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Edited by
Eleni Frangou, Motonobu Nakamura and Sayna Norouzi

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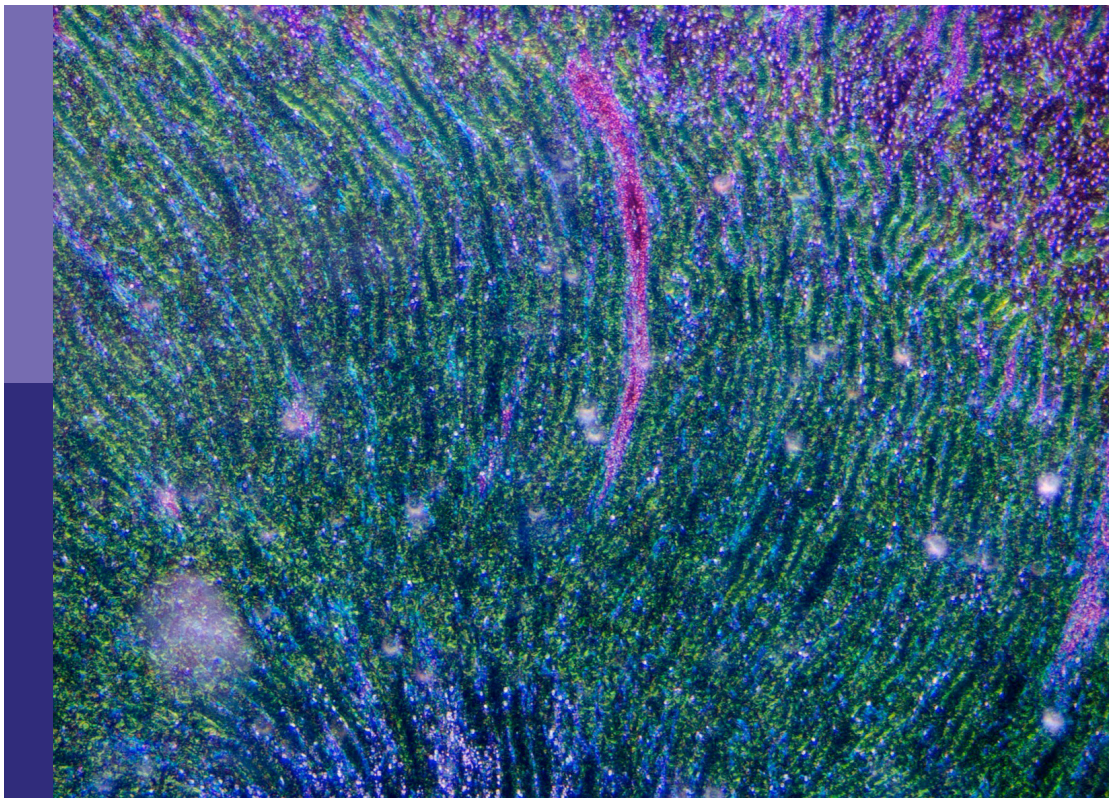

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Reviews in Frontiers in Nephrology

Topic editors

Eleni Frangou — General Hospital Limassol, Cyprus

Motonobu Nakamura — The University of Tokyo, Japan

Sayna Norouzi — Loma Linda University Medical Center (LLUMC), United States

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REVIEW
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Mechanism of *Abelmoschus manihot* L. in the Treatment of Contrast-Induced Nephropathy on the Basis of Network Pharmacology Analysis

Zhongchi Xu[1†], *Lichao Qian*[2†], *Ruge Niu*[1], *Yibei Wang*[1], *Ying Yang*[1], *Chunling Liu*[1] *and Xin Lin*[1*]

[1] Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China, [2] Nanjing Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China

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Edited by:
Michele Provenzano, Università di Bologna, Italy

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***Correspondence:**
Xin Lin
linxin@njucm.edu.cn

[†]These authors have contributed equally to this work

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Background: Contrast-induced nephropathy (CIN) is increasingly seen in patients receiving contrast medium. Abelmoschus manihot (L.) Medik. (Malvaceae) and its preparations are widely used and effective in the treatment of various chronic kidney diseases and CIN in China. It is supposed to be an important adjuvant therapy for CIN.

Methods: PubMed and CNKI were searched for the main compounds of *A. manihot* L. The Swiss target prediction platform, OMIM, GeneCards, DisGeNET, and DrugBank databases were mined for information relevant to the prediction of targets that *A. manihot* L. in the treatment of CIN. Subsequently, STRING database was applied for the construction of the PPI protein interaction network, meanwhile, the core targets were screened. DAVID database was used to perform the GO function and Kegg signal pathway enrichment analysis. AutoDockTools and PYMOAL were used for molecular docking. Vitro experiments were used to verify the effect of TFA, the main active component of *A. manihot* L., in the intervention of iopromide-induced cells injury.

Results: A total of 17 chemical components and 133 potential targets in *A. manihot* L. were obtained. The top 15 proteins with higher degree value were selected from the PPI network model, AKT1, PIK3R1, EGFR, SRC,AR, APP, TNF, GAPDH, MMP9, and PTPN1, etc. may be core targets. The enrichment analysis indicated that *A. manihot* L. was involved in the regulation of PI3K/AKT signaling pathway, FoxO signaling pathway, VEGF signaling pathway, HIF-1, TNF signaling pathway, melanoma, hepatitis B, and other signaling pathways which were mainly associated with the regulation of transcription and apoptosis, protein phosphorylation, inflammatory response, aging, and cell proliferation. Molecular docking indicated that the key components and core targets had a good binding ability. The vitro experiments illustrated that TFA reduces iopromide induced renal

tubular cell injury and apoptosis, which may be related to regulating the phosphorylation of AKT.

Conclusion: The study preliminarily revealed the multi-component, multi-target, and multi-pathway synergistic effects of *A. manihot* L. on CIN, which provide theoretical reference and basis for the study of the pharmacological mechanism of *A. manihot* L. in the treatment of CIN.

Keywords: contrast-induced nephropathy, Abelmoschus manihot L., network pharmacology, molecular docking, total flavonoids

INTRODUCTION

Contrast-induced nephropathy (CIN) is a sudden deterioration of renal function caused by intravascular injection of contrast medium (CM) for diagnosis and interventional operation. It is generally defined as renal function damage within 3 days after intravascular injection of CM without other causes, and serum creatinine (Scr) increases by more than 25% or 44μmol/L compared with baseline levels (1). With the wide application of CM in the field of radiation diagnosis and interventional therapy, the incidence of CIN is increasing year by year. It is a common complication of various ductus arteriosus diagnosis and treatment techniques represented by the percutaneous coronary intervention (PCI), and it is also a representative sign of poor patient prognosis. The incidence of CIN is estimated to range from 3.3% to 10.5% but can be as high as 10% to 20% or even 50% in high-risk patients (2, 3). Contrast-induced acute kidney injury (CI-AKI) is currently the third leading cause of hospital-acquired AKI (4, 5). The occurrence of CIN is related to a variety of factors, age, diabetes, renal insufficiency, progressive heart failure, low ejection fraction, acute myocardial infarction, cardiogenic shock, and kidney transplantation are fixed risk factors for CIN. Contrast agent dose, hypotension, anemia, and blood loss, dehydration, hypoalbuminemia, ACEI, diuretics, NSAIDs, nephrotoxic antibiotics, intra-aortic balloon counterpulsation are reversible risk factors for CIN (6, 7). Studies have shown that CIN increases the risk of major adverse events such as renal failure and cardiovascular events, such as acute myocardial infarction, stroke, and end-stage renal disease requiring kidney replacement (8–10). Current guidelines do not support pharmacological interventions to prevent CIN because none of the pharmacological practices has been shown to provide consistent protection (1). To date, there are no recognized effective preventive measures. At present, the prevention and treatment of CIN are mainly to monitor renal function, avoid the combined use of nephrotoxic drugs, maintain effective blood volume, postoperative hydration, and other non-specific treatments (11, 12). CIN is the culprit that leads to the rapid deterioration of renal function, and it is a sign of increased short-term and long-term cardiovascular events and adverse renal events in patients. It is critical for early intensive intervention in high-risk patients with CIN.

Traditional Chinese Medicine (TCM) is the most common form of alternative medicine and supplementary medicine in Asia, and has been widely used in the treatment of CKD. Abelmoschus manihot (L.) Medik. (Malvaceae) is a herb used in Traditional Chinese Medicine to treat some kidney diseases. Modern pharmacology has confirmed that the flavonoids of Abelmoschus manihot L. have the effects of anti-inflammation, antipyretic, analgesia, relieving cardio-cerebral myocardial ischemia, and hypoxia, protecting renal tubules and glomeruli (13). *A. manihot* L. and its preparations are widely used and effective in the treatment of various chronic kidney diseases and CIN, but the pharmacological mechanism of its treatment of CIN has not been fully elucidated. Therefore, this study undertook an in-depth analysis and prediction of the active component-target-pathway of Abelmoschus manihot L. in the treatment of CIN by the method of network pharmacology and explores the mechanism of *A. manihot* L. in the treatment of CIN.

MATERIALS AND METHODS

Collection of Active Components From *A. manihot* L.

All the chemical constituents of *A. manihot* L. were searched in CNKI and PubMed. The chemical constituents with pharmacological activities were selected and input into the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) to query the serial number of CAS and download the corresponding sdf molecular structures of the active components. The main active components of *A. manihot* L. were determined.

Target Prediction of the Main Active Components

The sdf molecular structures of active components were imported into the Swiss Target Prediction platform (14). The species was limited to "Homo Sapiens". Active components were subject to target enrichment prediction and the predicted genes were collected. All the genes were integrated and duplicates were removed. These genes constitute the prediction targets of the main active components of *A. manihot* L.

Collection of Targets Related to CIN

A search for target genes related to CIN was performed in the OMIM database (https://www.omim.org/), Gene cards database

(https://www.genecards.org/), DrugBank database (https://www.drugbank.ca/), DisGeNET database (https://www.disgenet.org/) with the keywords "Contrast Induced Nephropathy" and "CIN". Duplicates were deleted and the main genes related to CIN were integrated for further research.

Acquiring Targets of Main Active Components for CIN Treatment

Venny 2.1.0 (http://bioinfogp.cnb.csic.es/tools/venny/index.html) software was used to obtain the intersection between the predicted targets of *A. manihot* L. and the main targets of CIN. A Venn diagram was drawn. These intersection genes may be the related targets of *A. manihot* L. in the treatment of CIN.

Construction of Protein-Protein Interaction (PPI) Network and Screening of the Core Genes

The intersection of the predicted targets in the network model were imported into the String11.0 database (https://string-db.org/) (15), the species was limited to "Homo Sapiens". The highest confidence protein score value was >0.7. Unconnected single proteins were removed to construct the PPI diagram of these core targets. Then the relevant information of the PPI diagram is imported into the Cytoscape 3.6.1 software to construct a network model and perform topological analysis, and the node size, color, and edge thickness are adjusted according to the degree and comprehensive score. Taking the value as a reference, the core protein targets in the PPI network were screened.

Enrichment Analysis of Gene Ontology (GO) and Signaling Pathway

The core protein targets were Imported into DAVID online analysis platform (https://david.ncifcrf.gov/) (16) for enrichment analysis of the biological process (BP), molecular function (MF), and cellular component (CC). The Kyoto Encyclopedia of Genes and Genomes (KEGG) databases were used to enrichment analyze the signaling pathways related to the targets. The species and background were both limited to "Homo Sapiens". The main BPs, MFs, CCs, and pathways of *A. manihot* L. for CIN treatment were selected according to the criterion of $p<0.01$. The smaller the p-value, the higher the degree of enrichment. The top 20 GO biological functions were selected. The network model was established and the bar chart was drawn. Based on the results of BPs and signaling pathways related to the targets enriched in the GO-BP and KEGG database, the enrichment results were visualized and the bubble diagram was drawn.

Construction and Analysis of the Network Model of Main Active Components-CIN Treatment Related Targets-CIN Treatment Related Signaling Pathways

The main active components, the corresponding CIN related targets, and CIN treatment related signaling pathways were imported into Cytoscape 3.6.1 software. The main active component-target-signaling pathways network model was drawn. The topological analysis was used to analyze the network model and calculate the degree. The larger the value of the degree, the more important the node is in the network. The node size, color, and edge thickness are adjusted according to the degree, and visualization was carried out.

Molecular Docking Verification

Molecular docking was carried out between the key compounds of *A. manihot* L. and the core targets obtained from the PPI network. The receptor protein encoded by the gene was identified by the UniProt database (https://www.uniprot.org/), and its three-dimensional structure was obtained from the RCSB PDB database (https://www.rcsb.org/). The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) was used to download the two-dimensional structure of the molecular ligand. Then the structures were imported into the PyMOL2.4.0 software for receptor protein dehydration. The hydrogenation and charge calculation of the protein was carried out by AutoDockTool for structure optimization. The parameters of the receptor protein docking site were set to include active pocket sites that bind to small molecules of ligands. Finally, the AutoDockTools-1.5.6 software was used to dock the key active components with the corresponding targets, optimize the binding affinity between receptors and ligands and obtain the three-dimensional structures.

Preparation of Total Flavonoids of *A. manihot* L.

Total flavonoids of *A. manihot* L. (TFA) were extracted from the dry corolla of *A. manihot* L. TFA was extracted by the Department of Drug Preparation of the Affiliated Hospital of Nanjing University of Chinese Medicine. Briefly, 0.5 kg of raw *A. manihot* L. flowers was immersed in 8000mL 75% ethanol for 1 h and then heated to 90°C for 1 h to achieve alcohol extraction as ambrette fluid extract. After filtration, the extract was evaporated to produce a dry extract powder under vacuum at 60°C. The dried residue was dissolved in water for use in the experiments (17).

Experimental Verification

The data of network pharmacology show that the flavonoids are the key components of *A. manihot* L. in the treatment of CIN, and AKT is the core target. TFA inhibits the progression of Contrast-induced Nephropathy mainly by regulating apoptosis. Previous studies have successfully established the injury model of renal tubular epithelial cells (HK2) with iopromide. Iopromide can induce apoptosis of HK2 cells. Therefore, we used iopromide to establish an *in vitro* model of renal injury induced by a contrast medium. Then TFA was used to interfere with the model to evaluate whether it can regulate AKT phosphorylation and reduce apoptosis.

Reagents

Bcl-2 (lot no. AF6139) and Bax (lot no. AF0120) were purchased from Affinity Biosciences Co., LLC. (Cincinnati, USA). Caspase3

(lot no. 9662) and Cleaved Caspase-3 (Asp175) Antibody (lot no. 9661) were purchased from Cell Signaling Technology Co., Ltd. (Shanghai, China). Antibodies to AKT (lot no. 60203-2-Ig), antibody to phospho-AKT (Ser473)(lot no. 66444-1-Ig), antibody to GAPDH (lot no. 60004-1-Ig), horseradish peroxidase (HRP)-conjugated Affinipure goat anti-mouse IgG (H+L)(lot no. SA00001-1) and HRP-conjugated Affinipure goat anti-rabbit IgG (H+L) (lot no. SA00001-2) were purchased from Proteintech Biotechnology Co., Ltd. (Wuhan, China). Iopromide was purchased from Bayer Co., LLC. (Leverkusen, Germany). Fetal bovine serum (FBS), 0.25% trypsin-EDTA, phosphate buffered saline (PBS), and Dulbecco's modified Eagle medium/F-12 (DMEM/F-12) were purchased from Thermo Fisher Scientific (Scoresby, Australia). Cell Counting Kit-8 (CCK-8) was obtained from APExBIO (Houston, TX, USA). One Step TdT-Mediated dUTP Nick End Labeling (TUNEL) Apoptosis Assay Kit was purchased from Vazyme Biotechnology Co., Ltd. (Nanjing, Jiangsu). 4,6-diamidino-2-phenylindole (DAPI) staining solution and BCA protein assay kit were purchased from Beyotime Biotechnology (Shanghai, China).

Cell Line and Culture

Normal renal tubular epithelial cells (HK2) were obtained from Saiku Biotechnology Co., Ltd. The cells were maintained in DMEM/F-12 supplemented with 10% FBS and incubated at 37°C in 5% CO_2. The cells at approximately 80% to 90% confluency were digested and passaged.

Cellular Viability

HK2 cells were digested and seeded in 96-well plates at 1×10^4 cells per well. After 24 h of incubation, the cells were cultured in a serum-free medium and stimulated with iopromide (111mg I/mL) in the absence and presence of TFA (0.6 mg/mL). After 12 h of treatment, the medium was discarded, and 100μL serum-free medium containing 10% CCK-8 was added to each well. After incubating for another 1 h, the absorbance was measured using a model ELx800 spectrometer (BioTek Instruments, Winooski, VT, USA) at a wavelength of 450 nm. Cell viability is expressed as a percentage of the control group.

Fluorescence Staining of Apoptotic Cells

TUNEL staining kit and DAPI staining solution were used to assess the presence of apoptotic cells. Briefly, the cells were incubated and treated in accordance with the experimental protocol, washed three times with PBS, and fixed with 4% paraformaldehyde for 30 min. Then, they were permeabilized with 0.3% Triton X-100 in PBS for another 30 min and washed three times with PBS. 50μL of TUNEL staining solution was added to each well and incubated in the dark for 1 h at 37°C. Then, cells were washed three times with PBS, and 100μL of DAPI staining solution was added to each well, followed by incubation in the dark for 10 min and washing with PBS. Finally, cell fluorescent images were captured using a fluorescence microscope (Nikon Ni-U, DS-Qi2) equipped with standard red and ultraviolet fluorescence cubes. Fluorescent images were analyzed quantitatively using ImageJ software.

Western Blot Analysis

After incubation and intervention, the cells were lysed in RIPA buffer supplemented with a 2% protease and phosphatase inhibitor cocktail for 20 min on ice. After sonication, the samples were centrifuged at 4°C for 20 min, and each supernatant was collected for subsequent experiments. Total protein concentration was determined using a BCA protein assay kit. Equal amounts of protein (20μg) were separated by 10% or 12% sodium-dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The resolved proteins were electrophoretically transferred to polyvinylidene difluoride 9 (PVDF) membranes (Millipore, Billerica, MA, USA). The membranes were blocked with 5% non-fat dried milk in PBS containing Tween (PBST) buffer for 1 h at room temperature, washed three times with PBST, and incubated with primary antibodies overnight at 4°C. The membranes were washed again and incubated with HRP-conjugated anti-rabbit or anti-mouse IgG for 1 h at room temperature. The bands were flushed with chemiluminescent HRP substrate and imaged using a chemiluminescence system (ChemiDocTM XRS+ from Bio-Rad, CA, USA). Western blot images were analyzed quantitatively by Image Lab software. GAPDH was assayed to confirm equal loading of proteins.

Statistical Analyses

Statistical analyses were performed using SPSS software. All values were expressed as mean ± standard deviation (SD). Comparisons of two populations were made using an unpaired 2-tailed Student's t-test. For multiple groups, statistical significance was determined using a one-way analysis of variance (ANOVA) followed by Dunnett's test. Statistical significance was set at $p<0.05$.

RESULTS

Main Active Components of *A. manihot* L.

Through the collation of related papers (13, 18–23), a total of 17 chemical components such as flavonoids, organic acids and steroids in *A. manihot* L. were obtained as the main active components of study. The specific information is shown in **Table 1**.

Target Prediction of *A. manihot* L.

The sdf molecular structures of all the main active components in **Table 1** were imported into the Swiss Target Prediction platform, and the species was set up to "Homo Sapiens". The related targets of the above active components were predicted, all

TABLE 1 | Main active components of *A. manihot L.*.

Category	Molecule Name	CAS	Sdf
Flavonoids	Quercetin	117-39-5	
	Rutin	153-18-4	
	Hyperoside	482-36-0	
	Isoquercetin	482-35-9	
	Quercetin 3'-O-glucoside	19254-30-9	
	Quercimeritrin	491-50-9	
	Gossypetin	489-35-0	
	Myricetin	529-44-2	
	Myricetin-3-O-β-glucoside	19833-12-6	
Organic acids	Caffeic acid	501-16-6	
	Gallic acid	149-91-7	
	Protocatechuic acid	99-50-3	
	2,4-dihydroxybenzoic acid	89-86-1	
Steroids	β-sitosterol	64997-52-0	
	Sitgmasterol	83-48-7	
	α-spinasterol	481-18-5	
Nucleosides	Adenosine	58-61-7	

the information of targets was collected, and a total of 133 potential targets of *A. manihot* L. were obtained after deleting the integration of repeated invalid targets.

Related Targets of CIN

Search OMIM database, Genecards database, DrugBank database, and DisGeNET database with "Contrast Induced Nephropathy" and "CIN" as keywords. A total of 2832 CIN related targets were screened.

Key Targets of *A. manihot* L. in Treatment of CIN

The predicted related targets of *A. manihot* L. were mapped to the main targets related to CIN using Venny 2.1.0 software.

A Venn diagram was drawn (**Figure 1**). A total of 75 intersection targets were obtained. These may be the core targets of *A. manihot* L. for CIN treatment.

Construction of PPI Network Model

The 75 intersection targets of *A. manihot* L. in treatment of CIN were imported into the String database, and the species was limited to "Homo sapiens". The relationship diagram of protein-protein interaction was obtained, free targets were excluded, the highest confidence protein score value was set as > 0.7, a PPI network was constructed (**Figure 2**). The relevant information was obtained and imported into the Cytoscape software. The top 15 proteins with higher degree value were selected (**Figure 3**), including AKT1, Phosphatidylinositol 3-kinase regulatory subunit alpha (PIK3R1), epidermal growth factor receptor (EGFR), SRC, Androgen receptor (AR), Amyloid-beta A4 protein (APP), Tumor necrosis factor (TNF), Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Matrix metalloproteinase-9 (MMP9), Tyrosine-protein phosphatase non-receptor type 1 (PTPN1), and others. The PPI network was visualized and analyzed. The node color and size have been adjusted according to the degree, the bigger the node, the larger the degree value. The thicker the edge, the closer the relationship between the proteins. The darker the color, the more important the target. These targets may be core targets of *A. manihot* L. in the treatment of CIN. The targets are involved in the regulation of cell proliferation and apoptosis, metabolism, growth, and angiogenesis, and are closely related to the development and prognosis of CIN. It is suggested that the above targets may play a crucial role in the treatment of CIN. These findings confirmed the multi-component and multi-target synergistic mechanism of *A. manihot* L. in the treatment of CIN.

Enriched Gene Biological Functions and Signaling Pathways

The 75 related core targets were uploaded to the DAVID database for GO enrichment analysis and KEGG pathway enrichment analysis. A $p \leq 0.01$ was the screening parameter. 157 biological processes (BP), 40 cellular composition (CC), 36 molecular functions (MF), and 73 KEGG signaling pathways were obtained. GO and KEGG enrichment analyses were carried out to explore the potential function and mechanism of target genes related to the treatment of CIN in *A. manihot* L.

With $p<0.01$ as the screening criterion, the first 10 GO biological functions of these targets were shown in the form of a histogram (**Figure 4**). The top 20 BPs and KEGG signaling pathways enriched were plotted as bubble diagrams (**Figures 5**, **6**). In the bubble diagram, the node size represents the gene number, the larger the node, the more genes corresponding to the node. The color of the node represents the *p*-value. The smaller the *p*-value, the redder the color, otherwise, the values were depicted in shades of green. BPs enrichment analysis showed that these targets were involved in the composition of a variety of cell components and regulated the activities of a variety of kinases and transcription factors. The therapeutic effect of *A. manihot* L. on CIN may be related to the negative regulation of apoptosis, protein autophosphorylation, positive regulation of protein kinase B signal transduction, transmembrane receptor protein tyrosine kinase signaling pathway, cell proliferation, oxidative stress, MAPK activation and so on. The CCs may have therapeutic roles in CIN by affecting BPs, such as the regulation of transcription and apoptosis, protein phosphorylation, inflammatory response, aging, and cell proliferation.

KEGG signaling pathway enrichment analysis showed that *A. manihot* L. was involved in the regulation of PI3K/AKT signaling pathway, FoxO signaling pathway, VEGF signaling pathway, HIF-1, TNF signaling pathway, melanoma, hepatitis B, and other signaling pathways, which were closely related to the pathogenesis of CIN.

Construction and Analysis of the Network Model of Main Active Components-CIN Therapy Related Targets-CIN Therapy Related Signaling Pathways

The main active components, CIN therapy related targets, and CIN therapy related signaling pathways were imported into

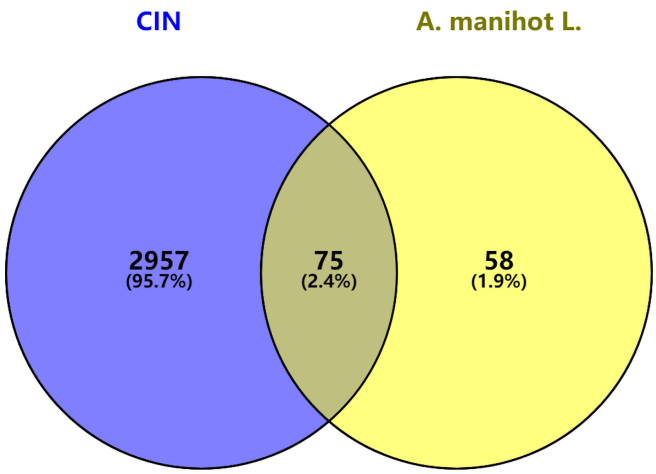

FIGURE 1 | Intersection targets of *A. manihot L.* in the treatment of CIN.

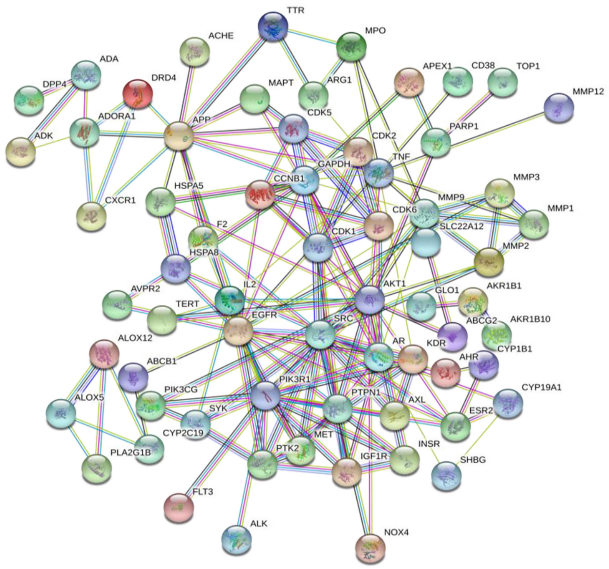

FIGURE 2 | The PPI network model.

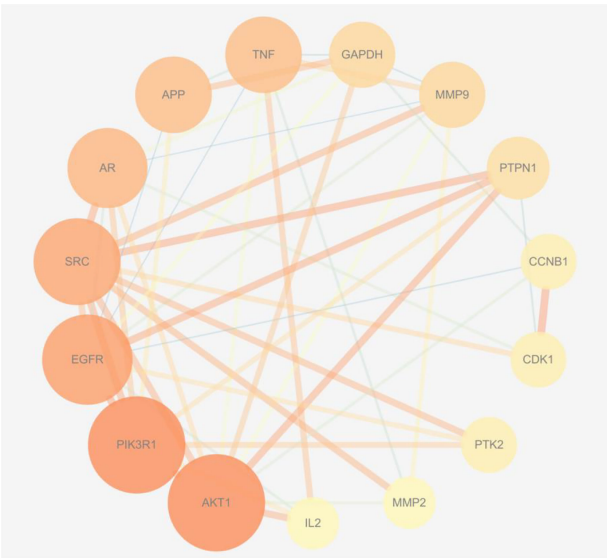

FIGURE 3 | The core targets in the PPI network. The bigger the node, the larger the degree value. The thicker the edge, the closer the relationship between the proteins. The darker the color, the more important the target.

Cytoscape 3.6.1 to build a main active component-target-signaling pathway network model (**Figure 7**). The topology analysis of the network model is carried out, the model included 170 nodes and 555 edges. In this model, 17 active components were shown as diamond-shaped yellow nodes, 133 targets were exhibited as blue regular hexagon nodes, 20 signaling pathways were marked as a red triangle. The edges represent the interaction between the components and the targets.

The network model shows the characteristics of cooperative regulation of multi-components, multi-targets, and multi-pathways in the treatment of *A. manihot* L. We found that the PI3K/AKT signaling pathway, FoxO signaling pathway, VEGF signaling pathway, HIF-1 signaling pathway, and TNF signaling pathway are important signaling pathways in the treatment of CIN. It is worth noting that most of the core targets in the PPI network participate in the PI3K/AKT signaling pathway, and the

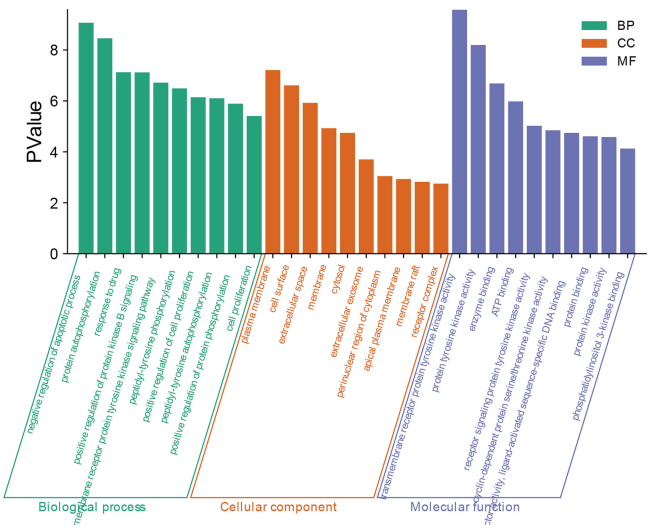

FIGURE 4 | Enrichment analysis of gene biological functions.

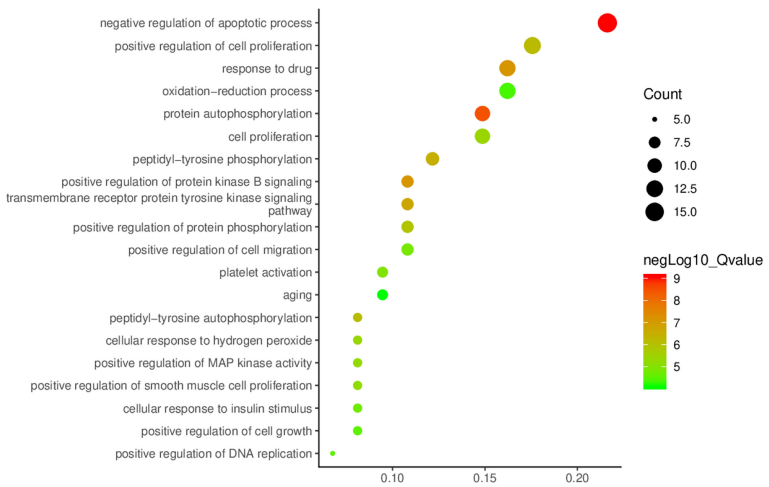

FIGURE 5 | Enrichment analysis of biological process.

results are consistent with the results of KEGG enrichment. Therefore, we chose the PI3K/AKT signaling pathway for further exploration to determine the potential mechanism of *A. manihot* L. for CIN treatment.

Docking of Core Components and Corresponding Main Targets of *A. manihot* L.

The top three components (Quercetin, Myricetin, Gossypetin) selected from the 17 key components were docked with the corresponding two targets (AKT1,PIK3R1) of the 15 core targets. The molecular docking showed that all these active compounds could easily enter and bind to the active pockets of pathway-related proteins. The binding affinity < 0 indicates that the receptor and the ligand have the ability of spontaneous binding. The lower the binding affinity score is, the more stable the crystal structure of the protein corresponding to the formation of the compound and the target is. The results of molecular docking show that the binding affinity between the key components and corresponding core targets of *A. manihot* L. did not exceed -4.5 kcal/mol, which indicated that the key components and core targets had a good binding ability (**Figure 8**, **Table 2**). The main active components of *A. manihot* L. may play a therapeutic role in CIN by intervening in the corresponding core targets.

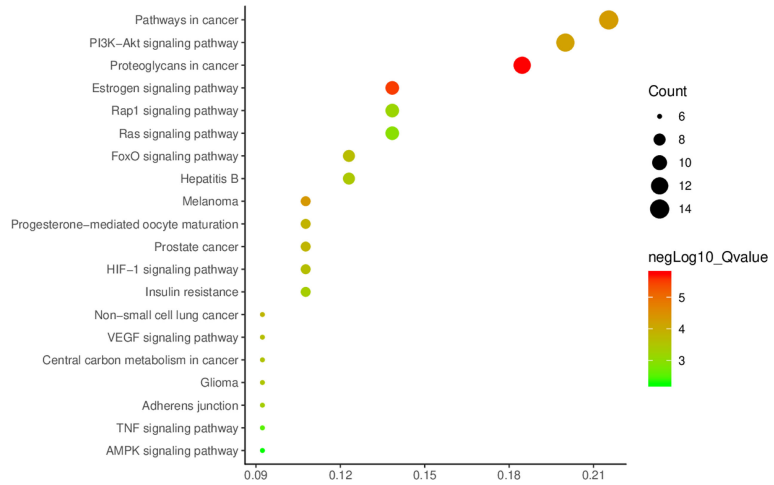

FIGURE 6 | Enrichment analysis of KEGG signaling pathway.

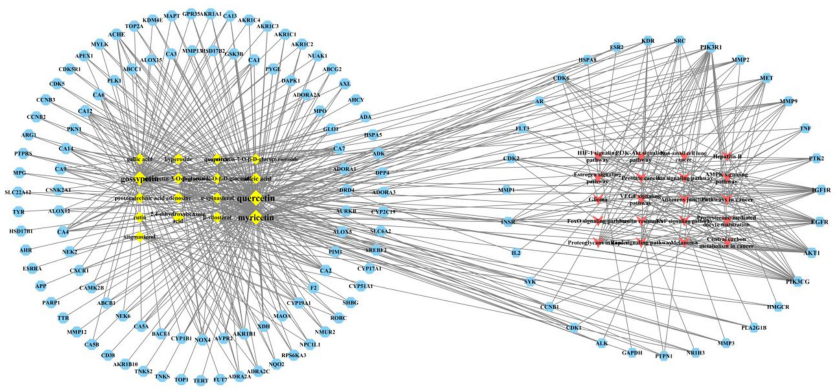

FIGURE 7 | Main Active Components-Targets-Signaling Pathways network model.

TFA Reduces Iopromide Induced Renal Tubular Cell Injury and Apoptosis by Regulating the Phosphorylation of AKT

To further observe the effect of CM on renal tubular epithelial cells, we established an *in vitro* model of CIN induced by iopromide. TFA was used to intervene iopromide-induced HK2 cells injury, and its effect on cellular viability was evaluated by the CCK8 method. Compared with the iopromide group (111mgI/mL), the TFA group (0.6mg/mL) significantly increased cell viability (**Figure 9A**), so TFA could reduce the cell injury induced by iopromide. The results of network pharmacology show that PI3K/AKT signaling pathway may be an indispensable pathway for *A. manihot L.* in the treatment of CIN. AKT is widely involved in a variety of physiological processes *in vivo*. AKT, as the core target of PPI network enrichment, has a good binding ability with the core components of *A. manihot* L. We found that TFA can significantly increase the phosphorylation level of AKT (**Figure 9B**), which indicates that AKT may be an important target for TFA to reduce the injury of renal tubular epithelial cells induced by iopromide. Meanwhile, TFA attenuated iopromide-induced apoptosis in HK2 cells, which was confirmed by TUNEL staining (**Figure 9D**). We further tested the expression of apoptosis-related proteins including Caspase3, Bcl2, and Bax (**Figure 9C**), and the results of Western blot confirmed the above conclusion.

DISCUSSION

Intravascular injection of CM is an irreplaceable step in percutaneous coronary intervention. With the wider application of CM, CIN has become a common complication after PCI. CIN has a significant negative impact on public health and finances and CIN-related diseases are a major healthcare problem. In the US healthcare system, more than 2 million cardiac interventional operations were performed each year, and more than 30 million doses of the iodine CM were used (24).

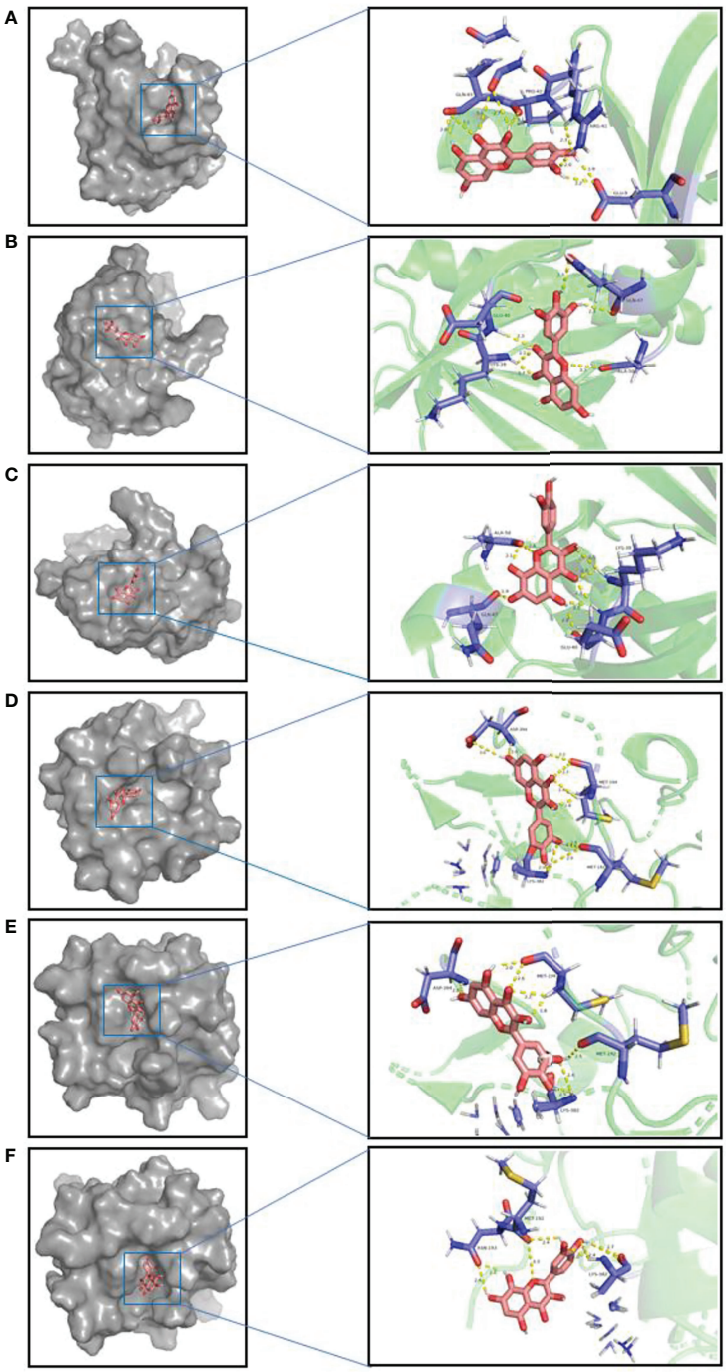

FIGURE 8 | Schematic diagram of molecular docking **(A)**. AKT1-Quercetin. **(B)** AKT1-Myricetin. **(C)** AKT1-Gossypetin. **(D)** PIK3R1-Quercetin. **(E)** PIK3R1-Myricetin. **(F)** PIK3R1-Gossypetin. Interacting amino acids and compound structures are shown on lines, in which hydrogen bonds are shown in yellow, amino acids are shown in purple, compound structures are shown in pink.

The pathophysiological mechanism of CIN is complex, and its explicit mechanism is far from clear, especially its cellular and molecular mechanism (25). The CM has a direct cytotoxic effect on vascular endothelial cells and renal tubular epithelial cells. After intravascular injection of CM, changes in renal hemodynamics occurred, characterized by rapid and transient vasodilation, accompanied by continuous vasoconstriction, increased renal vascular resistance, and decreased renal blood flow, resulting in a decrease in glomerular filtration rate and renal ischemia (26, 27). In addition, CM can cause osmotic

TABLE 2 | The binding affinity between components and targets in molecular docking.

Component	Target	Binding Affinity (kcal/mol)
Quercetin	AKT1	-5.47
	PIK3R1	-8.26
Myricetin	AKT1	-4.78
	PIK3R1	-7.57
Gossypetin	AKT1	-5.25
	PIK3R1	-6.41

diuresis, increase fluid excretion, increase renal tubular reabsorption, vasoconstriction is magnified by secondary renal insufficiency, resulting in a decrease in renal blood flow and oxygen supply, an increase in oxygen consumption and aggravation of ischemic and anoxic symptoms of the medulla (28), which eventually leads to renal tubule injury and tubule formation (29). Hypoxia induces the formation of reactive oxygen species (ROS) (30). A great deal of evidence shows that ROS plays an important role in the renal damage caused by CM (31, 32). ROS can directly damage renal tubular epithelial cells and vascular endothelial cells. CM increases the production of ROS and oxidative stress in kidneys and mediates cell membrane damage, which leads to apoptosis and necrosis, especially in renal tubular epithelial cells in the outer medulla (33, 34). CM induces apoptosis mainly through internal or mitochondrial cleavage of caspase-3 and caspase-9, these proteases are the executors of cutting key cellular proteins (35). This apoptotic pathway is regulated by members of the Bcl-2 family (36, 37).

Studies have shown that *A. manihot* L. can improve renal function, such as improving podocyte apoptosis, inhibiting immune response, reducing inflammation, improving renal fibrosis, and reducing renal injury (38, 39). Meanwhile, *A. manihot* L. has the effect of scavenging oxygen free radicals (40), which is helpful to improve the oxidative stress damage caused by CIN. Clinical randomized controlled trials show that perioperative prophylactic use of *A. manihot* L. and its pharmaceutical preparation during the percutaneous coronary intervention can effectively reduce the incidence of CIN (41, 42). Network pharmacology is an effective method to explore the relationship between plant medicine, targets, and diseases. at present, the network pharmacological analysis has been widely used to study the pharmacological mechanism of traditional Chinese medicine. *A. manihot* L. contains quercetin, rutin, myricetin, hyperin, and other 17 active components in the potential treatment of CIN, which are numerous and complex. This method is used to predict the mechanism of *A. manihot* L. in the treatment of CIN. Our study provides evidence that *A. manihot* L. ameliorates iopromide-induced CIN, which may be mediated by the activation of the PI3K/AKT signaling pathway.

The results of network pharmacology show that many pathways are closely related to the pathogenesis of CIN. PI3K/AKT, FoxO, VEGF, HIF-1, TNF, and other signaling pathways are vital pathways. The PI3K/AKT signaling pathway is related to cell growth and proliferation. FOXO is a key downstream factor of the PI3K/Akt signaling pathway, which induces the expression of death receptor ligands and Bcl-2 family members through negative regulation of the PI3K-Akt signaling pathway, and participates in cell survival, proliferation, growth, and angiogenesis (43, 44). Apoptosis signaling transduction plays an important role in the pathogenesis of CIN. Studies have confirmed the protective role of phosphorylation of AKT in the process of cell injury (45). Regulation of the PI3K/AKT signaling pathway can down-regulate cleaved caspase-3 and reduce the ratio of Bax/Bcl2, which can reduce apoptosis induced by CM (46).

Molecular docking was used to verify the binding ability of the main active components of *A. manihot* L. and its potential therapeutic targets. The results illuminated that there was a strong interaction between the active components and the proteins of the PI3K/AKT signaling pathway, which further verified the therapeutic effect of the main active components of *A. manihot* L. on CIN. We selected the TFA to verify the protective mechanism *in vitro*. By regulating the phosphorylation of AKT, TFA significantly reduced iopromide-induced apoptosis in HK2 cells. These results suggest that the treatment of *A. manihot* L. on CIN may be mediated by the regulation of the PI3K/AKT signaling pathway.

This study is a preliminary attempt to explore the effect of active components of *A. manihot* L. on the PI3K/AKT signaling pathway. It may provide a new direction for further study on the molecular mechanism of active compounds interfering with CIN. Nevertheless, there are some limitations to the study. The network pharmacology, which was based on the information collected in various databases, challenges the reliability of data collection and the accuracy of conclusions. Considering the importance of the PI3K/AKT signaling pathway in this network pharmacology, our experiment is limited to paying attention to the PI3K/AKT signaling pathway, and other pathways need to be further verified.

CONCLUSION

In this study, network pharmacology was used to explore the potential mechanism of *A. manihot* L. on CIN, which may be related to the regulation of the PI3K/AKT signaling pathway. Studies have shown that flavonoids are important active components of *A. manihot L.* in the treatment of CIN. AKT1 and PIK3R1 are the core target for the treatment of CIN. The results of molecular docking show that the main active components of *A. manihot* L. have good binding ability to the corresponding core targets. The vitro experiments confirmed that total flavonoids of *A. manihot* L. can significantly reduce iopromide-induced apoptosis of HK2 cells, which may be related to the up-regulation of AKT phosphorylation. In summary, this

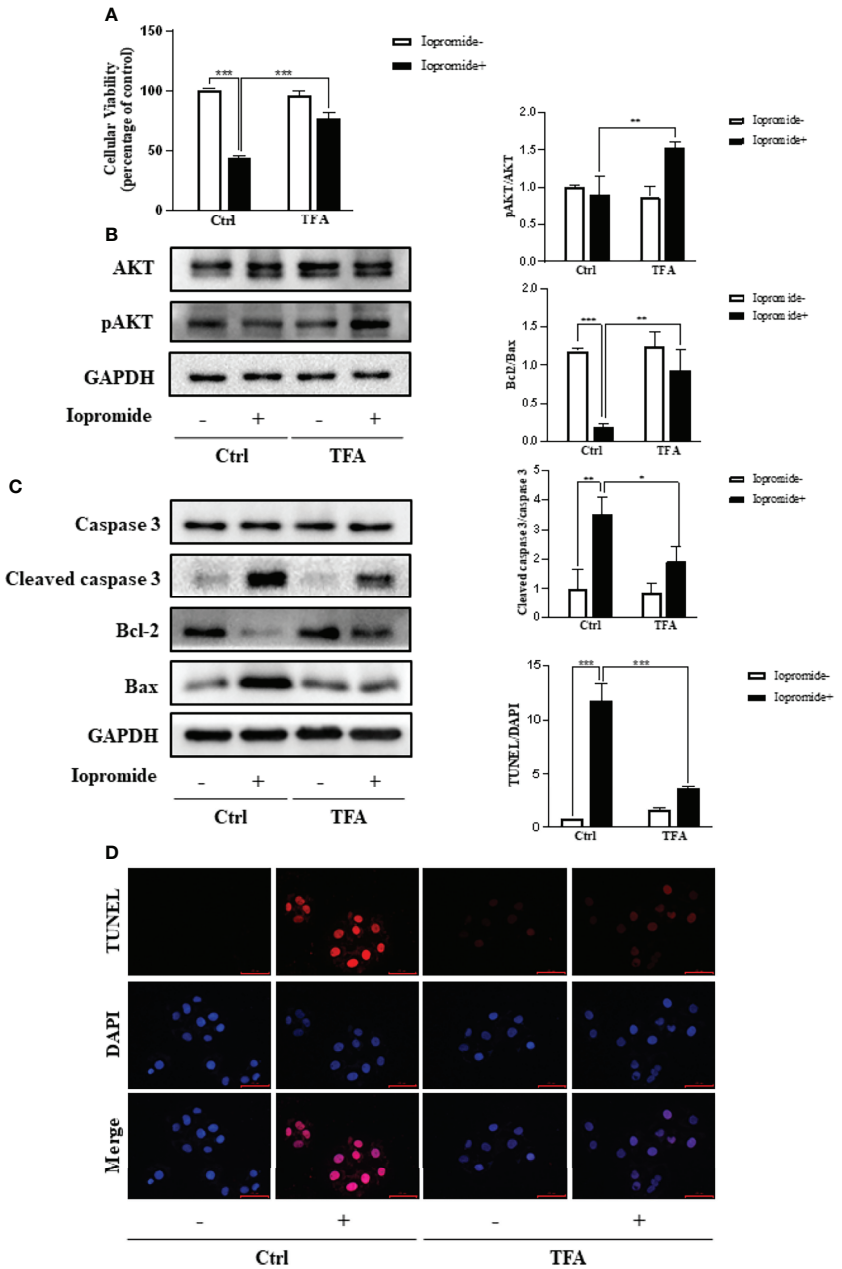

FIGURE 9 | TFA Reduces Iopromide induced Renal Tubular Cell Injury and Apoptosis by Regulating the Phosphorylation of AKT. **(A)** Effects of TFA on cellular viability of iopromide induced cell iniury. HK2 cells in 96-well plates were pretreated with TFA (0.6mg/mL) for 1 h and then challenged with or without iopromide (111mg I/mL) for another 12 h. Cellular viability was evaluated using a CCK-8 assay. Data are expressed as the percentages of living cells versus the control (Ctrl) (means ± SD, n=3, ***p<0.001 versus in Ctrl). **(B)** Effects on the phosphorylation of AKT in iopromide induced cells injury. HK2 cells were exposed to the indicated concentrations of iopromide with or without TFA for 12 h. Cellular lysates were subjected to western blot analysis of AKT, phosphorylated AKT and GAPDH. Statistical analysis opf phosphorylated AKT is shown on the right (means ± SD, n=3, **P<0.01 versus in Ctrl). **(C)** Effects of TFA on expressioin of apoptosis related proteins. HK2 cells werte pretreatred with TFA for 1 h and then challenged with or without iopromide for another 12 h. Cellular lysates were subjected to western blot analysis of cleaved caspase3, Bcl-2 and Bax. Statistical analysis of results are shown on the right (means ± SD, n=3, *P<0.05, **P<0.01, ***P<0.001). **(D)** Effects of TFA in iopromide induced cells apoptosis by TUNEL staining assay. HK2 cells were incubated with TFA for 12 h in the presence and absence of iopromide. Apoptosis cells were detected by TUNEL staining. Flourescence staining was observed by flourescence microscope (magnification x 200). Statistical analysis of results are shown on the right (means ± SD, n=3, ***P<0.001).

study preliminarily revealed the multi-component, multi-target, and multi-pathway synergistic effect of *A. manihot* L. on CIN, which provided a theoretical reference and basis for the study of the pharmacological mechanism of *A. manihot* L. in the treatment of CIN.

AUTHOR CONTRIBUTIONS

XL conceived and designed the experiments. ZX, YW, and RN collected and analyzed the data. LQ carried out the molecular docking analysis. ZX and YY performed the experiments. ZX and CL wrote the manuscript. XL proofread the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneph.2022.834513/full#supplementary-material

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REVIEW
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SGLT2 Inhibitors: A Broad Impact Therapeutic Option for the Nephrologist

Antonio Granata[1], Francesco Pesce[2], Massimo Iacoviello[3], Massimiliano Anzaldi[4], Francesco Amico[5], Maria Catalano[5], Giuseppe Leonardi[6], Carmela Gatta[7], Giusy Costanza[8], Salvatore Corrao[9] and Loreto Gesualdo[2]*

[1] Nephrology and Dialysis Unit, "Cannizzaro" Emergency Hospital, Catania, Italy, [2] Renal, Dialysis and Transplantation Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy, [3] Cardiology Unit, Department of Medical and Surgical Science, University of Foggia, Foggia, Italy, [4] Diabetes Unit, "Cannizzaro" Emergency Hospital, Catania, Italy, [5] Cardiology Unit, "Cannizzaro" Emergency Hospital, Catania, Italy, [6] Cardiology Unit, Azienda Ospedaliera Universitaria (A.O.U.) "Policlinico-San Marco", Catania, Italy, [7] Internal Medicine Unit, Azienda Ospedaliera Universitaria (A.O.U.) "Policlinico-San Marco", Catania, Italy, [8] Nephrology and Dialysis, "Vittorio Emanuele" Hospital, Gela, Italy, [9] Department of Internal Medicine, "Azienda di Rilievo Nazionale ed Alta Specializzazione (ARNAS) Civico, Di Cristina e Benfratelli", Palermo, Italy

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Edited by:
Michele Provenzano, Università di Bologna, Italy

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***Correspondence:**
Antonio Granata, antonio.granata4@tin.it

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Since their introduction as antidiabetic drugs, SGLT2 inhibitors (SGLT2i) have come a long way, proving to be beneficial on cardiovascular and renal outcomes independently of diabetes status. The benefits go far beyond glycemic control, and both the cardio- and nephroprotection are underpinned by diverse mechanisms. From the activation of tubule glomerular feedback and the consequent reduction in hyperfiltration to the improvement of hypoxia and oxidative stress in the renal cortex, SGLT2i have also been shown to inhibit hepcidin and limit podocyte damage. Likewise, they improve cardiac metabolism and bioenergetics, and reduce necrosis and cardiac fibrosis and the production of adipokines, cytokines, and epicardial adipose tissue mass. In terms of outcomes, the efficacy has been demonstrated on blood pressure control, BMI, albuminuria, stroke, heart disease, and mortality rate due to cardiovascular events. Patients with chronic kidney disease and proteinuria, with or without diabetes, treated with some SGLT2i have a reduced risk of progression. The analysis of subgroups of individuals with specific diseases such as IgA nephropathy has confirmed this solid effect on renal outcomes. Given these overarching activities on such a broad pathophysiological background and the favorable safety profile that goes with the use of SGLT2i, it is now certain that they are changing our approach to clinical interventions for important outcomes with an impressive impact.

Keywords: SGLT 2 inhibitors, diabetes, CKD - chronic kidney disease, glycemic control, Cardioprotection, Nephro- protection

INTRODUCTION

Diabetic kidney disease (DKD) is a microvascular complication associated with at least 30% of the diabetes cases worldwide and a well-established leading cause of chronic kidney diseases (CKDs) and the end-stage renal disease (ESRD) (1).

DKD is a global burden, and in 2012, its mortality rose by 94% (2). DKD risk factors can be classified into three major categories: susceptibility risk factors (such as age, sex, family history, ethnicity), initiation factors (such as hyperglycemia), and progression factors (such as hypertension, diet, obesity) (3).

DKD is associated with numerous structural alterations in the kidney, as reported by different authors. Most common structural alterations include an increased thickness in different kidney compartments, such as glomerular, capillary, tubular, and basement membrane (4–6). Moreover, the pathophysiology of DKD consists of different critical metabolic changes, which promote inflammation and fibrosis. These changes include hyper aminoacidemia, glomerular hyperfiltration, glomerular hyper infusion, and hyperglycemia (7–9).

Diagnosis of DKD is mostly clinical but also includes the measurement of eGFR and albuminuria. In fact, during DKD, blood tests for kidney function result in a persistent high urinary albumin/creatinine ratio (≥30 mg/g) and a reduction in eGFR (<60 ml/min per 1.73 m^2) (10). However, Klessens et al. conducted a study, which revealed that both proteinuria and a reduced eGFR failed in the DKD diagnosis (11).

Unfortunately, long-term therapies aimed at glycemic control are not sufficient to reduce the DKD risk. Nowadays, new therapeutic strategies aim to reduce glomerular hyperfiltration, inflammation, and fibrosis (12–15). Sodium-glucose cotransporters type 2 inhibitors (SGLT2i) have been suggested as a novel, insulin-independent therapeutic approach for managing T2DM (16).

RENAL SODIUM-GLUCOSE COTRANSPORTERS AND THEIR INHIBITION

The kidney plays an important role in the maintenance of glucose homeostasis. In fact, it is involved in gluconeogenesis and glucose reabsorption at the glomerular level. Glucose is a polar molecule, able to cross the cell membrane from the lumen to the tubule through an active transport mediated by two sodium/glucose carriers, called SGLT2 and SGLT1. SGLT2 is located in the first segment of the proximal tubule, and it is responsible for the reabsorption of 90% of the filtered glucose. On the contrary, SGLT1 is located in the third segment of the proximal tubule, and it is responsible for the reabsorption of the remaining 10%. The filtered glucose is totally reabsorbed into the tubule, reaching a maximal reabsorption threshold corresponding to 180–200 mg/dl of blood glucose (17–19).

When the blood glucose levels are above the threshold, the system capacity will be exceeded, and glucose in the urine will be observed (20).

In diabetic patients, in a condition of hyperglycemia, the amount of glucose filtering into the glomerulus is enhanced, leading to a condition called glomerular hyperfiltration (21).

Glomerular hyperfiltration consists of an alteration of the early stages of the CKD in both T2DM and T1DM (22). However, glomerular hyperfiltration is not always the leading cause of DKD (23). SGLT2i belong to the gliflozins class and had initially been developed to improve glycemic compensation in T2DM patients. In the last years, the rationale for using this class of drugs has changed due to the emerging favorable effects on cardiovascular (CV) and kidney outcomes (24).

SGLT2i mechanism of action is insulin independent (25–28) and acts by blocking the filtered glucose reabsorption and increasing urinary glucose excretion (29–31).

SGLT2i can be administered as monotherapy or in combination with other classes of glucose-lowering drugs (16).

So far, numerous SGLT2i have been studied. To date, the available formulations are classified according to their selectivity for the SGLT2/1 transporters. Selective compounds include dapagliflozin, empagliflozin, and ertugliflozin, which are involved in the exclusive inhibition of the SGLT2 transporter. On the other hand, canagliflozin and sotagliflozin present an inhibitory effect even on SGLT1 (32). To date, four different oral formulations have been approved in the US and many more regions, including European Union (EU) and Japan for daily administration [alone or in combination with metformin or dipeptidyl peptidase 4 (DPP4)] (**Table 1**) (24).

TABLE 1 | SGLT2i approved by the European Medicines Agency.

Drug	Association	Commercial name	Dosage
Empaglifozin	/	Jardiance©	10 mg 25 mg
	Metformin	Synjardy©	5 mg + 850 mg 12.5 + 850 mg 5 + 1,000 mg 12.5 + 850 mg
	Linagliptin	Glyxambi©	10 mg + 5 mg 25 mg + 5 mg
Canaglifozin	/	Invokana©	100 mg
	Metformin	Vokanamet©	50 + 850 mg 150 + 1,000 mg 50 + 1,000 mg 150 + 850 mg
Dapaglifozin	/	Forxiga©	10 mg
	Metformin	Xigduo©	5 + 850 mg 5 + 1000 mg
	Saxagliptin	Qtem©	5 mg + 10 mg
Ertugliflozin	/	Steglatro©	5 mg 15 mg
	Metformin	Segluromet©	2.5 mg + 850 mg 2.5 mg + 1,000 mg 7.5 mg + 850 mg 7.5 mg + 1,000 mg
	Sitagliptin	Steglujan©	5 mg + 100 mg 15 mg + 100 mg

[Adapted from Costanza et al., 2020 (24)].

Various registrative trials have been conducted to evaluate the safety of these molecules. Interestingly, they demonstrated to be not only safe but also able to significantly reduce major CV events, hospitalizations, and the exitus due to CV events (24).

Three clinical trials have been conducted to evaluate the CV safety of SGLT2i: EMPA-REG OUTCOME, CANVAS, and DECLARE TIMI 58. In total, 34,322 patients were included. The EMPA-REG OUTCOME enrolled patients with 0% of multiple risk factors and 100% previous CV event, while this proportion rose in the CANVAS program (34%) and in the DECLARE TIMI 58 (59%). Diabetic patients with a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 (25.9% in the EMPA-REG OUTCOME, 20.1% in the CANVAS program and 7.4% in the DECLARE TIMI 58) have been recruited. In particular, the EMPA-REG OUTCOME included CV benefits in patients with a GFR of 30–60 ml/min/1.73 m^2. Results showed that patients treated with SGLT2i presented a reduced risk of CV events than the placebo group. In particular, SGLT2i reduced the establishment of major CV events by 11%, as well as the CV death and hospitalizations (33). The relative risk reduction ranged between 27% and 35% (34). Moreover, some benefits for the kidney have been registered (33).

These results encouraged new retrospective studies and new clinical trials to evaluate the protective effect of SGLT2i on the kidney. In particular, Toyama et al. conducted a metanalysis including 27 studies and 7,363 diabetic patients. SGLT2i demonstrated to be involved in the improvement of numerous outcomes, such as blood pressure control, BMI and albuminuria reduction, CV risk reduction, stroke, and heart disease reduction, as well as a decrease in the mortality rate due to CV events. Moreover, SGLT2i were safe and well tolerated (35).

The DAPA CKD study confirmed the efficacy of dapagliflozin to reduce the risk of sustained decline in the eGFR with a hazard ratio of 0.56 (95% CI, 0.45 to 0.68; $p < 0.001$), end-stage kidney disease, and death from renal or cardiovascular causes in a broad population, regardless of the presence or absence of diabetes (36).

SGLT2I NEPHROPROTECTION

Current evidence suggests that numerous mechanisms can contribute to establishing kidney protection by SGLT2i. These mechanisms can be direct or indirect, as well as local or systemic. The first mechanism consists of glycemic control. In fact, SGLT2i promote glucose elimination with urine, but they also improve the use of glucose in the liver and reduce insulin resistance at the muscle level (37, 38). To evaluate this aspect, numerous studies have been conducted. In 2013, Vasilakou et al. conducted a systematic review and meta-analysis to assess the efficacy and safety of SGLT2i in adults with T2DM. Results demonstrated a reduction of HBA1c of 0.66% in patients with T2DM (39).

Moreover, Heerspink et al. reported that GFR decline was slowed down and that the proteinuria was reduced in T2DM patients treated with SGLT2i (40).

Overall, these data suggest that improved glycemic compensation certainly contributes but cannot alone explain the effectiveness of SGLT2i in kidney protection. These elements support the multifactorial nature of nephroprotection from SGLT2i, but, on the other hand, it opens new horizons on the possible effectiveness of these molecules in non-diabetic kidney disease. **Table 2** shows the main clinical studies conducted with SGLT2i, which have revealed pleiotropic effects of great interest in terms of kidney protection. Due to the limited correlation between clinical benefits from SGLT2i and glycemic control, the most recent work shows growing attention to the favorable effects of gliflozins even in the absence of DM.

Furthermore, SGLT2i are characterized by various systemic mechanisms involved in kidney protection and are unrelated to glycemic control. In fact, SGLT2i can contribute to the weight and BMI reduction (44, 48) since the first dose (49).

SGLT2i can modulate the activation of the tubuloglomerular feedback through the increase in sodium delivery to the macula densa. This reduces the afferent arteriole vasodilatation, glomerular hypertension and the subsequent albuminuria (50). SGLT2i could also exert, by glycosuria, a diuretic osmotic effect (51–53) without inducing renin–angiotensin system activation. On the contrary, the increased delivery of sodium at the level of macula densa is associated with the activation of tubule-glomerular feedback and the consequent vasoconstriction of the glomerular afferent arteriole and the reduction of renin activity (54). In addition, the increased elimination of sodium and water acts in the blood pressure control and the cardiac load reduction (55). The mechanisms involved in the blood pressure reduction include the diuretic action (56), as well as the bodyweight and total sodium reduction (57). The reduction in the stiffness of the blood vessels might also play a role (58).

Several hypotheses have been postulated to explain the cardioprotective role of SGLT2i. Firstly, SGLT2i might induce a reduction in preloading and after loading conditions through the osmotic diuresis, reducing blood pressure and improving CV function. Other mechanisms might involve the improvement of cardiac metabolism and bioenergetics, the inhibition of the myocardial Na+/H+ exchange, the reduction of necrosis and cardiac fibrosis, and the alteration in the production of adipokines, cytokines, and epicardial adipose tissue mass (51).

Moreover, according to some animal model studies, SGLT2i might also play an anti-inflammatory role. In fact, SGLT2i demonstrated to be involved in reducing inflammatory markers production in the kidney (59). Finally, other favorable effects have been hypothesized at the cardiac level (51). SGLT2i could improve the myocardial energetics by increasing hematocrit (60) and oxygen delivery as well as the changes of energetic substrates (61). In fact, SGLT2i are able to fix the imbalance between oxygen demand and oxygen supply that is commonly seen in diabetic patients.

The increase in hematocrit may be due to EPO upregulation induced by intensified hypoxia at the renal cortico-medullary junction (62). In addition, the inhibition of hepcidin by SGLT2i may increase iron bioavailability and utilization (63).

There is evidence that SGLT2i limits podocyte damage (64), and the efficacy in glomerulonephritis is becoming apparent, as dapagliflozin has been shown to reduce the risk of CKD progression in patients with IgA nephropathy (65).

TABLE 2 | Main clinical studies involving SGLT2i.

Trial	Type of Study	Population	Drug	Main results
EMPAREG OUTCOME	Trial	7,020 patients with T2DM	Empaglifozin	↓ CV-related death↓hospitalization↓ death for any cause
CANVAS	Trial	10,142 patients with T2DM and high CV risk	Canaglifozin	↓ composite endpoint CV death, non-fatal myocardial infarction or stroke
CREDENCE	Trial	4,401 patients with T2DM, CKD, and microalbuminuria	Canaglifozin	↓ kidney composite endpoint↓ ESKD, GFR decline, albuminuria↓ hospitalization↓ composite endpoint CV death, non-fatal myocardial infarction or stroke.
Yagi et al. (41)	Observational	13 patients with con T2DM	Canaglifozin	↓ pericardial fat
Sato et al. (42)	Observational	40 patients with T2DM and coronopathy	Dapagliflozin	↓ pericardial fat, body weight, tumor necrosis factor alpha (TNF-α), plasminogen activator inhibitor type 1 (PAI-1)
Bouchi et al. (43)	Pilot	19 patients with T2DM	Luseogliflozin	↓ pericardial fat, body weight, BMI, blood pressure, triglycerides, RCP
Heerspink et al. (40) **Blonde et al.** (44)	Trial	1,450 patients with T2DM	Canaglifozin	↓ GFR decline↓albuminuria in patients with microalbuminuria and macroalbuminuria↓ BMI, body weight
McGurnaghan et al. (45)	Observational	8,566 pz con DM2	Dapagliflozin	↓ body weight BMI, blood pressure
Kario et al. (46)	Trial	132 patients with T2DM and hypertension	Empaglifozin	↓ blood pressure, body weight
Solini et al. (47)	Trial	40 patients with T2DM	Dapagliflozin	↓ blood vessels stiffness
DAPA-HF	Trial	4,744 patients with heart failure with and without T2DM	Dapagliflozin	↓ worsening heart failure or CV death with and without T2DM
DAPA-CKD	Trial	4,245 patients with CKD and microalbuminuria, with and without T2DM	Dapagliflozin	↓ composite endpoint of eGFR decline ≥50%, ESKD and CV or renal death
DECLARE TIMI-58	Trial	17,160 patients with T2DM and patients con DM2, high-risk or with atherosclerotic vasculopathy	Dapagliflozin	↓ composite endpoint CV death↓ hospitalization for heart failure
VERTIS	Trial	8,246 patients with T2D and established atherosclerotic cardiovascular disease	Ertugliflozin	Noninferior for CV, trends beneficial effect on renal outcomes

[Adapted from Costanza, 2020 (24)] ↓: reduction.

The most important beneficial effects of SGLT2i are reported in **Table 3**.

In summary, SGLT2i seem to act on multiple systemic aspects, known CV risk factors, and CKD development and progression. Similarly, the local mechanisms underlying nephroprotection also appear to be manifold. De Nicola et al. have suggested that SGLT2i can counteract glomerular hyperfiltration, regardless of the hypoglycemic effect, while having benefits related to albuminuria, inflammation, and nephromegaly secondary to the improvement of glycemic control (66). The effects of SGLT2i will certainly be investigated in depth in large cohorts of patients now that FDA and EMA have granted the approval of dapagliflozin to reduce the risk of kidney function decline, kidney failure, cardiovascular death, and hospitalization for heart failure in adults with CKD (67).

TABLE 3 | Most important beneficial effects of SGLT2i.

Most important beneficial effects of SGLT2i
Increased glycemic control
Reduction of afferent arteriole vasodilatation
Reduction of glomerular hypertension
Reduction of albuminuria
Increase of Na elimination
Reduction of blood pressure
Increased hematocrit and oxygen delivery
Reduction of preloading and after-loading condition
Reduction of myocardial Na/H exchange
Increased cardiac metabolism
Reduction of epicardial adipose tissue mass
Reduction of necrosis and cardiac fibrosis
Reduction of epicardial adipose tissue mass
Decrease in production of adipokines and cytokines
Weight loss
BMI reduction
Anti-inflammatory activity

SGLT2I KIDNEY PROTECTION AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES

As confirmed by a lot of evidence mentioned above, patients with T2DM present a high risk for heart failure, ischemic events, and CKD (24, 47).

The EMPAREG OUTCOME trial evaluated the effects of empagliflozin on CV mortality and morbidity in T2DM patients at high CV risk. Patients were randomized to receive empagliflozin or placebo once daily. This trial suggested that T2DM at high CV risk and treated with empagliflozin had a lower rate of primary outcomes than the placebo group (68).

Two years later, the CANVAS program integrated the data of 10,142 T2DM patients at high CV risk. Patients were randomized to receive canagliflozin or placebo. After a mean period of 188.2 weeks, primary outcomes were analyzed. Results showed that patients treated with canagliflozin presented a lower

risk of CV events compared to the ones receiving placebo. However, the amputation rate was higher in the treatment group, but the reason is not yet fully understood (69).

The DECLARE TIMI 58 trial conducted by Wiviott et al. evaluated the CV efficacy of dapagliflozin in patients with T2DM at risk for atherosclerotic cardiovascular diseases. Participants were randomized to receive dapagliflozin or placebo. The primary outcome was a composite of major CV events (MACE) and death or hospitalization for heart failure. Secondary outcomes were a renal composite (which included ≥40% decrease in eGFR to <60 ml/min per 1.73 m^2 of body surface area, new end-stage renal disease, or death from renal or CV causes) and death from any cause. Results from the study highlighted a lower rate of CV death or hospitalization for heart failure and renal outcome in patients treated compared to the ones treated with placebo (70). The renal outcome described in the DECLARE TIMI 58 study was not included in the original protocol so, even though encouraging, these results need to be confirmed.

Moreover, pericardial fat is involved in the establishment of coronary artery disease, especially as a concurrent condition during DM2 and obesity (42). In 2018, Sato et al. evaluated the relationship between SGLT2i and pericardial fat in 40 T2DM patients. Results showed a decrease in the pericardial fat volume, potentially caused by the improvement of systemic metabolic parameters due to the SGLT2i treatment (42). Promising results have been obtained with luseogliflozin (43).

In 2019, Perkovic et al. published the results collected from the CREDENCE study, a double-blind, randomized trial aimed to evaluate the efficacy of canagliflozin in the CV and renal protection in T2DM patients. All patients were treated with renin–angiotensin system (RAS) blockage and presented both albuminuria and an eGFR of 30 to <90 ml/min per 1.73 m^2 of body surface area. As a result, in T2DM patients affected by kidney disease, the CV and kidney failure risk were lower in the treatment group compared to the placebo one. The median study follow-up was 2.62 years (71).

In 2020, Bhatt et al. conducted a study to evaluate the effects of sotagliflozin on CV and renal events in patients with T2DM and moderate renal impairment (SCORED). The trial aimed to verify whether sotagliflozin was non-inferior to placebo in terms of heart failure events. SCORED was a multicenter, double-blind trial that enrolled T2DM patients with chronic kidney disease and CV risk. Patients were randomized 1:1 to receive sotagliflozin or placebo. Due to a loss of funding, the trial ended up early. However, results showed that sotagliflozin was able to reduce the risk of death for CV causes, in patients with diabetes and chronic kidney disease, with or without albuminuria (47).

Interestingly, SGLT2i might change CV biomarkers in patients with CKD and T2DM. Lawler et al. performed a *post hoc* analysis among 231 participants from the eValuation of ERTugliflozin efficacy and Safety (VERTIS) renal trial affected by T2DM and stage 3 CKD. Patients were randomized 1:1 to receive ertugliflozin 5 or 15 mg daily or placebo. Clinical biomarkers have been measured at three time points: baseline, 26 weeks, and 52 weeks. The analysis included cardiac troponin, renin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), atrial natriuretic peptide (ANP), human erythropoietin (EPO), ACE, ACE2, and aldosterone. Results showed that plasma aldosterone was significantly higher at 26 weeks in patients treated with ertugliflozin. However, the effect was no longer significant at 52 weeks.

On the contrary, NT-proBNP concentration was lower in patients treated with ertugliflozin at 26 and 52 weeks. Finally, the treatment with ertugliflozin did not cause any significant changes in cardiac troponin, EPO, ACE, ACE2, HbA1c, potassium, blood pressure, and eGFR. This study showed that the effects of ertugliflozin are maintained even in patients with moderate CKD (72). In VERTIS-CV, patients with T2D and micro- or macroalbuminuria were likely to benefit from HF risk reduction with an SGLT2i (73).

Recently, the EMPEROR-REDUCED trial aimed to evaluate the effects of SGLT2 inhibition with empagliflozin on major heart failure outcomes in patients with heart failure and a preserved ejection fraction. Results showed that a CV event occurred in 13.8% of the patients treated with empagliflozin and in 17.1% of patients included in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; $p < 0.001$), regardless of the presence of diabetes. Moreover, the total number of hospitalizations for heart failure was lower in the treatment group compared to the placebo group (hazard ratio, 0.73; 95% CI, 0.61 to 0.88; $p < 0.001$) (74).

SGLT2I KIDNEY OUTCOMES IN NON-DIABETIC PATIENTS

Because of the benefits demonstrated in renal and CV protection, SGLT2i are likely to be incorporated as part of the guideline-directed medical therapy (GDMT) (75).

Several clinical studies have evaluated kidney outcomes in non-diabetic patients with and without heart failure.

Recently, two trials have tested dapagliflozin and empagliflozin in a population of patients affected by heart failure with reduced ejection fraction (HFrEF). In both trials, patients were in stable clinical conditions, with an NYHA class mainly between II and III, LVEF ≤ 40%, high levels of NT-proBNP, and recommended medical therapy. In both trials, patients with and without diabetes were enrolled and, among secondary endpoints, kidney outcomes were evaluated.

In DAPA HF, which enrolled 4,744 patients, during a median follow-up of 18 months, dapagliflozin (10 mg once daily), compared with placebo, significantly reduced the primary combined endpoint (76), i.e., cardiovascular death, hospitalization, or urgent visit for heart failure [16.3 vs. 21.2%, HR: 0.74 (95% CI: 0.65–0.85); $p < 0.001$]. Analogously, in EMPEROR-reduced (77), during a median follow-up of 16 months, empagliflozin (10 mg/daily) when compared with placebo significantly reduced the primary endpoint, i.e., CV deaths and heart failure hospitalizations [15.8 vs. 21%, HR: 0.75 (95% CI: 0.65–0.86); $p < 0.001$]. The favorable effect was mainly driven by the reduction of heart failure hospitalization

(13.2 vs. 18.3%; HR: 0.69; 95% CI: 0.59 to 0.81), whereas no significant reduction was observed when CV death (10% vs. 10.8% HR 0.92; 95% CI: 0.75 to 1.12) and death for all causes were analyzed. In both DAPA-HF and EMPEROR-reduced, the favorable effects of SGLT2i were significant in diabetic as well as in non-diabetic patients (78).

Interestingly, in EMPEROR-reduced but not in DAPA-HF, a significantly slower decline of GFR was observed [mean slope of change in eGFR (ml/min/1.73 m^2) per year: absolute difference 1.73 (95% CI: 1.10–2.37); $p < 0.001$]. This could be due to the lower baseline eGFR in the EMPEROR-reduced trial population (78).

In general, it is known that SGLT2i can decrease albuminuria and the risk of kidney disease progression in TD2M patients. However, Cherney et al. conducted the DIAMOND study, a randomized, double-blind, placebo-controlled, crossover trial, with the aim to evaluate the kidney effects of dapagliflozin in patients with proteinuria but without DM. Participants were enrolled among six hospitals in Canada, Malaysia, and Netherlands. Baseline characteristics included CKD, no DM diagnosis, a 24-h urinary protein excretion between >500 but ≤3500 mg, and an eGFR of at least 25 ml/min per 1.73 m^2. All the participants were on stable renin–angiotensin system blockade (79).

Participants were randomized to firstly receive dapagliflozin 10 mg/once daily and then placebo, or *vice versa*, according to a 1:1 ratio. Each treatment lasted 6 weeks with a 6-week washout. The primary outcome was the change in the 24-h proteinuria, while secondary outcomes were changes in the measured GF (mGF), body weight, blood pressure, and the concentration of neurohormonal biomarkers (79).

Results showed that 6-week treatment with dapagliflozin did not affect proteinuria but induced a decline in mGFR and a bodyweight reduction in patients with CKD but without DM (79).

Notably, a large trial (DAPA-CKD), stopped early due to data showing benefits, has shown that the use of dapagliflozin in patients with CKD, with and without type 2 diabetes, was associated with less progression of CKD, renal mortality, and all-cause mortality. As mentioned above, the primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. The primary outcome event occurred in 9.2% of patients treated with dapagliflozin and 14.5% of patients treated with placebo (hazard ratio, 0.61). Moreover, the hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56, and the one for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71. Finally, 4.7% of the participants in the treatment group and 6.8% of the patients in the control group died. It is worth mentioning that all patients received ACE inhibitor/ARB and presented albuminuria. Thus, generalization to further categories of patients is needed. Nonetheless, this indication covers a broad range of patients with impaired kidney function and proteinuria, including patients with non-diabetic CKD (36).

SGLT2I AND OTHER BENEFITS: FOCUS ON THE LIVER AND RESPIRATORY FAILURE IN COVID-19

As reported above, SGLT2i showed numerous beneficial effects in different body locations, which extend beyond glycemic control. These beneficial effects include a reduction in body weight and blood pressure, and an improvement in uric acid concentration, oxidative stress, inflammation, and liver steatosis (80).

Also, dapagliflozin has been investigated to evaluate organ protection in high-risk patients affected by COVID-19 (81, 82). In fact, it has been hypothesized that dapagliflozin may reduce the risk of multi-organ failure and death and improve recovery in patients hospitalized with COVID-19 and have cardiometabolic risk factors (81).

In 2020, Akuta et al. conducted a retrospective study among 7 Japanese patients with non-alcoholic fatty liver disease (NAFLD) and T2DM receiving long-term treatment with canagliflozin (100 mg/day). The study aimed to determine the long-term effects of SGLT2i in NAFLD patients in the clinical outcomes and the liver histopathology (83).

During the study, liver biopsies were collected at the beginning of the trial, after 24 weeks, and after more than 1 year. As a result, the treatment with SGLT2i improved the scores of steatoses, lobular inflammation, ballooning, and fibrosis (83).

In 2020, the COVID-19 pandemic challenged the global health system since SARS-CoV-2 may lead to the development of severe pneumonia and may cause multiorgan failure. Cardiovascular and kidney complications are the most common, leading to poor outcomes, including death (82).

Since the important benefits showed by dapagliflozin in the cardio- and renal protection in patients with T2DM, the DARE-19 trial has been conducted. The study aimed to evaluate the organ protection provided by dapagliflozin in high-risk patients affected by COVID-19. DARE-19 was an international, multicenter, randomized, double-blind, placebo-control study, which involved hospitalized patients among the US, Brazil, Mexico, Argentina, India, Canada, and UK (81). Inclusion criteria included hospitalization with confirmed/suspected SARS-CoV-2 for ≤4 days, an O_2 saturation of ≥94% on ≤5 L/min, a CXR finding c/w COVID-19, and ≥1 risk factor (HTN, Type 2 Diabetes, ASCVD, HF, and CKD). Primary endpoints consisted of preventing respiratory, cardiovascular, renal, or death events and the recovery in terms of hospitalization and clinical status in case of organ failure.

In this study, after the initial screening to confirm the COVID-19 diagnosis, patients were treated with dapagliflozin 10 mg or placebo once daily for 30 days, in addition to the local standard therapy. All patients had daily assessments until hospital discharge, death, or end of the 30-day treatment period, followed by a 60-day observational follow-up (82).

Results showed that organ dysfunction or death occurred in 11.2% of the patients treated with dapagliflozin and 13.8% of the patients included in the placebo group (hazard ratio 0.80). Moreover, 87.5% of the patients in the dapagliflozin group and

85.1% in the placebo group showed clinical status improvement (82).

In conclusion, the study showed that numerically fewer patients treated with dapagliflozin experienced organ failure and death and that dapagliflozin was well-tolerated, allowing the use of SGLT2i even in a setting of COVID-19 (82).

SGLT2I SAFETY PROFILE AND ADVERSE EVENTS

SGLT2i are generally well tolerated (84). **Table 4** summarizes tolerability in the four main trials. SGLT2i present a low risk of hypoglycemia, a very fearsome and non-infrequent adverse event with some classes of hypoglycemic drugs, especially in people with diabetes with CKD (85). The reason could be the reduction of blood glucose levels by SGLT2i, which is closely linked to the amount of glucose filtered. The glucose load that goes into the pre-urine at the glomerular level depends on blood glucose and GFR. Thus, modest glycosuria is expected, as well as a milder hypoglycemic action in subjects with better glycemic compensation and impaired kidney function.

Urinary tract infections (UTIs) are a common side effect among SGLT2i, and they are frequently observed during treatments with other glycosuric drugs (86). In 2015, the US Food and Drug Administration (FDA) issued a notice reporting 19 cases of UTI and pyelonephritis (87). Similarly, the EMA indicated UTIs as a common adverse effect. In fact, clinical trials reported conflicting data: EMPA-REG OUTCOME, CANVAS, and DECLARE TIMI-58 did not show a significant difference in risk of UTIs compared to placebo, while in the CREDENCE canagliflozin study, it was associated with a 3-times increased risk (68–71). Moreover, a recent metanalysis that included 86 randomized clinical trials and over 50,000 subjects highlighted that SGLT2i, in relation to the risk of UTIs, are comparable to other hypoglycemic drugs (GLP-1 agonists and DDP-4 inhibitors). Compared to the placebo, canagliflozin and empagliflozin were not associated with an increased risk, while dapagliflozin showed a relative risk of 1.23 (95% CI, 1.03–1.46). In fact, secondary analyses revealed that dapagliflozin increased the risk of UTIs only at the dosage of 10 mg/day, thus outlining a dose-dependent side effect (88). According to the current evidence, the problem of UTIs is significantly reduced compared to the past. This reduction leads to several implications in clinical practice. Since DM itself is a risk factor for UTIs and their evolution is more frequently unfavorable than in non-diabetic patients (89), the fear of such adverse events and any complications could lead the clinician to significantly limit the prescription of SGLT2i. Many people with diabetes would not enjoy the cardiovascular and kidney benefits in this scenario. Realistically, further studies on populations with independent risk factors for UTIs, such as advanced age and CKD, will better clarify the safety profile of these molecules. On the other hand, educating patients to take care of personal hygiene and recognizing the suggestive symptomatology of UTIs can represent very useful interventions for prevention and prognosis (24).

Genital infections are mostly related to increased urinary glucose excretion (86). The EMPAREG OUTCOME, CANVAS, DECLARE TIMI-58, and CREDENCE trials agreed on increased risk from SGLT2i compared to placebo. In these trials, genital infections were between 4 and 9 times more frequent, although the number of events recorded was limited (68–71).

Fournier's gangrene is a severe necrotizing infection of the external genitals and perineum that often requires a complex surgical approach, with a fatal prognosis in 7.5% of patients. Since their approval, several authors have reported cases of Fournier gangrene in subjects treated with SGLT2i (90). However, DECLARE TIMI-58, the only trial designed to assess the impact of Fournier's gangrene, showed a reduced risk with dapagliflozin compared to placebo (70).

Surprisingly, in the CANVAS study, canagliflozin was associated with a double risk of foot and leg amputations (69). Volume depletion and increased blood viscosity have been postulated as possible responsible mechanisms. The known risk factors were the previous history of amputations, peripheral vascular disease, and neuropathy. According to the EMA request, the DECLARE TIMI-58 study collected the amputation data and concluded that there was no statistically significant difference in dapagliflozin compared to placebo (70). The increased risk has not been confirmed even in the CREDENCE, DAPA-HF, and OBSERVE-4D studies, an observational study that involved over 700,000 patients treated with the different SGLT2i (71, 75, 91).

During the CANVAS study, an increased risk of non-vertebral fractures, mainly of the limbs, emerged with canagliflozin already after 3 months of treatment. This result has not been confirmed in CANVAS-R or in DECLARE TIMI-58 (69, 70). Following retrospective studies have reported a very low or absent risk of fractures, comparable to other hypoglycemics

TABLE 4 | Tolerability of SGLT2i across the main trials.

	EMPAREG OUTCOME	CANVAS	DECLARE-TIMI 58	CREDENCE	DAPA HF	DAPA CKD	VERTIS
Hypoglycemia	-	-	-	-	-	-	-
Urinary infections	-	-	-	-	-	-	-
Genital infection	+	+	+	+	-	-	+
Amputations	-	+	-	-	-	-	-
Fractures	-	+	-	-	-	-	-
Diabetic ketoacidosis	-	+	+	+	-	-	+
AKI	-	-	-	-	-	-	-

[Adapted from Costanza et al., 2020 (24)].

such as GLP-1 agonists and DDP-4 inhibitors, in low-risk populations (92).

The scientific literature agrees on the increased risk of diabetic ketoacidosis associated with treatment with SGLT2i. However, a small number of events have been reported (24).

Moreover, some potential deleterious events on kidney function have been reported, such as the SGLT2i impact on electrolyte balance in exposed subjects (93).

In conclusion, SGLT2i showed a good safety profile. The knowledge of possible adverse events must guide the clinician in identifying those at increased risk and, where possible, intervene on modifiable risk factors, educate the patient to implement effective prevention, and ensure adequate follow-up for the early identification of side effect (24).

SGLT2I: CURRENT GUIDELINES AND RECOMMENDATIONS

According to the growing evidence that highlights the benefits of SGLT2i, various scientific societies have gradually updated guidelines and acts of direction, progressively expanding the indications of using these molecules. According to the new Standards of Medical Care in Diabetes 2021 of the American Diabetes Association (ADA), metformin remains the first-line therapy in the diabetic subject, also nephropathic, without prejudice to conditions of intolerance or adverse reactions and for GFR > 30 ml/min/1.73 m^2.

Nowadays, SGLT2i are also indicated in subjects where metformin has earned a good glycometabolic compensation, therefore even when HbA1c is targeted. In addition, whereas previously, the use of these molecules was recommended in the presence of heart failure, chronic kidney disease, and/or atherosclerotic vasculopathy, the existence of CV risk factors that pose a high risk is now sufficient. In people with diabetes with CKD, SGLT2i are preferred to GLP-1 agonists due to stronger evidence in terms of slowing the decline of GFR. In fact, GLP-1 agonists have reduced albuminuria and the risk of composite renal endpoints, while the effects on GFR are controversial (94, 95).

Since the CV and renal benefits from SGLT2i are only to a small extent attributable to the improvement of blood glucose control, it has been hypothesized that even non-diabetic subjects with CV pathology and/or MRC can benefit from this therapy (96).

In parallel with DAPA-HF, DAPA-CKD was a randomized, double-blind, placebo-controlled trial that also recruited diabetic and non-diabetic patients, as mentioned above. Arguably, obesity-induced CKD, which recognizes glomerular hyperfiltration as one of the main pathogenic factors, could benefit from the use of SGLT2i (97, 98).

In this direction, DAPA-HF was the first trial with SGLT2i to recruit non-diabetic subjects as well, assessing the effectiveness of dapagliflozin in the treatment of heart failure, in addition to the standard of care. Dapagliflozin emerged as a powerful therapy, with an excellent safety profile and a great efficacy even in subjects without DM (75). According to these results and those of the EMPEROR-reduced trial, the ESC Guidelines of the European Society of Cardiology for Heart Failure 2021 include SGLT2i as recommended therapy for patients with HFrEF (98).

Based on the currently available data, SGLT2i show important benefits at the socio-health and pharmacoeconomic levels. In fact, although their cost is higher compared to other hypoglycemics, the advantages are greater (24).

CONCLUSIONS

Despite current measures against DM, the residual risk of ESKD, CV morbidity, and mortality remain high. SGLT2i have shown very promising results on renal outcomes and good safety profile. Therapeutic efficacy, tolerability, and costs support the broad use of these drugs in the diabetic population. In addition, SGLT2i can be widely used even in non-diabetic patients, and patients with risk factors and/or CV disease, nephropathy to different etiopathogenesis, and up to the more advanced stages of CKD. Of course, the evidence in CKD patients is still relatively limited and additional data are needed to draw a robust conclusion.

Further studies are needed to clarify any differences between different SGLT2i in CKD and between the different phenotypes (albuminuric and non-albuminuric). The SGLT2i represent another challenge to create an integrated management model and to apply therapeutic care diagnostic pathways, which lead to the involvement of a multidisciplinary team of professionals to ensure the optimization of the treatment and the follow-up management.

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All authors contributed to the research, development, and content of the manuscript.

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REVIEW
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Obesity, Weight Gain, and Fluid Overload in Peritoneal Dialysis

Jack Kit-Chung Ng[1], *Win Hlaing Than*[1,2] *and Cheuk Chun Szeto*[1,2*]

[1] Carol & Richard Yu Peritoneal Dialysis Research Centre, Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China, [2] Li Ka Shing Institute of Health Sciences (LiHS), Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China

Obesity is a global epidemic that has a complicated pathogenesis as well as impact on the outcome of peritoneal dialysis (PD) patients. In this review, the prevalence of obesity in incident PD patients as well as the phenomenon of new-onset glucose intolerance after PD will be reviewed. Published literature on the effect of obesity on the survival and incidence of cardiovascular disease in PD patients will be discussed. Particular emphasis would be put on literature that compared the impact of obesity on the outcome of hemodialysis and PD, and the confounding effect of dialysis adequacy. Next, the complex concept of obesity and its relevance for PD will be explored. The focus would be put on the methods of assessment and clinical relevance of central versus general obesity, as well as visceral versus subcutaneous adipose tissue. The relation between obesity and systemic inflammation, as well as the biological role of several selected adipokines will be reviewed. The confounding effects of metabolic syndrome and insulin resistance will be discussed, followed by the prevalence and prognostic impact of weight gain during the first few years of PD. The differences between weight gain due to fluid overload and accumulation of adipose tissue will be discussed, followed by the current literature on the change in body composition after patients are put on chronic PD. The methods of body composition will be reviewed, and the clinical relevance of individual body component (fluid, fat, muscle, and bone) will be discussed. The review will conclude by highlighting current gaps of knowledge and further research directions in this area.

Keywords: chronic kidney disease, atherosclerosis, metabolic syndrome, inflammation, cardiovascular disease

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***Correspondence:**
Cheuk Chun Szeto
ccszeto@cuhk.edu.hk

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INTRODUCTION

Peritoneal dialysis (PD) is widely used for providing home-based dialysis (1, 2). Traditionally, PD-related peritonitis has long been the Achilles heel of PD and the major cause of technique failure (3, 4). With the advances in connection system and standardization of treatment protocol, the focus of improving the longevity of PD patients has shifted to metabolic complications and cardiovascular diseases (5, 6). In addition to the high prevalence of traditional cardiovascular risk factors, it is increasingly recognized in recent years that non-traditional risk factors play important roles in the pathogenesis of cardiovascular disease in PD patients (7, 8). Specific uremic toxins, anemia, disturbances in divalent ion metabolism, sympathetic nerve over-activity, gut dysmotility, circulating bacterial metabolites and fragments, and various treatment-related factors may all

contribute to the pathogenesis of cardiovascular disease in CKD (9, 10). More recently, obesity has emerged as the key modifiable risk factor that bridges the traditional and non-traditional pathogenic pathways of cardiovascular disease.

DEFINITION OF OBESITY

Obesity is most commonly defined by body mass index (BMI). The World Health Organization (WHO) considers a BMI between 20 and 25 kg/m^2 as normal weight, a BMI between 25 and 30 kg/m^2 as overweight, and a BMI of >30 kg/m^2 as obese (11). However, the Asian population have a higher body fat content for the same BMI than the western population (12), and the International Obesity Task Force recommended the lower cut-offs of BMI ≥23 kg/m^2 for overweight, and ≥25.0 kg/m^2 for obese for Asian people (13). To complicate the matter, BMI is a poor estimate of fat mass distribution in CKD (14). Although waist-hip ratio (WHR) and skin fold thickness are superior to BMI for the correct classification of obesity in CKD (15), skin fold thickness is not readily available in most centers, and WHR may not be a valid estimate in PD patients (16).

EPIDEMIOLOGY OF OBESITY

Following the trend in the general population (17–21), obesity is increasingly common among incident PD patients. In a retrospective study of 1681 incident adult PD patients from a single center, Than et al. (22) reported that 37.7% were obese or overweight at the initiation of PD over a 25 years period of observation. In this study, the prevalence of obesity or overweight at the initiation of PD increased from 21.9% before 2000 to 47.3% after 2015 (22). Notably, the absolute increase in the prevalence of obesity or overweight was more pronounced in diabetic patients (from 33.7% to 59.6%) than non-diabetic ones (from 13.2% to 32.3%), although the relative increase was actually more marked in the non-diabetic group (22). However, the prevalence of obesity as well as the magnitude of its increase was slightly lower among PD patients than that observed in the general population (21), which is probably the result of the common coexistence of protein-energy malnutrition in patients with advanced CKD (23, 24).

ASSESSMENT OF OBESITY AND BODY FAT CONTENT

Traditionally, body mass index (BMI) is the most commonly used marker for obesity (17–21). BMI is simple and easily understood by patients. However, BMI tends to over-diagnose obesity in tall patients (12567), and does not distinguish the cause of a high body weight, which may be due to the increase in muscle mass or fluid retention (25). In recent years, a number of specific tests, notably multi-frequency bioimpedance spectroscopy and dual-energy X-ray absorptiometry (DXA) scan, have been developed for the measurement of individual body compartments (26). Multi-frequency bioimpedance spectroscopy measures the resistance and reactance of the body under the flow of electrical current and provides a reproducible and non-invasive method to determine the adipose tissue mass and volume of overhydration in the body (27). Since the equipment is simple and the method is suitable for frequent repeated measurements, the technique has been extensively used in hemodialysis as well as PD patients (28–30), but the technique is more commonly used for the monitoring of body fluid status rather than fat content of dialysis patients. DXA scan uses two X-ray beams with different energy levels to perform spectral imaging that allows the measurement of bone mineral density as well as body fat and muscle distribution (31). However, the equipment is expensive and the application in the dialysis population is less well reported.

WEIGHT GAIN DURING PD

Not only that obesity is common in incident PD patients, a large proportion of PD patients have substantial weight gain after the initiation of PD (32–34). In a study of 444 consecutive incident PD patients, Choy et al. (35) found that the mean weight gain after one year of PD was 1.34 kg, and nearly 25% patients had weight gain over 3 kg. Nonetheless, previous studies that compared the magnitude of the weight gain after the initiation of dialysis showed either no significant difference in the change in body weight after started on PD or hemodialysis, or actually a slightly higher probability of substantial weight gain after started on hemodialysis (36, 37). In the study of Choy et al. (35), there were no significant correlations between body weight gain and glucose load or peritoneal transport parameters, but patients without any peritonitis episodes during the first year of PD had significantly more weight gain than patients who experienced peritonitis during that time (35). Taken together, these data indicate that improvement in uremia and general health is the more important cause of weight gain, while glucose absorption from the PD solution plays only a minor role. Consistent with this notion, weight gain during the first year of PD in this study was not associated with adverse clinical outcome in the subsequent follow up, while weight loss during the first year of PD predicted poor patient survival (35). Similarly, analysis of 1911 adult incident PD patients recruited from 114 dialysis centers that participated in the Brazilian Peritoneal Dialysis Multicenter Cohort Study, Fernandes et al. (38) found that weight gain during the first year of PD was not associated with a higher subsequent mortality. In contrast, in an observational study of 148 incident PD patients, Kim et al. (39) noted that excess weight gain during the first year of PD was closely linked to systemic inflammation, diabetes and rapid decline in residual renal function, although the effect on subsequent mortality was not significant. In another prospective study of 109 incident PD patients, Castro et al. (40) found that 61% had an increase in waist circumference after 6 months of PD, and a significant increase in waist circumference was only observed among patients who died in the subsequent 4 years of follow up,

suggesting that weight gain after PD may not be an entirely benign phenomenon.

With a longer duration of observation, our recent analysis of 954 consecutive incident PD patients found that the average weight gain was 1.2 kg after the first 2 years of PD, and the magnitude of weight gain after PD increased progressively over the past 25 years (41). In this analysis, there was a significant interaction between baseline body mass index (BMI) and subsequent weight change on technique survival but not on patient survival. For the patients with baseline BMI <23 kg/m2, weight gain ≥3 kg was associated with a better 5-year technique survival, while for patients with baseline BMI >25 kg/m2, weight gain ≥3 kg was associated with a trend of worse technique survival (41). On the other hand, weight gain ≥3kg was associated with a worse subsequent patient survival rate irrespective to the baseline BMI (41). Taken together, available literature does not show a consistent effect of weight gain after the initiation of PD, prognostic impact probably depends on the baseline nutritional status of the patient.

THE OBESITY PARADOX IN ADVANCED CKD

In the general population, obesity is a well-known risk factor of metabolic diseases (e.g. type 2 diabetes mellitus, non-alcoholic fatty liver disease) and cardiovascular diseases, as well as Alzheimer disease, depression, osteoarthritis, and several types of cancer (17, 42, 43). In addition, obesity is also well reported to contribute to the pathogenesis and progression of CKD (44, 45). In CKD patients, however, the role of obesity as a cardiovascular risk factor is less well studied. In a cross-sectional study of 1740 patients with stage 3 CKD, the degree of central obesity, as defined by the waist-hip ratio, had a strong and independent correlation with arterial pulse wave velocity (46). In another observational study of 1669 patients with stage 2 to 4 CKD followed for an average of 9.3 years, Elsayed et al. (47) found that waist-hip ratio, but not BMI, was associated with cardiovascular events, indicating that central obesity is more important than BMI as a cardiovascular risk factor.

Contrary to the observations in the general population, obesity is often reported to be associated with a better outcome in patients receiving kidney replacement therapy (KRT), which is mostly chronic hemodialysis in the published literature. In a review of the US Renal Data System data in 418,055 hemodialysis patients, Johansen et al. (48) found that high BMI was associated with increased patient survival, including the subgroup with extremely high BMI. In this study, high BMI was also associated with a reduced risk of hospitalization and a lower rate of mortality in all mortality categories (48). Notably, different methods for measuring adiposity, including the Benn index and estimated fat mass, yielded similar results, and adjustments for lean body mass did not affect the findings (48). Similarly, a systemic review of 10 studies with over 1 million patients showed that hemodialysis patients with higher body weight or BMI were associated with a lower all-cause mortality and cardiovascular mortality, and the benefit was consistent across all ethnic groups (24). In another meta-analysis of 22 studies on hemodialysis patients, the relationship between BMI and mortality was linear (49). In this analysis, 1 kg/m^2 increase in BMI was associated with a 3% reduction in all-cause mortality, and 4% reduction in cardiovascular mortality (49).

IMPACT OF OBESITY ON THE OUTCOME OF PD PATIENTS

Published data on the relation between obesity and the outcome of PD patients are limited and showed conflicting results (**Table 1**). Snyder et al. (50) and Ramkumar et al. (51) reported that overweight and obese PD patients have better survival rates than those with lower BMI, while McDonald et al. (52) noted that obesity was associated with higher risks of death and technique failure. Other early studies did not find any association between obesity and the outcome of PD patients (53–55). In a study of 280 PD patients, Liao et al. (56) found that metabolic syndrome was a significant predictor of cardiovascular events in non-diabetic patients. However, when the 5 components of metabolic syndrome were separately analyzed, only hypertriglyceridemia, low high-density lipoprotein levels, and hyperglycemia predicted adverse cardiovascular outcomes, while central obesity was not a significant prognostic indicator (56). The conflicting results may be explained because BMI may not be a marker of obesity but that of nutritional status. Incident PD patients with high BMI may have better survival if they have a high skeletal muscle mass rather than adipose tissue mass (51). In a systematic review, Ahmadi et al. (57) concluded that the relation between BMI and mortality was linear during the first year of PD. In this analysis, being underweight was associated with higher mortality, and being overweight or obese, as defined by BMI, was associated with lower mortality. The relation, however, became an insignificant J-shape one after 2 years on PD, and both underweight and obesity seemed to increase the mortality risk (57). The same J-shape relationship between BMI and mortality was also noted in another meta-analysis that focused on Asian PD patients (58). It is important to note that all these studies focused on all-cause mortality, and there are few published data on the association between obesity and cardiovascular mortality in PD patients (49), although a high BMI was protective for all-cause mortality as well as cardiovascular mortality in the hemodialysis populations (49). Although obese PD patients had higher risk for complications than non-obese PD patients, their survival was similar to matched HD patients (59), indicating that obesity is not a contraindication for PD.

There are recent data to further show that the prognostic impact of obesity is affected by the coexistence of frailty. In a study of 267 prevalent Chinese PD patients, Chan et al. (60) noted that frail patients had a higher waist-hip ratio (an indicator of central obesity) but not BMI. Although waist-hip ratio did not predict patient survival in this study, there was a significant

TABLE 1 | Relation between obesity and the outcome of PD patients.

Author	No. of case	fFllow up (year)	Findings
Snyder (50)	41,197	3	obese patients have better survival: adjusted HR of mortality 0.89 ($p < 0.05$), 0.99, and 1.00 for the obese in the first, second, and third year, respectively
Ramkumar (51)	10,140	1.5	new PD patients with high BMI/skeletal muscle mass have best survival: HR of all-cause mortality 0.90 (95%CI 0.83-0.97); HR of CV mortality 0.88 (95%CI 0.79-0.97)
McDonald (52)	9679	2	obesity associated with death (HR 1.36; 95%CI 1.14-1.54; $p < 0.05$) and technique failure (HR 1.17; 95%CI 1.07-1.26; $p < 0.01$)
Abbott (53)	1662	5	BMI over 30 not associated with survival risk or advantage (adjusted HR 0.99; 95%CI, 0.86-1.15; p=0.89)
Stack (54)	17,419	1	higher mortality for BMI < 20.9 (RR 1.20, 95%CI 1.00-1.43 for diabetic; RR 1.39, 95%CI 1.19-1.64 for nondiabetic); no difference in mortality between BMI quintiles 20.9-23.5, 23.5-26.1, 26.1-30.0, and >30.0
De Mutsert (55)	688	5	new PD patients with BMI >30 have similar survival with those with BMI 18.5-25: HR 0.8 (95%CI 0.5-1.3)
Liao (56)	280	4	metabolic syndrome was independently associated with increased risk for CV death (HR 13.3) and fatal or non-fatal CV events (HR 10.5); obesity (BMI >25) did not affect all cause mortality (HR 1.45; 95%CI 0.57-3.70; p =0.43), CV death (HR 2.02; 95%CI 0.59-6.88; p =0.26), and fatal or non-fatal CV events (HR 1.76; 95%CI 0.69-4.52; p=0.24)
Ahmadi (57)	156,562 (9 studies)	5	first year of PD: BMI 25-30 was associated with lower mortality than BMI 18-25 (HR 0.83, 95%CI 0.79-0.89) 3 to 5 years after PD: insignificant J-shape relationship with BMI 18-25 as the reference, i.e. BMI >30: HR 1.07 (95%CI 0.93-1.23); BMI < 18: HR 1.17 (95%CI 0.95-1.44)
Liu (58)	3610 (7 studies)	variable	J-shape relationship: obese group (BMI 25-29.9) associated with higher risk of all-cause mortality (HR 1.46; 95%CI 1.07-1.98; $p = 0.02$) and CV mortality (HR 2.01; 95%CI 1.14-3.54; $p = 0.02$); underweight group (BMI < 18.5) also had higher all-cause mortality (HR 2.11; 95%CI 1.46-3.07; $p < 0.001$).
Obi (59)	15,573	4	obese PD patients had higher risk for hospitalization for peritonitis and technique failure (i.e. need of transfer to hemodialysis) (P for trend < 0.001 for both analyses)

PD, peritoneal dialysis; BMI, body mass index (in kg/m^2); CV, cardiovascular; HR, hazard ratio; CI, confidence interval.

interaction between waist-hip ratio and frailty on patient survival and cardiovascular survival (60). For patients without frailty, the two-year cardiovascular survival was significantly better for those with a high waist-hip ratio (91.3% versus 74.4%), and they had fewer hospital admission for cardiovascular disease in 2 years, while waist-hip ratio did not predict the cardiovascular survival or need of hospital admission for cardiovascular disease in frail patients (60). The result of this study seems to indicate that there is a protective role of obesity in non-frail PD patients but not the frail ones (60).

IMPACT ON PD CATHETER INSERTION AND COMPLICATIONS

Obesity is well reported to be associated with PD catheter-related complications, which include catheter malfunction and various mechanical complications. Common sense and clinical experience suggest that obese patients have more technical difficulty with PD catheter insertion because of the deeper operating field, but published literature in this area is limited (61, 62). Visceral adiposity is associated with an increased volume of omentum, which theoretically increases the risk of catheter malfunction due to omental wrap. Again, there are no good data to support this notion, and results are conflicting from published study regarding the benefits of prophylactic omentectomy or omentopexy at the time of catheter insertion (61). A study that compared PD catheter insertion by mini-laparotomy, simple laparoscopy, or advanced laparoscopic techniques (with rectus sheath tunneling, selective omentopexy, and adhesiolysis) found no difference in the rate of catheter malfunction rates in the entire study population as well as the subgroup of obese patients (63). An observational study suggests that extended catheters have satisfactory survival compared with conventional catheters (64), but extended catheters are not generally available in many countries.

IMPACT ON DIALYSIS ADEQUACY

An important reason that obesity may affect the outcome of PD patients is the impact of body size on dialysis adequacy. In essence, the capacity of the peritoneum as a dialysis membrane is intrinsically limited by its relatively low permeability (as compared to synthetic membrane of hemodialyzers) and the maximal time allowed for dialysis each day (i.e. 24 hours). In the scenario of continuous ambulatory peritoneal dialysis (CAPD), the problem is aggravated by a generally fixed dialysis regimen of 3 or 4 daily exchanges, or 6 to 10 L/day for the usual 2 to 2.5 L exchange volume (65). The surface area of peritoneal membrane is similar to body surface area, which is proportional to the square root of body weight (66), implying that obese patients have a proportionally "smaller peritoneal dialyzer" (i.e. lower area of peritoneal membrane for dialysis). Assuming complete equilibration of urea in the PD effluent, a CAPD regimen of four 2-L exchanges per day in a patient with body weight 50 kg (i.e. total body water 30 L) would achieve a weekly peritoneal Kt/V 1.87 (67). The same CAPD regimen in a patient with body weight 70 kg would achieve a weekly peritoneal Kt/V 1.33, which would increase to 1.67 if the regimen is adjusted to four 2.5-L exchanges (67). For a 100 kg patients, a regimen of four 3-L exchanges (which is the maximal tolerable dwell volume without respiratory compromise) would only have a peritoneal Kt/V 1.4.

Clinical observations are in line with the above-mentioned theoretical considerations. Obesity generally has little adverse effect on the all-cause mortality of incident PD patients (49, 57). In a meta-analysis of 9 studies, Ahmadi et al. (57) found that being overweight or obese was associated with lower 1-year mortality and no significant association with 2-, and 3- to 5-year mortalities. Given the above discussion on the limitations of PD in providing adequate solute clearance for patients with a higher body weight, the gradual loss of survival benefit for PD in obese patients could possibly due to the loss of residual renal function. More importantly, the probability of conversion to hemodialysis increases substantially with the BMI. In an observational study of 15,573 incident PD patients from 2007 to 2011, Obi et al. (59) found that obese patients had faster declines in residual kidney function and consistently achieved lower total Kt/V over time despite greater increases in dialysis Kt/V than non-obese patients. More importantly, higher BMI was significantly associated with shorter time to transfer to hemodialysis (59), suggesting that dialysis adequacy and small solute clearance are the major concern of obese PD patients.

OBESITY AND INFLAMMATION

The major mechanism that explains the potential link between obesity and the adverse clinical outcome in the general population is systemic inflammation (68), but the data dedicated to the PD population in this area are scarce. In essence, obesity should be considered as a chronic inflammatory state because adipocytes secrete a panel of peptides mediators, commonly referred to as adipokines (69), that play important roles in the pathogenesis of insulin resistance, endothelial dysfunction, and cardiovascular disease (68, 70). Traditional cytokines released by the adipose tissue include tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor (PAI-1), monocyte chemotactic protein-1 (MCP-1), and macrophage migration inhibitory factor (MIF) (71–74). They play important roles in the local regulation of adipose tissue metabolism as well as triggering a pro-inflammatory state in distant sites (75–79).

Adipocytes also secrete a panel of mediators that are usually not produced by other cell types. Notable candidates include leptin, adiponectin, resistin, omentin-1, and vaspin. Leptin, the best known adipokine, affects nitric oxide production and activates the sympathetic system (80, 81). Increases in serum leptin levels during PD are associated with inflammation and a decrease in lean body mass (82). Adiponectin is another major adipokine that is involved in regulating glucose levels and fatty acid breakdown (83). Resistin was first described to be involved in the pathogenesis of obesity-associated insulin resistance in mice (84). Omentin-1, also known as intelectin-1, is a novel adipokine produced mostly in visceral adipose tissue (85). Vaspin (visceral adipose tissue-derived serpin) is a member of serine protease inhibitor family first isolated by from visceral white adipose tissues of Otsuka Long-Evans Tokushima fatty rat (86). Although not often considered as an adipokine, adipose tissue releases free fatty acids to the systemic circulation, which contribute to the development of insulin resistance, pro-inflammatory, and pro-thrombotic state (87). In addition, obesity also leads to disturbances in the gut microbiota, which result in the leakage of lipopolysaccharide and other bacterial fragments to the systemic circulation, eventually leading to an inflammatory response (88, 89). Although the pathophysiological roles of these adipokines have been well studied in diabetic and obese patients, data on their relevance in the PD population are scarce.

INSULIN RESISTANCE AND METABOLIC SYNDROME

Another major mechanism that obesity leads to adverse clinical outcome is the concomitant insulin resistance and metabolic syndrome. Obesity is well reported to be associated with insulin resistance, and the major mechanism is *via* its effect on the incretin axis, and glucagon-like peptide 1 (GLP-1) is probably the most important mediator. In essence, GLP-1 is a 30-amino acid peptide hormone produced in the intestinal epithelial endocrine L-cells by differential processing of proglucagon, and is the major incretin hormone (90). One of the most important functions of GLP-1 is to, *via* its specific receptor, amply the post-prandial insulin secretion (91). The activity of GLP-1 is regulated by its degrading enzyme dipeptidyl peptidase-4 (DPP-4), which is also known as the T-cell antigen CD26. DPP-4 is an integral membrane protein expressed on many cell types, and is also shed from the membrane and circulates as a soluble protein in the plasma (92). Under physiological conditions, GLP-1 is the major substrate of the circulating DPP-4 (92). In obese patients, the secretion of GLP-1 is reduced, while that of DPP-4 is increased (93, 94). The alteration in the incretin axis is the major contributing factor of insulin resistance, dyslipidemia, and atherosclerosis in obesity (95, 96). In addition to its metabolic effects, the incretin axis is also involved in inflammation (97). In monocytes and macrophages, GLP-1 agonists and DPP-4 inhibitors suppresses the action of protein kinase A, which leads to a reduction in inflammatory cell infiltration into the arterial wall (97). In addition, DPP-4 also has many substrates other than GLP-1 that are implicated in the generation of inflammation (98). Dedicated data on insulin resistance and the alterations of incretin axis in PD patients, however, are scarce.

First recognized in its extreme form as Reaven's syndrome X (99), metabolic syndrome began as a loosely defined clustering of major risk factors for cardiovascular diseases and type 2 diabetes (100). With the improving case recognition and definition, obesity has become a key element of the constellation of metabolic syndrome, as emphasized by the revised criteria for metabolic syndrome by International Diabetes Federation (IDF) (100). In the general population, metabolic syndrome is strongly associated with overall mortality, cardiovascular disease, and stroke (101). It has been suggested that any adverse outcome associated with obesity is the result of metabolic syndrome rather

than obesity per se (102, 103). However, the definition of metabolic syndrome and its prognostic implication in PD remain controversial (71, 104). Traditional criteria for metabolic syndrome is not applicable to PD patients because they tend to have a larger waist circumference, there is never a genuine "fasting" state, and the confounding effect of excessive body fluid is considerable. In a retrospective analysis of 329 prevalent PD patients, the agreement between four sets of diagnostic criteria for metabolic syndrome was at best fair to moderate (104). In this study, metabolic syndrome was present in 53.2%, 53.8%, 60.5%, and 66.3% of the PD patients according to the original World Health Organization (WHO) criteria, the International Diabetes Federation (IDF) criteria, the original National Cholesterol Education Program (NCEP) criteria, and the modified NCEP criteria, respectively (104). However, the overall survival, cardiovascular survival, or technique survival did not differ between patients with and without metabolic syndrome, irrespective to diabetic status and diagnostic criteria being used (104), indicating that unlike the general population, metabolic syndrome may not be an important prognostic indicator of PD patients.

NEW-ONSET GLUCOSE INTOLERANCE AFTER PD

A major cause of weight gain in PD patients is glucose absorption from the PD solution, and an important confounding factor that the weight gain may lead to adverse clinical outcome is the development of new-onset diabetes after PD. Since glucose is the most commonly used osmotic agent in commercial PD solution, it has been estimated that PD patients derive about 20% of their total daily energy intake from the glucose in PD solutions, which corresponds to a daily energy intake of 4 to 13 kcal/kg body weight (105). Our previous study of 252 non-diabetic incident patients found that fasting plasma glucose was above 7.0 mmol/l in 27.3% non-diabetic incident PD patients (106). In this study, obese patients did not have a higher risk of new-onset diabetes after PD, but even mild fasting hyperglycemia (fasting plasma glucose >5.6 mmol/l) was associated with a worse survival (106). In contrast, Dong et al. (107) examined total of 612 non-diabetic PD patients, and found that new-onset diabetes after PD was present in only 32 patients (5.2%). In this study, high BMI and C-reactive protein levels are major predictive factors for the development of new-onset diabetes and impaired glucose tolerance in PD patients (107). In a recent analysis of 1681 incident PD patients, Than et al. (22) noted that the fasting plasma glucose level after initiation of PD in patients without pre-existing diabetes rose gradually from 5.9 ± 2.0 to 6.4 ± 2.2 mmol/l from 1995 to 2019, and the incidence of new-onset diabetes increased from 18.0% to 23.3% during this period (22). In this study, there was a modest but statistically significant correlation between post-dialysis fasting plasma glucose level and baseline BMI in non-diabetic patients; new-onset diabetes was present in 37.9% patients with baseline BMI 19.0 to 23.9 kg/m2, but 59.0% of those with baseline BMI above 25.0 kg/m2 (22). However, outcome data were not analyzed in this study, and it remains uncertain whether the new-onset diabetes after PD directly causes any adverse outcome, or the glucose load from PD simply unmasks the underlying occult metabolic problems that is associated with CVD.

FLUID OVERLOAD AS A CONFOUNDING FACTOR

Another important factor that confounds the relation between obesity and clinical outcome is the effect of fluid overload. A patient with a large body weight may be the result of being obese or having fluid overload, and any weight gain in PD patients may be due to increase in adipose tissue mass or worsening of fluid overload. In an early case control study of predominantly CAPD patients, diabetes as well as noncompliance with fluid restriction, salt restriction, and performance of dialysis exchange were important predictive factors of symptomatic fluid overload (108). As expected, peripheral edema, pulmonary congestion, pleural effusions, and arterial hypertension were all common manifestations of symptomatic fluid overload in this study (108).

In the context of obesity assessment, asymptomatic fluid overload is also common in PD patients (109). In the Initiative for Patient Outcomes in Dialysis-Peritoneal Dialysis (IPOD-PD) study that examined 1092 patients from 135 centers in 32 countries, only 38.7% patients had normal hydration, while fluid overload of over 1.1 L was present in 56.5% of them, and the median fluid overload was 2.0 L for male patients (110). Notably, most of the patients were already overhydrated before the initiation of PD, including those without a documented diagnosis of congestive heart failure (110). In a study that recruited 122 asymptomatic prevalent Chinese PD patients, Kwan et al. (111) reported that fluid overload, defined as over-hydration volume ≥1 L, was present in 72.1% patients, while 20.5% patients had over-hydration ≥5 L. Another study that recruited 307 prevalent Chinese CAPD patients with a median duration of PD 14.6 months found that fluid overload, as defined by extracellular to total body water ratio ≥0.40, was present in 66.8% patients, and over half of them had no symptom related to fluid overload (112). Kim et al. (113) further reported from a study of 284 prevalent PD patients that 68% patients who had fluid overload at baseline remained persistently hypervolemic one year later, and nearly 20% of the entire cohort had chronic fluid overload.

Fluid overload is a well reported predictor of adverse outcome in PD patients. Guo et al. (112) found that the cardiac event rate after 1 year of follow-up was significantly higher in the patients with fluid overload than those with normal hydration (17% vs 7%). In a study of 529 patients, O'Lone et al. (114) noted that the overhydration indices (including the absolute volume of overhydration, and its ratio with extracellular water volume) were independent predictors of all-cause mortality. Fluid overload is directly linked to increased cardiovascular morbidity and mortality (114, 115). Even among asymptomatic PD patients, Ng et al. (29) found that the volume status

independently predicted patient survival and cardiovascular events (29). In this study of 311 incident PD patients, each 0.1 unit increase in extracellular-to-intracellular volume ratio was associated with 24.5% decrease in overall survival and 18.7% decrease in cardiovascular event-free survival (29). Longitudinal study with repeated bioimpedance spectroscopy measurement further showed that PD patients who remained persistently hypervolemic had a 2.8-fold increase in risk of transferring to chronic hemodialysis (113).

Traditionally, fluid overload is considered as a result of underlying cardiac disease or inadequate dialysis. More recently, it is increasingly recognized that fluid overload per se directly contributes to the pathogenesis and progression of cardiovascular disease. Specifically, fluid overload causes dysfunction of the gut permeability barrier dysfunction, a phenomenon that is particularly prominent in the context of CKD (116). It has long been reported that plasma levels of endotoxin, the major bacterial cell fragment that is implicated in the generation of systemic inflammatory response and cardiovascular disease, were higher in edematous heart failure patients than in non-edematous patients and healthy volunteers (3). In CKD, small intestinal water content correlated with plasma endotoxin level, suggesting that bowel wall edema leads to gut permeability barrier dysfunction (117, 118), which is postulated to facilitate the translocation of bacterial fragments to the systemic circulation, leading to systemic inflammation and cardiovascular diseases.

OBESITY IN DIFFERENT COMPARTMENTS

In the recent years, it is increasingly recognized that obesity is an over-simplified concept. In the general population, it has long been recognized that central obesity, i.e. the accumulation of fat around the mid-body section, increases the risk of glucose intolerance, dyslipidemia, cardiovascular disease, Alzheimer's disease, and several types of cancer (119, 120). Patients with a waist-to-height ratio exceeding 0.5, despite a normal BMI, had elevated mortality risk for cardiovascular and metabolic disease (121). It has been proposed that the accumulation of fat in the body close to vital organs in the abdomen leads to a low-grade systemic inflammatory state (122, 123). In PD patients, the assessment of central obesity by waist circumference is theoretically confounded by the instillation of PD solution into the peritoneal cavity. Nonetheless, waist conference remains a reasonable marker of abdominal adiposity in PD patients. In a study of 107 prevalent PD patients, Kamimura et al. compared waist circumference measured at umbilicus level to formal trunk fat measurement by dual-energy x-ray absorptiometry, the agreement (as determined by the kappa statistic) between waist circumference and trunk fat was 0.59, and the change in waist circumference significantly correlated with changes in trunk fat after 6 months ($r = 0.49$), both indicate a moderate agreement between the methods (124).

However, the differentiation between central and peripheral obesity may not be sufficiently accurate because adipose tissue in human body could be divided into several distinct compartments (125). Traditionally, adipose tissue is classified by morphology into white, brown, or beige subsets (126). Although brown and beige adipose tissue contribute little, if any, to the total body adipose tissue mass in normal adults (126), white adipose tissue per se could be further classified by its location into subcutaneous and visceral ones, which constitutes 80% and 20%, respectively, of the white adipose tissue mass (127). The usual concept of central obesity, therefore, encompasses visceral adipose tissue (located intra-abdominally, in the omentum, and adjacent to internal organs) as well as subcutaneous adipose tissue in the abdominal wall (127). There is, however, emerging evidence that subcutaneous and visceral adipose tissues are different in their metabolic profile and clinical implications. In essence, current data suggest that visceral adipose tissue is the key determinant of insulin resistance, metabolic disturbance, and probably adverse cardiovascular outcome in obesity, while subcutaneous adipose tissue appears to have a small protective effect (125, 128–130).

It is important to note that the differential effect and prognostic implications of visceral and subcutaneous fat have not been explored in the PD population, but in an observational study of 115 PD patients, Bazanelli et al. (124) examined the change in body fat distribution over time by dual-energy x-ray absorptiometry. In this study, the overall BMI gradually increased with the vintage of PD, but there was a gradual decline in the amount of truncal fat simultaneously (124). The mechanism and prognostic implication of the progressive change in body fat distribution in PD patients require further studies.

CHANGE IN BODY COMPOSITION AFTER PD

As discussed above, a large body weight may be the result of excessive body water rather than a higher adipose tissue or muscle mass. Similarly, progressive weight gain after PD may be caused by fluid overload rather than obesity. Nonetheless, early reports showed that the content of body fat, especially intra-abdominal fat, increases after PD treatment (131–133), while the magnitude of overhydration did not appear to increase during the first two years of PD (134). In a prospective study of 19 PD patients, Fernström et al. (131) measured the body fat by serial computed tomography (CT) and dual energy x-ray absorptiometry (DEXA) and found that although the overall body weight increased insignificantly from 67.1 to 68.4 kg over an average of 7 months on PD, the intra-abdominal fat area increased by 22.8%, and the percentage of total body fat content increased from 27.8% to 30.9%. In a study with an extended follow up of 79 months, Søreide et al. (132) examined the percentage of total body fat of 8 PD patients by means of a computerized model of near infrared interactance and found that the total body fat content increased from 19.8% to 22.5%, while the body weight had no change. When individual adipose tissue compartments were monitored over 12 months in 60 Korean PD patients by bioelectric impedance analysis and computed tomogram, Choi et al. (133) found that their body weight continued to increase in during the first 12 months on PD, but

visceral and subcutaneous fat mass increased only during the first 6 months, and then decreased from 6 to 12 months. In this study, patients with more visceral fat mass at the start of PD had less gain of visceral fat mass during the first 6 months, and those with more subcutaneous fat mass at the start of PD had less gain of subcutaneous fat mass, indicating that regression-to-mean is an important confounding factor (133). More importantly, the change in body weight was not associated with the change in visceral or subcutaneous fat, suggesting that hydration status was the major determinant of body weight change (133).

The best data in this aspect came from the Initiative for Patient Outcomes in Dialysis-Peritoneal Dialysis (IPOD-PD) study (135), which recruited 1054 incident PD patients in 135 centers from 28 countries, and their volume status was measured by bioimpedance spectroscopy before the start of PD and then every 3 months for 3 years. In this study, the mean volume overload was 1.9 L before the initiation of PD, which was reduced to 1.2 L after one year of PD, and it remained stable at year 2 and 3 (135). Baseline clinical parameters and PD prescription did not predict the change in volume status over first 6 months in this study, but a relative volume overload over 17.3% was independently associated with a higher risk of death (adjusted hazard ratio 1.59) (135). In a prospective study of 155 incident PD patients with a median follow-up of 12 months, Jaques et al. (136) noted that although fluid overload is common, volume status could be reasonably controlled when the PD prescription was tailored to patient's individual characteristics, while the level of residual renal function, modality of PD (CAPD versus machine-assisted PD), and peritoneal characteristics are not decisive in this matter.

Although fluid status may be an important confounding factor, there is emerging evidence that the progressive accumulation of fat in PD does have clinical impact, even though it may be "masked" by the concomitant changes in other body composition. In an observational study of 160 PD patients followed for 2 years, Kim et al. (137) showed that although the body weight appeared to be static, loss of lean tissue mass (i.e. muscle mass) and gain in adipose tissue mass were observed after 2 years of PD in over 30.5% and 44.3% of patients, respectively. However, the impact of obesity in sarcopenic patients has not been well-studied. The loss of lean tissue and gain in adipose tissue mass were both reported to be independent risk factors for all-cause mortality after adjusting for demographic, biochemical, and cardiovascular parameters (137). In the IPOD-PD patient cohort, the use of hypertonic and glucose solutions were significantly associated with a decrease in lean tissue mass and an increase in adipose tissue mass over time (138). In this analysis, lean tissue mass inversely correlated with the risk of death, while a high adipose tissue mass (as represented by the fat tissue index) was associated with a higher sub-distributional hazard ratio for the risk of death when compared with the median as a reference (138).

CONCLUSION

The above discussion indicates that the relationship between obesity and the outcome of PD patients is complicated, and body weight is not a reliable measurement for obesity. In essence, obesity has variable clinical effects along the journey of PD patients, as summarized in **Figure 1**. Obesity is associated with various complications during PD catheter insertion. At the initiation of PD, obesity is probably a marker of better nutrition, which explains its association with improved clinical outcome in some observational studies. Nonetheless, adipose tissue secretes a number of inflammatory mediators, and obesity aggravates the problem of inadequate dialysis in anuric patients. With time on PD, there is usually weight gain due to increase in body fat and fluid accumulation, each of them independently leads to adverse outcome, especially an increase in cardiovascular risk. The concomitant decline in skeletal muscle mass may be masked, but will also contribute to the adverse clinical outcome.

STRATEGIES OF WEIGHT LOSS

In obese patients with type 2 diabetes, weight loss is known to reverse the underlying metabolic abnormalities and improve glycemic control (139). In this group of patients, weight loss of 15% has a disease-modifying effect that could not be achieved by insulin or oral hypoglycemic agents (139). Furthermore, weight loss improves risk factors for cardio-metabolic disease and quality of life in this population (139). Given the complex relationship between obesity and the clinical outcome of PD, it remains to be determined whether weight loss confers an equivalent clinical benefit in obese PD patients.

If weight loss is considered desirable, dietary restriction and exercise is difficult to achieve and sustain the target body weight (140). In obese adults with normal kidney function, phentermine-topiramate and glucagon-like peptide-1 (GLP-1) receptor agonists, especially semaglutide, are the most effective drugs in reducing weight (141). Neither phentermine-topiramate nor GLP-1 receptor agonists, however, has been tested in obese PD patients. Given the accumulating evidence that GLP-1 receptor agonists reduce the cardiovascular events in patients with moderate to severe CKD (142), it would be important to explore the efficacy and benefit of using GLP-1 receptor agonists for obese PD patients. Surgical options, such as gastric bypass and sleeve gastrectomy, are highly effective in body weight control and have well documented metabolic benefits (143–145), but conversion to long term hemodialysis is necessary. Adjustable intragastric balloon is a minimally-invasive alternative that is feasible for the PD population but further studies are required.

GAPS OF KNOWLEDGE AND FURTHER RESEARCH DIRECTIONS

The above discussion reviewed a wealth of literature on the complex relation between obesity and the prognosis of PD patients. Suffice to say, the impact of adipose tissue mass on

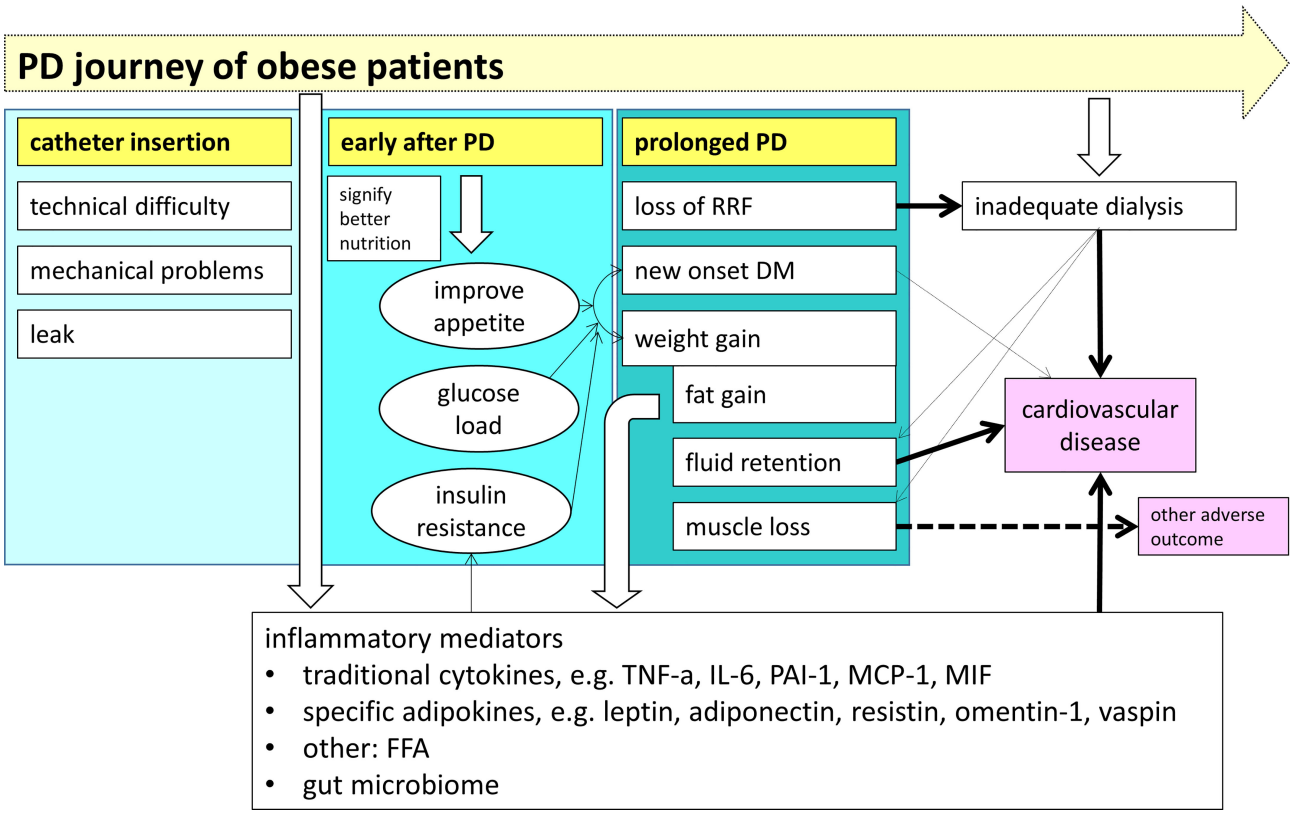

FIGURE 1 | The impact of obesity on the clinical outcome along the journey of patients treated with peritoneal dialysis (PD). Before PD is started, obesity is associated with several specific problems during dialysis catheter insertion. During the early phase of PD, obesity is a surrogate marker of a better nutritional status. With time on PD, there is a gradual decline in skeletal muscle mass and an increased in body fat and fluid, resulting in a progressive overall weight gain. Obesity directly contributes to the systemic inflammatory state *via* a panel of inflammatory mediators, and also aggravates the problem of inadequate dialysis when the patient become anuric, both lead to the adverse outcome of chronic PD patients. (PD, peritoneal dialysis; RRF, residual renal function; DM, diabetes mellitus; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor type 1; MCP-1, monocyte chemoattractant protein-1; MIF, macrophage migration inhibitory factor; FFA, free fatty acids).

the clinical outcome is not linear, is different from the relation observed in the general population, includes the risk of cardiovascular disease as well as that of conversion to hemodialysis, and there is a considerable confounding effect from the concomitant changes in other aspects of body composition (notably decline in muscle mass and fluid overload). There are many questions to be answered in this field, and we outlined in **Table 2** some of them which we considered particularly interesting. Notably, recent data showed that glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, as well as dual gastric inhibitory peptides (GIP) and GLP-1 receptor agonist, such as tirzepatide, are effective treatment of obesity and probably reduce the risk of cardiovascular events in obese or diabetic patients (111, 146–148). It would be interesting to explore whether these agents are equally beneficial in PD patients.

TABLE 2 | Gaps of knowledge and further research directions.

■ What are the adipocyte dysfunctions in CKD and PD patients?
■ Differentiate the functions and abnormalities between adipocyte and stromal cells in the adipose tissue.
■ How does acute events (notably peritonitis) affect body fat content of PD patients?
■ What are the prognostic impact of different body components (i.e. fat content, muscle mass, and fluid overload)?
■ How to measure specific compartments of adipose tissue (especially visceral fat content)?
■ What is the optimal treatment of new onset diabetes after PD? What should be the target of glycemic control?
■ How to preserve muscle mass and avoid excessive fat accumulation at the same time?
■ What is the role of non-pharmacological therapy (e.g. exercise training)?
■ Is there any role of the novel anti-obesity agents (e.g. glucagon-like peptide-1 receptor agonists) in PD patients?

AUTHOR CONTRIBUTIONS

JN and WT were responsible for literature review and writing the first draft of the manuscript. CS was responsible for the overall idea, organization and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Sodium First Approach, to Reset Our Mind for Improving Management of Sodium, Water, Volume and Pressure in Hemodialysis Patients, and to Reduce Cardiovascular Burden and Improve Outcomes

Bernard Canaud[1,2†], Jeroen Kooman[3], Andreas Maierhofer[4], Jochen Raimann[5†], Jens Titze[6] and Peter Kotanko[5,7]*

[1] School of Medicine, Montpellier University, Montpellier, France, [2] Global Medical Office, Freseenius Medical Care (FMC)-France, Fresnes, France, [3] Maastricht University Maastricht Medical Center (UMC), Maastricht University, Maastricht, Netherlands, [4] Global Research Development, Fresenius Medical Care (FMC) Deutschland GmbH, Bad Homburg, Germany, [5] Research Division, Renal Research Institute, New York, NY, United States, [6] Cardiovascular and Metabolic Disease Programme, Duke-National University Singapore (NUS) Medical School, Singapore, Singapore, [7] Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, United States

New physiologic findings related to sodium homeostasis and pathophysiologic associations require a new vision for sodium, fluid and blood pressure management in dialysis-dependent chronic kidney disease patients. The traditional dry weight probing approach that has prevailed for many years must be reviewed in light of these findings and enriched by availability of new tools for monitoring and handling sodium and water imbalances. A comprehensive and integrated approach is needed to improve further cardiac health in hemodialysis (HD) patients. Adequate management of sodium, water, volume and hemodynamic control of HD patients relies on a stepwise approach: the first entails assessment and monitoring of fluid status and relies on clinical judgement supported by specific tools that are online embedded in the HD machine or devices used offline; the second consists of acting on correcting fluid imbalance mainly through dialysis prescription (treatment time, active tools embedded on HD machine) but also on guidance related to diet and thirst management; the third consist of fine tuning treatment prescription to patient responses and tolerance with the support of innovative tools such as artificial intelligence and remote pervasive health trackers. It is time to come back to sodium and water imbalance as the root cause of the problem and not to act primarily on their consequences (fluid overload, hypertension) or organ damage (heart; atherosclerosis, brain). We know the problem and have the tools to assess and manage in a more precise way sodium and fluid in HD patients. We strongly call for a sodium first approach to reduce disease burden and improve cardiac health in dialysis-dependent chronic kidney disease patients.

Keywords: chronic kidney disease stage 5D, hemodialysis, fluid overload, hypertension, cardiac disease, sodium and water imbalance

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****Correspondence:***
Bernard Canaud
canaudbernard@gmail.com;
Bernard.Canaud@fmc-ag.com

†ORCID ID:
Bernard Canaud
orcid.org/0000-0001-6854-2816
Jochen Raimann
orcid.org/0000-0002-8954-278

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1 INTRODUCTION

Despite recent improvements in dialysis patient outcomes (1–3), cardiovascular events remain the leading cause of death accounting for 50 to 55% of mortality according to estimates of the United States Renal Data System (3). Severe arrhythmias and sudden cardiac death account for almost 28% of cardiac death while coronary ischemic disease, congestive heart failure or vascular events are responsible for the rest (3).

Findings of recent studies may be taken as examples to highlight the burden of this problem. Fluid overload is quite common in hemodialysis patients. In a large cohort of incident hemodialysis patients (>40.000), moderate fluid overload (>2.5 l) assessed by multifrequency bioimpedance was noted in 46% of patients, while a more severe one (>6 l) was observed in about 10% (4, 5). Hypertension, even when set as a predialysis systolic blood pressure >160 mmHg, was noted in 20% of patients in the same cohort and more frequently associated with fluid overload (4). In addition, cardiac health issues tended to aggravate over the next 12 months in about half of the patients, contributing to worsened outcomes and almost doubling the relative risk of death (4). Left ventricular hypertrophy (LVH), a surrogate marker of chronic fluid overload and/or hypertension was detected up to 75% in patients starting dialysis with a continuous increase over time (6–8). Hyponatremia, a biomarker strongly associated with poor outcome in dialysis patients, is observed in 10 to 19% of hemodialysis patients in recent cohort reports (9, 10). In a recent study, it has been shown that hyponatremia was in fact associated with combined fluid overload (EC and IC fluid excess) with intercompartmental fluid imbalance, translating into the occurrence of an intercurrent illness (cardiac failure, inflammation, oxidative stress) being likely associated with protein energy wasting (10–12). This observation is in line with findings large cohort studies (13, 14) and confirm validity of a recent proposed workflow algorithm to explore hyponatremia in dialysis patients (15). A high prevalence of cardiac arrhythmias was shown in studies using implanted loop recorders (16–18). Recent cardiac rhythm monitoring study involving sixty-six patients using continuous monitoring of such loop recorders have identified that 1678 clinically significant arrhythmias (CSA) were observed in 44 (66.7%) dialysis patients (16, 19). The majority were bradycardia not necessarily with hyperkalemia (19.7%) followed by asystole (9.1%) and ventricular tachycardia (1.5%). Confirmed arrhythmia subtypes were represented by atrial arrhythmia (90.9%) with atrial fibrillation (30%) followed by ventricular arrhythmia (71.3%) and bradyarrhythmia (25.8%). Five patients of this cohort with serious bradyarrhythmia required pacemaker implantation to prevent cardiac sudden death. Lastly, pulmonary edema and related congestive heart decompensation episodes are among the most frequent causes of hospitalization (44%) and readmissions creating a significant burden both on patient and healthcare system (20, 21).

Fluid volume depletion and care management of hemodialysis patients is another critical point that may affect outcomes (22, 23). As documented in recent reports, too aggressive dry weight policy based on high ultrafiltration rate (24, 25) (> 13 ml/hr/kg, for example), is associated with critical hypovolemia and serious intradialytic hypotension (IDH) (26), that may lead to repetitive systemic hemodynamic stress episodes with end-organ damage (27, 28). Repetitive ischemic insults result from inadequate hemodynamic response to volume depletion but not only (24, 29). In fact, ischemic insult is part of a broader multifactorial stress condition, namely dialysis-induced systemic stress syndrome, that includes hemobiological reactions, hypoxemia, thermal imbalance, osmotic and electrolytic shifts (27). As recently summarized, dialysis-induced systemic stress may contribute to morbidity and mortality in dialysis patients as a potent disease modifier including protein energy wasting process (27, 29). A call for action is needed to mitigate this additional cardiovascular risk in maintenance hemodialysis patients (27).

In this context, it is easily recognized that sodium and water related disorders contribute significantly to cardiac burden in hemodialysis patients, either from chronic fluid overload exposure during the interdialytic period or from acute fluid depletion during dialytic time (30, 31). Now, it must be highlighted that sodium and fluid accumulation is a long-standing process aggravating along chronic kidney disease progression with a culminant point at the end stage of kidney disease. In addition, specific conditions (i.e., aging) or diseases (i.e., hypertension, diabetes) are strong enhancers of this risk as indicated in recent population-based studies (32–34). A more careful attention should be paid to this cause to address their consequences and better manage patients in order to mitigate their risks (35). The aim of this narrative review is to address new physiological and pathophysiological findings related to sodium and water disorders in chronic kidney disease (CKD) patients and to propose clinical action points to improve cardiac health in dialysis patients.

2 SODIUM AND WATER PHYSIOLOGY: NEW FINDINGS

2.1 Sodium Homeostasis: From Two to Three Compartment Model

In healthy humans, sodium and water homeostasis relies on a precise balance between sources (external dietary, internal metabolism) and losses (kidney, gut) in which kidney function and neuroendocrine factors play a major role. Traditionally, total body sodium (TBS) distributed in the extracellular volume (ECV) and bone, was thought to remain relatively constant over time and adjusted to intake changes. This fine regulation of TBS depends on kidney function and blood pressure as described in a kidney-centric model elaborated by Guyton et al (36). According to this view, sodium distributes in two compartments, circulating (volemia) and Interstitium, and ensures extracellular volume and hemodynamic homeostasis (36). In this setting, natremia reflects the effective plasma tonicity (natremia x 2) acting as the main driving force for water repartition within extra- and intracellular compartments. This two-compartment model depicts sodium in solution (i.e.,

osmotically active sodium), that controls blood pressure and hemodynamics to ensure adequate tissue perfusion. In the past decade, this conventional model has been challenged by new physiological findings that demonstrated the existence of a tissue sodium storage compartment, thus expanding the TBS concept into a three-compartment model (37–39). Initially, this model has been suspected from discrepancies in sodium mass balance studies conducted in healthy astronauts as part of the MARS 500 project (40). In conditions of strictly isolated and controlled conditions, the investigators observed that subjects submitted to precise diet salt intakes exhibited cyclic variations of TBS which were not translated in body weight or urinary sodium excretion changes but correlated with aldosterone and cortisol changes (40–43). This observation suggested that sodium accumulates in a third compartment without commensurate water retention. Later, this hypothesis was confirmed by means of sodium MRI imaging of (23)Na showing sodium stored in skin and muscle (42, 44). Tissue sodium concentration may be then quantified by (23)Na MRI (34, 44). From reference studies, tissue sodium is estimated between 10 and 40 mmol/l increasing with aging and under pathologic conditions (e.g., diabetes, hypertension, chronic kidney disease) (32–34). Further interventional studies confirmed that skin sodium storage is an active process that may be modulated according to sodium and water needs and conditions. Skin sodium is stored under the keratinocyte layer in a hypertonic environment that may regulate its own electrolytic microenvironment by means of sodium gradient and adjustment of lymph flux *via* angiogenic factors (45–48). Phagocytes sense hypertonic sodium accumulation and trigger tonicity-responsive enhancer binding proteins (Nuclear Factor of Activated T Cells 5, NFAT5) that stimulate in turn secretion and release of vascular endothelial growth factor C (VEGFC) (49). This mechanism has a dual action: first, it increases tissue sodium clearance *via* lymphatic flow; secondly, it acts on systemic blood pressure by modulating vascular tone *via* a stimulation (endothelial Nitric Oxide Synthase, eNOS expression. In addition, muscle sodium content tends to parallel skin behavior contributing to the overall tissue sodium storage with the same consequences. It has been suggested that tissue sodium content may contribute to blood pressure control independently from traditional neuroendocrine mechanisms *via* a skin immune-mediated mechanism (37). This interesting pathway of hypertension has been recently challenged by transgenic mouse models (50, 51). In these animal models, hypertension was induced by pathological losses of free water. Interestingly, hypertension was due to cutaneous vasoconstriction to limit epidermal water loss, and metabolic adaptation (muscle and protein catabolism) to enhance production of urea and organic osmolytes. This concept of pathogenesis of hypertension is antipodal to the classic view relying on salt retention (52). All these finding open new pathways for understanding better and managing hypertension resistant to traditional approaches (37).

In anuric chronic kidney disease dialysis patients, sodium and water balance rely mainly on renal replacement treatment schedule, dietary intake and likely on skin, gut, lungs and oxidative process. Conventional, short and intermittent hemodialysis treatment schedules create cyclic fluctuation alternating between a slow loading phase (interdialytic) and a fast-unloading phase (intradialytic), making fluid and volume management quite challenging (27, 29). As discussed earlier, fluid volume and pressure management expose patients to dialysis-induced systemic stress and morbidity. On one hand, chronic fluid overload is associated with mechanical and functional cardiac stress leading to structural changes contributing to cardiac remodeling (i.e., left ventricular hypertrophy, concentric or asymmetric, myocardial fibrosis, arrhythmias) and vascular consequences (atherosclerosis). On the other hand, acute fluid depletion secondary to ultrafiltration induces hypovolemia leading likely to intradialytic hypotension depending on patient's hemodynamic response. In that setting, repetitive silent ischemic cardiac insults (i.e., myocardial stunning) may aggravate and accelerate damaging processes. Subsequently, further factors (i.e., arrhythmia, hypoxemia, ionic fluxes) may precipitate cardiac events and potentiate the effects of dialysis-induced systemic stress. Today, it is well recognized that maintenance conventional hemodialysis may act as a disease modifier likely contributing to end organ damage and cardiac burden (29). Aside management of volume and pressure, reflecting sodium osmotically active, a component that has been extensively studied, the role of tissue sodium accumulation and its management remain unexplored in maintenance hemodialysis patients (28, 53, 54). This new identified issue should be addressed more precisely in future clinical research (55). Indeed, it is speculated that restoration of tissue sodium homeostasis will be integrated in a more comprehensive management of sodium, water and blood pressure to improve cardiac health.

2.2. Pathophysiological Consequences of Sodium and Water Disorders in Advanced CKD and Dialysis Patients

Impairment of the sodium metabolism in patients with ESRD often results from longstanding pathologic processes that start early with kidney disease and aggravates steadily over time with progredient loss of kidney function. Sodium imbalance reflects the inability of the diseased kidney to handle daily sodium and water load.

Sodium accumulation in the extracellular space is the most common and diagnosable consequence of sodium imbalance in CKD patients. This refers to sodium in the extracellular fluid volume, the so called osmotically active sodium, which tends to increase thirst with subsequent expansion of the extracellular volume in the circulation and the interstitial space. Edema, hypervolemia, hypertension and congestive heart failure are among the most common manifestations of sodium accumulation and fluid overload translating into consequent cardiac and vascular damages. This pathophysiological dynamic has rendered chronic fluid overload with or without hypertension to be recognized as one of the main causes of morbidity in CKD patients. However, as summarized in recent reviews, next to sequelae on fluid and hemodynamics, sodium imbalance also associates with multiple end organ damages including cardiac remodeling (left ventricular hypertrophy), proarrhythmic condition, white matter brain damage, atherosclerotic lesion, protein energy wasting, inflammation and lung disorder with pulmonary hypertension (37, 55).

On the other hand, predialysis hyponatremia, reflecting hypotonicity and sodium-free water excess, is observed in 10 to 15% HD patients (56). Hyponatremia is a strong marker of poor outcomes (9, 13, 56, 57). Recent studies have shown that hyponatremia is in fact a mixed fluid disorder, consisting of extracellular fluid excess and water compartment repartition imbalance, reflecting an underlying illness such as congestive heart failure, liver disease or inflammatory protein energy malnutrition (10, 13, 15, 58). Interestingly, recent observational studies have shown that clinical outcomes might be improved by intensifying fluid and sodium depletion [negative dialysate-to-plasma (d-p) Na gradient] rather than correcting plasma sodium concentrations while loading patient by applying a positive (d-p) Na gradient (9).

Sodium accumulation in tissue, as discussed in the previous paragraph, also associates with chronic kidney disease progression. As documented through functional (23)Na MRI imaging, skin and muscle sodium content increase steadily over time as kidney function deteriorates (32). Interestingly, several metabolic consequences of salt tissue accumulation and organ damage have been identified as an independent component of its mechanical action (55). However, this is a new field of research with fast growing and fascinating findings in which more must be discovered. Few examples will be used to illustrate this new pathophysiologic link. Left ventricular hypertrophy has been shown to be positively correlated with skin sodium content, almost independently from blood pressure level, in a prospective study conducted in advanced non-dialysis CKD patients (53). In HD patients, pulse wave velocity (PWV) changes may likely reflect vascular sodium content changes and endothelial function improvement as suggested by acute changes in PWV following sodium depletion by dialysis (59–61). Insulin resistance, assessed by means of euglycemic clamps, has been found to be inversely correlated to skin sodium content in HD patients, suggesting that tissue sodium interacts with insulin pathways independent of uremic toxin levels (62). Salt loading and tissue storage activate an adaptive regulatory network mechanism in the muscle that enables reprioritization of local energy metabolism and induces muscle wasting in healthy subjects (63). In a recent clinical case report, refractory pruritus has been linked to a massive skin sodium accumulation in a HD patient and improved after large sodium depletion through expanded hemodialysis (64). This latter observation led investigators to speculate on a possible link between skin salt accumulation and local immune mechanisms activating keratinocytes (64).

3 IMPLICATIONS OF INTERMITTENT TREATMENT OF MAINTENANCE HEMODIALYSIS: UNPHYSIOLOGICAL PROFILE INDUCED BY INTERMITTENT THERAPY

The unphysiological profile of intermittent HD is recognized as a leading cause of dialysis intolerance and multiorgan morbidity (65, 66). This phenomenon is worsened by short or very short dialysis treatment schedules. Intermittent HD generates periodic and cyclic changes in volume and blood pressure, osmotic shifts, and fluctuations of waste products and electrolytes (67). Cyclic profiles are contrasting with closely regulated and relatively stable conditions of the internal milieu in healthy or even non dialysis CKD patients.

The HD cyclic phenomenon may refer to a tide phenomenon with two phases of loading (interdialytic) and unloading (intradialytic) as described in more details below (27, 35, 67).

During the interdialytic period, anuric HD patients tend to accumulate sodium and fluid according to fluid and dietary intake, leading to chronic fluid overload. In this condition, fluid overload has two consequences: the first is marked by weight gain and progressive increase of systemic arterial pressure and pulmonary arterial pressure with cardiac stretching during the interdialytic phase; the second reflects fluid accumulation and translates into cardiac stretching and structural cardiac remodeling (68).

During the intradialytic period, sodium and fluid are removed mainly through ultrafiltration (intradialytic weight loss) and negative dialysate-to-plasma sodium gradient. Volume depletion leads to hypovolemia that triggers adaptative hemodynamic response to preserve arterial pressure. To face hypovolemia and cardiac stroke reduction, hemodynamic stability (blood pressure and tissue perfusion) tends to be preserved by increasing vascular tone, mainly through vasoconstriction of alpha-adrenoceptor territories, and increase vascular refilling including venous return. Hemodynamic response and full adaptive response may be limited by critical hypovolemia (ultrafiltration to refilling imbalance) or cardiac impairment (diastolic and systolic dysfunction, arrhythmia, heart failure) or vascular refilling capacity (hypoalbuminemia, capillary albumin leakage, inflammation). Recent functional dialytic imaging studies have shown that reductions in myocardial perfusion and contractility (myocardial stunning) are directly linked to ultrafiltration rate (69–72). In addition, it has been shown also that this phenomenon starts very early during HD session even before ultrafiltration has reach a significant level that may reduce volemia (73, 74). Several observational studies have documented a strong association between mortality and high ultrafiltration rate or volume changes, drop in blood pressure, and end-organ ischemic insult (75, 76). Indeed, hemodynamic response to hemodialysis is more complex than a simple reaction to hypovolemia, since it includes other factors such as vascular refilling capacity, bioincompatibility reactions, thermal balance, electrolyte fluxes, nutrient losses and individual patient's characteristics (cardiac reserve, neurohormonal stress responses) (28, 29). Interesting, this response may be mitigated by various factors (e.g., age, gender, comorbidity, autonomous neuropathy, and medication) explaining also individual or temporal variations in hemodynamic response.

Whatever the exact pathophysiologic consequences of this phenomenon, volemic changes (hyper- and hypo-volemia) provoke rapid alternating cycles of cardiac loading and unloading but still maintaining overtime an abnormal high pulmonary pressure level (68, 77). Such cycling phenomenon is responsible for repetitive and chronic myocardial stretching, a mechanism that has been recognized by cardiologists as the main mechanism of

inflammatory mediator release (78, 79). This mechanism contributes to cardiac remodeling and further fibrosis, a proarrhythmogenic condition (79).

4 ACTIONS TO MITIGATE CV RISK ASSOCIATED WITH SODIUM, WATER, VOLUME AND HEMODYNAMIC MANAGEMENT

Adequate management of sodium, water, volume and hemodynamic control of hemodialysis patients relies on a stepwise approach (28, 67, 80): the first entails assessment and monitoring of fluid status and relies on clinical judgement supported by specific tools; the second consists in acting on correcting fluid imbalance mainly through dialysis prescription but also on diet and thirst guidance; the third consist in fine-tuning treatment prescription to patient response and tolerance.

4.1. Monitoring Sodium, Water and Fluid Status

Sodium and fluid balance assessment and monitoring in HD patients is not an easy task (81). However, this is the first step from a clinician's perspective to ensure a better and more precise salt and volume management. Patient monitoring relies on a clinical judgment supported by several tools depending on the complexity of the case as depicted in **Figure 1**.

4.1.1 Clinical assessment

Clinical management is currently summarized in the dry weight probing approach (82–84). The concept of dry weight was introduced by Scribner and colleagues in the 1960s, as the main pathway to control fluid overload and blood pressure in HD patients. Dry weight probing involves a stepwise reduction of post dialysis weight over time to achieve an adequate control of systemic blood pressure, disappearance of fluid overload symptoms and prevention of intra- or peri-dialytic hypotension. This clinically-oriented approach has been shown to be associated with indisputable value in clinical nephrology (85). As just confirmed recently in interventional studies this clinical approach allows for good control of blood pressure and to improve long-term patient outcomes (86). However, sensitivity and specificity of clinical assessment in detecting fluid imbalance as set by clinically determined 'dry weight' is challenged when compared to instrumental tools such as bioimpedance (87, 88). On the other hand, excessive or too fast fluid depletion has led to some concerns as being associated with higher risks including cardiac stunning or severe cardiovascular events (88–90). This is now being recognized as being part of dialysis-induced systemic stress. Volemia management remains a critical concern in HD patients that has been recently highlighted by the KDIGO controversy conference (91). Therefore, if dry weight policy remains still valid and necessary from a clinician perspective, it is not sufficient to ensure optimal sodium volume and pressure management in dialysis patients. Further tools are required to support clinical decision making on a daily practice.

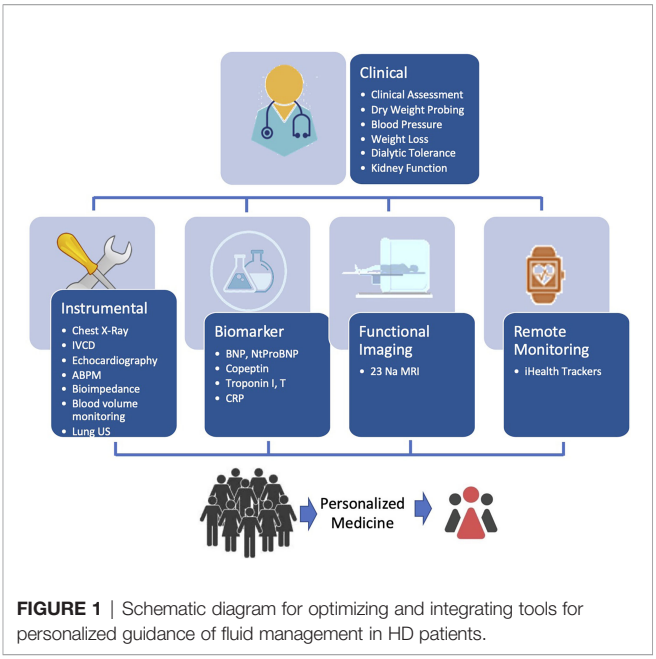

FIGURE 1 | Schematic diagram for optimizing and integrating tools for personalized guidance of fluid management in HD patients.

4.1.2 Instrumental Tools

Non-invasive technology-based tools have been shown helpful to assess volemia, fluid status, or hemodynamic indicators (67).

Inferior vena cava diameter (IVCD) and collapsibility index have been proposed to monitor intravascular volume and right atrial pressure or central venous pressure changes in dialysis patients with positive outcomes (92). However, the practical difficulty in implementing these methods, factors affecting reading and the poor predictive value on blood pressure response in probing dry weight have precluded its generalizability in chronic patients setting (93).

Relative blood volume change (RBV) and refilling rate capacity during dialysis assessed by online blood volume sensor embedded in HD machines has been also proposed to guide fluid management (94, 95). In expert hands, this tool may provide at bed side useful information on individual patient intravascular volume status to handle hemodynamic guidance (96). Blood volume monitoring may be used to better characterize patient's critical volemia beyond which occurrence of severe intradialytic hypotension is likely to occur (97). Absolute blood volume measurement, based on non-invasive measurement either by dilution or online calculation, has been proposed recently for a better assessment of this crucial parameter (98). To date, only one limited study has explored the clinical benefits of monitoring precisely this parameter. An observational study in 842 hemodialysis patients has shown the existence of certain "favorable" RBV ranges at specific timepoints during dialysis that are associated with improved patient survival (99). These RBV ranges have been recently integrated as control targets in an automatic UFR feedback concept (100).

Bioimpedance has been proposed over the last few years as a more precise way to assess fluid status in dialysis patients (101, 102). Several approaches (segmental versus total body, single versus multifrequency) using various devices and algorithms have been developed with interesting results (103). In a systematic review, multifrequency bioimpedance spectroscopy (BIS) analysis [National Institute for Health and Care Excellence, (NICE, UK)] was recognized as the most precise and reliable tool in a clinical setting for guiding fluid management in dialysis patients (104). In addition, extensive use of BIS in clinical studies has generated substantial evidences showing that BIS was able to detect subtle fluid volume variation and to support clinical decision making in terms of dry weight reduction (105). Although some studies showed positive effects of fluid management based bioimpedance on clinical endpoints, there are most based on observational data while controlled interventional studies are still lacking for generating stronger evidences.

Echocardiography is a reliable tool in expert hands to monitor cardiac impact of fluid depletion both on functional and morphological aspects (106–108). It has been shown that several cardiac key parameters such as ejection fraction, left ventricular mass, left ventricular end diastolic volume, peak strain, aortic distensibility or pulmonary arterial pressure or right atrial volume have associations to chronic fluid overload and are useful or be regularly assessed in dialysis patients. However, while their use for dry weight determination has been proposed, most agree on their limitations for that particular purpose.

Regional chest bioimpedance cardiographic device (NICaS), a non-invasive device, has been recently introduced to assess patient's hemodynamic response to ultrafiltration (109). The device relies on skin electrodes and sophisticated proprietary algorithms integrating ECG and blood pressure parameters and claims the remarkably ability to determine stroke volume, cardiac index and power and total peripheral vascular resistance. Based on this set of parameters, it is possible to identify different profiles of hemodynamic response in terms of peripheral vascular resistance and cardiac function (110). In this pilot study, the authors identified that hemodynamic response to fluid depletion and/or hypovolemia (ultrafiltration) may differ substantially according to patient profile. Based on NICas, three groups of patients were identified: firstly, predominant decrease of cardiac power index (reduction of blood pressure and cardiac output reflecting preload reduction); secondly, predominant decrease of peripheral vascular resistance (autonomous dysfunction); thirdly, both decrease of cardiac power index and total peripheral vascular resistance (combined phenomenon). Such assessments in dialysis patients may facilitate interpretation of hemodynamic response (cardiac dysfunction, insufficient vascular refilling capacity, autonomous dysfunction) and then help nephrologists to optimize fluid removal preventing intradialytic hypotension.

Lung ultrasound has been proposed more recently to track silent fluid accumulation in the lung Interstitium (extravascular edema) reflecting both volume overload and cardiac dysfuntion (111, 112). Interlobular septa thickening due to water accumulation reflects US beam and generates visible B line bundles (comet- like tails). A simple counting of these B lines provides an estimate of lung water excess and may support clinical decision-making in terms of dry weight probing (113, 114). The approach has been shown beneficial to reduce fluid overload and blood pressure levels in a recent controlled trial investigating the management of dialysis patients with resistant hypertension (112). A recent interventional trial has explored the clinical interest of using predialysis lung ultrasound scan (Lung Ultrasound Study, LUST study) including 183 patients in the active arm versus 180 in the control arm, to titrate ultrafiltration during dialysis. Lung congestion was significantly more frequently relieved in the active (78%) than in the control (56%) arm. However, risk for all-cause and cardiovascular hospitalization and the changes of left ventricular mass and function did not differ among the two groups suggesting that better volume control is not sufficient per se to reduce cardiac burden in dialysis patients. In addition, a *post-hoc* analysis for recurrent episodes of decompensated heart failure (HR 0.37) and cardiovascular events (HR 0.63) showed a significant risk reduction in the active arm. In hemodialysis patients with high cardiovascular risk, fluid management guided by lung ultrasound may help to reduce lung congestion more effectively than usual clinical care (115).

4.1.3 Cardiac Biomarkers

Cardiac biomarkers have been extensively explored in hemodialysis patients to disentangle fluid status and cardiac function or remodeling (116). Atrial natriuretic peptides (ANP, BNP, and NT-proBNP) are the most commonly used ones for assessing fluid overload (117–119). More recently, copeptin (a vasopressin precursor) has been recently introduced to assess fluid depletion (120). Cardiovascular biomarkers reflecting cardiac or endothelium injury are also of interest to set a more precise and personalized fluid management approach. Sensitive troponin from the family of troponin molecules (troponin I and T) have been used to detect or to prevent critical cardiac injury in response to fluid depletion (121, 122). Several endothelial biomarkers (e.g., ADMA, FG23, ROS, NO pathways) or inflammatory mediators (CRP, IL1, IL6) or oxidative stress markers have further been proposed, either isolated or combined, to assess cardiac and vascular risk as part of the fluid management strategy with promising results (123, 124). As shown in the few prospective cohort studies, Brain Natriuretic Peptides (BNP) or their surrogates were used successfully to better guide fluid management in incident dialysis patients with past cardiac history or when hospitalized for cardiac decompensation (118, 119, 125).

4.1.4 Functional Imaging Tools

Quantification of sodium accumulated in the tissue (skin and muscle) using sodium (23)MRIs in dialysis patients have become the focus of several investigations to assess tissue sodium (32, 44). As outlined before, accumulation of sodium in the tissue may contribute to systemic toxicity *via* local or remote tissue

organ damage. Consequences such as left ventricular hypertrophy and vascular stiffness positively associate with the amount of tissue sodium stored and may ultimately increase the risk of cardiac failure. In addition, sodium tissue accumulation contributes to metabolic and inflammatory disorders that enhance cardiovascular risk. In recent study assessing tissue sodium (skin, muscle) by (23)Na MRI in dialysis patients, it has been shown that tissue sodium and water were mobilizable by hemodialysis (54). A reduction of almost 50% of tissue sodium concentration (skin and muscle) was observed contributing to the net salt mass recovered from a direct dialysate quantification. However, tissue Na removal was apparently not linked to dialysate-plasma Na gradient. Sodium (23)MRI remains clinical research tool with restricted access due to its complexity. However, it is envisioned that dedicated segmental sodium MRI device will be available in the near future (126).

4.1.5 Remote Monitoring Tools

New remote technology, so called ihealth trackers, offer convenient and interesting tools for monitoring in a fully automated and non-obstructive mode, HD patients during the interdialytic period (127). Long-term remote monitoring of vital signs, blood pressure, heart rate, respiration rate, physical activity appears to be a valuable approach for assessing high risk dialysis patients knowing that sudden cardiac death occurs mostly during interdialytic phases. In addition, home based connected devices such as electronic weighting scale with integrated bioimpedance may facilitate monitoring of fluid volume gain in the future (128). Best use of these tools may help clinicians to identify earlier clinical conditions of fluid imbalance or cardiac conditions in order to act on, before they reach critical stage.

4.2. Acting on Sodium, Water and Fluid Management

4.2.1 Dry Weight Probing Approach: Clinical Management

Dry weight clinical management must be conceived as the overarching workflow aiming to ensure optimal fluid and hemodynamic management in dialysis patients (83, 129). This process relies on four main components that include diet, hemodialysis prescription, residual kidney function and adjunctive medication. Success of dry weight achievement is then evaluated at short term on objective key parameter indicators (i.e., lack of clinical symptoms, optimal blood pressure, euvolemia, normal BNP levels) and patient well-being. This is visually outlined in **Figure 2**.

4.2.2. Diet Counseling: Reduce Salt Intake

Reduce dietary salt intake is associated with clinical benefits, better cardiac outcomes in chronic kidney disease and hemodialysis patients. Adherence to a low-sodium diet is challenging but well established as crucial element for treatment success (130). Salt dietary counselling should be better implemented through renal dietitian educational support on an individual basis accounting for lifestyle and diet habits. It is not our intent to review salt dietary recommendations, we refer interested readers to recent reviews (131, 132). In brief, it is currently recommended to restrict salt (sodium chloride) diet intake to about less than 5 g (85 mmol) per day that it equivalent to 10 g (170 mmol) between two HD session (91). Apart from cardiac health, salt diet restriction has additional benefits in HD patients since it reduces thirst and interdialytic weight gain facilitating HD management.

4.2.3. Treatment Time and Frequency: Reduce Ultrafiltration Rate While Increasing Net Ultrafiltration

Reducing ultrafiltration rate is obviously the most logical approach to reduce cardiac morbidity in HD patients (71, 133, 134). Aggressive management of sodium and fluid excess to restore fluid homeostasis either by applying high ultrafiltration rate and furthermore associating hypertonic dialysis (high dialysate-to-plasma sodium concentration gradient) to facilitate refilling rate has been associated with increased risk of mortality. The optimal and rational approach to improve excess fluid volume is to increase, either HD frequency and/or dialysis time or to have additional isolated ultrafiltration sessions. Daily or nocturnal dialysis treatment schedule have been proved to be

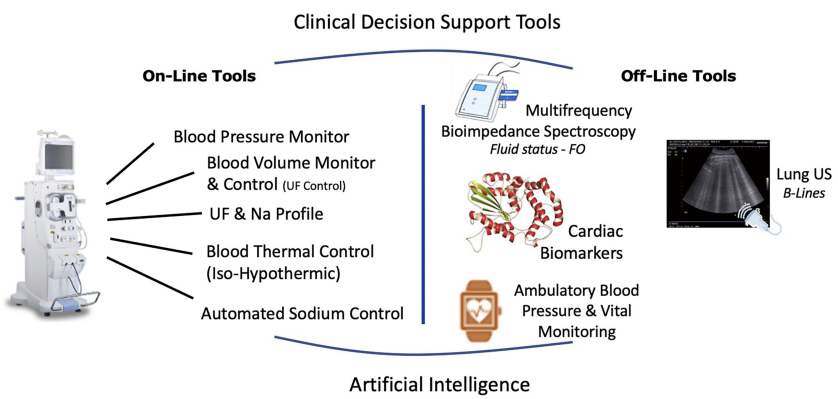

FIGURE 2 | Integrated approach to reduce intradialytic hypotension and to reduce dialysis induced systemic stress relying on current available integrated tools on HD machines and potentially supported by specific cardiac intervention.

associated with significant improvement in fluid and hemodynamic management in HD patients (135–138). Nevertheless, these approaches may not always be accepted by patients or applicable by care providers for organizational or economic reasons.

4.2.4. Blood Volume Control: Prioritize Blood Volume Preservation

Modulating a patient's hemodynamic response through various tools embedded in HD machines is an appealing approach to maintain hemodynamic stability (94). Monitoring blood volume changes during HD session is useful to identify critical volemia (i.e., intradialytic hypotension risk), to estimate remaining fluid in the Interstitium, or to quantify vascular refilling capacity, but it is not sufficient to optimize hemodynamic response (139, 140). Additional feedback-controlled loop algorithm set on critical volemia threshold and acting on ultrafiltration is better suited to provide a precise preservation of effective volemia (ultrafiltration control) (141). This tool could be coupled to other options such as sodium management and profile (142, 143). Ultrafiltration control tool improves patient's hemodynamic tolerance, reduces intradialytic hypotension and cardiac stunning risks (144). In brief, ultrafiltration control tends to reduce cardiac insult but its long-term clinical benefits remain to be proven.

4.2.5. Thermal Balance: Favor Iso or Hypothermic Dialysis Condition

Adjusting dialysis thermal balance to preserve peripheral vascular resistance and cardiac output is also a simple strategy to improve hemodynamic tolerance and reduce organ damage that has been proven clinically effective including systematic literature review (142, 145, 146). In brief, the main objective is to deliver isothermic (patient's neutral thermal balance) or hypothermic dialysis (patient's negative thermal balance), to prevent thermal gain during a dialysis session which is associated with an inappropriate hemodynamic response (vasodilation, tachycardia, fall of ejection fraction) (147). Hypo-or isothermic HD could be manually achieved by setting dialysate temperature 0.5-1°C below predialysis patient's core temperature. Automated thermal control of dialysis sessions requires the use of an online blood temperature monitor that can control more precisely thermal balance of patients to a preset target. Both approaches tend to reduce hypotension incidence, hemodynamic stress and organ insult as shown in recent studies (145, 146).

4.2.6. Sodium and Water Control: Prioritize Isonatremic HD and Sodium Mass Removal

Optimizing sodium and water imbalance by means of hemodialysis is crucial to restore fluid and tonicity homeostasis (148, 149). This process relies on convective and diffusive sodium flux times treatment time. The sum of convective and diffusive fluxes determines total salt mass removed per session (55, 150). Convective sodium flux is dragged through ultrafiltration (weight loss), while diffusive sodium flux is driven by a dialysate-plasma sodium gradient. In that setting, dialysate sodium concentration plays a particular role in sodium management since it acts both on sodium mass removal and on plasma tonicity changes. Dialysate-plasma sodium gradient prescription rather than dialysate sodium concentration alone should be considered for personalizing dialysis prescription (150). Indeed, there is no medical rationale today to prescribe dialysate sodium on a fixed concentration basis except to facilitate facility practice. In all cases, predialysis plasma sodium concentration (or mean value) should be used as reference value for choosing dialysate sodium prescription. Manual dialysate sodium alignment to predialysis plasma sodium concentration may be then reconsidered on a periodically basis according to results (151, 152). An innovative approach for dialysate sodium prescription has been proposed recently relying on an automated sodium balancing module that has capacity to align dialysate sodium concentration to plasma sodium according to physician prescription (153–156). Based on this new tool, care givers have the opportunity to customize dialysate sodium prescription according to patient needs (sodium mass and tonicity adjustment) in an easy and timely appropriate manner without the cumbersome task of laboratory testing. Accordingly, one may identify three prescription options: positive gradient (or hypertonic dialysis), neutral gradient (or isonatremic dialysis) or negative gradient (or hypotonic dialysis). For safety reason, positive gradient will be preferably ranging between +1 to +5 mmol/l; negative gradient will be ranging between -1 and -5 mmol/l. Isonatremic dialysis will be then ranging between -1 and +1 mmol/l. Isonatremic dialysis may represent default basic prescription for the majority of patients. Hypotonic dialysis may be favored in patients with resistant or paradoxical hypertension, fluid overload or tissue sodium excess to enhance sodium depletion. Hypertonic dialysis may be indicated in hypotensive prone or hypovolemic patients in order to improve hemodynamic tolerance. In addition, it is expected that continuous fine tuning of dialysate sodium alignment on plasma sodium concentration may facilitate sodium mobilization from tissue storage addressing more adequately total body sodium homeostasis (157). Further focused clinical studies are clearly required to better identify potential benefits or risks associated with these personalized prescriptions. Alternatively, the use of sodium control module to deliver isotonic dialysis is likely expected to reduce thirst by preserving the patient's tonicity set point (158). Potential benefits of isotonic or zero-diffusive dialysis are currently explored in various prospective studies (159).

4.3. Predictive Medicine, Advanced Analytic and Artificial Intelligence

Big data and artificial intelligence have already been successfully applied at the point of care to support physicians in the decision-making process. Availability of accurate, longitudinal, data set is a key factor for the development of reproducible predictive algorithms. In that setting, artificial intelligence relying on machine learning, neuronal network and deep learning, can be used to predict on an individualized, session-based, patient hemodynamic response (intradialytic hypotension) to dialysis-

related prescriptions (ultrafiltration, dialysate sodium, treatment time, dialysis modality) on multiple relevant hemodynamic and dialysis adequacy parameters (160). Based on this information, clinician can choose on time at the point of care the best dialytic strategy to reduce hemodynamic stress for a given patient. Value of this approach deserves further clinical trials.

4.4. Adjunctive Actions: Cardiac Management: Medications, Synchronization

Additional specific actions may be further required in cardiac compromised patients or to satisfy specific patient's needs (161). It is not our intent to make an in-depth review of cardiac interventions to improve cardiac health. However, few examples may be presented to illustrate our purpose. Renin angiotensin blockers or calcium channel blockers may be indicated in case of refractory hypertension (162). Betablockers, renin angiotensin inhibiting agents or mineralocorticoid receptor antagonists may be also indicated in ischemic cardiac disease or in obstructive or diastolic cardiac failure (163–165). In that setting, the right medication (preferably non-dialysable) with the appropriate dosing is needed to prevent clearing and loss during dialysis. Coronary angioplasty, or coronary bypass as well as valve replacement should be envisaged as needed (166). Cardiac resynchronization relying on pacemaker implantation may be indicated in case of severe cardiac dysfunction. Implantable defibrillator may be indicated in case of severe and repetitive arrhythmia associated with risk of sudden cardiac risk (167). Cardioversion may be indicated in selected cases of atrial fibrillation resistant to medication with interesting results (168).

In brief, indications of these medications and/or cardiac intervention should remain in the hand of cardiologists. At this stage, our point is to emphasize the fact that sodium, water and fluid imbalance should be the first line of action in HD patients. Medications and cardiac interventions are likely to be useful but should remain as second line of action and nevertheless used in combination with optimized sodium and water management.

5 PERSPECTIVE FOR FUTURE IMPROVEMENT

A comprehensive and integrated approach is needed to improve further cardiac outcome in HD patients. From clinical research, it is obvious that none of the tool described earlier used alone has the capacity to address issues raised by sodium, water and fluid imbalance. Future research should address this challenge by associating different levels of action as briefly schematized in **Figure 3**. firstly, relying on online tools embedded in HD machines (i.e., ultrafiltration-controlled volume, thermal balance, sodium control module) and secondly, on offline tools (i.e., bioimpedance, lung US, ihealth trackers) for fluid and pressure status monitoring. In that perspective, biosensors use has to be orchestrated and integrated into specific algorithms and feedback loops control as part of smart HD machine providing immediate support to care givers; secondly, using offline tools (bioimpedance, biomarkers) feeding network data system, benefiting from advanced analytics and artificial intelligence, supporting in almost real-time clinical decision making; thirdly, optimized functioning of these tools will rely on large web based networking system (big data, cloud computing) that can integrate data from all sources of information and propose clinical guidance to care giver.

6 CONCLUSION

As delineated in this comprehensive essay, new findings related to sodium homeostasis and pathophysiologic links require a new

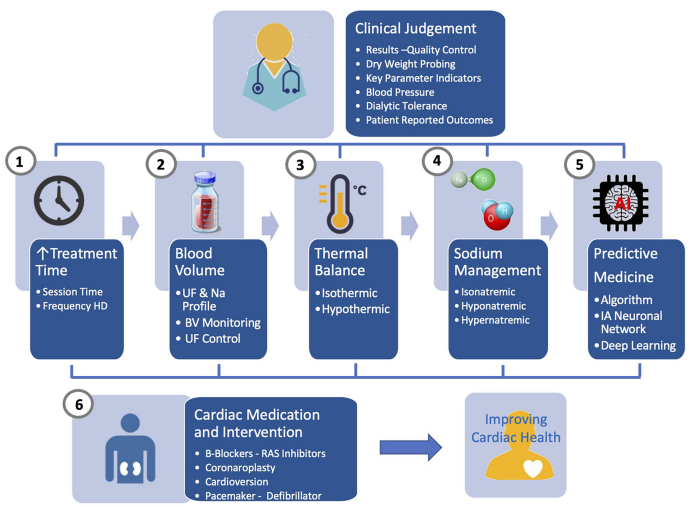

FIGURE 3 | Advanced management of sodium, fluid and blood pressure in hemodialysis patients integrating currently available online and offline tools under the clinical supervision and supported by artificial intelligence.

vision for sodium, fluid and pressure management in dialysis dependent chronic kidney disease patients. The traditional dry weight probing approach that has prevailed for many years must be reviewed in the light of these new findings and enriched by availability of new tools for monitoring and handling sodium and water imbalance. It is time to come back to sodium and water imbalance as cause root of the problem and not to act on their consequences (fluid overload, hypertension) or organ damage (cardiac, atherosclerosis, brain damages). We know the problem and have the tools to assess and manage in a more precise way sodium and fluid disorders in hemodialysis patients. We strongly call for a sodium first approach to reduce disease burden and improve cardiac health in chronic kidney disease patients.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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EDITED BY
Jorge E. Rojas-Rivera,
University Hospital Fundación Jiménez Díaz, Spain

REVIEWED BY
Sophia Lionaki,
National and Kapodistrian University of Athens, Greece

*CORRESPONDENCE
Gabriella Moroni
gabriella.moroni@hunimed.eu

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Severe lupus nephritis in the present days

Gabriella Moroni[1,2]*, Marta Calatroni[1,2] and Claudio Ponticelli[3]

[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele Milan, Italy, [2]Nephrology and Dialysis Division, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Humanitas Research Hospital, Milan, Italy, [3]Independent Researcher, Milan, Italy

Lupus nephritis (LN) is one of the most frequent and severe organ manifestations of systemic lupus erythematosus (SLE) that is a chronic autoimmune disease. Despite improvement in patient and renal prognosis, the disease continued to be associated with a high rate of end stage kidney disease. Along the last decades, it seems that the epidemiology of LN and its clinical presentation have progressively changed. The forms with renal insufficiency at presentation seem to have progressively reduced in developed countries in favour of more mild clinical presentations with urinary abnormalities only. To this clinical change does not correspond a less severe histological lesions, in fact, the extent of active lesions at kidney biopsy are unchanged, whereas chronic lesions are becoming less frequent and less severe. Meanwhile, new types of severe LN defined by the variable association of demographic, clinical, histological characteristics at diagnosis or during the follow-up are gradually emerging and require attention in assessing the therapy and prognosis.

During the last years, randomized controlled trials have reported the efficacy of new drugs in association with standard therapy to improve the rate of short- and medium-term renal response. One of the advantages is that these results were obtained with reduced dosage of corticosteroids whose protracted use is associated with increase of chronic organ damage. Optimization of therapeutical strategies, tailored on the demographic clinical and histological characteristics, with combination of old and new drugs are urgently needed for severe LN.

KEYWORDS

severe lupus nephritis, systemic lupus erythematosus, immunosuppression therapy, kidney biopsy, renal insufficiency

Introduction

Despite progressive improvement in renal prognosis (1, 2), proliferative lupus nephritis (LN) is still associated with a 6-fold increase in mortality compared with the general population (3). Around 10% of patients develop end-stage kidney disease (ESKD) within 5 years from the diagnosis (4). Therefore, a prompt clinical and histological

identification of LN patients at risk of progression and appropriate treatment in the initial and maintenance phases of the disease are critical to improve the outcome of patients with severe forms of LN. In this paper, we will review the clinical and therapeutic approaches to "severe LN", mainly based on the last European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/EDTA) recommendations (5) and recent randomized controlled trials.

What is severe lupus nephritis?

The term severe LN may be used to indicate the absent or the incomplete response to first-line conventional therapy with corticosteroids and immunosuppressive agents. However, LN can also be defined "severe" in the presence of clinical, histological, and/or demographic features that can predict a poor outcome, at diagnosis or during the disease course.

Clinically, increased levels of serum creatinine, high grade proteinuria, and active urine sediment are important prognostic signs of progressive and severe forms of LN (6). The occurrence of renal flares along the course of the disease is another predictor of poor kidney prognosis (7, 8).

Histologically, six classes of glomerular lesions have been defined in LN at kidney biopsy (9). Of them, class III (focal proliferative lupus nephritis), class IV (diffuse proliferative LN), and class III or IV plus class V are considered the most severe forms (10). Chronicity index can further contribute to define the possible outcome. The presence of tubulo-interstitial injury, glomerular sclerosis or fibrous crescents at basal kidney biopsy is a strong predictor of kidney function impairment (11, 12).

Apart from glomerular classification, other rare histologic forms may lead to severe LN, including vascular lesions in patients with antiphospholipid syndrome and thrombotic microangiopathy (TMA). In patients with antiphospholipid antibodies (aPL), glomerular and vascular lesions over-imposed to those of LN can be present and may lead to severe acute kidney injury (AKI) or chronic irreversible lesions (13–15). However, in a recent prospective cohort of 64 patients with biopsy-proven LN, aPL was associated with renal dysfunction in the short-term but had no deleterious effect on long-term renal survival (16). TMA is characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia. It is an uncommon pathological finding in LN, with a prevalence below 10% (17). The characteristic vascular lesions consist in endothelial cells swelling with narrowing of vascular lumen and formation of thrombi. Renal TMA in LN is more frequent in patients with aPL antibodies, thrombotic thrombocytopenic purpura, malignant hypertension, or presence of anti-Ro antibodies (18). Complement activation by classical or alternative pathways plays a key role in the pathogenesis of secondary TMA (19). Whatever the cause, TMA in LN is associated with severe clinical presentation and bad long-term renal prognosis (20).

Among the demographic characteristics male gender, young age, non-Caucasian/Asian ethnicity, and poverty may be associated with more frequent and severe LN. Males account for 4% to 22% of SLE patients, with 30% in studies on familial aggregation (21). The incidence of males with LN seems to be increased in the last decades (2). Some investigators reported that males have more severe disease, showing more frequent clinical presentation with nephrotic syndrome or renal dysfunction, higher renal activity index at kidney biopsy, and more frequent progression to renal failure (22–26). Other studies demonstrated that appropriate therapy allows a benign course in males with LN (27). A review of 16 studies, reported that 6 studies pointed to an increase in incidence of LN in males, 9 studies demonstrated no disparity in gender, and one study showed contradicting results. In addition, 4 studies pointed that male had a more severe renal outcome as revealed by laboratory tests. However, the risk of dialysis and remission were similar between both genders. Young age is another predisposing factor of LN development in SLE (4) and it is associated with more severe presentation and outcome (28–30). In comparison with adults, juvenile-onset SLE has more frequently severe clinical manifestations of LN, a higher risk of flares, organ damage and higher mortality rates (31, 32). A poor adherence to therapy is frequent in children and adolescents with LN and can contribute to unpredictable flares and high levels of morbidity and mortality (33, 34). Ethnicity has a relative impact on the outcome of the patients and their response to treatment, but it needs to be taken into consideration in treatment decisions. SLE is more common and it is associated with a higher level of disease activity and poorer outcomes in Black, Hispanic and Asian patients (35). The severe lupus phenotype in those populations can be explained by increased autoantibody reactivity, higher frequency of arterial hypertension, and the genetic risk burden. Ethnicity remains a key determinant of poor SLE outcome, including, flares, ESKD and mortality, even after adjustment for socio-economic factors (36, 37). Low socio-economic status and poverty are associated with frequent flares, poor quality of life and increased morbidity and mortality in patients with SLE (38–40). Altogether, young age at onset(<30years), male sex, African-American ethnicity, and delayed treatment initiation are the main factors associated with the risk of renal relapses in a population-based study on SLE patients enrolled between 2000 and 2015 in the United States. The leading causes of death were the young age in women, (mainly between 15–24years) and the African-American and Hispanic origin (41).

Standard treatment of severe lupus nephritis

Increased awareness of severe forms of LN can help to improve the treatment and outcome. According to the Joint

EULAR/ERA-EDTA, patients with class III or IV LN and high activity index should start therapy with three intravenous (iv) methylprednisolone pulses (MPP) and an immunosuppressive agent, mycophenolate mofetil (MMF) or cyclophosphamide (CYC). After MPP, patients should receive oral prednisone at progressive lower dosage (5). The Aspreva Lupus Management Study (ALMS) demonstrated that 3 g of MMF and monthly iv CYC pulses have the same efficacy and similar side effects in Caucasians and in Asian patients while in "other ethnicities", including African-Americans and Hispanics participants, MMF was significantly more effective than CYC (42). After these results, MMF became the drug of choice in LN patients with these ethnicities. However, in the ALMS, only half of patients achieved response at six months, defined as ≥50% reduction of proteinuria and stabilization of renal function (43).

For severe nephrotic syndrome, the recent EULAR/EDTA recommendations suggest the combination of glucocorticoids with 1-2 g/day of MMF and a calcineurin inhibitor (CNI), preferably tacrolimus [5]. This association of drugs, called multitarget therapy, demonstrated a significant higher rate of response at six months than high monthly dose of iv CYC, in a Chinese study (44). The efficacy of CNI in reducing proteinuria is well known and is due to two different mechanisms: the vasoconstriction of the afferent arteriolas leading to reduced GFR and reduced urine protein excretion, and the stabilization of podocyte cytoskeleton (45, 46). However, CNI are not easy to handle and may be responsible of important side effects including hypertension, diabetes, and nephrotoxicity.

The rare cases of AKI with normal glomeruli at light microscopy that can develop during lupus podocytopathy, usually respond well to corticosteroids and immunosuppressive agents but may show a high rate of relapses. Instead, in case of AKI and focal segmental glomerulosclerosis(FSGS) the response to therapy is worse with a low rate of complete remission (47). Collapsing variants of FSGS in LN, with poor response to aggressive therapy have been reported (48).

Until few years ago patients with Lupus TMA were treated with plasma infusions or plasmapheresis. This treatment reduced the mortality in comparison with patients who did not receive these treatments, but many patients did not respond to this therapy (49). Eculizumab, a recombinant, fully humanized IgG2/IgG4 monoclonal antibody that inhibits C5activation, proved to be a very efficacious therapy in lupus TMA (50).

New treatments for severe lupus nephritis

New drugs have been tested to increase the rate of response, diminish the risks of flares, and reduce the doses and side effects of corticosteroids and CNI (Table 1).

The long-term use of glucocorticoids may increase the risk of obesity, glucose intolerance, hypertension, dyslipidaemia, and other atherogenic factors, with consequent elevated cardiovascular morbidity and mortality (55–58). In addition, glucocorticoids are among the most important determinants of chronic damage development in LN (59–62). A multivariate analysis on 187 biopsy-proven LN patients followed for around 18 years showed that an average prednisone dosage>5mg/day evaluated along the whole follow-up was one of the independent predictors of the first increase in the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage index(LICC/ACR DI) (63). Belimumab, a recombinant human IgG-1λ monoclonal antibody that inhibits B-cell activating factor, can increase the rate of response in SLE, decrease the rate of flares, and reduce the

TABLE 1 Results of recent randomized controlled trials in Lupus nephritis.

TRIAL	Criteria for response	Study drug	Placebo	Difference	Results
	Results at 1 year				
LUNAR **Rituximab** (51)	UPCR <0.5, creat <15%, <5 RBC	30.6	26.4	4.2%	Failure
NOBILITY CRR **Obinotuzumab** (52)	UPCR <0.5, creat <15%, <10 RBC	34.9%	22.6%	12.3%	Failure
NOBILITY ORR **Obinotuzumab** (52)	UPCR <0.5 creat <15%,	40%	18%	22%	Success
AURA III **Voclosporin** (53)	UPCR<0.5 eGFR ≥60ml/min	40.8%	22.5%	18.5%	Success
BLISS-LN **Belimumab** (54)	UPCR<0.7, eGFR <20% and≥60ml/min	46.6%	35.4%	11%	Success

UPCR, urinary protein/creatinine ratio; creat, serum creatinine; RBC, red blood cells; eGFR, estimated glomerular filtration rate.

corticosteroid dosage (64). In a phase III randomized controlled study, participants were assigned to receive standard therapy (corticosteroids and 3g MMF or low-dose ivCYC) plus placebo or standard therapy plus Belimumab 10mg/kg administered intravenously once a month for two years. At the end of the follow-up, more patients in the belimumab group than in the placebo group had a primary efficacy renal response (43%vs.32%; P=0.03) and a complete renal response (30%vs.20%;P=0.02). The results were even better when belimumab was associated with MMF in class III and in Class IV LN in comparison to mixed and membranous forms and in non-black patients. The risk of a renal-related events or death was lower with belimumab than placebo (hazard ratio, 0.51;P=0.001). At the last observation (104 months) a significantly higher number of patients in belimumab were in treatment with ≤5mg prednisone. No difference with placebo was reported in side effects (65). A secondary analysis of this study demonstrated that belimumab significantly reduced the risk of renal flares and attenuated the annual rate of estimated glomerular filtration rate (eGFR) decline (54). On the other hand, response was significantly more frequent when urine protein/creatinine ratio was <3g/g than when proteinuria was higher. These results suggest that adding belimumab to standard initial therapy in severe LN not only can improve the response but may also reduce renal flares and the corticosteroids dosage. Based on these results, belimumab in association with MMF can be added to induction therapy in active class IV LN, in patients with history of renal relapses and in those who require a reduction/withdrawal of corticosteroids.

Recently, in a phase III randomized controlled trial a new CNI, voclosporin, employed at the dosage of 23,7g twice a day, in association with 2g of MMF and glucocorticoids, demonstrated the superiority at six and at 12 months in comparison to placebo plus MMF and glucocorticoids in inducing complete or partial remission of LN. Of interest, these results were obtained with very low dosage of corticosteroids; 20-25mg/day of prednisone at the start of the study rapidly reduced to 2.5 mg/day at week 12. Instead, no changes from baseline in immunological parameters (serum levels of C3, C4, anti dsDNA antibodies) were observed. The results were less good in Caucasians than in other ethnicities and in membranous than proliferative LN. Serious side effects, mainly pneumonia, were similar in the two groups (66). Voclosporin is reported to be more potent than cyclosporin *in vitro*, with a more stable pharmacodynamic and pharmacokinetic that avoids the need of blood monitoring; the lipid and glucose metabolic profiles have been reported to be better than those observed with the old formula of cyclosporine (53). No change in GFR after 52 weeks was demonstrated in the two groups. However, patients with an eGFR ≤ 45mL/min/per1,73m^2 at screening were excluded from the study. The potential nephrotoxicity of CNI is well known. To verify the superiority of voclosporin over other CNIs in LN a randomized trial should compare the efficacy of voclosporin vs low- dose cyclosporine or tacrolimus. Long term data and the identification of eGFR cut-off for voclosporin contraindication are necessary (67, 68). Waiting for these results, the combination of CNI, and low dose MMF and low dose corticosteroids can be helpful in patients with active proliferative LN and severe proteinuria, with the aim to induce a rapid resolution of proteinuria particularly if kidney function is normal, good control of arterial hypertension, and low chronicity index at kidney biopsy (69). Similarly, voclosporin can be started in association with MMF and with low dose corticosteroids in active proliferative LN particularly in presence of severe nephrotic syndrome. Although it seems not necessary to check the blood levels of voclosporin, renal function monitoring is necessary particularly during the first months of therapy to modulate the dosage of the drug.

Severe LN based on severe clinical/ histological presentations

Although presentation with nephritic syndrome or with rapidly progressive renal insufficiency seem to have progressively reduced during the last forty years at least in developed countries (2), kidney dysfunction at presentation is an important predictor of CKD (70). Even if discrepancies between clinical and histological presentations exist, impaired kidney function at presentation is usually associated with the presence of cellular crescents, tuft fibrinoid necrosis and/or severe diffuse interstitial infiltrations at kidney biopsy (11, 71). In these cases, the complete response to therapy is difficult to achieve and renal prognosis is poor. In our personal experience of 213 biopsies proven LN patients followed for around 10 years, those with eGFR<60ml/min/per1,73 m^2 at time of renal biopsy developed a significantly higher rate of ESKD (17.6%) than those presenting with eGFR ≥60mil/min/per 1,73 m^2 (2.7%, P=0.001) (Table 2**).** Whether MMF and CYC are equally effective in treating the severe forms of LN is an open question. Before the advent of MMF, many units used monthly administration of high doses of iv CYC, as suggested by the results of randomized, controlled, trials in which a large percentage of patients with severe LN were included (72, 73). More recently, LN patients at high risk were excluded from clinical trials or were included in very low percentage. However, a sub analysis of the Aspreva study included patients with an eGFR<30 ml/min at randomization treated with either high-dose iv CYC (12 patients) or 3gMMF (20 patients). At the start of that study there were no significant differences in the clinical characteristics between the two groups. Scarring at kidney biopsy were present in 42% of patients in the CYC group and in 35% of MMF group. The difference was not significant but the score of chronicity index in the two groups was not reported, although chronicity index is one of the best predictors of kidney function deterioration in the long-term (12). The more rapid response in MMF group was probably due to more active lesions in MMF than in CYC participants. At six months, no difference in the response was demonstrated between the two groups, but only few patients responded to treatment 16.7% in the CYC arm vs 20% in MMF (74). A pooled analysis reported the effects of CYC or MMF

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TABLE 2 Rate of ESKD and death in patients with Lupus Nephritis with eGFR < or ≥ 60/mil/min at kidney biopsy.

	eGFR <60ml/min/	eGFR≥60ml/min/	p
Patients	68	145	
eGFR ml/min	47.7 (28.1-50.4)	101 (79-122)	0.0001
Proteinuria g/day	4 (1.9-55)	2.9 (1.9-4.9)	0.30
Histologic classes II/III/IV/V	0/13/49/6	2/33/66/44	0.0002
Arterial hypertension	66.2%	42.1%	0.002
Activity index	8 (4.75-10)	4 (1-8)	0.0001
Chronicity index	2 (1-5)	1 (0-3)	0.0001
Follow-up years	10.7 (2.1-22.1)	11-8 (4.2-20.1)	0.91
ESKD	17.6%	2.7%	0.0001
Deaths	13.2%	4.1%	0.02

Personal experience. eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

in all the published cases with impaired kidney function at presentation and/or crescents in more than 15% of glomeruli and fibrinoid necrosis. The two drugs appeared to be equally effective in inducing remission in the short term. Among 139 participants to this analysis, the average partial remission (48% MMF;51%CYC) and complete remissions (9%MMF;6%CYC) at 6 months were similar (75). However, in the maintenance phase, relapse rates and risk of developing ESKD were higher for MMF than for CYC (75–77). Looking at those rates of response it seems that neither CYC nor MMF can successfully manage patients with severe LN. In our experience, the induction therapy of severe forms consisted of three intravenous MPP (500-1000 mg/die) followed by oral prednisone 0.75-1 mg/kg/die for 2-4 weeks tapered to 10 mg/day, associated with oral cyclophosphamide (1.5-2 mg/kg/die) for at most 3 months. We checked every 7-10 days the number of white blood cells and adjusted the dosage of cyclophosphamide accordingly. One important point is the regular monitoring of the patients particularly during the first months. If renal function did not recover within two/three months a new course of methylprednisolone pulses, or, more recently, a rituximab infusion of 1g was added. In case of worsen of renal function, a repeat kidney biopsy can be of help to exclude over-imposed TMA.

It is possible, and even likely, that an add-on therapy with a novel agent may be helpful, especially in presence of low chronicity index.

Many hopes rest on the efficacy of Rituximab (RTX) a chimeric monoclonal antibody directed against CD20. The Explorer trial failed to show the superiority of RTX over placebo in lupus patients treated with azathioprine, mycophenolate mofetil, and methotrexate (78) and the Lunar trial showed that RTX therapy did not improve clinical outcomes of LN after 1 year of treatment (79). However, it is possible that the inclusion of patients with mild-moderate LN can have influenced the results, since most patients assigned to the control arm obtained a high rate of response with standard therapy, so obscuring the potential superiority of RTX. Despite these negative results of randomized, controlled trials, RTX continues to be used with success in refractory or frequently relapsing forms of LN (51, 80–82). Cases of good response of the association of CYC and RTX in severe and refractory LN have also been reported in literature (83, 84). In a study, 84 patients with severe and refractory LN were randomized to CYC or to the association of CYC+RTX. The response occurred in 83.3% of participants assigned to the combined therapy and in 57.1% of those assigned to CYC alone, the difference being significant. Proteinuria, serum C3 fractions and SLEDAI score were significantly improved in RTX group (85).

Obinotuzumab, a humanized type II anti-CD20 monoclonal antibody, demonstrated to be superior to RTX in the treatment of follicular lymphoma (86). Recently, Obinotuzumab at the dosage of 1g at day 1, at week 2, 24, and 26 in association with methylprednisolone pulses and 2-2.5 g of MMF was compared with placebo in a phase II randomized trials on 125 patients with proliferative LN. The primary end-point, complete renal response, was not achieved at week 52, despite a percentage difference of 12% in favor of Obinotuzumab. Instead, in an exploratory analysis conducted at week 104, complete renal response was reported in a significantly higher number of patients in Obinotuzumab (41%) in comparison to placebo (23%,P=0.026) (87). If these mid-term results will be confirmed by further studies, one can hope that this monoclonal antibody in association with standard therapy may improve the current results in severe forms of LN. A phase III randomized trial are under way. Among other drugs in study, anirolumab a monoclonal antibody against type I interferon is ongoing (52), a Janus-kinase inhibitor suppressing signals from multiple cytokines, and secukinumab a selective inhibitors of interleukins-17 are under way (88).

Conclusions

Despite progressive improvement in renal survival, lupus nephritis continues to be a disease with high risk of ESKD and death. The management of severe LN is a real challenge. It requires a careful clinical/histological assessment to predict the

short-term and long-term outcomes, the choice of a treatment that may couple efficacy and safety, and a regular monitoring of patients by a dedicated team.

The simultaneous or alternate combination of time-honored and new promising drugs might allow to interfere with different pathogenetic mechanisms of the disease, achieve higher rate of complete and stable response, prevent flares, and reduce the dosage of corticosteroids. Further drugs for the treatment of LN are under investigation.

Author contributions

GM contributed to conception and design of the review and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Samar Abd ElHafeez,
Alexandria University, Egypt

REVIEWED BY
Alex Siu-Wing Chan,
Hong Kong Polytechnic University,
Hong Kong SAR, China
Karem Salem,
Fayoum University, Egypt

*CORRESPONDENCE
Wen Zhang
306762827@qq.com

†These authors have contributed equally to this work and share first authorship

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Mechanisms underlying acupuncture therapy in chronic kidney disease: A narrative overview of preclinical studies and clinical trials

Xinyin Liu[1†], Xiaoran Wang[2†], Hongzhen Ma[3†] and Wen Zhang[3*]

[1]The First Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, China, [2]Department of Nephrology, The First People's Hospital of Hangzhou Lin'An District, Hangzhou, China, [3]Department of Nephrology, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), Hangzhou, China

Chronic kidney disease (CKD) is associated with high incidence, low awareness, and high disability rates among the population. Moreover, the disease significantly affects the physical and mental health of patients. Approximately 25% of patients with CKD develop end-stage renal disease (ESRD) within 20 years of diagnosis and have to rely on renal replacement therapy, which is associated with high mortality, heavy economic burden, and symptoms including fatigue, pain, insomnia, uremia pruritus, and restless leg syndrome. Currently, the means to delay the progress of CKD are insufficient; therefore, developing strategies for delaying CKD progression has important practical implications. In recent years, more and more people are accepting the traditional Chinese medical technique "acupuncture." Acupuncture has been shown to improve the uncomfortable symptoms of various diseases through stimulation (needling, medicinal moxibustion, infrared radiation, and acupressure) of acupoints. Its application has been known for thousands of years, and its safety and efficacy have been verified. As a convenient and inexpensive complementary therapy for CKD, acupuncture has recently been gaining interest among clinicians and scientists. Nevertheless, although clinical trials and meta-analysis findings have demonstrated the efficacy of acupuncture in reducing albuminuria, improving glomerular filtration rate, relieving symptoms, and improving the quality of life of patients with CKD, the underlying mechanisms involved are still not completely understood. Few studies explored the correlation between acupuncture and renal pathological diagnosis. The aim of this study was to conduct a literature review summarizing the currently known mechanisms by which acupuncture could delay the progress of CKD and improve symptoms in patients with ESRD. This review help provide a theoretical basis for further research regarding the influence of acupuncture on renal pathology in patients with CKD, as well as the differences between specific therapeutic mechanisms of acupuncture in different renal pathological diagnosis. The evidence in this review indicates that acupuncture

may produce marked effects on blocking and reversing the critical risk factors of CKD progression (e.g., hyperglycemia, hypertension, hyperlipidemia, obesity, aging, and anemia) to improve the survival of patients with CKD *via* mechanisms including oxidative stress inhibition, reducing inflammatory effects, improving hemodynamics, maintaining podocyte structure, and increasing energy metabolism.

KEYWORDS

complementary therapy, acupuncture, therapeutic mechanism, chronic kidney disease, end-stage renal disease

1 Introduction

Chronic kidney disease (CKD) refers to abnormal renal structure or function caused by various reasons or an unexplained decrease in the glomerular filtration rate (GFR<60 mL/min) for >3 months (1). In 2012, the *Lancet* published the first nationwide cross-sectional survey of CKD in China, showing that there were approximately 120 million patients with CKD, which had a 10.8% prevalence rate among adults (2). According to the five insights of the 2019 Global Disease Burden Study, exposure rate to the risk factors of injury and disability caused by CKD has also increased, second only to hypertension, hyperglycemia, obesity, environmental pollution, and social factors (3). Furthermore, approximately 25% of patients with CKD develop end-stage renal disease (ESRD) within 20 years of diagnosis (4). Patients with ESRD have a high mortality rate and require long-term maintenance dialysis, which incurs substantial medical costs and places a heavy economic burden on families, society, and the country. Currently, the etiology and pathogenesis of CKD are unclear, and there is a lack of effective treatments.

1.1 Treatment of CKD in Western medicine

The main treatments of CKD target preventing ESRD to reduce mortality. Modern medicine has made several attempts to treat this disease, including dealing with its complications (e.g., renal hypertension, hyperlipidemia, proteinuria) using glucocorticoids, cytotoxic drugs, immunosuppressants, and biological agents based on individual patient characteristics and renal pathology (5). However, there are currently no ideal treatment schemes, and this disease has become a significant public health concern worldwide. Hence, it is necessary to explore novel methods for its prevention and treatment.

1.2 Associated symptoms and symptomatic treatment

The considerable symptomatic burden associated with CKD greatly affects the quality of life of patients. Common symptoms include fatigue, pain, sleep disorders, restless leg syndrome (RLS), and chronic pruritus, although with considerable variations related to symptom definition, period of prevalence, and levels of severity (6–8). The first-line intervention of pain and pruritus is mainly medication, but their use and management have limitations, and nonpharmacologic approaches have therefore attracted attention. For example, replacement therapy has been shown to be feasible and effective against fatigue and sleep disorders (9).

1.3 Acupuncture and CKD

Acupuncture is an essential component of traditional Chinese medicine (TCM) and substitute auxiliary therapies. According to the TCM theory, there are 12 main and collateral channels on the human body surface and 361 classical acupuncture points on these channels (10). Acupuncture can adjust the qi and blood of the meridians and viscera, improve various uncomfortable symptoms, and treat diseases by stimulating different acupoints. For the purpose of this review, acupuncture is considered as a generalized concept, including procedures involving insertion of fine needles into the skin or deeper tissues at specific locations (acupoints) of the body which are then manipulated manually, electrically, or with combined moxibustion; pressure on the acupoints with fingers; or application of infrared radiation on acupoints instead of fine needles.

1.3.1 Effectiveness

Acupuncture has been proven to reduce urine protein levels and improve estimated GFR (11–18). Meanwhile, some studies

also focused on the effects of acupuncture on hemodynamics (19) and renal interstitial fibrosis (20–24). Factors such as hyperglycemia, hypertension, hyperlipidemia, obesity, pain, aging, and anemia have a profound relationship with CKD progression (25). Considering that acupuncture can be effective in improving these aspects (26–30), it is believed that acupuncture may improve the prognosis of patients with CKD by controlling the above risk factors. In addition, acupuncture has the potential to alleviate various ESRD-related symptoms (e.g., pain, uremic pruritus [UP], RLS, and sleep disorders) (31–33). The therapeutic effect of acupuncture on CKD cannot be explained entirely by the bidirectional regulation of nerves, which is generally considered the main effective mechanism (34). However, a number of large-scale, randomized controlled clinical trials are still needed to clarify the indications of acupuncture before it can be used widely in clinical practice, especially as the mechanisms by which acupuncture affects disease mechanisms can be quite complex.

1.3.2 Security

The safety of acupuncture has been widely confirmed in clinical practice. A prospective observational study on acupuncture for chronic pain in Germany included 454920 patients, of whom more than 30% were over 60 years old, and reported mild side-effects (pain, hematoma, and bleeding) in 7.9% of patients. Only 13 patients suffered serious adverse events, including pneumothorax, hypertension, hypotension, asthma attacks, and aggravation of suicidal thoughts (35). The safety of acupuncture for CKD has also been proved. A systematic review of 55 randomized controlled trials showed that the most common side-effects associated with needling therapy and acupressure therapy were elbow soreness and bleeding and intradialytic hypotension and dizziness, respectively, and that no adverse effects were reported for moxibustion therapy (36). Some researchers believe that some side-effects of acupuncture are due to malpractice by acupuncturists, which can be avoided by strengthening training (37). The World Health Organization recommends at least 1568 hours of training to meet the basic requirements of acupuncture practitioners of ensuring clinical efficacy and patient safety (38).

However, although acupuncture is one of the safest replacement therapies, especially when provided by well-trained acupuncturists, to the best of our knowledge, the recent progress related to the use of acupuncture in treating CKD has not been summarized. This review aimed to assess the beneficial effects and current known mechanisms of acupuncture with regard to CKD and ESRD-related symptoms. We believe that acupuncture may have a significant impact on the associated risk factors for blocking or reversing the progress of CKD and alleviating the discomfort of patients, thus improving their prognosis.

2 Methods

We designed our literature review to include basic and clinical studies that addressed the effects and mechanisms underlying the effects of acupuncture treatment in CKD. The PubMed databases were queried for full-text studies published between January 1, 2000 and August 31, 2022 in English or Chinese using the following keywords: “acupuncture” and “kidney”.

Inclusion criteria:

1. Description of specific mechanisms of how the acupuncture treatment exerted its effects
2. Exclusive use of acupuncture to treat CKD and related symptoms
3. Related studies cited in these articles

Initially, 747 published articles were identified, of which only 46 articles matched the inclusion criteria and were reviewed. We excluded one withdrawn article, two articles unable to find partial results of changes in renal function, and two articles with imprecise test design that does not control variables. The references of the remaining 41 articles identified an additional 6 articles that also matched our inclusion criteria, which were also included in the final review, resulting in 47 articles in total (Table 1). The studies included randomized controlled animal experiments and clinical experiments and involved kidney injury. Additionally, we conducted a supplementary literature search on hyperlipidemia, which was not identified in the previous search but has been proved to be an important independent risk factor for the development of CKD.

3 Results

The 47 studies included in this review employed the use of Sprague Dawley rats, Wistar rats, Golden Syrian hamsters, New Zealand white rabbits, which were used to model ischemic nephropathy, diabetic nephropathy (DN), or hypertensive nephropathy. According to the risk factors of CKD, including hyperglycemia, hypertension, hyperlipidemia, obesity, aging, and anemia (25), we classified and summarized the potential mechanisms of action of the beneficial effects of acupuncture on the progress of CKD (Figure 1) and the common symptoms of ESRD.

3.1 Risk factors of CKD and the corresponding mechanism of acupuncture

3.1.1 Hyperglycemia

DN is rapidly becoming the most common cause of ESRD worldwide (25). The pathogenesis of DN is complex and

TABLE 1 Summary of studies in chronic renal injury, and renal physiological function and ESRD-related symptoms (2000-2022).

Ref.	Type of study	Species	Sample size	Related disease/ symptom	Acupuncture therapy	Result	Conclusion	Mechanism
(12) Yu et al.	RCT	Human	59	CKD	Needling at Hegu (LI4), EA at "Zusanli" (ST36) and "Taixi" (KI3) for 20 minutes, once per week, for 12 weeks	Reduced Scr and increased estimated GFR level	Improved renal function	None
(15) Zhu et al.	RCT	Human	106	CKD	Needling at "Shenguan", "Dihuang", and "Renhuang" for 30 minutes, MO at these acupoints for 20 minutes, once per day, the interval of 2 days once every 10 treatments, for 2 months	Reduced 24h-UP and red blood cell count of urinary sediment, and increased creatinine clearance rate	Improved renal function	None
(16) Paterno et al.	Preclinical study	Male Wistar rats	21	CKD	EA at "Zusanli" (ST36) and "Taixi" (KI3) for 20 minutes, EA and MO at "Shenshu" (BL23) for 2 minutes, twice a week, for 8 weeks	Improved urine volume, Scr, decreased 24h-UP, blood pressure, glomerulosclerosis and tubulointerstitial fibrosis indices	Attenuated the progression of renal disease	None
(17) Nie et al.	RCT	Human	180	Chronic allograft nephropathy	Needling at "Sanyinjiao" (SP6), "Diji" (SP8), "Yinlingquan" (SP9), "Xuehai" (SP10), etc. in spleen-meridian group; "Taixi" (KI3), "Zhaohai" (KI6), "Fuliu" (KI7), "Ciliao" (BL32), etc. in kidney-meridian group, for 30 minutes, once per day, the interval of 2 to 3 days once every 10 treatments, for 20 treatments	Reduced 24h-UP in all groups, and decreased Scr in spleen-meridian group	Relieved the damage of transplant kidney	None
(18) Mao et al.	RCT	Human	60	Idiopathic membranous nephropathy	MO at "Shenshu" (BL23), "Pishu" (BL20), "Guanyuan" (CV4), "Zusanli" (ST 36) and "Sanyinjiao" (SP6), for 30 minutes, once a day, 5 days a week, the interval of 2 days once every 5 treatments, for 6 months	Decreased the total TCM syndrome scores, the levels of 24h-UP, the blood coagulation indexes, TC and TG, increased the levels of ALB	Improved the clinical symptoms, renal function and renal microcirculation	None
(19) Matsumoto-Miyazaki et al.	RCT	Human	43	CKD	MO at "Shenshu" (BL23), for 4 minutes, 3 times in succession	Reduced resistive index	Decreased renal vascular resistance	None
(21) Li et al.	Preclinical study	Male SD rats	51	FSGS	MO at "Shenshu" (BL23) in one group and "Geshu" (BL17) in another group, for 30 minutes, every other day, for 12 weeks	Reduced UP, Scr, urea nitrogen, and serum uric acid, decreased renal α-SMA, fibronectin and TGF-β, increased podocin protein, nephrin protein and mRNA	Alleviated podocyte injury and inhibits RIF, improved renal function	Increase renal podocin and nephrin protein expressions, maintain the structural integrity of podocyte septa. Regulate renal tubular epithelial-mesenchymal transition and ECM integrity

(Continued)

TABLE 1 Continued

Ref.	Type of study	Species	Sample size	Related disease/ symptom	Acupuncture therapy	Result	Conclusion	Mechanism
(22) Zuo et al.	Preclinical study	Male adult New Zealand white rabbits	30	CRF	Needling at "Shenshu" (BL23), "Mingmen" (DU4) and "Pishu" (BL20), for 30 minutes, once a day, for 36 days	Reduced the levels of TNF –α, Smad3, ILK and TGF –β expression, decreased the concentrations of TGF –β, IL–8, TNF–α and IL –1β in blood serum, and increased eNOS expression	Relieved RIF, promoted the recovery of renal function	Regulate TGF-β-related pathways, decreased the levels of inflammation-associated cytokines, and attenuated RIF *via* the TGF-β/Smad pathway
(23) Zhang et al.	Preclinical study	Male SD rats	20	CRF	EA at "Sanyinjiao" (SP 6), "Taixi" (KI3) and "Shenshu" (BL23) for 20 minutes, once daily, for 30 days	Decreased the body weight, Scr and BUN levels and the expression of beta-catenin in the renal tissue	Relieved RIF, improved the renal function	Reduce the expression of beta-catenin in the renal tissue
(24) Li et al.	Preclinical study	Male SD rats	36	FSGS	EA at "Sanyinjiao" (SP 6), "Taixi" (KI3) and "Shenshu" (BL23) for 10/20/30 minutes, every other day, for 30 days	Decreased the contents of urinary microglobulin-α1, micro-albumin, transferrin and IgG, and Scr, BUN and uric acid, improved the injury of the renal tissue	Improved the kidney function and pathological changes	None
(27) Zhang et al.	Preclinical study	Male SD rats	36	DN	Needling at "Zhongwan" (CV12), "Quchi" (LI11), "Hegu" (LI4), "Zusanli" (ST36), "Yinlingquan" (SP9), "Xuehai" (SP10), "Diji" (SP8), "Sanyinjiao" (SP6), "Fenglong" (S40), and "Taichong" (LR3) for 30minutes, once daily, for 4, 8, or 12 weeks	Improved 24h-UP, BUN, TC, and triglycerides levels, the density of slit diaphragms. Promoted the renal expression of nephrin, CD2AP, and podocalyxin and decreased the expression of desmin	Improved the kidney function, and prevent the progression of DN	Ameliorated podocyte lesions
(29) Zhao et al.	Preclinical study	Male SD rats	40	Aging	Acupuncture at "Guanyuan" (CV4) and "Zusanli" (ST36) for 30 minutes, once daily, for 28 days	Reduced the contents of H_2O_2 and MDA in kidney tissue and kidney cell apoptosis rate	Delayed aging	Regulate peroxidation and apoptosis
(30) Cao et al.	RCT	Human	38	CRF, Anemia	Injected rHuEpo subcutaneously at "Shenshu" (BL23) and "Zusanli" (ST36), 3 times a week, for 2 months	Decreased the values of CRP, IL-6, TNF-α, Scr and BUN, increased Hb and SF levels	Improved EPO resistance and enhanced EPO efficacy, improved renal function and anemia	Alleviate micro-inflammatory state of the body
(31) Karjalian et al.	RCT	Human	90	Uremic pruritus	Applied symmetrical pressure on "Sanyinjiao" (SP6), "Xuehai" (SP10), "Zusanli" (ST36) and "Quchi" (LI11), for one minute, followed by three intermittent pressures on each point	Reduced the severity of pruritus and the levels of serum phosphorus and parathyroid hormone	Improve the severity of pruritus	None
(32) Mohammadi et al.	RCT	Human	60	RLS	NIR light was applied to "Zusanli" (ST36), "Sanyinjiao" (SP6), "Yanglingquan" (GB34) and "Chengshan" (BL57), for 2 minutes, 3 times a week, for 4 weeks	Decreased the mean RLS scores during the intervention sessions	Attenuated the symptoms of RLS in hemodialysis patients	None

(Continued)

TABLE 1 Continued

Ref.	Type of study	Species	Sample size	Related disease/ symptom	Acupuncture therapy	Result	Conclusion	Mechanism
(39) Wang et al. (2022)	Preclinical study	Male Wistar rats	60	DN	EA at "Guanyuan" (RN4), "Zusanli" (ST36), "Zhongwan" (RN12) and "Fenglong" (ST40) acupoints, for 15 minutes every other day, for 8 weeks	Increased the levels of body mass, SOD activity, and FoxO1 and PGC-1α expression, decreased the contents of blood glucose, Scr, BUN, ALB, MDA and ROS, and reduced pathological damage	Improved renal function, reduced the oxidative stress response and protected the kidneys	Rise the levels of forkhead transcription factor O1 and peroxisome proliferators-γ Coactivator-1α in rat mesangial cells
(40) Gao et al.	Preclinical study	Male SD rats	40	DN, Contrast-induced nephropathy	Needling/MO/needling & MO at "Sanyinjiao" (SP6), "Shenshu" (BL23) and "Pishu" (BL20), for 5/3/5&3 minutes, once daily, for 7 days	Needling & MO treatment down-regulated BUN and Scr levels, and Fas and FasL mRNA and protein expression levels, and up-regulated renal MDA, NOS, SOD and T-AOC activity	Reduced the oxidative stress and renal injury. Needling and MO has a synergistic effect	Down-regulate the expression of renal Fas and FasL genes and proteins
(41) Wang et al.	RCT	Human	120	DN	EA at "Zhongwan" (CV12), "Fenglong" (ST40), "Xuehai" (SP10) and "Taichong" (LR3), "Guanyuan" (CV4) and "Zusanli" (ST36), for 30 minutes, for 5 times a week, for 8 weeks	Decreased the levels of UAER, Scr, BUN, CysC, ηbL, ηbM, ηbH, ηp and FIB, increased serum eNOS and NO levels	Improved renal function and reduced microcirculation disorders	Up-regulate the levels of serum eNOS and NO
(42) Huang et al.	Preclinical study	Male Wistar rats	40	DN	EA at "Shenshu" (BL23) and "Zusanli" (ST36) for 20 min, 5 times a week, for 6 consecutive weeks	Decreased the levels of 24h-UP, FBG, BUN and p62, up-regulated the expression levels of LC3II, Beclin-1 and Nephrin proteins and ratio of LC3II/I. No significant change was found in the level of Scr. Improved the number of autophagosomes or autophagobubbles in podocytes	Alleviated kidney damage and improved facilitating autophagy	Improve facilitating autophagy
(43) Zhang et al.	Preclinical study	Mice	36	DN	EA at "Shenshu" (BL23), "Zusanli" (ST36) and "Sanyinjiao" (SP6), etc. acupoints for 20 minutes, once daily, for 3 weeks	Decreased the serum levels of TNF-α, IL-6, IL-1β and IL-18 in DN mice, reduced the number of renal mononuclear macrophage differentiation, changed the mRNA expression of NOS2 and Arg1, and NO production levels of renal mononuclear macrophage differentiation, suppressed the protein expression of HMGB1, NLRP3 and NF-κB in renal mononuclear macrophage	Reduce DN-induced inflammation and protect renal function	Suppressed HMGB1/NLRP3/ NF-κB pathway at renal mononuclear macrophage to attenuate inflammation
(44) Zhang et al.	RCT	Human	130	DN	Needling at "Quchi" (LI11), "Zhigou" (TE6), "Hegu" (LI4), "Xuehai" (SP 10), "Zusanli" (ST36), "Yinlingquan" (SP9), "Fenglong" (ST40), "Diji" (SP 8), "Sanyinjiao" (SP6), "Taichong" (LR3), "Tianshu" (ST25),	Improved symptoms of the patients, and had benign regulative action on metabolism of blood sugar and lipids, and GFR, renal blood flow and urinary albumin level, inhibited over expression of MCP-1	Improved renal blood flow and renal function, and protected glomerulus and renal tubules, so as to delay renal lesion	None

(Continued)

TABLE 1 Continued

Ref.	Type of study	Species	Sample size	Related disease/ symptom	Acupuncture therapy	Result	Conclusion	Mechanism
					"Gaohuang" (BL43), "Shenshu" (BL23), "Zhongwan" (CV12) and "Zhongji" (CV3), for 30 minutes, twice a day, for 42 days			
(45) Zhang et al.	RCT	Human	130	DN	Needling at "Zhongwan" (RN12), "Quchi" (LI11), "Hegu" (LI4), "Zusanli" (ST36), "Yinlingquan" (SP9), "Sanyinjiao" (SP6), "Fenglong" (ST40), "Xuehai" (SP10), "Diji" (SP8), "Taichong" (LR3), "Baihuanshu" (BL30), "Shenshu" (BL23), "Gaohuang" (BL43) and "Zhongji" (RN3), for 30 minutes, twice a day, for 6 weeks	Improve clinical symptoms and signs, FBG, UAER, beta2-microglobulin, MCP-1, lymphocyte membrane cholesterol, MDA, 8-OHdG, SOD, CD3+, CD4+, CD8+, and CD4+/CD8+	Improved glycometabolism disturbance-induced progressive kidney injury	Restrain overexpression of MCP-1, adjust level of oxidative stress, prohibit oxidation of protein, increase protectiveness of membrane, adjust quantity and activity abnormity of T lymphocyte subgroup, leading to repairing lymphocyte damage and improving immune expression
(46) Li et al.	Preclinical study	Male Wistar rats	12	None	EA at "Taixi" (KI3) for 20 minutes, once daily, for 7 days	Increase NAD-dependent isocitrate dehydrogenase and quinone reductase expression in the kidney	"Taixi" (KI3) has a relationship with Kidney	None
(47) Chen et al.	Preclinical study	Male Wistar rats	12	None	EA at "Taixi" (KI3) for 20 minutes, once daily, for 7 days	Increase NAD-dependent isocitrate dehydrogenase and quinone reductase expression in the kidney	"Taixi" (KI3) increased energy metabolism, and has a close relationship with kidney	None
(48) Li et al.	Preclinical study	Male C57BL/6 mice	80	DN	EA at "Zusanli" (ST36) and "Shenshu" (BL23), once daily, for 7 successive days	Down-regulated the blood glucose, alleviated the renal tissue injury, and decreased the expressions of TRPC6 and Nephrin in glomerulus and renal tissue	Alleviated renal injury	Reduce renal TRPC6 and Nephrin expressions and inhibiting podocyte activation
(49) Li et al.	Preclinical study	Male C57BL/6 mice	80	DN	EA at "Zusanli" (ST36) and "Shenshu" (BL23), once daily, for 7 successive days	Down-regulated the blood glucose, alleviated the renal tissue injury, and decreased the expressions of TRPC6 and related apoptotic proteins Caspase-3, Bax and Bcl-2 in the renal tissue	Alleviated renal injury	Down-regulate the expression of TRPC6 and Caspase-3 and up-regulating the ratio of Bcl-2/Bax
(50) Song et al.	RCT	Human	152	CKD, renal hypertension	Needling at s "Jiangya" and "Shenbing" acupoints, once daily, the interval of 3 days once every 2 weeks, for 24 weeks	Lowered blood pressure, reduced UP, decreased Scr	Improved renal function and lowered blood pressure	None
(51) An et al.	Preclinical study	New Zealand white rabbits	50	glomerulonephritis	Needling at "Fengmen" (BL12) and "Shenshu" (BL23) for 30 minutes, once daily, for 8 weeks	Lowered blood pressure, parameters of renal function and improved podocyte injury, increased the protein expression of phosphorylated ERK1/2.	Lowered blood pressure and halted deteriorating renal function	Inhibit the ERK1/2 MAPK pathway to reduce renal sympathetic nerve activity

(Continued)

TABLE 1 Continued

Ref.	Type of study	Species	Sample size	Related disease/ symptom	Acupuncture therapy	Result	Conclusion	Mechanism
(52) Paterno et al.	Preclinical study	Male Wistar rats	56	CKD	EA at "Zusanli" (ST-36) and "Taixi" (KI-3) and MO at "Shenshu" (BL23), for 20 minutes, twice a week, for 8 weeks	EA-MO reduced proteinuria, lowered Scr and urea concentrations, reduced glomerulosclerosis and tubulointerstitial fibrosis indices, increased in serum and renal NO levels, attenuated the elevation of TBP, MAP and RSNA	Lowered blood pressure, improved renal function and alleviated pathological damage of renal tissue	Regulate renal sympathetic nerve activity and NO level
(53) Kim et al.	Preclinical study	Male golden Syrian hamsters	12	Renal hypertension	EA at "Zusanli" (ST-36) for 30 minutes, once daily, for 5 days	Reduced MAP, increased periarteriolar NO concentration, and prevented the reduction of eNOS and nNOS	Reduced blood pressure	Activation of eNOS and nNOS reduces blood pressure through the stomach meridian
(54) Oh et al.	Preclinical study	Male SD rats	50	Renal failure, Renal hypertension	EA at "Zusanli" (ST36) and "Taixi" (KI3) acupoints, for 10 minutes, once daily, for 10 days	Reduced blood pressure, albuminuria, serum BUN and Scr concentrations, attenuated the increments of glomerulosclerosis and tubulointerstitial fibrosis, increased IGF-I mRNA and protein levels in both the kidney and the serum, and decreased the expressions of oxidative stress-related substances	Reduced blood pressure and protected renal function	be related to the effects of oxidative stress on IGF-I in renal failure-induced hypertension
(55) Yang et al.	Preclinical study	Male SHR rats	40	Hypertensive nephropathy	EA at "Shenshu" (BL23), "Geshu" (BL17) or both "Shenshu" (BL23), "Geshu" (BL17) for 15 minutes, every other day, for 12 weeks	Decreased the blood pressure and the expression levels of renal TIMP-1, PAI-1 and α-SMA proteins. Improved renal pathological damage	Reduced the blood pressure and alleviated pathological damage of renal tissue	Down-regulate expression of TIMP-1, PAI-1 and α-SMA proteins
(56) Chen et al.	Preclinical study	Male SHR rats	24	Hypertensive nephropathy	EA at "Quchi" (LI11) and "Zusanli" (ST36) acupoints for 20 minutes, once daily, for 6 weeks	Decreased the blood pressure, positive depositional area of type I and III collagen and the expression of semi-quantitative analysis of TGF-β1 mRNA	Lowered the blood pressure and improved the damage of kidney morphology	Intervenes the process of RIF by reducing synthesis of kidney type I, III collagen and restraining expression of TGF-β1.
(57) Che-Yi et al.	RCT	Human	40	Uremic pruritus, ESRD	Needling at the "Quchi" (LI11) acupoint, thrice weekly, for 1 month	Lowered pruritus scores	Relieved uremic pruritus	None
(58) Akça et al.	RCT	Human	75	Uremic pruritus, ESRD	Acupressure at the "Quchi" (LI11) acupoint, thrice weekly, for 4 weeks	Reduced the levels of discomfort from uremic pruritus	Relieved uremic pruritus	None
(59) Rehman et al.	RCT	Human	58	Uremic pruritus, ESRD	Acupressure at "Yongquan" (KI1), for 6 minutes, once daily, for 8 weeks	Reduced the PSQI score and improved the mean EQ5D index score	Improved the sleep quality and quality of life	None
(60) Arab et al.	RCT	Human	108	Uremic pruritus, ESRD	Acupressure at "Shenmen" (HT7) acupoint, for 8 minutes, 3 times a week, for 4 weeks	Reduced the total PSQI score	Improved the sleep quality	None
(61) Shariati et al.	RCT	Human	48	Sleep disorder, ESRD	Acupressure at "Shenmen" (HE7), "Hegu" (Li4) and	Improved the scores of PSQI, subjective sleep quality, sleep latency, sleep	Improved the sleep quality	None

(Continued)

TABLE 1 Continued

Ref.	Type of study	Species	Sample size	Related disease/ symptom	Acupuncture therapy	Result	Conclusion	Mechanism
					"Sanyinjiao" (SP6) acupoints, for 9 minutes, 3 times a week, for 4 weeks	duration, sleep efficiency, sleep disturbance, the use of sleeping medication, and daytime dysfunction		
(62) Tsay et al.	RCT	Human	106	Fatigue, ESRD	Acupressure at "Yongquan" (KI1), "Zusanli" (ST36), "Yanglingquan" (GB34) and "Sanyinjiao" (SP6) acupoints, for 12 minutes, 3 times a week, for 4 weeks	Improved the results of the revised PFS, VAS of Fatigue, PSQI and the Beck Depression Inventory	Improved fatigue	None
(63) Eğlence et al.	RCT	Human	118	Fatigue, ESRD	Acupressure at "Zusanli" (ST36), "Yanglingquan" (GB34), "Sanyinjiao" (SP6) acupoints and electrically stimulate at "Yongquan" (KI1) acupoints, 3 times a week, for 1 month	Lowered the subscale and total fatigue scores for the VAS and PFS, except for the score of cognitive subscale on the PFS	Decreased fatigue	None
(64) Wang et al.	RCT	Human	109	Comprehensive symptoms, ESRD	MO at "Zusanli" (ST 36) and "Sanyinjiao" (SP 6), 2 to 3 times a week, for 12 weeks	Increased the survival quality scores of physical functioning, general health, mental health, social functioning, vitality, effects of kidney disease and cognitive function	Improved the survival quality of physical functioning, general health and vitality, which benefits the psychological condition of the patients	None
(65) Kim et al.	RCT	Human	24	Comprehensive symptoms, ESRD	Individualized acupuncture treatments were provided twice a week, for 6 consecutive weeks	Improved the results of some subscales of KDQOL-SF, including effects of kidney disease, burden of kidney disease, role-limitations physical, emotional well-being, energy/fatigue and physical functioning	Improved the survival quality of life	None
(66) Li et al.	RCT	Human	97	Comprehensive symptoms, ESRD	MO at "Zusanli" (ST 36) and "Sanyinjiao" (SP 6) acupoints, 2 to 3 times a week, for 12 weeks	Improved the symptom scores of lassitude and fatigue, short breath and aversion to talk, poor appetite, soreness and softness of waist and knees, aversion to cold, cold extremities, etc.	Improve the clinical symptoms	None
(67) Su et al.	RCT	Human	69	Comprehensive symptoms, ESRD	FIR or HP at "Qihai" (RN6), "Guanyuan" (RN4) and "Zhongji" (RN3) acupoints, for 30 minutes, 3 times a week, for 12 weeks	Improved some parameters of the HRVA. Improved the scores of the psychological domain and the environmental domain of the WHOLQOL-BREF questionnaire	Decreased both stress and fatigue levels and stimulated autonomic nervous system activity	None
(68) Sun et al.	RCT	Human	71	Comprehensive symptoms, ESRD	MO at "Zusanli" (ST 36), "Guanyuan" (CV4) and "Sanyinjiao" (SP 6) acupoints, for 6 minutes,	Improved some fields of the KDQOL-SF, including role-emotional, role-physical, energy, social support, work	Improved physical strength and mood in the quality of life	None

(Continued)

TABLE 1 Continued

Ref.	Type of study	Species	Sample size	Related disease/ symptom	Acupuncture therapy	Result	Conclusion	Mechanism
					2 to 3 times a week, for 12 weeks	status, quality of social interaction, etc.		
(69) Tsay et al.	RCT	Human	106	Comprehensive symptoms, ESRD	Acupressure/TEAS at "Zusanli" (ST 36), "Guanyuan" (CV4) and "Sanyinjiao" (SP 6) acupoints, for 13 minutes, 3 times a week, for 1 month	Improved the scores of PFS, PSQI and the Beck Depression Inventory	Lowered the levels of fatigue, a better sleep quality and less depressed moods	None
(70) Bullen et al.	RCT	Human	101	ESRD	Individual needling or massage for 20 minutes, once a week, for 8 weeks	Improved PROMIS mental raw score	Improved the health-related quality of life	None

RCT, randomized controlled study; CKD, chronic kidney disease; EA, electroacupuncture; Scr, serum creatinine; GFR, glomerular filtration rate; MO, moxibustion; 24h-UP, 24-hour urine protein; TCM, traditional Chinese medicine; TC, total cholesterol; TG, triacylglycerol; ALB, albumin; SD, Sprague Dawley; FSGS, focal segmental glomerulosclerosis; α-SMA, alpha-smooth muscle actin; TGF-β, transforming growth factor-beta; ECM, extracellular matrix; CRF, chronic renal failure; TNF−α, tumor necrosis factor−α; ILK, integrin linked kinase; IL−8, interleukin-8; eNOS, endothelial nitric oxide synthase; RIF, renal interstitial fibrosis; BUN, blood urea nitrogen; DN, diabetic nephropathy; CD2AP, CD2-associated protein; H_2O_2, hydrogen peroxide; MDA, malondialdehyde; CRP, C-reactive protein; Hb, hemoglobin; SF, serum ferritin; EPO, erythropoietin; NIR, near-infrared; RLS, restless legs syndrome; SOD, superoxide dismutase; FoxO1, forkhead box O1; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; ROS, reactive oxygen species; T-AOC, total antioxidant capacity; UAER, urine albumin excretion rate; CysC, cystatin; ηbL, whole blood low-cut viscosity; ηbM, whole blood mid-cut viscosity; ηbH, whole blood high-cut viscosity; ηp, plasma viscosity; FIB, fibrinogen; NO, nitric oxide; FBG, fasting blood glucose; LC3, microtubule-associated protein light chain 3; Arg1, arginase-1; HMGB1, high mobility group box-1; NF-κB, nuclear factor-kappaB; MCP-1, monocyte chemoattractant protein-1; 8-OHdG, 8-hydroxydeoxy guanosine; NAD, nicotinamide adenine dinucleotide; TRPC6, transient receptor potential-6 channels; ERK1/2, extracellular signal-regulated kinase 1/2; TBP, tail-cuff blood pressure; MAP, mean arterial pressure; RSNA, renal sympathetic nerve activity; nNOS, neuronal nitric oxide synthase; IGF-I, insulin-like growth factor-I; SHR, spontaneously hypertensive rats; TIMP-1, tissue inhibitor of metalloproteinase 1; PAI-1, plasminogen activator inhibitor-1; PSQI, pittsburgh sleep quality index; PFS, piper fatigue scale; VAS, visual analog scale; KDQOL-SF, kidney disease quality of life-short form; HP, heat pad; HRVA, heart rate variability analyzer; WHOLQOL-BREF, a questionnaire authenticated and approved by the World Health Organization; TEAS, transcutaneous electrical acupoint stimulation; PROMIS, patient-reported outcomes measurement information system.

involves various mechanisms, resulting in poor therapeutic outcomes (71). It is generally accepted that the developmental mechanism of DN results from abnormal homeostasis (72). There are many critical links in the progression of DN, e.g., oxidative stress, inflammation, and podocyte structural damage. A reciprocal relationship exists between inflammation and oxidative stress (73, 74). Various Chinese meta-analyses point out that acupuncture can reduce the urine protein, serum creatinine, fasting blood glucose, postprandial blood glucose, glycosylated hemoglobin, total cholesterol, and triglycerides of patients with DN, as well as enhance the efficacy when combined with conventional drugs (26, 75, 76).

3.1.1.1 Oxidative stress

The increase in reactive oxygen species (ROS) caused by blood glucose is at the core of the pathogenesis of DN. Hyperglycemia-induced oxidative stress is believed to cause both local and systemic inflammation (77).

Forkhead transcription factor O1 (FOXO1) overexpression reduced ROS in rat mesangial cells and protected mitochondrial function by activating peroxisome proliferator γ coactivator 1 α (PGC-1α) (78). A study on rats with DN showed that electroacupuncture (EA) increased the levels of FOXO1 and PGC-1α in kidney tissue, thus improving renal function (39).

Nitric oxide synthase (NOS), superoxide dismutase (SOD), and malondialdehyde (MDA) are essential indicators of oxidative stress. Reactive species may also be produced enzymatically by uncoupled NOS (79). SOD is an antioxidant that can effectively remove superoxide anions and protect cells from oxidative damage (80). MDA is a metabolite of lipid peroxidation, which can reflect the level of free radicals in tissues and lipid peroxidation caused by free radicals, and indirectly reflects cell damage (40). A study on rats with DN showed that acupuncture and moxibustion have synergistic effects on antioxidant stress, which may be related to their function in downregulating the expression of MDA and upregulating the expressions of NOS and SOD in the kidney (40). Another trial revealed that EA could improve renal function and reduce microcirculation disorders in early DN by up-regulating the levels of serum endothelial NOS and NO (41).

Oxidative stress can directly damage podocytes, mesangial cells, and endothelial cells, resulting in proteinuria and tubulointerstitial fibrosis. One study suggested that EA may effectively alleviate renal injury in rats with DN by promoting renal autophagy. The number of podocytes in rats with DN treated with EA was more than that in the untreated group, while the levels of 24-h urine protein, blood urea nitrogen, and serum creatinine were lower (42).

Nuclear factor 2 related factor 2 (Nrf2) regulates oxidative stress in the antioxidant response system by controlling the expression of more than 250 genes (72, 79). A study on rabbits with acute kidney injury revealed that EA treatment enhanced the expression of phosphorylated Akt, heme oxygenase-1 protein, Nrf2 total protein, and nuclear protein to resist oxidative stress (81).

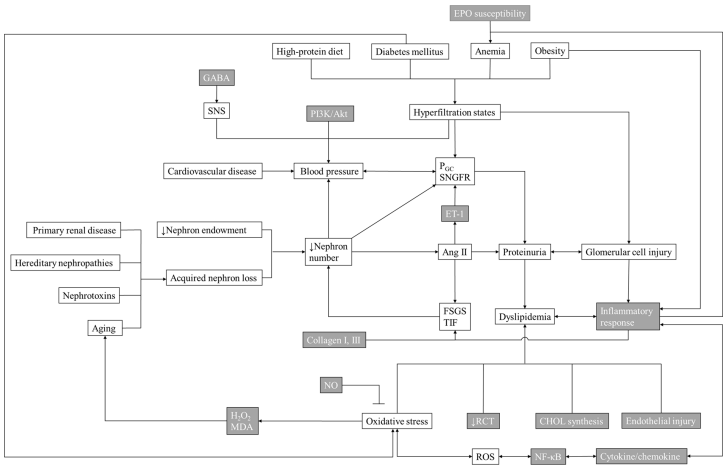

FIGURE 1
Mechanisms Underlying the Effects of Acupuncture Therapy in Chronic Kidney Disease. The gray grids are the known possible main mechanism/target/downstream product of acupuncture in treating chronic kidney disease. EPO, erythropoietin; GABA, γ-aminobutyric acid; SNS, sympathetic nervous system; PGC, proliferator γ coactivator; SNGFR, single nephron glomerular filtration rate; ET-1, endothelin-1; Ang II, angiotensin II; FSGS, focal segmental glomerulosclerosis; TIF, tubulointerstitial fibrosis; MDA, malondialdehyde; RCT, reverse cholesterol transport; CHOL, cholesterol; NF-κb, nuclear factor-kappa B; ROS, reactive oxygen species.

3.1.1.2 Inflammation

Continuous inflammation of the circulatory system and renal tissue is the fundamental pathological basis for the development of DN (82). Inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), transforming growth factor-β, IL-1, and IL-18 are elevated in the blood and have been related to the occurrence and progression of DN (83, 84). Several studies have shown that acupuncture can improve insulin resistance by reducing serum IL-6, IL-8, and IL-1β levels, which might help protect islet B cell function (43, 85).

Increasing evidence has shown the central role of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway (71) in DN pathogenesis. JAK and STAT subtypes expressed on the renal tubulointerstitial increase along with the development of DN and negatively correlated with the estimated GFR. Nuclear factor-kappa B (NF-κB) is a key transcription factor in the inflammatory process of DN and is activated by the JAK-STAT pathway. NF-κB regulates inflammatory cytokines and chemokines, e.g., monocyte chemoattractant protein-1 (MCP-1) and cell adhesion proteins, leading to kidney damage. A study on diabetic mice revealed that acupuncture could suppress the inflammatory response of DN through the NF-κB-related pathway (43). Zhang et al. designed a series of multicenter, randomized, and blinded studies, showing that the needling method of harmonizing the spleen and stomach on patients with early DN might inhibit the NF-κB-related pathway by inhibiting the expression of MCP-1, which can improve renal blood flow and GFR, decrease urinary albumin secretion, protect the glomerulus and renal tubules, thus reducing the inflammatory levels and delaying the progress of DN (44, 45).

3.1.1.3 Energy metabolism

The kidney requires a large number of mitochondria to provide the energy to remove waste from the blood and regulate fluid and electrolyte balance. Mitochondrial dysfunction leads to a decrease in ATP production, alterations in cellular functions and structure, and the loss of renal function (86, 87). Figueiredo et al. (88) found that in non-exercised hyperglycemic rats, under the same dose of anesthesia (ketamine, 90 mg/kg body weight), the lactic acid concentration and blood glucose level of the experimental group treated with EA decreased significantly, indicating that acupuncture might reduce blood glucose by enhancing aerobic metabolism and increasing ATP output.

NAD-dependent isocitrate dehydrogenase is present in the mitochondria. It is a momentous rate-limiting enzyme of the tricarboxylic acid cycle (TCA) and plays a crucial role in energy production and anabolism. As the most important source of adenosine triphosphate (ATP), TCA is closely related to the occurrence of nephropathy. Two other studies reached similar conclusions; after needling the "Taixi" (KI 3) point, increased expression of NAD-dependent isocitrate dehydrogenase and quinone reductase was observed in rat kidney tissue, suggesting that targeted acupuncture improves energy metabolism (46, 47).

Metabonomics has also been applied to study EA's effects on renal metabolism. Alanine is a characteristic metabolite in the kidney, an important energy source for human beings, and is involved in lymphocyte regeneration, thus maintaining immune

homeostasis (89). Threonine participates in energy metabolism and promotes the cellular immune system's defense function (89). Research suggested that the levels of the two metabolites in the kidneys of mice with premature ovarian failure were elevated, and the levels were down-regulated after electroacupuncture stimulation of "Sanyinjiao" (SP6) and "Guanyuan" (CV4), close to the level of healthy mice (90). Another study revealed that the effect of EA on the abnormal increase of metabolites might suggest that it can regulate the disordered amino acid metabolism, thereby improving energy metabolism and regulating the kidney's immune function (91).

3.1.1.4 Maintaining the podocyte structure

Podocytes are important functional cells in the glomerulus that cannot regenerate when they suffer from injury. Their damage and apoptosis could result in the destruction of the glomerular filtration membrane and induce DN (92). Podocalyxin is one of the main structures responsible for the negative charge on the glomerular membrane (93). CD2-associated protein (CD2AP) is a transmembrane protein that interacts with nephrin to maintain cytoskeleton and slit diaphragm function. Damage to CD2AP leads to the destruction of the podocyte skeleton and marked proteinuria (94). Desmin also maintains the mechanical stability of podocytes to enable morphological changes on the tensile glomerular capillary wall (95). Zhang et al. found that acupuncture partly prevented DN rats from podocyte foot process effacement—which exhibited fusion, complete destruction, or disappearance—and thick glomerular basement membrane. It also upregulates nephrin expression, CD2AP, and podocalyxin but downregulates desmin, thus protecting and maintaining podocytes' physical and chemical structure (27).

The transient receptor potential-6 channel (TRPC6) is an integral player in the calcium processing in podocytes and in the maintenance of their cellular structure (96, 97). Möller et al. reported that overexpression of TRPC6 in healthy mice leads to the restructuring of the podocyte actin cytoskeleton and alterations in calcium flux, which causes proteinuria (97). Hyperglycemia and elevation in angiotensin II (Ang II) levels are sufficient to cause overexpression of TRPC6, resulting in increased calcium influx and eventual podocyte dysfunction and death (98). Li et al. proved that EA preconditioning could alleviate renal injury in hyperglycemic mice by reducing renal TRPC6 and nephrin expression and inhibiting podocyte activation (48, 49).

3.1.2 Hypertension

Hypertension is considered a result of renal damage and a significant contributor to the progression of CKD (25). Approximately 80–90% of patients with CKD have renal hypertension, which accelerates renal dysfunction (99, 100). Therefore, controlling blood pressure is critical in preventing progressive deterioration of renal function. Renal hypertension is difficult to cure and usually requires the combined use of several antihypertensive drugs with possible non-compliance. The pathological mechanism of renal hypertension is complex, including activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), oxidative stress, increased endothelin-1 (ET-1), and inflammation. Acupuncture has been shown to have certain clinical effects on renal hypertension (50). A network meta-analysis on acupuncture therapy for essential hypertension, which included 31 trials with 2,649 patients, revealed that acupuncture might have similar effects as common medication. However, the quality of this evidence is not high (101).

3.1.2.1 Angiotensin II type 1 receptor-ET-1-endothelin-1 type A receptor pathway

ET-1 is a crucial molecule that regulates renal hypertension, and its release is induced by the combination of Ang II and angiotensin II type 1 receptor (AT1R). ET-1 combines with endothelin-1 type A receptor (ETAR), which causes marked renal vasoconstriction (102). A previous study revealed that Ang II and ET-1 receptor blockers could reduce blood pressure in animal models and patients (103). Acupuncture reduces blood pressure by lowering the ET-1 level (104, 105). Additionally, long-term EA blocks the AT1R-ET-1-ETAR pathway by inhibiting the expression of AT1R and ETAR (106). Therefore, it is believed that the AT1R-ET-1-ETAR pathway may be a target for acupuncture treatment of renal hypertension.

3.1.2.2 Renin-angiotensin-aldosterone system

The RAAS is a vital blood pressure regulation system that maintains the homeostasis of water and electrolytes in the internal environment. There are two main pathways. 1) The angiotensin-converting enzyme/Ang II (ACE/Ang II) pathway constricts blood vessels and promotes tissue proliferation and remodeling (107). 2) The ACE2/Ang-(1-7) pathway has the opposite effects (108). Moreover, Liu et al. found that acupuncture and moxibustion showed good antihypertensive effects by reducing the content of Ang II and atomic layer deposition in the plasma of hypertensive rats (109).

3.1.2.3 SNS

The development of hypertension partly depends on the increased sympathetic outflow and impaired baroreflex function. The nucleus tractus solitarii (NTS) is the main integration center regulating the autonomic reflex and sympathetic outflow. In the NTS, inhibition of γ-aminobutyric acid (GABA) is essential for pressure reflection signal processing. Evidence shows that an increase in GABA inhibition leads to hypertension (110–112). Therefore, neuronal activity in the NTS is a significant target for acupuncture to regulate the sympathetic excitatory reflex

function. A study revealed that EA could reduce sympathetic activity and significantly inhibit the sympathetic excitatory reflex in rats, which may be achieved by regulating functional GABA (113). Moreover, acupuncture reduced local renal sympathetic nerve activity by inhibiting the extracellular regulated protein kinase ½-MAPK pathway to lower blood pressure (51). Another study also verified the relationship between acupuncture and renal sympathetic activity (52).

3.1.2.4 Oxidative stress

Renal hypertension induced by ischemic nephropathy is affected by oxidative stress mechanisms involving molecules such as NOS and heme oxygenase (HO-1/2) (114–116). In one study, EA was shown to prevent the reduction of endothelial NOS and nitric NOS levels associated with hypertension (53).

Inducible NOS (iNOS) and HO-1/2 expression is involved in the secretion of insulin-like growth factor-I (IGF-I) in MCF-7 cells (117). IGF-I has been proved to be related to proliferation, differentiation, survival, apoptosis, and cell protection related to oxidative stress (118). Another study showed that EA can reduce the levels of iNOS and HO-1/2 and upregulate IGF-1 levels, thus reducing glomerulosclerosis and renal interstitial fibrosis as well as blood pressure in rats with renal failure (54). Additionally, the possibility of acupuncture being able to directly affect the process of renal fibrosis in hypertensive rats has also been suggested (55, 56).

3.1.3 Hyperlipidemia/obesity

Recent studies have shown that hyperlipidemia and obesity are two adverse factors associated with the progression of CKD *via* different mechanisms. However, obese patients are typically at higher risk of hyperlipidemia (119). Obesity is associated with high glomerular filtration and other glomerular hemodynamic alterations, which may aggravate CKD progression (120, 121). Adipocytes produce various hormones and pro-inflammatory molecules, which may lead to progressive renal damage (122). According to the lipid nephrotoxicity hypothesis, hyperlipidemia can lead to inflammation, oxidative stress, and endogenous electrical stress (123).

A study on 1528 obese patients with hyperlipidemia treated with acupuncture suggested that acupuncture had dual effects on obesity and hyperlipidemia. The patients not only effectively lost weight (the total effective rate of the mild obesity group was 98.9%), but they also reduced their levels of total cholesterol, triglycerides, and low-density lipoprotein and improved their high-density lipoprotein (HDL) level (28). Some scholars believe that acupuncture combined with moxibustion reduces the adverse effects of hyperlipidemia and obesity better than acupuncture alone (124). Another study found that different acupoint combinations had different effects on reducing blood lipid levels. The "Quchi" (Li 11), "Zhongwan" (CV 12), and "Fenglong" (ST 40) points had a superior performance on blood lipid metabolism (125).

3.1.3.1 Anti-oxidative stress

Nitric oxide (NO) is an endothelium-derived messenger molecule that alleviates oxidative stress. Several studies revealed that EA and moxibustion increase the level of NO to resist oxidative stress and that the effect of moxibustion is regulated by temperature (126–130). Transient receptor potential vanilloid subfamily 1 (TRPV1) is an essential molecular regulator that provides moxibustion with temperature dependence of its hypolipemic properties. There is a relationship between the cholesterol-lowering effect of moxibustion and the activation of TRPV1 (131).

3.1.3.2 Reverse transport mechanism

Reverse cholesterol transport (RCT), which is partly mediated by ATP-binding cassette transporter A1 (ABCA1), is a significant physiological link that delays hyperlipidemia progression. ABCA1 regulates intracellular RCT and HDL production, thereby controlling lipid metabolism. As transcription factors, activated peroxisome proliferator-activated receptor (PPAR)-α and liver X receptor α (LXRα) enhance ABCA1 transcription activity (132, 133). Zou et al. believed that moxibustion upregulated PPARγ and scavenger receptor B1 (SR-B1) protein and gene expression in the liver to promote cholesterol reversal (134). HDL binds to SR-B1 and transports cholesterol to the liver for selective metabolism. Another research study found that EA stimulation of the "Fenglong" (ST 40) point contributed to increased expressions of ABCA1, PPARα, LXRα, and retinoid X receptor α messenger RNA, thus contributing to RCT, and somehow had a therapeutic effect on hyperlipidemia (135, 136).

ABCA1 dysfunction leads to excessive cholesterol ester accumulation as lipid droplets in macrophages, thereby contributing to foam cell formation (137). EA at the "Fenglong" (ST 40) point can prevent macrophage transformation into foam cells and increase cholesterol outflow rate in macrophages, thus preventing and reversing foam cell formation (138).

3.1.3.3 Lipids synthesis reduction

Sterol regulatory element binding protein-1C (SREBP-1C) is a transcription factor involved in the transcriptional regulation of the fatty acid synthase (*FAS*) gene that controls the synthesis of lipids from glucose in the liver (139). Recent research indicated that *FAS* could catalyze the *de novo* synthesis of fatty acids and impact liver physiology through signaling and energy storage (140). It is believed that acupuncture downregulates SREBP-1C and *FAS* to control the expression of key enzymes regulating cholesterol synthesis in the liver to prevent hyperlipidemia (141).

3.1.3.4 Inflammation reduction

CKD is an inflammatory state that results in glomerular and tubular lesions and adversely affects lipid balance (142, 143). Several inflammatory markers have been associated with lipid levels (144). Some studies revealed that acupuncture could reduce intercellular cell adhesion molecule-1, MCP-1, TNF-α, IL-6, and IL-1γ, slowing the inflammatory process (145–147).

Adiponectin (ADPN) is the only adipocyte-specific protein negatively associated with obesity. It has anti-diabetic, antiatherosclerotic, anti-inflammatory, and antiangiogenic properties. Hand acupuncture and EA intervention positively affect hyperlipidemia by reducing blood fat content and upregulating serum HDL-C and ADPN levels in hyperlipidemic rats (148).

3.1.4 Aging

A longitudinal study among individuals without nephropathy found that the GFR decreases with age, indicating that nephron loss might be part of normal aging (149). Other studies have shown that proteinuria, CKD, and ESRD incidence rates increase with age (149–151). Acupuncture can delay the aging of the kidney tissue by suppressing oxidative stress and reducing apoptosis. An experiment suggested that the apoptosis rate of renal cells and the levels of hydrogen peroxide and malondialdehyde decreased after acupuncture in adult rats (29).

3.1.5 Anemia

Renal anemia is one of the most common complications of CKD and affects the quality of life and survival time of patients with CKD (152). In a study of 131 patients with CKD, elevated hemoglobin levels were independently associated with reduced mortality (153). Renal anemia is usually caused by the hyposecretion of erythropoietin (EPO). EPO is a protein hormone synthesized by proximal convoluted tubular cells, essential for erythrocytes' growth. Medical treatments sometimes show poor efficacy, including recombinant human erythropoietin and polysaccharide iron complexes (154). Therefore, there is an urgent need for supplemental therapies to improve the curative effect. One study found that acupoint injection could reduce the level of C-reactive protein, improve the micro-inflammatory state, and help reduce EPO dosage, which is better than the traditional injection method (30). Acupoint injection reduces costs and meets the requirements of patients' health and the economy.

3.2 Control of ESRD-related complications

CKD and ESRD have attracted attention worldwide, and the number of patients on hemodialysis (HD) has increased dramatically. Patients on HD often have many painful complications, such as UP, RLS, insomnia, fatigue, sleep disorders, and hypotension. Acupuncture can alleviate these problems. A systematic review of randomized controlled trials showed that acupuncture had demonstrated efficacy in alleviating sleep disturbance, fatigue, and UP symptoms among patients with CKD (36).

3.2.1 Pain

Pain can be one of the most debilitating symptoms of CKD (155). Patients suffer several types of pain, including peripheral neuropathic pain, joint pain, autosomal dominant polycystic kidney disease (ADPKD)-related pain, and pain caused by renal biopsy. A multicenter, cross-sectional study evaluated the impact of pain on the quality of life of patients with ESRD on HD, with the results suggesting that pain significantly impacted their life quality (156). Pain management in patients with CKD is challenging. Non-opioid analgesia using acetaminophen, topical analgesics, and gabapentinoids is preferred, but cannot relieve pain to a great extent (155). Furthermore, the long-term use of non-steroidal, anti-inflammatory drugs poses a risk of liver and further kidney damage. A study on over 400,000 patients with ESRD showed that an opioid prescription was accepted by over half of them (157), even though opioid use is associated with an increased risk of altered mental status, falls, fractures, hospitalizations, and mortality, in a dose-dependent manner (158, 159).

Nevertheless, opioids play a central role in the analgesic mechanism, desensitizing peripheral nociceptors, reducing pro-inflammatory cytokines, and activating the descending inhibitory system (160). A previous study showed that high- and low EA frequencies could relieve heat, mechanical, and spontaneous pain by regulating μ and δ opioid receptors (161). This shows that acupuncture has the prospect of reducing or even replacing opioid use.

Besides, the role of acupuncture in the treatment of chronic lower back pain has been well proven and addressed in the Clinical Practice Guideline of the American College of Physicians (162). It is also effective against chronic lower back pain caused by polycystic kidney disease (163). Unfortunately, at present, there is a lack of large-scale studies on verifying the efficacy of acupuncture and moxibustion on lower back pain in other types of CKD.

3.2.2 Uremic pruritus

Chronic pruritus associated with ESRD is one of the most important causes of systemic pruritus (164). UP is an unpleasant and painful condition causing the desire to scratch, invalidating the skin's protective barrier, and affecting patients' health-related quality of life (HR-QOL) (31). A large multicenter study of 18801 patients on HD showed that 42% of them had UP (165). The pathogenesis of UP may involve inflammatory

states, such as increased levels of pro-inflammatory cytokines (IL-6, IL-2, and TNF-α), immune changes, and neuropathy. Current drug treatment regimens (e.g., antihistamines, bupropion, and tacrolimus) often lead to many side-effects, including sleepiness, nausea, vomiting, and epilepsy. Patients are unlikely to extract many benefits, and the symptoms usually recur after drug discontinuation (164). Acupuncture, an economical and safe complementary therapy, has obvious advantages in treating pruritus, with one meta-analysis even suggesting the potential of acupuncture to treat UP (166). Studies have shown that one of the mechanisms of acupuncture in treating chronic pruritus is regulating inflammatory cytokines, including reducing IL-4 and IL-2 levels in serum, enhancing the anti-inflammatory cytokine IL-10, and inhibiting the level of the inflammatory cytokine TNF-α (the acupoints are all "Quchi" (LI11), "Hegu" (LI4), "Xuehai" (SP10), and "Yinlingquan" (SP9)) (167–169). Another animal study found that EA increased the serum levels of interferon-γ of mice with atopic dermatitis, with no significant change in IL-4 levels (the acupoints are "Quchi" (LI11) and "Neiguan" (PC6)) (170). This finding suggests that different acupoints lead to different effects.

Karjalian et al. conducted a randomized, double-blind, pre- and post-control clinical trial among 90 patients on HD and found that acupoint pressing could effectively reduce pruritus in patients on HD (31). Four other randomized controlled trials showed that acupuncture, acupoint pressing, transcutaneous acupoint electrical stimulation, and auricular finger pressing could reduce UP symptoms (57–59, 171). Yi et al. believed this effect could continue after the treatment course (57).

3.2.3 Restless leg syndrome

RLS is a common chronic sensorimotor disorder characterized by a strong demand to move the legs during rest and bedtime. The development of this disease in patients undergoing HD is progressive (32). The prevalence among European and American adults varies from 7% to 10% (172, 173). Further, the prevalence of RLS has been reported to increase with age (174). RLS affects sleep quality and leads to dysfunction of emotion, cognition, energy, and other daily activities. RLS is associated with an increased risk of cardiovascular disease, osteoporosis, musculoskeletal pain, and mortality (175–177). A single-center, single-blinded, randomized controlled study attempted to treat 60 HD patients with RLS by irradiating lower limb acupoints with near-infrared light, but the symptoms of RLS recurred after irradiation was stopped (32). The mechanism was unknown, and the effects might have been related to the selection of acupoints, treatment cycle, and treatment mode, which require further study.

3.2.4 Sleep disorders

Sleep disorders in patients on HD can lead to psychosocial function and interpersonal relationship disorders and reduce their HR-QOL (60). More than 85% of patients on HD experience serious sleep problems (178). Zahra et al. and Shariati et al. found that acupoint pressing positively affects sleep quality in patients on HD, but the specific mechanism is still unknown (60, 61).

Acupuncture has been proved to have a significant effect on sleep disorders. Various meta-analyses, which included thousands of patients each, suggested that acupuncture could improve the sleep quality of patients with primary insomnia and patients with insomnia-related primary diseases and conditions (stroke, ESRD, perimenopause, pregnancy, and mental illness) of all ages, with few and mild adverse reactions (33, 179–182). However, because most of the included studies were heterogeneous and the sample size of each experiment was small, and there are few studies related to ESRD, it is still necessary to design randomized controlled trials with larger sample sizes to prove the essential of acupuncture to treat sleep disorders in patients on HD.

3.2.5 HR-QOL

HR-QOL is a measure of the value assigned to duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy (183). Due to the progress of ESRD, the lifestyle restrictions and changes imputed to HD usually lead to fatigue, depression, anxiety, which have a profound impact on HR-QOL. The mental health of elderly patients is an especially serious problem (184). Mid- and long-term fatigue may even increase the risk of cardiovascular events and is associated with higher mortality (185). The clinical trials of this subsection were evaluated through the following questionnaires: Pittsburgh Sleep Quality Index, Piper Fatigue Scale; Visual Analog Scale, Kidney Disease Quality of Life-Short Form, a questionnaire authenticated and approved by the World Health Organization and Patient-Reported Outcomes Measurement Information System. Two studies showed that acupoint pressing could improve the fatigue state of HD patients (62, 63), and several randomized controlled studies found that moxibustion, acupressure, transcutaneous electrical acupoint stimulation, and acupuncture had positive impacts on aspects such as physical functions, general health, and vitality (64–69). However, in 2018, a study on living conditions of 101 HD patients who received short-term acupuncture/massage suggested that although the original Patient-Reported Outcomes Measurement Information System psychological scores of patients improved, the improvement was not significant, and might have been related to the sample capacity and treatment duration (70).

4 Discussion

CKD is a significant public health problem worldwide and is characterized by a high incidence rate and complex pathogenesis. The clinical treatment scheme needs to be improved urgently, as currently the main clinical therapeutic strategy is to delay the progress of CKD, which mostly relies on medication. According to Kidney Disease Improving Global Outcome (KDIGO) guidelines, dealing with the complications of CKD (e.g. renal hypertension, hyperlipidemia, proteinuria) is essential, and the use of angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and statins is common (5). Different medication schemes, including glucocorticoids, cytotoxic drugs, immunosuppressants, and biological agents are used to treat patients with CKD after assessing their renal pathologies and personal conditions (5). Moreover, if the kidney damage is secondary to other basic diseases, such as diabetes, it is necessary to control the primary disease (186). However, an ideal treatment plan has not yet been found, and the drugs used are usually accompanied by several side-effects, including digestive tract reaction, obesity, liver and kidney damage, bone marrow suppression, and reproductive damage; furthermore, the therapeutic effects may take weeks to months to manifest, which often leads to intolerance (187). About 25% of patients with CKD will eventually progress to ESRD within 20 years of diagnosis and need renal replacement therapy (4).

The evidence of this review reveals several beneficial effects of acupuncture on CKD and ESRD-related symptoms, and a summary of studies on acupuncture therapy in chronic renal injury, renal physiological function and ESRD-related symptoms is presented in Table 1. It is believed that acupuncture may have a significant impact on the risk nodes of the progress of CKD through multiple pathways, so as to improve the prognosis of patients with CKD. This is mainly realized through the following mechanisms: 1. reduced inflammatory reactions and protection of podocytes, mesangial cells, and endothelial cells from antioxidant stress; 2. delaying glomerular and tubular lesions by downregulating inflammatory factors to regulate relevant signal pathways, including NF-κB-related pathways; 3. reducing podocyte apoptosis and protecting the glomerular filtration membrane by reducing renal TRPC6 levels and maintaining podocyte structural proteins; 4. improving glomerular hemodynamics through blood pressure regulation systems (SNS, RAAS, etc.); 5. improving energy metabolism to regulate renal immune function *via* regulating enzymes involved in aerobic metabolism in mitochondria. The major mechanisms by which acupuncture can relieve ESRD-related symptoms are: 1. activating the descent inhibition system to relieve pain by regulating the release of bioactive chemicals, especially opioids; 2. regulating inflammatory cytokines to relieve chronic pruritus.

This review fully illustrates the advantages of acupuncture in treating CKD. First, acupuncture can act in cooperation with drug therapy to improve its the curative effects (18). Second, the potential mechanisms by which acupuncture may help in treating CKD are diverse; compared with single target therapy, acupuncture improves CKD prognosis through various pathways. Third, acupuncture is a simple supplementary therapy with mild side-effects, which prevent patients from taking additional drugs, especially opioids (161), to improve patient compliance. Fourth, the schedule of acupuncture treatment is flexible and varied (Table 1). Fifth, acupuncture has a wide range of applications with few contraindications and is suitable for the elderly and children (35, 188). Sixth, the cost of acupuncture in China is low, which most patients can afford regardless of economic status.

Furthermore, we focused on other methods that have the potential to help improve the quality of life or relieve symptoms of CKD, including taking TCM prescriptions and Chinese patent medicine, including *Tripterygium Wilfordii Hook. f.* and *Artemisinin*, which can effectively reduce albuminuria and protect kidney tissue (189, 190). However, the compositions of traditional Chinese herbs are extremely complex; moreover, patients with advanced CKD may suffer from electrolyte disorders due to metabolic issues. Therefore, more detailed studies and monitoring is required to ensure the safety of patients. The KDIGO guidelines suggest that proper exercise and dietary management, including low sodium, high-quality protein, and low-fat diets, can help improve patients' quality of life; acupuncture should also be recommended as an effective physical therapy (5).

There are some obvious limitations of this literature review. First, because of the involvement of various acupuncture points, complex physiological aspects, and differing patient characteristics and disease processes, acupuncture-based treatment of CKD is highly personalized, and the specific therapeutic mechanism and indications needs further study. Second, there is still a lack of large-scale, double-blind, multicenter, large sample size, randomized studies to verify the observed effects and provide a high-quality theoretical basis for them. Third, the mechanisms of acupuncture in improving ESRD-related symptoms, especially RLS and sleep disorder, cannot be clarified for now. Finally, the review could only cover studies that focused on therapeutic mechanisms that were not specific to renal pathology, on which there are very few studies. Some literatures mentioned renal interstitial fibrosis without specific pathological diagnosis. Only one clinical trial revealed the effectiveness of moxibustion on membranous nephropathy. Two animal studies mentioned focal segmental glomerulosclerosis (FSGS), one research revealed that moxibustion delay the progress of FSGS *via* alleviating podocyte injury, the other one did not mention the underlying mechanism.

5 Conclusions

This review suggests that acupuncture can be beneficial for CKD through several mechanisms, including oxidative stress inhibition, reducing inflammatory effects, improving

hemodynamics, maintaining podocyte structure, and increasing energy metabolism. In general, acupuncture has the potential to become a new, simple, safe, and inexpensive treatment modality that can be used to treat CKD, slow the progress of renal dysfunction, and improve patient symptoms. However, the review only covers non-specific therapeutic mechanisms, lacking content related to renal pathology due to a lack of studies on this topic. Moreover, it is unclear whether acupuncture can improve CKD with different pathologies, and rigorous clinical and mechanistic studies are required to design future protocols for the use of acupuncture in such cases. This could prove conducive to understanding the potential mechanisms involved in different renal pathological diagnosis as well as the impact that acupuncture may have on them.

Author contributions

All authors contributed to one or more of the following aspects of the manuscript: conception, acquisition of data, drafting, and revising the article. WZ and XL researched data and wrote the manuscript. XW and HM reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ilse Sofia Daehn,
Icahn School of Medicine at Mount Sinai,
United States

REVIEWED BY
Amir Shabaka,
Hospital Universitario Fundación Alcorcón,
Spain

*CORRESPONDENCE
Enrique Morales
emoralesr@senefro.org

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Lupus nephropathy beyond immunosuppression: Searching for nephro and cardioprotection

Enrique Morales[1,2,3]*, Justo Sandino[1,2] and María Galindo[2,3,4]

[1]Department of Nephrology, University Hospital "12 de Octubre", Madrid, Spain, [2]Research Institute of University Hospital "12 de Octubre" (imas12), Madrid, Spain, [3]Department of Medicine, Complutense University of Madrid, Madrid, Spain, [4]Department of Rheumatology, University Hospital "12 de Octubre", Madrid, Spain

Renal involvement in systemic lupus erythematosus (SLE) represents one of the most frequent organ manifestations, often leading to end-stage kidney disease (ESKD). Several therapies have been tested in patients with lupus nephritis (LN) to prevent further organ damage. The effectiveness of immunosuppressive therapy as a treatment for LN is abundant, supported by multiple clinical trials that have shown its efficacy in preventing the development of chronic kidney disease (CKD). In addition to immunosuppressive therapy, several traditional and recent therapies aimed at nephroprotection in patients with proteinuric chronic kidney disease are gaining importance in the setting of LN. Thus, immunosuppressive therapy should be accompanied by nephro- and cardioprotective measures to control cardiovascular risk factors and proteinuria to ensure a better renal prognosis. Despite this, the literature on these specific measures is relatively scarce, with recommendations focused on the blockade of the renin-angiotensin-aldosterone system (RAAS). This review explores the pharmacological options available for cardiovascular and renal protection outside the usual treatment schemes.

KEYWORDS

lupus nephritis, proteinuria, RAAS blockade, diuretics, lsglt2

Introduction

Systemic lupus erythematosus (SLE) is defined as a chronic autoimmune disease with alternating periods of quiescence and disease flares (1). Approximately 30% to 50% of SLE patients will develop some level of organ injury within five years of diagnosis and 50% or more within ten years of diagnosis (2).

SLE patients frequently develop lupus nephritis (LN) that can progress to end-stage renal disease (ESKD), with a risk between 10% and 30% at 15 years in patients with severe LN (classes III, IV, and V) (3).

According to the European Alliance of Associations for Rheumatology (EULAR) recommendations for disease management, the goals of SLE treatment are control of disease activity; prevention of flares and organ damage and, ultimately, prolongation of life (4). Treatment goals in patients with LN include preserving renal function and preventing ESKD; these outcomes can be assessed by renal biopsy and other clinical indicators of

damage, such as estimated glomerular filtration rate (eGFR) slope and chronic kidney disease (CKD) staging (5).

In addition to immunosuppressive therapy, all classical and modern therapies aimed at nephroprotection in patients with proteinuric chronic kidney disease are gaining importance (6). Some novel treatments like the use of finerenone or sodium-glucose cotransporter-2 inhibitors (SGLT2i) in combination with the classical renin-angiotensin-aldosterone system (RAAS) blockers are promising therapies (7). Patients with LN are excluded from studies with new nephroprotective agents, leading to a gap in knowledge about the effect of these drugs on LN. For this reason, knowledge of these new therapies outside the nephrological world may significantly impact the preservation of renal function.

Non-immunological factors for the progression of lupus nephropathy

By definition, all LN patients have CKD, but CKD progresses to ESKD in only some cases (3). Patients with LN who started life with a low number of nephrons, or have nephron loss beyond physiologic aging, have a shorter renal life span, especially in aging populations. Therefore, patients with LN and low birth weight or a previous episode of acute kidney injury are at risk for developing ESKD independent of LN disease activity. On the other hand, delay in diagnosis and adequate treatment, nonadherence to therapy, and, in the worst case, LN recurrence are factors that would lead to further nephron loss and further progression of CKD (8). On the other hand, some patients with adequate control of SLE activity may progress to ESKD after a single episode of LN, possibly due to the presence of high-risk genetic variants for CKD progression. For example, CKD risk variants of the apolipoprotein L1 (APOL1) gene are highly prevalent in afro-American individuals (9).

Classical nephroprotective treatment

SLE patients have a higher mortality rate than the general population, with infections, cardiovascular (CV) complications, and especially renal failure as the leading causes of death (10) SLE patients present both traditional (dyslipidemia, smoking, obesity) and non-traditional (proteinuria, inflammation) CV risk factors. It is known that dyslipidemia accelerates the progressive decline of renal function in patients with CKD (11). The latest KDIGO guidelines on lipids and CKD recommend regular evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) and to initiate statin or statin/ezetimibe combination on patients aged ≥ 50 with non-dialysis-dependent CKD or a kidney transplant (12). Evidence that statins may retard CKD progression in humans is insufficient, with different outcomes reported based on the type and dose of the statin used (13). These recommendations, although strongly evidenced-supported, cannot be extrapolated to patients with CKD and SLE since data on this group of patients Is scarce.

Moreover, glucocorticoid therapy, mainly when high doses are used for a prolonged period, increases bone loss, incidence of CV events and infections, risk of malignancies, especially non-Hodgkin's lymphoma, lung, and skin cancer (14–16). The use of hydroxychloroquine in SLE is widely extended since the benefits of this drug include lower flare rates and, particularly, lower incidence of CV events (17). Regular assessment of these risk factors and opportune treatment is crucial to avoid CV complications in patients with LN; some tools such as the Framingham risk score and the recalibrated SCORE prediction model are two widely used tools that provide estimates of the risk of developing CV events (18); however, these scales did not include lupus nephritis or steroid use into their models. Some studies (19, 20) show that the QRISK3 calculator could be more accurate in predicting cardiovascular events in SLE patients, recommending measures during the initial stages of disease.

Pregnancy in patients with LN is associated with increased maternal complications compared to the healthy population (21) Prompt contraceptive and pregnancy counseling are strongly advised in SLE patients of childbearing age. Furthermore, low-dose aspirin has been shown to have a protective effect in patients with SLE during pregnancy and reduce the incidence of CV events in patients with associated antiphospholipid syndrome (APS) (4).

The amount of proteinuria is a decisive factor in the prognosis of patients with LN. The goal is to achieve proteinuria <0.7 g/24h (or protein/creatinine ratio <0.7 g/g) within the first year of treatment and complete remission (proteinuria <0.5 g/24h or PCR <0.5 g/g) during the clinical course (4). Treating LN and proteinuria with RAAS blockade at maximum tolerated doses is recommended, complemented with a sodium-poor diet to optimize its effect (10). Moreover, the 2019 EULAR-ERA EDTA recommendations for the management of LN suggest that RAAS blockade is recommended (in non-pregnant patients) due to its anti-proteinuric and antihypertensive effects; with no specific recommendation for any particular drug, either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) (4, 6) In fact, recent studies suggest that early RAAS blockade introduction is associated with an earlier rate of glucocorticoid discontinuation (22). Kanda and collaborators demonstrated that proteinuria decreased after ARB treatment in 83% of the patients with LN (PCR decrease from 2530 to 459 g/g [P = 0.03]). In addition, serum albumin and cholesterol levels were significantly improved. Systolic blood pressure significantly decreased, with no symptoms of hypotension. The anti-proteinuric effect of ARB did not correlate with blood pressure reduction. Interestingly, higher total complement activity levels before ARB treatment were associated with a more significant reduction of proteinuria. These findings show that adding ARB would be a safe and effective treatment for LN with persistent proteinuria despite corticosteroids and immunosuppressive treatment (23).

The evidence on RAAS inhibition in recent immunosuppression-based trials shows that treatment in terms of nephroprotection is usually poorly optimized before induction therapy is initiated; both BLISS-LN and AURORA 1 trials, essential and recent studies on the use of belimumab and voclosporin on patients with LN, show that not all patients had RAAS blockade prior to randomization (66% of patients on the belimumab arm in BLISS-LN) (24, 25).

Additionally, we must remember that diuretics can be an essential tool to mitigate proteinuria, especially if combined with RAAS blockade. The use of thiazide diuretics can be particularly beneficial in patients on a high-sodium diet or as an add-on therapy in cases with significant residual albuminuria, with similar effects for thiazide-like agents. The role of loop diuretics as anti-proteinuric agents is not entirely clear, but

their mechanism to reduce proteinuria is probably related to RAAS blockade and intra-glomerular pressure reduction. Data on other diuretics like amiloride, acetazolamide, and triamterene as anti-proteinuric agents are partially clear (26).

The role of mineralocorticoid receptor (MR) antagonist (MRA) in treating proteinuric kidney disease is widely known and has been described extensively (27–29). Most landmark trials did not include patients with LN since active immunosuppressive treatment is a common exclusion criterion.

Evidence indicates that the use of spironolactone on top of ACEIs and ARBs induces a proteinuria reduction of approximately 30–40% (30, 31), with an initial decline of (eGFR) with subsequent stabilization (29). Hyperkalemia is a frequently feared side effect of MRA treatment, especially when combined with RAAS blockade. However, evidence supports that discontinuation of MRA after an episode of hyperkalemia is associated with higher mortality compared to continuing MRA therapy, an option to be considered, especially since the new potassium binders became available (32).

Non-steroidal anti-inflammatory drugs (NSAIDs) are a cornerstone therapy for several symptoms of SLE, although it must never be overlooked that NSAIDs are nephrotoxic. In addition, LN is a risk factor for NSAID-induced acute kidney injury, and NSAID-induced hepatotoxicity is increased in SLE patients (33). This makes it crucial to minimize or avoid using NSAIDs and other nephrotoxic agents in patients with SLE and established CKD, with special care on dose adjustment for several agents commonly used for nephro-protection. (Table 1)

Future perspectives in terms of nephro-protection in lupus nephritis

Finerenone

Novel MRA, like finerenone, are known to block MR-mediated sodium reabsorption and MR overactivation with additionally demonstrated anti-inflammatory and anti-fibrotic effects (34). Recent data from the FIDELITY pooled analysis of the FIDELIO and FIGARO trials found reductions in CV events and kidney failure outcomes with finerenone in type-2 diabetic patients with CKD. In fact, in the FIDELIO-DKD trial, finerenone was associated with a more significant reduction in albuminuria from baseline to month 4, which was maintained subsequently (35). These beneficial effects on reducing proteinuria and cardiovascular events may be extrapolated to patients with LN. However, there are no data on the use of finerenone in this specific population, so proper clinical trials are needed to establish accurate recommendations.

SGLT2i

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have recently been demonstrated to exert profound cardio and nephroprotection in large cardiovascular outcome trials (36). In patients with heart failure, independent of whether they have or not type 2 diabetes, SGLT2i reduces the progression of CKD and improves CV outcomes (36). Since many aetiologies of non-diabetic nephropathy are characterized by intraglomerular hypertension (37), we hypothesize that SGLT2i acutely decreases GFR and proteinuria in patients without diabetes at risk of progressive kidney function loss *via* a glucose-independent hemodynamic mechanism. Furthermore, distinct complications of SLE are also amenable to the therapeutic potential of SGLT2i, such as the increased occurrence of pulmonary hypertension, metabolic syndrome, and increased blood pressure. Patients with LN were excluded from such studies due to the potential necessity of acute immunosuppression (36).

Recently, we have published a pilot study in patients with LN on stable immunosuppressive treatment and non-immunosuppressive treatment with RAASi to whom a 10-mg dose of empagliflozin was added, obtaining a 50% reduction in residual proteinuria with minimal changes in eFGR and with few side effects (38).

TABLE 1 Commonly used drugs for nephro and cardioprotection in patients with lupus nephritis.

Drugs commonly used in patients with SLE	Special considerations on patients with CKD
NSAIDs	Avoid or minimize its use
Antimalarial (Hydroxychloroquine)	Dose adjustment might be necessary to avoid retinopathy.
RAAS blockers *ACEi* *ARB* *MRA*	Might induce AKI High risk of hyperkalemia and hypotension Special care in patients with known renal artery stenosis Hepatic toxicity
Diuretics	Might induce AKI Electrolytic disorders (hypokalemia, hypomagnesemia) High risk of hypotension
Metformin	Avoid when GFR is < 30 ml/min Risk of hypoglycemia and lactic acidosis
SGLT-2i	Avoid when GFR is < 25 ml/min. Risk of hypotension and diabetic ketoacidosis Risk of urinary tract and skin infections.
GLP-1RA	No dose adjustment is required but not recommended in patients on dialysis.

SLE, Systemic lupus erythematosus; CKD, chronic kidney disease; NSAIDs, Non-steroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; ACEi, Angiotensin-converting enzyme (ACE) inhibitors; ARB, angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonist; AKI, acute kidney injury; GFR, glomerular filtrate rate; SGLT-2i, Sodium-glucose cotransporter-2 inhibitors; GLP-1RA, Glucagon-like peptide-1 receptor agonists.

GLP-1RA

Glucagon-like peptide one receptor agonists (GLP-1RA) is a class B G protein-coupled receptor expressed in the pancreas and central nervous system but is also present in other organs such as the gut, kidneys, lungs, liver, heart, muscle, and peripheral nerves. GLP-1 increases insulin secretion in response to nutrients and suppresses glucagon secretion from pancreatic islet cells, reducing postprandial glucose levels (39).

Some studies suggest that GLP-1 RAs may benefit kidney outcomes, especially in improving albuminuria (40). The REWIND trial studied the effect of dulaglutide vs. placebo on the type 2 diabetic population. Only 7.9% of patients had microalbuminuria at baseline, and after a median follow-up of 5.4 years, dulaglutide proved to have a protective effect (HR 0.77, 95% CI 0.77-0.93; p=0.0004) for the appearance of new-onset albuminuria (41). Furthermore, in the AWARD-7 study, dulaglutide was shown to halt kidney disease progression and prevent the worsening of albuminuria in the diabetic population with CKD (42). As mentioned, proper clinical trials involving patients with LN are needed to establish accurate recommendations on using GLP-1 RAs as nephroprotective agents.

Others

Endothelin receptor antagonists (ERAs) such as atrasentan and eprosartan have been associated with renal protection when combined with RAAS blockade (43). A low dose (0.75 mg/d) of atrasentan has been shown to lower albuminuria by 36% without significant side effects in subjects with type 2 diabetes with CKD who were already treated with the maximal tolerated dose of ACE inhibitors or ARBs (44). The mechanism of their renoprotective effect is believed to be based on their vascular effects, which cause glomerular vasodilation, lowering the tubular load of albumin. Moreover, endothelin has been associated with renal inflammation; endothelin receptor blockade controls renal inflammation by moderating the inflammatory effects of albuminuria reabsorption. Furthermore, the endothelin system has been implicated in the deposition of collagen and fibrosis (45). This can be of particular interest to patients with LN.

Conclusions

Nephroprotection is a cornerstone in preserving renal damage in patients with lupus nephritis (Figure 1). In the search for comprehensive treatment, knowledge of the different therapeutic alternatives aiming at a double nephro and cardioprotection effect is crucial to avoid excessive immunosuppression and to achieve personalized and precise medical practice in our patients with lupus nephritis.

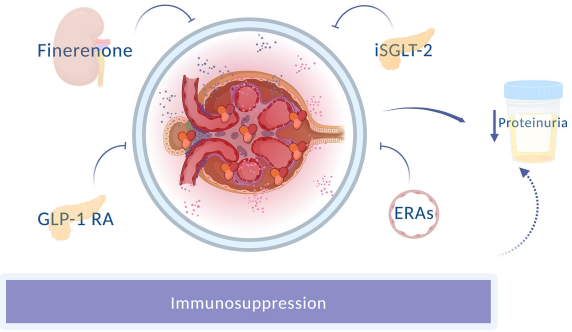

FIGURE 1
Novel nephron-protective strategies in lupus nephritis. Different drugs with an anti-proteinuric effect improve renal prognosis, apart from the usual immunosuppression. GLP-1RA, Glucagon-like peptide 1 receptor agonists; SGLT-2i, Sodium-glucose cotransporter-2 inhibitor; ERAs, Endothelin receptor antagonists.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Rafidah Abdullah,
Consultant, Putrajaya, Malaysia

REVIEWED BY
Matthew Aaron Sparks,
Duke University, United States

*CORRESPONDENCE
Urmila Anandh
uanandh@gmail.com

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The changing landscape in nephrology education in India

P. S. Vali[1], Namrata Parikh[2], Krithika Mohan[3] and Urmila Anandh[4]*

[1]Asian Institute of Nephrology and Urology, Hyderabad, India, [2]The Ottawa Hospital, Ottawa, ON, Canada, [3]Hosmat Hospitals India, Bangalore, India, [4]Department of Nephrology, Amrita Hospitals Faridabad, Delhi, India

Digital tools have revolutionized education in nephrology in India. All forms of in-person learning are moving online. Social media have taken over the world, with clinicians learning and promoting multidirectional education methods. E-learning is better equipped to keep up with the rapid pace of new knowledge generation and dissemination. The use of digital multimedia tools to enhance rapid learning is backed by science, viz., dual-coding theory. Digital tools such as Twitter, blogs, podcasts, YouTube, and Nephrology Simulator (NephSIM) have had an impact in facilitating nephrology education among medical professionals and the general public. Digital tools, such as NephMadness, have resulted in the gamification of nephrology learning. Social media usage by the nephrology community in India is growing at a rapid pace. Everyday Cases in Nephrology (#ECNeph), a monthly Twitter-based discussion focused on academically challenging clinical cases, has its origins in India. The Women in Nephrology, India (WIN-India) initiative is very active in facilitating digital education in India and has, in a short space of time, created phenomenal momentum. Furthermore, non-governmental organizations in India, such as the Kidney Warriors Foundation and the Multi Organ Harvesting Aid Network (MOHAN) Foundation, have successfully tapped into social media to educate and aid kidney disease patients. All technologies come with some drawbacks. Despite their acceptance and validation, digital tools have their own pitfalls. These relate to (1) accessibility and connectivity, (2) accuracy of the scientific information, (3) social media noise, and (4) patient privacy. All pitfalls of digital education can be addressed by avoiding excessive social media overload and adopting an appropriate peer-review process. It is advisable to seek written consent from patients whenever patient data are posted online, to avoid privacy issues.

KEYWORDS

social media, Twitter, digital tools, nephrology education, pitfalls

Introduction

The internet has played a pivotal role in revolutionizing the world and transforming it into a global village: almost 60% of the global population has access to the internet (1). Digital tools have revolutionized education, especially since the emergence of the COVID-19 pandemic. Books are being replaced by e-books, lectures by YouTube videos, and regular

in-person discussions by podcasts. Digital tools, especially social media, have taken over the world, with educators developing innovative teaching methods. The target audience of these tools is not only healthcare workers, but also patients and caregivers. With an estimated average daily usage of 147 minutes per person, social media has reinvented the way people communicate and decipher information (2).

Social media are increasingly being used for e-learning, and may be better equipped to keep up with the rapid pace of new knowledge generation and dissemination, as well as the desire for learning at any time and from any location (3). On social media, a network of educators contribute to digital sources by explaining concepts, answering questions, or creating durable content in a variety of formats, whereas others serve as curators, organizing content and directing people to the right answers (4). In a systematic review, it was found that use of social media was associated with improved knowledge, attitudes, and skills (5). The use of social media was also reported to promote collaboration, feedback, and professional development.

This shift to e-learning has also paved the way for the introduction of a diverse set of digital resources, which can be used as educational tools. The medical profession is no exception when it comes to capitalizing on these digital tools to harness mutual learning and educate the public (4).

Several scientific organizations, such as the International Society of Nephrology (ISN) and, locally in India, Women in Nephrology (WIN) and the Indian Society of Organ Transplantation (ISOT), have dedicated social media teams covering their conferences on platforms such as Twitter, Facebook, YouTube, and Instagram, which enables them to reach a wider audience.

Why digital tools?

The use of a digital multimedia methodology as a learning tool is based on dual-coding theory (6). This theory states that the working memory of a human brain has two parallel channels with regard to information acquisition, processing, and retention: the visual/pictorial channel and the auditory/verbal processing channel. The efficacy of information processing and retention is amplified when both of these channels receive input. Therefore, the purpose of integrating digital tools into medical education is to enhance the efficacy of learning by incorporating both visual and auditory inputs into the conventional medium of teaching.

Digital tools in nephrology education

The nephrology community took to social media with alacrity, and over the years many platforms have been used to propagate nephrology knowledge. These initiatives have met with considerable success. Presented below is a brief review of the digital tools of greatest importance in the field of nephrology education.

A: Twitter

Twitter is a digital micro-blogging platform that allows users to post text content in the form of a tweet, which has a maximum character limit of 280 characters. The ability to post text and multimedia content in a tweet is well suited to the delivery of education in small, easily consumed segments. The medical profession quickly adopted Twitter as a medium for educational tools and professional networking. A series of tweets threaded around a core theme constitutes a "tweetorial." These tweetorials have evolved into interesting educational compilations that provide on-the-spot comprehensive educational content in an "easy-to-grasp" format (4).

Hashtags are also used to maximize Twitter's potential. A hashtag is used to categorize content in a consistent way. For example, searching for #NephPearls in the Twitter search window will instantly capture and display a wealth of nephrology-related information. In addition to allowing for more focused browsing of educational content, hashtags are used to discuss scientific papers in online journal clubs and to tweet conference-related content. However, in order to reap the greatest benefit from hashtags, one must use popular hashtags. The ability to conduct polls is also a convenient Twitter tool and aids in the gamification of the educational content (7). In addition, @Ask Renal is an innovative Twitter account that provides users with quick answers to questions related to renal sciences. It is a crowdsourced Twitter bot that will automatically propagate any tweets with the hashtag #askrenal (8).

The best part of Twitter is its interface, which allows the expression of content with a limited number of characters and real-time synchronization. These two features aid in the creation of conversations almost in real time, which in turn has made Twitter a dependable tool for hosting real-time scientific conversations and online journal clubs.

B: Blogs

A blog is a web page with content that is displayed in reverse chronological order and is expected to be more dynamic than a website (9). Every blog has an inbuilt search window that displays all the content related to the search phrase, thereby facilitating the quick retrieval of the content being sought (10).

The *American Journal of Kidney Diseases* (AJKD) blog (https://ajkdblog.org/), maintained under the aegis of the AJKD, is a content-loaded blog. The objective of this blog is to present the journal's practice-changing content in an engaging format. Another feature of the AJKD blog is the Atlas of Renal Pathology, a rich collection of

renal histopathology topics presented in a systematic and lucid format.

Another noteworthy renal blog that deserves special mention is the Renal Fellow Network (RFN). It is a first-of-its-kind, peer-reviewed online forum that is contributed to and maintained by nephrology fellows, and is supervised by faculty advisors (11). It is intended to foster interest in the field of nephrology. The RFN blog has a vast number of bite-sized posts on subjects across clinical nephrology and established a partnership with the American Society of Nephrology (ASN) in 2018 to expand its reach. The Kidney Reports Community is another useful nephrology blog that facilitates the publication of educational content in a visually appealing format (12).

C: Podcasts

Podcasts are themed collections of digital audio files that are made available for downloading and listening. The ASN podcast hosts interviews with experts, with a focus on advances in nephrology. The National Kidney Foundation's podcast series "Life as a Nephrologist" focuses on the decision to pursue nephrology as a career and the excitement that comes with it. "Freely Filtered" is a Nephrology Journal Club (NephJC) podcast series and presents a twice-monthly summary of the online journal club. Other interesting nephrology podcasts include "Kidney 360", "Channel Your Enthusiasm", "The Nephron Segment", "NephTalk", "Throwback Thursday with Dr. Fred Silva", and "Kidney Essentials".

D: YouTube

YouTube is a video-on-demand hosting platform that has had an unprecedented impact in connecting multimedia content with the human race. Not only is it the second most commonly visited website, but it also has a robust user base of more than 2.5 billion monthly users and records more than 1 billion hours of video-watching each day (13).

YouTube is being utilized by educators in nephrology to educate patients, the public, and health professionals, including nephrologists (14). An early such channel was "Nephrology on Demand", which served as an educational resource for nephrology caregivers and patients. The Glomerular Disease Study & Trial Consortium (GlomCon) YouTube channel is a popular forum that aims to provide a unified platform for all clinicians and pathology researchers interested in glomerular disorders.

It should be noted that, although YouTube is flooded with a wide range of patient education content, very little of it is of high quality. In a study in which 295 peritoneal dialysis videos were evaluated systematically for the quality of their content, only 17% of the videos targeted at patient education were of reliable quality (15).

YouTube has enormous promise as a digital instructional resource, given its accessibility and popularity. However, in a manner similar to the existing popular YouTube Kids app, it is time to develop a subsidiary scholarly section that will permit the display of multidisciplinary academic content in a focused manner. In addition, the time has come for the nephrology community to consider generating patient-centric YouTube videos in multiple local languages.

E: NephSIM

NephSIM is a digital educational simulator tool (www.nephsim.com) that was launched in 2018. It is essentially a mobile-optimized website that aims to facilitate case-based teaching (16). It is based on a framework of interactive cases and iterative feedback. On this platform, a real-life case will be presented in a systematic pattern in which it is ultimately funneled through a differential diagnosis pathway, following which the final diagnosis and management are discussed. In a survey assessing the impact of NephSIM on academic learning in nephrology, 96% of respondents reported that they enjoyed using NephSIM, and almost all of them intended to continue using this tool in the future (16).

F: NephMadness—the power of gamification

NephMadness is a popular initiative that uses a gamification strategy to disseminate nephrology information. In this virtual competition, 32 nephrology concepts compete against each other (17). These ideas are chosen to be representative of the most important ideas and scientific papers from the past few years. Structured along the lines of the college basketball playoff model, NephMadness is a single-elimination contest in which concepts compete against one another and participants predict the winning concepts. A distinguished panel of judges selects the winning concepts, and contestants see how their predictions compare. The objective is to facilitate learning about advances in nephrology. The roadmap of NephMadness is structured so that the contestants and their advocates create propaganda on various social media platforms, such as Twitter, the AJKD blog, and podcasts, to increase awareness on their topics of choice. In this way, this virtual gamification strategy amplifies and propagates nephrology education.

The free open-access medical education (FOAMed) community for nephrology has made NephMadness an annual event for the past 10 years. Every year, over a thousand people enter the competition to engage in fun-based learning (18).

G: Other digital tools

Visual abstracts have revolutionized the way in which work published in medical journals is delivered and disseminated. First introduced by Professor Andrew Ibrahim, visual abstracts aid the viewer in rapid screening of the available scientific articles in a visually appealing format, and can persuade viewers to embark on a deeper

analysis of a particular work. Over the past 9 years, all major nephrology journals have adopted visual abstracts as a standard digital supplement to their published content (19, 20).

Platforms such as Facebook Live and Zoom allow audiences to interact with the educator and have great potential to facilitate education of target audiences, especially professional peers, patients, and caregivers, in a flexible way (21). Questions are answered, concepts are explained, and expert feedback is provided to learners, thus providing a digital mentorship (4). Instagram and LinkedIn allow two-way conversations, although not in real time. The major digital tools in nephrology education are depicted in Figure 1.

Digital education of patients and caregivers

Over 850 million people worldwide are affected by chronic kidney disease (CKD) (22). Digital education has been used to create awareness of CKD in the general population. Freely available applications (apps) such as the app by the Renal Health Project aim to help patients undergoing dialysis or a renal transplant better understand their disease, organize their treatment, and control their tests, diet, and all aspects of their therapy (23). The Renal Health Project also provides regular health education for patients through social networks such as YouTube and Instagram. This helps them learn more about all aspects of their kidney disease, including risk factors, causes, prevention, treatment, dialysis, and transplantation. Through these projects, patient self-care and management have been shown to improve. Several phone apps, such as "Care after Kidney Transplant", "Kidney Diet", and "Find My Dialysis", are available to help disseminate information to patients (24).

Several organizations, such as the Kidney Warriors Foundation, which is an India-based network of kidney patients, caregivers, healthcare professionals, and social workers, utilize social media widely to advocate for policies that improve access to quality healthcare for patients with kidney disease (25).

Nephrology and social media—the Indian experience

In January 2022, the number of internet users in India (that is, the number of people with access to digital information) was estimated at 658 million, about 47% of the Indian population. Various social media platforms, such as Facebook, Twitter, Instagram, and LinkedIn, enjoy tremendous popularity in India. In January 2022, of these 658 million citizens with internet connectivity, 467 million were actively participating in social media (26). These statistics demonstrate the immense potential of social media in India. If this is harnessed effectively, it could have far-reaching consequences.

Healthcare professionals in general, and nephrologists in particular, have come to realize this potential and, in recent years, have brought about a minor revolution in our country. Social media have eliminated geographic barriers, and Indian nephrologists have taken advantage of this. For example, the International Society of Nephrology has a dedicated social media team that includes many nephrologists of Indian origin. They have worked together on several occasions and published their experiences (27–29).

The use of online digital tools in nephrology education in India began with the Twitter-based chat "Everyday Cases in Nephrology" (#ECNeph), where academically challenging real- world cases are discussed, with strict measures to ensure patients' privacy. This initiative quickly gained popularity and won the NephJC Kidneys award for Nathan Hellman Social Media Project of the Year 2017 (30). Now in its fifth year since its conception, #ECNeph continues to draw audiences from several countries for its monthly discussions (31).

"Last Month in Nephrology" is a similar brainchild of Indian nephrologists. It takes the form of a newsletter that provides

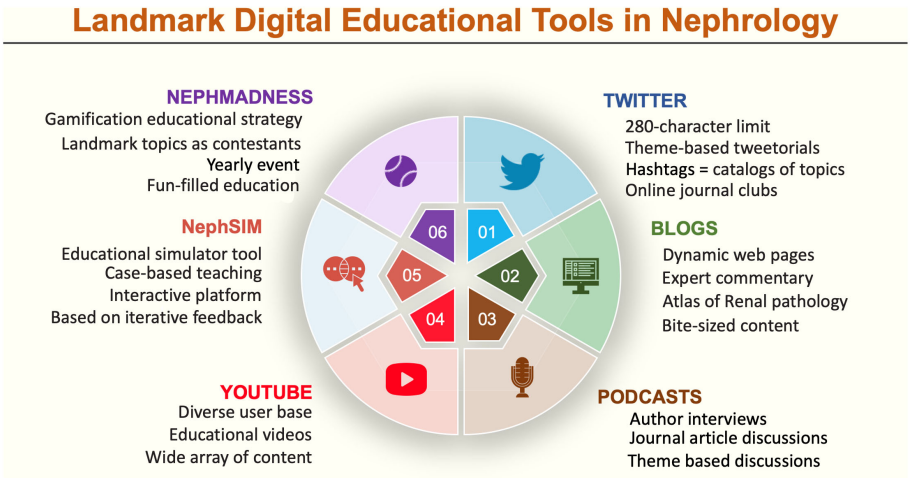

FIGURE 1
Landmark digital tools in nephrology.

commentary on recently published evidence. The aim is to change the way nephrologists approach patient care, armed with recent advances in their subspecialty (32).

Indian nephrologists were among the first to use the services of dedicated social media teams to report on their conferences. In 2017, the Association of Vascular Access and inTerventionAl Renal Physicians (AVATAR) conference attracted extensive social media coverage (33). Since then, numerous conferences have achieved excellent coverage in the form of live tweets and livestreams (34, 35).

The Women in Nephrology, India (WIN-India) initiative, launched in 2021, aims to offer mentorship to many aspiring early-career nephrologists. Since its launch, WIN-India has successfully organized several impactful teaching activities. Recently, it held its first international conference Women IN Nephrology-India Conference (WIN-ICON) as a hybrid program, where female nephrologists in the early stages of their careers were given the opportunity to share the stage with speakers of international renown. This is a good example of how social media can bring together mentors and mentees from different corners of the world.

In India, social media tools have also been successfully used for advocacy, especially in the area of organ donation. The Multi Organ Harvesting Aid Network (MOHAN) Foundation in India utilizes Facebook as a channel to drive organ donation. Many non-governmental organizations use social media to create awareness of organ donation. All these organizations practice a certain amount of tact and discretion in their activities, to avoid the spread of misinformation. In 2021, Basu et al. created "best practice" recommendations for social media use concerning organ donation (36). These guidelines can serve as a foundation for the use of social media for advocacy of other initiatives as well.

Pitfalls of digital education

It is also important to realize the tremendous impact of social media and the implications of social media misuse. The message that can be disseminated to 50 million people via television over 13 years can be disseminated through social media to the same number of people in 3 months. (37) This makes it very important to maintain a strong sense of responsibility and restraint while utilizing these apparently "fun" tools, and to be aware of the pitfalls of this social media. These pitfalls are summarized in Table 1.

In response to this issue, the Nephrology Social Media Collective (NSMC) provides a dedicated year-long internship promoting the effective use of social media, which alerts its students to the pitfalls of social media (38, 39). Some of the leading names in the Indian social media scene have participated in this program and now hold important positions in the faculty of the NSMC.

Future directions

While Indian nephrologists have been quick to engage with social media, there still appears to be a significant gap between its potential and the extent to which it has been harnessed. Possible reasons include a lack of awareness and interest. The near absence of formal peer review for the majority of posts is also a concern. Clearly, all these lacunae will have to be addressed before we can move forward as "digital" nephrologists. Furthermore, digital tools have been proven to increase treatment adherence in a few non-renal chronic disorders (40). Therefore, it would be prudent to develop such digital tools and algorithms aimed at enhancing treatment adherence among patients with chronic kidney disease.

TABLE 1 Pitfalls of social media use.

Pitfalls	Comments
Accessibility, connectivity, and adaptability	40% of the world still lacks basic internet facilities (e.g., countries with lower socioeconomic status and remote places). Digital tools are popular among the younger population, but elderly people may still hesitate to be a part of this revolution. There are many who are not willing to do away with traditional educational training.
Accuracy of scientific information	Traditionally, data undergo peer review by experts in the field before publication. With digital education, this is not the case; the accuracy of the information can be questioned. Bias may occur in the form of opinions and inaccuracies. Exceptions exist, such as NephJC and NephMadness, which are internally peer reviewed. Large numbers of "fake messages" are circulated on social media.
Social media noise	Constant buzzing and pinging of posts, notifications, and messages leads to anxiety and exhaustion. This can cause time to pass without awareness, resulting in anxiety and exhaustion (31). Social media use can result in a sense of unhealthy competition and can increase peer pressure as users are exposed to a high volume of knowledge.
Patient privacy	Infringement of patient privacy is a major concern in the evolving digital world. Often, patient information is shared in order to disseminate knowledge to learners (often without consent).

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All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Lily Mushahar,
Tuanku Ja'afar Seremban Hospital, Malaysia

REVIEWED BY
Eoin Daniel O'Sullivan,
Royal Brisbane and Women's Hospital, Australia

*CORRESPONDENCE
Mythri Shankar
mythri.nish@gmail.com

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The evolution of social media in nephrology education: A mini-review

Mythri Shankar[1]* and Matthew A. Sparks[2,3]

[1]Department of Nephrology, Institute of Nephro-urology, Bengaluru, India, [2]Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, NC, United States, [3]Renal Section, Durham VA Health Care System, Durham, NC, United States

Social media is defined as "a group of Internet-based applications that build on the ideological and technological foundations of Web 2.0, that allow the creation and exchange of user-generated content". Social media can be used in medical education to enhance knowledge sharing among peer groups and the public in general. The internet revolutionized learning by allowing easier dissemination of knowledge that did not depend on printing and physical distribution of books, journals, or magazines. According to a report from 2018, 95% of students have access to smartphones and 45% are online at any given time. Social media platforms are powerful tools to spread knowledge by the way of stories, videos, and educational games. Both formal and informal learning can be achieved with the use of social media. The microblogging website Twitter has become a popular social media platform by many in medical education including the nephrology community. Twitter, for example, is used to build communities, discuss journal articles, inform the community of conferences, share infographics and visual abstracts of original research work. As an example, it can be difficult for women in nephrology to connect and travel to make a physical presence. The use of social media allows women to connect *via* webinars and Women in Nephrology (WIN) India live Twitter chats. Thus, social media can help facilitate networking and collaboration with nephrologists all over the world. Social media has limitations as well. Insensitive posts can have a detrimental effect on one's career. A survey has shown that increased use of social media can contribute to addiction, anxiety, diminished self-esteem, and even depression. Hence, in order to effectively use social media to contribute positively to one's career, we recommend considering the positive and negative aspects of social media.This review will discuss the various social media platforms and how they have been applied to nephrology education.

KEYWORDS

blogs, Twitter, Facebook, medical education, social media

Introduction

The world has continued to embrace digitalization and the internet. Social media platforms such as Facebook, Twitter, Instagram, YouTube, and TikTok are a part of daily routine and thus intertwined in the social fabric of lives. As of 2021, 4.26 billion people were using social media worldwide, which is projected to increase to 6 billion by 2027 (1). Today, 72% of Americans and 47% of Indians use some form of social media (2, 3). Social media has become a de facto town square where unique ideas are discussed, debated, and disparate groups are able to come together and build like-minded communities. Moreover, social media has given a voice, diminished barriers, and resulted in more equitable opportunities. One of the advantages of social media is that it empowers the end user to share, discuss, and educate. Thus, social media has dismantled the traditional hierarchical approach to education, including medical education, where only the select few could teach *via* textbooks, at conferences, or in journal articles. Social media allowed for anyone to join the conversation. An educational needs assessment of US nephrology fellows in 2021 showed diminished use of traditional educational resources and a greater use of digital free open-access medical education (FOAMed) resources from 2016 to 2021 (4). Thus, showing the transformation that has occurred in nephrology education over the last decade.

The ubiquitous spread of smartphones and increasing access to the internet in remote rural areas has allowed medical education *via* social media to spread throughout the world. The coronavirus disease 2019 (COVID-19) pandemic further accelerated the use of social media to share medical information and discuss the fast-paced and ever changing information regarding the pandemic. In parallel, there was an immense increase in the submission of papers to preprint servers which ignited public discussions and peer review on social media platforms like Twitter, blogs, podcasts, and YouTube were the norm (5). However, social media has both positive and negative effects. Here we discuss the influential role of social media in education and its pitfalls.

Social media can empower students, teachers, and patients to build a community and share information. Moreover, social media can allow people to connect and learn from other groups typically siloed in different disciplines and institutions. According to a report, 96% of students with internet access use at least one social media platform for educational purposes (6). The nephrology community has embraced social media over the last several decades (7).

Traditionally, nephrology has been identified as filled with challenging concepts (8). The standard teaching is by didactic lectures, which have formed the backbone of medical education, are often ineffective, passive, and fail to achieve widespread dissemination (9). Active learning techniques have the potential to provide in-depth comprehension and better concept retention (10–12). Bonwell and Eison have defined active learning as "involving students in doing things and thinking about the things they are doing" (12). Social media is one of the promising platforms for implementing active learning in nephrology education.

Social media

Social media is a collective term for internet-based applications and websites focusing on interaction, communication, sharing content, and collaboration. In the early 2000s, the advent of Web 2.0 allowed users to interact and collaborate in a virtual community as creators of user-generated content. Throughout the years social media platforms have been created to allow individuals to stay in touch with family, friends, and the larger community. Businesses use social media platforms to promote their products and track customer insights. There are various social media platforms with unique attributes. Facebook, launched in 2004, is a social networking website with the largest number of users worldwide. Meta, the umbrella company, now owns Facebook, Instagram, and WhatsApp. Registered users create their profiles, upload photos and videos, and send messages to keep in touch with their community. However, in order to follow an individual on Facebook, both parties must accept the invitation. YouTube, (founded in 2005) a social media platform for individuals to upload original videos. It is currently the second most commonly used platform. WhatsApp (2009) is a multi-platform messaging application that allows users to share photos, videos, text messages, and their status. It works on a wide range of platforms and is an inexpensive way to connect with people across the globe. However, WhatsApp is a closed group of individuals, thus limiting the ability to disseminate information widely. Instagram (2010) is a free photo and video sharing application where registered users share photos or short videos with their followers. They can also view, like, and comment on the photos or short videos shared by their friends. While video, and photos can be shared widely, two-way conversation is limited. TikTok (2011) brands itself as "the leading destination for short-form mobile video" to inspire creativity and spread joy. Pinterest (2010) is a go-to place for rich visuals. Twitter (2006) is a micro-blogging site and undoubtedly the birthplace of nephrology education. Users interact with short messages that have a 280 character limit called "tweets". The unique aspect to Twitter is that you are able to follow individuals without the other person's permission (unlike Facebook). Thus, allowing for more diverse followers and instantaneous adding and deleting of one's social media feed. Twitter allows its users to participate actively or passively in the learning process. Users can passively view others' tweets or connect and produce their own content. The content is free, real-world, dynamic, original, and diverse. This is directly opposite of a textbook, which is reviewed, oftentimes already outdated, and comes at a cost. The content on Twitter is unpolished making it more real-world, however, users can link to the primary journal articles. Twitter provides an instant audience with multiple users providing feedback on the content posted enriching the learning process (13, 14).

Free open-access medicine education (FOAMed) is the primary product of Web 2.0 with many forms such as discussions (on Twitter), podcasts (audio content), live conference tweeting, visuals (Twitter, Instagram, Facebook, etc), video content (YouTube), and essays (blog posts). Social media also simplifies collaboration among healthcare workers around the world (15) (Figure 1).

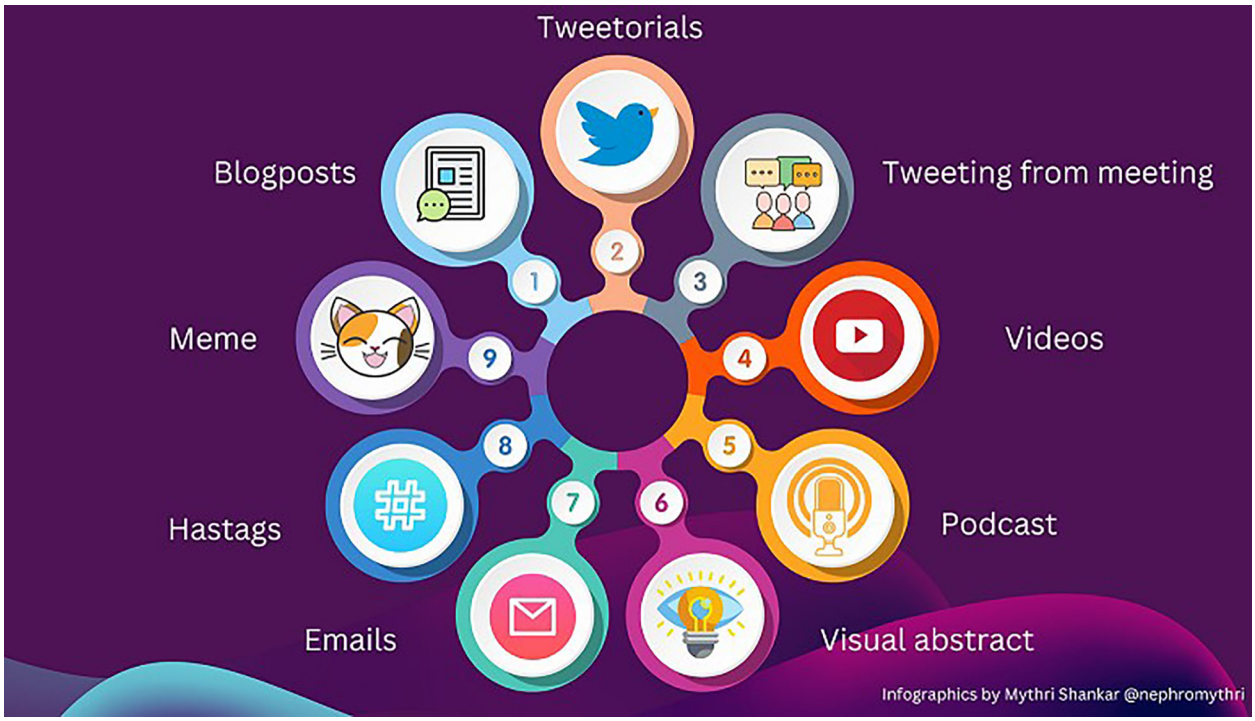

FIGURE 1
Various modes of social media.

Blog posts and Tweetorials

The term "blog" was first coined in 1997 by Peter Merholz who shortened the term web log to blog. A blog is a user generated website used to share short (or long) articles with no publishing paywall or impediment to publishing. Blogs may or may not be peer reviewed. However, the comment section serves as a peer review forum. A blog is a great starting point to keep up with the latest developments and innovations in the field. It allows the user to update the contents by just uploading and attaching files to it. A blog can become interactive if the author allows readers to comment. Posts are archived and organized in reverse chronological order, so the latest ones are visible first to the readers. The Renal Fellow Network was one of the earliest blogs (originally hosted by the Google platform, Blogger now on Wordpress) in nephrology, started by the late Dr. Nathan Hellman in 2008 as a nephrology fellow (16). The content is peer-reviewed by a team of nephrologists and fellows before publication. Glomcon pubs is another blog, where the content focuses primarily on glomerular diseases and is peer-reviewed by editors before publication. Glomcon pubs is an online educational library of blog posts, infographics, and short videos catering to glomerular diseases (17). A few other nephrology blogs of interest for nephrologists are Precious Bodily Fluids by Dr. Joel Topf (18), Nephron Power by Dr. Kenar Jhaveri (19), The Nephrologist by Dr. Vanessa Grubbs (20), the NephJC blog (21), and Landmark Nephrology (22). These websites were the earliest meeting places for nephrologists which invited debates and discussions. Many of these discussions moved to Twitter in ~2010. The tweets were sporadic and displaced. Hence, NephMadness was created as an attempt to focus the conversation during a discrete time point. NephMadness is an online interactive educational tool based on a single elimination tournament occuring during the month of March each year. Similar topics are pitted against each other, and a winner is chosen by a blue ribbon panel of judges. Topics are debated on social media and winners and losers and named, sparking more debate online (23). NephMadness uses the entire gamut of FOAMed; blogs, Twitter and tweetorials, Instagram, Facebook, visual abstracts, memes, podcasts, and emails list serves.

As mentioned above, Twitter has been a popular social media site for nephrology education. Twitter currently has a character limit of 280, along with the addition of hyperlinks, hashtags, pictures, and videos. Producing high-quality content in 280 characters is challenging. To overcome this, the tweetorial was developed. A tweetorial is a combination of tweets threaded (attached) together to form a series of tweets in the form of a tutorial, thus called a Tweetorial. It is defined as a "collection of threaded tweets aimed at teaching users who engage with them" (24). They help understand the pathophysiology and mechanism of the disease by answering the "why" question, which increases readers' curiosity. The tweetorials may include polls, links to primary resources, graphics, and short one-minute videos to make them more engaging (25).

Twitter hashtags

With a tsunami of information and tweets available on Twitter, it becomes difficult to search for a topic of interest. Hence, tweets have hashtags for categorization. For example, #NephMadness, #ISNwebinars, #NephPearls, and so on (26). The use of hashtags aids in categorization of the content which makes it easy to search.

#AskRenal is a popular hashtag created by Nephrology Social Media Collective (NSMC) faculty, which can be used to ask any nephology-related query. The @AskRenal Twitter handle is a bot programed to search for any tweets using the #AskRenal hashtag (27). The @AskRenal Twitter account then retweets the original tweet containing the #AskRenal hashtag to the entire nephrology community on Twitter. Since having a large number of followers is crucial for conversation and thus is an impediment to joining Twitter, The @AskRenal bot allows for individuals who are new to Twitter and have a small number of followers to receive high quality answers to queries. An analysis of tweets using the #AskRenal hashtag demonstrated that users who tagged tweets with the #AskRenal hashtag resulted in high yield referenced answers that were quickly replied to and were not dependent on follower count (27, 28).

Nephrology Journal Club (NephJC) is a biweekly nephrology online journal club that occurs on Twitter. It is an hour-long discussion about the latest literature occurring in two time zones. A blog post serving as an editorial is published before the discussion accompanied with a visual abstract. Anyone can join the discussion by using the hashtag #NephJC. Often, the author of the publication participates in the chat. Users directly post queries related to the study and get instant answers. Regular participation in journal clubs helps to build networking relationships and collaboration (22). Many NephJC chats are then featured as a publication in the journal *Kidney Medicine* (29, 30).

Everyday cases in nephrology (ECNeph), using the hashtag #ECNeph, is a discussion of everyday cases in nephrology by nephrologists in India and across the globe. A fascinating case history slowly unwinds, keeping participants involved with active discussion about the case. It is a monthly, hour-long discussion on Twitter. Participants can participate and discuss using the hashtag #ECNeph (31).

Twitter polls

Embedded polls allow for participants to interact with tweets. Several examples in nephrology have successfully used Twitter polls to teach. The editors of NephSIM used Twitter polls to teach acid-base disorders and examples of others using them for point of care ultrasonography in nephrology (32).

Tweeting the meeting

Prior to 2017, conference content at ASN Kidney Week was limited to people who could physically attend, which was difficult due to financial constraints and geographical distance. Moreover, many conferences had strict policies that prohibited sharing of meeting content outside of the venue. This changed in 2017 as a result of policy change originating from the ASN Media and Communications Committee (33). This ushered a shift in which many conferences followed suit, actively encouraging the sharing of conference presentations. Thus, many conferences now use hashtags to increase engagement and enhance dissemination. Name tags are now provided with Twitter handles. A person attending one session can now follow what is happening in the other session by following the hashtag of the conference name (#KidneyWk for example). Those who are far away and cannot attend, can just follow the tweets with the help of conference hashtag and stay connected and uptodate with the latest innovations in the field. Some examples are #ISNFrontiers #ISNWCN #ERAEDTA #KidneyWk, #NKFClinicals, #KIDNEYcon (33, 34).

Video contents

Video contents in the form of lectures, chalk talks, live and recorded webinars are accessible from YouTube and Vimeo. Glomcon has a web-based, clinical video case conference with peer group discussion involving nephrologists, nephropathologists, trainees, basic science, and clinical scientists (35). In collaboration with other societies, WIN-India, organizes live webinars, panel discussions, and debates regularly which gives an opportunity for live participation and the videos are also posted YouTube for later consumption (36, 37). WIN India strives to support women to advance their careers by providing mentorship, promoting research and collaboration (32). ISN conducts a Nuances in Nephrology live webinars on nephrology topics where the members can interact with the expert speaker and clarify the queries (38). Similar websites include NephroPOCUS.com (39) which advocates for point of care ultrasound based physical examination, "Washington University in St. Louis nephrology teaching series" (40) and "Arkana Live" (41) - videos that discuss nephropathology, "John Roberts" (42) videos on YouTube - a series for pencasts catering to medical students and internal medicine residents.

Podcasts

It might take a lot of work for a busy nephrologist to find time to read articles, journals, books, and blog posts to stay up-to-date. With access to any personal digital device, one can access a universe of podcasts at one's fingertips. Podcasts are a very efficient way to consume information while you are on the go - during a commute to the workplace, during a lunch break and in between meetings (43, 44). There are several podcasts for nephrologists to choose from are listed in the Table. Additionally, ISN is using Twitter space to discuss high yield nephrology topics with experts, which can be attended by any of the registered Twitter users (Table 1).

Visual abstracts

A visual abstract is a visual summary of key points of the journal article. Similar to the abstract section of a journal article, it summarizes the article with essential points. The purpose is to create interest in readers to read the full article. The visual abstract is not a substitute for reading the full article. In the fast-moving digital world, we have just a few seconds to capture the audience's attention,

TABLE 1 List of Nephrology Podcasts.

Podcast Name	Launch Date	Group	Subject
ASN Podcast	2009	ASN	General Nephrology, Policy
CJASN	2017	ASN	Nephrology Advances
The Sediment	2017	American Society of Pediatric Nephrology	Pediatric Nephrology
Throwback Thursdays	2017	Arkana, Fred Silva	Nephropathology, History of Nephrology
NephTalk	2017	Satellite Healthcare	General Nephrology
Life as a Nephrologist	2018	NKF	Nephrology Careers
Freely Filtered	2019	NephJC	Nephrology Advances
Global Kidney Care	2020	ISN	General Nephrology
Kidney360	2020	ASN	Nephrology Advances
JASN	2020	ASN	Nephrology Advances
Kidney Essentials	2021	Sarah E Young, Sophia L Ambruso, Judy Blaine	General Nephrology
Channel Your Enthusiasm: The Burton Rose Book Club	2021	NephJC	Acid Base, Electrolytes, General Nephrology
Nephrology Nursing Perspectives	2021	ANNA	Nephrology Nursing
Fast Facts Nephrology	2021	Karger	General Nephrology
NANT	2021	National Association of Nephrology Technicians/ Technologists	Nephrology Technicians
The Nephron Segment	2022	Samira Farouk, Matthew A. Sparks, Sam Kant, Elinor Mannon	General Nephrology
The Kidney Chronicles	2022	Emily Zangla, Annie Kouri	Pediatric Nephrology
Kidney Commute	2022	NKF	General Nephrology
Let's Talk About Kidneys	2022	Dallas Nephrology Associates	General Nephrology
The PD Exchange	2022	Peritoneal Dialysis International	Nephrology Advances, Peritoneal Dialysis

and high-impact visual abstracts serve this purpose. A study by Ibrahim et al., in 2017 showed that visual abstracts had 7-fold higher impressions and 3-fold higher website visits compared to text-only tweets (45). Oska et al. conducted a prospective case-control cross over study where 40 research articles were tweeted in 3 formats; citation only, citation with key figure, and citation with visual abstract. The results showed that tweets with visual abstracts had twice as many article views as those that contained citations alone and citations with key figures (46).

Emails

Email listservs are one of the first forms of two-way real time communication that developed between educators in nephrology (47). One of the first examples was the ASN Renal Educators Listserv was started in 2011 as a way for educators to communicate and share ideas (48). Even though it is an older technology, of late, it has been increasingly used to deliver newsletters directly to the recipient. One need not search the internet for content; the blog posts get directly delivered to the subscriber's email account. The release of new episodes of podcasts, reminders of upcoming webinars, publications of new journal articles, and visual abstracts are delivered to the subscribers immediately by email (49).

Memes

A meme is visual which is witty, ironic, gains popularity instantaneously, and spreads quickly *via* social media platforms. They were started in the middle of the 21st century and have become a global internet cultural phenomenon. A study by Vivekananth et al, compared physiology students who created memes with those who created concept maps to learn complex topics. They inferred that memes ignited interest in the subject, increased peer interactions, enhanced retention of concepts, simplified complex topics, and created a positive learning environment (50).

Interactive learning

The NSMC internship (launched in 2015) is a year-long, mentored program where interns (ranging from medical students, residents, and attendings) participate in a curriculum of activities, lectures, and capstone projects to increase confidence, proficiency, and knowledge in social media. The NSMC internship is currently composed of 4 rotations; graphical communications, podcasting, NephJC Twitter journal club, and blogging/tweetorial. Modern communication skills are taught during this internship, which empowers interns to create FOAMed and become future leaders in medicine (51) (Figure 2).

The Glomcon fellowship (launched in 2020) admits fellows to be educated in diagnosing and managing glomerular disease from experts worldwide.The fellows present their assignments and cases, followed by an interactive discussion with expert nephrologists (52).

The International Society of Nephrology (ISN) American Nephrologists of Indian Origin (ANIO) clinical nephropathology certification program is another such year-long online program. It comprises of recorded and live videos to learn the basics of nephropathology (53).

NephSIM is a mobile-optimized tool that uses interactive nephrology cases and real time feedback to teach pathophysiology, diagnosis and management of the case (54). Additionally, NephSIM Nephrons (Launched in 2021) is a year-long mentorship program tailored for trainees who are interested in pursuing a career in nephrology (55).

Global nephrology community

The ASN has a forum for members called ASN Communities aiming to provide a meeting place for nephrologists to discuss cases, debate controversies, and notify any upcoming opportunities for members (56). The forum also provides opportunities for educators to discuss upcoming challenges and strategies (57).

Balancing gender inequities

Gender inequities are known to impact a woman's career and advancement negatively. Social media platforms have helped achieve gender parity in a significant way. It provides access to mentorship, education, and research. Creating a community such as WIN, which advocates for gender equity, has played a significant role (37). The goal is to nurture interest in nephrology for young doctors and implement patient advocacy programs as well. It provides a platform for young women nephrologists to interact with senior women nephrologists and seek mentorship and collaboration (36, 37, 58). It is imperative that the social media community continue to ensure gender balance and diversity.

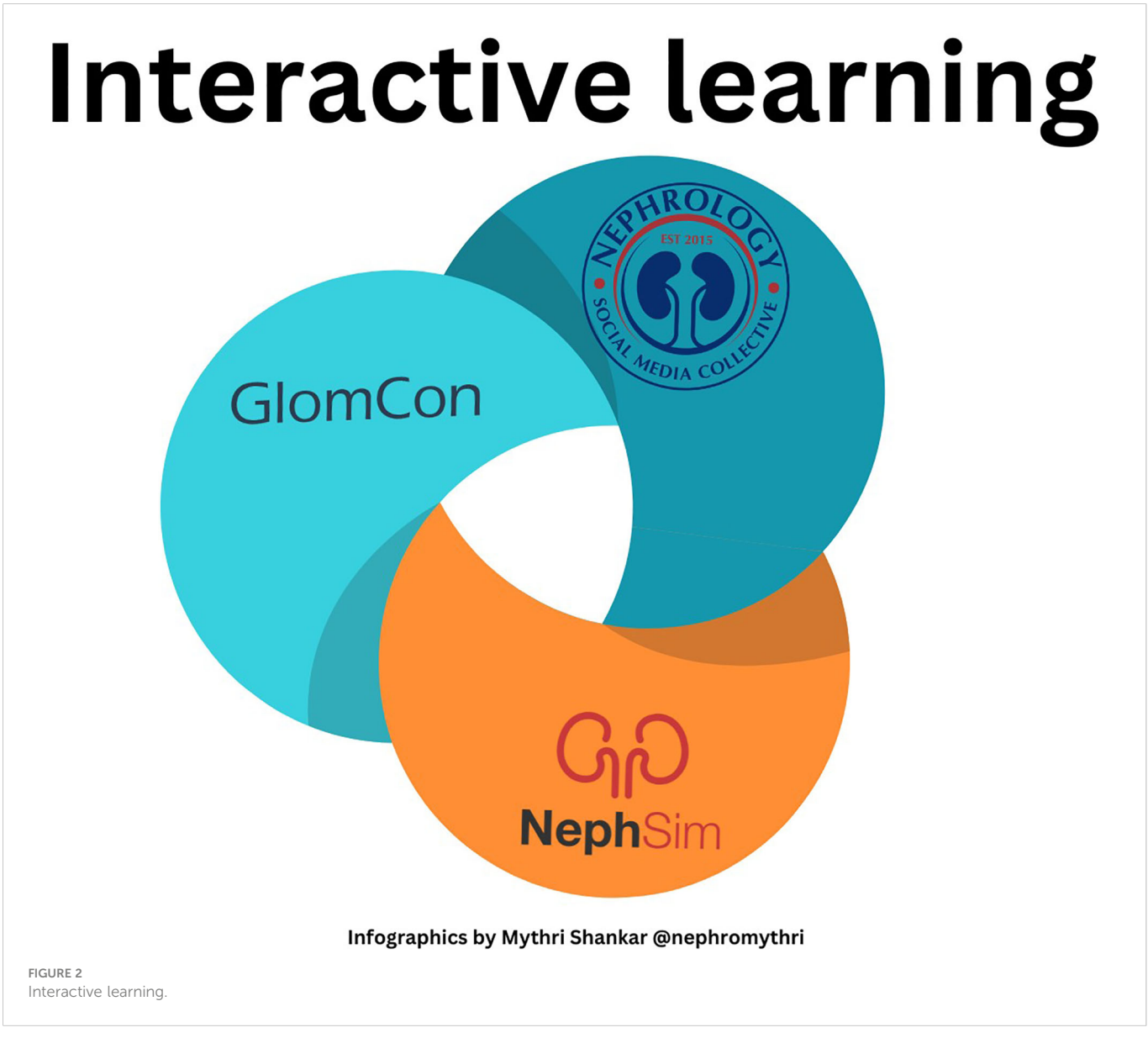

FIGURE 2
Interactive learning.

Guide for first time social media users

1. Users should choose one platform that suits them the most based on the desired content and target audience (eg., Facebook, Twitter, Instagram, YouTube, LinkedIn). Similar to medicine, one should have a personalized approach, and it is best to keep professional and personal social media accounts separate as much as possible. However, one should recognize that this is challenging to accomplish completely. The level of engagement can range from passive viewing to the active creation of FOAMed content. Initially, one may find it intimidating, but as the comfort level increases, the engagement level also increases. Based on our experience, the nephrology social media community (#NephTwitter) is warm, welcoming, uplifting, and non-threatening (59).
2. Be cordial and support your peer group by sharing content created by them. Always use high-quality images and videos. Provide credit and provide appropriate citations. Join Twitter chat groups such as #NephJC, #ECNeph to learn and network (59).
3. Take breaks from social media. Strategies are to use social media during certain times of the day or certain days of the week. According to a study by Pirdehghan et al, social media use can lead to anxiety, insomnia, addiction and fear of missing out (60).
4. Follow people with shared professional interests, experts, and leaders in nephrology. It is essential to stay focused and not get carried away with distractor tweets such as politics, movies, and so on. However, it must be noted that your social media feed is your feed and it should be curated to how you want to use it.
5. Create a social media scholarship portfolio describing the content created and the associated analytics, which can be critically assessed for improvement of the content and published. The scholarship portfolio can help in job placements and promotions.

The future

Worldwide, engagement of nephrologists with social media continues to increase (4). Many are using social media for educational purposes, and more established institutions are beginning to recognize it for promotion and tenure (61, 62). Many international nephrology organizations are investing in social media. ISN organized online coverage of the World Congress of Nephrology (WCN) in 2017. Since then, the WCN conferences have been live-streamed. The ASN has created ASN Communities to capture the interaction between its members across the globe. The University of California, San Francisco, has a rotation where a medical student reviews the medical entries to the Wikipedia website on Web 2.0 (63). The Duke University Clinical Research Training Program offers a Masters degree course titled Scientific Communication where physicians and researchers learn modern communication skills such as social media and visual abstract creation (64). Beth Israel Deaconess Medical Center offers a digital education curriculum for 2nd and 3rd year residents in the internal medicine residency program (65). The future will see more programs focused on social media education aimed at trainees.

Platforms such as TikTok, Instagram, and Facebook are still ripe for innovation, and they have a lot of potential to be explored with a robust audience. Two-way communication is limited in these social media platforms, which could be a pitfall with scope for improvement (15). Newer platforms, like Mastodon, are also gaining popularity and could threaten the popularity of Twitter.

Nephrology has been the leader in FOAMed. Intensivists, cardiologists, and endocrinologists are catching up. We should take advantage of our early start and continue to lead others in FOAMed. While uptake of social media has been swift, there is a an urgent need and important opportunity for educational research to assess the impact of social media in education (8).

Limitations

While the use of social media for education has many positive attributes, it is important to consider the negative consequences. Using social media for education can be a double-edged sword. The posted content is often not peer reviewed; hence, there is a threat of dissemination of inaccurate and/or commercially biased information. Fact checking and feedback is provided by a robust network of experts in the audience (16). However, loud voices can sometimes drown out other perspectives. One can directly communicate with the author and corrections can be performed immediately, this bypasses the red tape which requires a structured letter to the editor. The feedback may be sporadic and imperfect but at least it's transparent and accessible. Several scoring systems have been studied to critically appraise blog posts and podcasts, especially in critical care medicine (66). The nephrology online community has yet to adopt these metrics.

While tweeting educational material such as imaging, laboratory values, urinary sediment examination, pathology images, and case history, it is essential to obtain patients' consent and/or ensure confidentiality. Patients may not be willing to share their data online as it may breach their confidentiality (67). Although the content is purely for educational purposes, other people, such as the patient themself, the patient's family members, may find it offensive. Even if one deletes a tweet, someone might have already downloaded the image and reposted it later. Hence, watermarking the copyright holder on the images is one way to prevent the misuse of images. Also, one should remember that they represent their institution and remain courteous in conversations. There are instances where people have lost their jobs due to insensitive remarks made on social media platforms. An essential mantra for online users is to remember that "once an image or tweet is released, it is in the public domain forever." (66) While it is common to place statements like, "tweets are my own and do not represent my employer" on Twitter or social media profiles, it must be noted that

individuals can never completely dissociate their online behavior from their employer, family, or peer group. Thus, it is important to maintain a high degree of professionalism when engaging in social media.

Another inevitable limitation of social media is leaving a public data trail. Our online behavior is being constantly tracked and monitored by marketing companies to sell their products or political influencers to increase their vote base (68).

Despite all the limitations, nephrologists can use social media to their advantage.They can use it to reach and collaborate with the target audience. With consistent and focused creation of FOAMed, one can gain visibility and credibility. This, in turn, can open up offline opportunities, such as an invitation to become speakers, editors, research collaborations, and publications, ultimately advancing one's career (59). Meeting nephrologists from around the world, sharing ideas, forming teams and collaborations is a huge benefit and much of our current landscape emerged from such online relationships (for example NephJC led to NephJC Freely Filtered and so on). Not to forget, people's clinical and research careers have started through just online messages.

Conclusion

Medical media is ever-evolving. There is a growing interest in nephrologists to consume educational content from social media and create and disseminate original content. There is increasing involvement of nephrologists in real-time debates, discussions, and analysis of data presented. With the growing interest, knowing how to use social media platforms effectively to one's leverage is crucial. Lastly, it is time to study how social media and FOAMed have impacted education in both the short and long term. The nephrology community should continue to invest money, time, and energy into research, best practices, and the creation of new content.

Author contributions

MS conceptualized and wrote the article. MAS edited and reviewed the document. Both authors contributed to the article and approved the submitted version.

Conflict of interest

MAS reports receiving honoraria from Elsevier–Nephrology Secrets; serving as a scientific advisor or member of the American Board of Internal Medicine Nephrology Board, Board of Directors, NephJC; serving on the editorial boards of American Journal of Kidney Diseases, ASN Kidney News, Kidney360, Advances in Kidney Health and Disease, and Kidney Medicine; serving as program director of the Nephrology Social Media Collective Internship; serving as associate director of NephSIM Nephrons; and serving on KCVD Membership & Communications Committee of AHA, KCVD Scientific & Clinical Education Lifelong Learning Committee of AHA, and the National Kidney Foundation North Carolina Medical Advisory Board. MS is Associate Program Director of Nephrology Social Media Collective, Glomcon Instructor, Member - ISN Education, ISN young, ISN social media team, ISN ACT trial, Secretary - WIN - India Karnataka Chapter. Member of Editorial board - Kidney medicine, KIReports, Glomcon pubs.

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EDITED BY
Lily Mushahar,
Tuanku Ja'afar Seremban Hospital, Malaysia

REVIEWED BY
Elvira Gosmanova,
Albany Medical College, United States

*CORRESPONDENCE
Rumeyza Kazancioglu
drkazancioglu@yahoo.com

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The optimization of peritoneal dialysis training in long-term

Meltem Gursu[1], Larisa Shehaj[1,2,3], Omer Celal Elcioglu[1] and Rumeyza Kazancioglu[1]*

[1]Department of Nephrology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Türkiye, [2]Department of Internal Medicine, Salus Hospital, Tirana, Albania, [3]ISN fellow in Department of Nephrology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Türkiye

Peritoneal dialysis is a home based therapy for patients with advanced chronic kidney disease. This method provides adequate clearance of uremic toxins and removal of excess fluid when a proper dialysis prescription is combined with patient adherence. Peritonitis is the most frequent infectious complication among these patients and may render the continuity of the treatment. Training patients and their caregivers have prime importance to provide proper treatment and prevent complications including infectious ones. The training methods before the onset of treatment are relatively well established. However, patients may break the rules in the long term and tend to take shortcuts. So, retraining may be necessary during follow-up. There are no established guidelines to guide the retraining of PD patients yet. This review tends to summarize data in the literature about retraining programs and also proposes a structured program for this purpose.

KEYWORDS

peritoneal dialysis, training, re-training, outcome, peritonitis

1 Introduction

Chronic kidney disease is a growing global health issue, with an increasing number of patients requiring kidney replacement therapy. Approximately 11% of patients choose peritoneal dialysis (PD) as their kidney replacement therapy, with this number varying from country to country and center to center (1, 2). Compared to hemodialysis, PD offers several advantages, including fewer hospital visits, fewer hypotension episodes, no anticoagulation requirements, a more independent lifestyle, and greater affordability (3, 4). Peritoneal dialysis is technically simpler to apply (5), minimizes hospital admission and hospital infection (6), is more feasible in rural and remote areas (7), and preserves better the residual kidney function (8, 9) – factors that affect the survival of patients on dialysis (10, 11). Additionally, PD positively affects patients' quality of life allowing them to maintain employment and daily activities (12). Studies have shown that patients are motivated to select PD because it can be performed independently at night, does not affect their lifestyle, and does not prevent them from traveling (12, 13). However, patients also cite disadvantages of PD therapy, such as catheter care, fear of peritonitis, frequent cycles of

bag exchange during the day, lifestyle changes, problems with PD machines, the intensity of cycles, abdominal pain, sleep disturbance and annoyance of other people (14, 15).

Peritonitis is the most critical complication of PD therapy and can lead to a permanent transfer to hemodialysis. Even with effective treatment, it still is associated with mortality (16, 17). The hazard ratio for death due to infection, cardiovascular complications, and noncompliant dialysis is elevated within the first month of a single peritonitis episode and remains raised for up to six months (18). To decrease peritonitis rates, the International Society for Peritoneal Dialysis (ISPD) guidelines recommend preventive measures to decrease peritonitis rates like systemic prophylactic antibiotics application before PD catheter insertion, daily application of antibiotics ointment to the catheter exit site and an itemized training program (19, 20).

Over the past 30 years, the rates of peritonitis have decreased thanks to improvements in connection systems and the use of prophylactic antibiotics before catheter insertion (21). However, despite these advances, the rates still remain high. Reported rates of peritonitis vary greatly between countries, ranging from 0.2 episodes per patient per year (22, 22) to between 0.6 and 0.9 episodes per patient-year (23–25). In addition, the rate differs between different dialysis centers within a country (23, 26, 27). The factors that contribute to this variability are undefined, but it is thought to be due to differences in patient training, infection prevention protocols, and follow-up schedules (28, 29).

Proper training of patients who start treatment with PD is fundamental for achieving a successful technique and a low rate of peritonitis (30). Studies have shown that correct techniques for training patients about PD can significantly reduce the peritonitis rate (31–33). Moreover, re-training programs have been found to be necessary, as peritonitis rates tend to rise over time on PD (34). This may be due to patients becoming more self-confident and neglecting to follow the exact rules taught by medical professionals. Studies analyzing this problem found that improper hand-washing was the most common issue among about 50% of patients, and incorrect mask-wearing was prevalent in around 10-15% of patients (31, 34, 35).

2 Exit site care and bag exchanges

The most common factors contributing to the risk of peritonitis are exit site care and connection technique. Patients should be educated on proper techniques and frequently monitored to ensure they are following best practices. Retraining should be provided as necessary. In a randomized controlled study, re-training was shown to lower the rate of exit site infection caused by gram-negative microorganisms per patient per year (36).

According to the 2017 ISPD guidelines, careful consideration should be given to the location of the exit site to ensure it can be easily cleaned and is less prone to trauma (37). After catheter insertion, incisions should be covered and dressing should remain undisturbed for 3-5 days to promote proper epithelialization and wound healing (37). Proper exit site care, including the use of topical antibiotics, avoiding immersion of the peritoneal catheter in water, and immobilization to prevent trauma, plays a crucial role in preventing peritonitis. It is important to follow a sterile dressing technique and wash the exit site with water and antiseptic soap during showers to maintain sterility (37). Exit site cleansing should be performed at least twice a week and after each shower, once the exit site is fully matured (37) Antimicrobial soap and water are commonly used to cleanse the exit site, while povidone iodine and chlorhexidine are common disinfectants (37). Alcohol-based disinfectants should be avoided (37). Although evidence is insufficient to support the use of one solution over another, the guidelines recommend the daily topical application of antibiotic ointments at the exit site to prevent infection (37).

Proper hygienic care including hand washing, use of face masks, and new technologies such as bags with Y set and flush before fill, as well as proper exchange methods are also mandatory to prevent peritonitis in addition to exit site care.

It is important to emphasize the proper performance of bag exchanges during initial training for new PD patients, including checking fingernail cleanliness, bag expiration date and leakage, and avoiding any suspected contamination. Patients should also be instructed on the correct steps to connect and disconnect the bag, flushing before filling, and the importance of wearing a face mask and cap during exchanges. All patients should receive this primary education program covering these issues. The ISPD recommends a training program lasting five days, with each session lasting approximately three hours (20). The VARK learning style questionnaire (Visual, Auditory, Read and write, and Kinesthetic) may be used to facilitate learning (31).

However, a critical question is whether patients apply the taught techniques in the long term. Previous studies have shown that over 50% of patients deviated from the standard procedure, especially in terms of hand washing, during bag exchange in the sixth month of PD, and these errors predicted a higher risk of peritonitis during follow-up (32, 35). To improve adherence, it is important to focus on prevention of infections, signs and symptoms of infections, hydro-electrolytic balance, hand washing, and exchanging/preparing the cycler (32).

Patients may forget the skills they have learned or become overconfident and depart from the standard protocol due to long-term PD treatment (38). Periodic re-training on bag exchange can reduce the risk of contamination by ensuring proper follow-up of the steps of the procedure. However, the guidelines do not specify the content, frequency, or location of the re-training process, as these may vary depending on the characteristics of the patients in each unit.

3 The frequency of re-training

The TEACH study compared two groups, frequent re-training (with a home visit every 1-3 months) and conventional re-training (with only two home visits after starting PD), for 24 months. It showed that frequent re-training reduced the risk of exit site infection and peritonitis rate. The study also suggested that older patients are at a higher risk of peritonitis, and repeated training/re-training could benefit this patient subpopulation (39).

The most recent ISPD guidelines recommend re-training after hospitalization, peritonitis, or catheter infection, changes in

dexterity, vision, or mental acuity, changes in caregiver for PD exchange, after other interruptions in PD treatment (such as transient transfer to HD), and 3 months after initial training and routinely thereafter (at least once yearly) (40).

4 The technique of re-training

A study conducted on pediatric patients found that longer total training time that included theory and practical/technical content was associated with lower peritonitis rates (41). The duration of each training session may also impact the effectiveness of the training. The BRAZPD II study analyzed 2243 incident PD patients from 122 centers in Brazil between 2008 and 2011 and revealed that shorter training sessions (<1 hour/day) and longer total training duration (>15 hours) were associated with lower peritonitis risk (42).

Therefore, extending the total training time with frequent, shorter sessions may allow for the identification and correction of mistakes made during PD therapy implementation.

In a study conducted between December 2010 and June 2016, re-training with technique inspection was compared to oral education. The results showed that repeat training under technique inspection may help correct improper steps during bag exchange and thus reduce the risk of peritonitis (43).

On the other hand, re-training through oral education, which mostly focused on the theoretical part, did not significantly impact the risk of peritonitis, despite patients showing good adherence with the training program (43). Every step of the exchange procedure, including motor skills and memory learning, is stored in the cerebellum and cerebellar cortex (33). This process is more active during technique inspection than it is with oral education. Thus, correcting mistakes during technique inspection can help the patient's mind store and recall the steps more effectively (33, 44).

5 Re-training location

The regular home visits during PD therapy are crucial for follow-up, as both the patient and their family need to receive ongoing support. Early identification and treatment of problems can help keep the patient healthy and reduce hospitalizations. Studies have shown that frequent home visit training can lower the peritonitis rate (45, 46). Since PD is performed in the patient's home, home visits can provide valuable information on the patient's environment and how they are carrying out the exchange procedure. Kazancioglu et al. recommended frequent home visits for training, which can help maintain a safe environment and reduce the risk of peritonitis (47).

6 Whom to re-train?

Although peritoneal dialysis (PD) is a patient-driven therapy, some patients require assistance from family members or healthcare workers, especially nurses. While the impact of assistance on PD patients is unclear, several observational studies have reported a decreased rate of peritonitis in patients supported by family members or nurses (48, 49). Conversely, studies have shown that patients cared for by private caregivers are more predisposed to peritonitis than those cared for by family members (50, 51).

A study conducted in France between 2000 and 2004 revealed that patients cared for by private nurses had a higher risk of peritonitis compared to those cared for by family members (51). Family members may have a greater personal investment in achieving positive PD outcomes by carrying out the exchange procedures themselves when patients are unable to perform them accurately. When comparing subgroups (family-assisted PD, nurse-assisted PD, and private nurse-assisted PD), family-assisted and nurse-assisted PD had a lower risk of peritonitis (52). Similarly, another study showed that family-assisted PD had a lower risk of peritonitis compared to other groups (53). Therefore, re-training should apply to all participants in the patient's treatment, including assistants who are healthcare workers.

7 The content of the re-training program

We should also consider the content of the re-training program. Should it include all subjects or be limited? In a multicenter study by Ljungman S et al., which included 671 PD patients, all patients received baseline training according to the guidelines (36). Patients were randomized to the re-training group and the control group. Patients in the re-training group performed an exchange with the supervision of a PD nurse without interruption and completed a questionnaire containing 24 multiple-choice questions on hygiene, infection prophylaxis, exchange technique, exit-site infection, and peritonitis. If the patient did not meet the test goals, further training was provided until they were achieved (36). According to the results of the questionnaire, 29% of the patients required re-training. The total incidence of peritonitis and exit-site infection per patient year, as well as outcomes, were similar in both groups. However, peritonitis caused by gram-negative microorganisms was less frequent in the re-training group (36). Although this study was prospective and included a high number of patients, the results were not consistent with previous observational studies. This may be due to differences in patient characteristics, protocols of antibiotic prophylaxis, and compliance with the guidelines. Although there is not enough evidence to follow a certain way, we believe that the content of re-training should be tailored to the patient's needs.

8 Messages from the authors

For both patient and technique survival in PD patients, training of the patients and/or carers is crucial. The training program should be extended throughout the duration of the ongoing PD treatment rather than being restricted to the time when the treatment first began.

While the most recent ISPD guidelines recommended performing re-training three months after initial training and

regularly thereafter (once a year at a minimum) and after certain conditions described in the guidelines, we advise closely monitoring the technical capabilities of the patients at the clinic or at home at each visit and performing re-training sessions even more frequently.

Adding more frequent, shorter training sessions may enable health professionals to evaluate patients' method, identify any deficiencies, and fix them during PD therapy. So, the focus of the retraining session needs to be goal-oriented.

Retraining is applicable in both the hospital and at home. House visits provide useful information regarding the environmental aspects, such as the position of the baths and the cleanliness of the exchange room, which could lead to error during the exchange procedure.

Every participant in the patient's treatment, notably the patient's family members, should undergo retraining. The social structure of the family and the community should be considered when making this decision. Even if the assistant is a healthcare professional, retraining should be taken into account.

The re-training program's content should be adaptable and tailored to the patient's needs as determined by the PD nurse or the doctor.

Every unit may need to identify the requirements in relation to the patient characteristics.

Author contributions

All authors contributed equally to collection of knowledge, drafting the manuscript and revision of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Irma Tchokhonelidze,
Tbilisi State Medical University, Georgia

REVIEWED BY
Matthias Zeiler,
"C. e G. Mazzoni"Hospital,
Italy
Pankaj N. Maheshwari,
Fortis Hospital, India

*CORRESPONDENCE
Sana F. Khan
sk4yp@virginia.edu

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Optimizing peritoneal dialysis catheter placement

Sana F. Khan* and Mitchell H. Rosner

Division of Nephrology, University of Virginia Health System, Charlottesville, VA, United States

Long-term success of peritoneal dialysis as a kidney replacement therapy requires a well-functioning peritoneal dialysis catheter. With ongoing reductions in infectious complications, there is an increased emphasis on the impact of catheter-related and mechanical complications. There is currently a marked variation in the utilization of various types of catheters (double cuff vs single cuff, coiled tip vs straight tip), methods of catheter insertion (advanced laparoscopic, open surgical dissection, image guided percutaneous, blind percutaneous), timing of catheter insertion, location of catheter placement (pre-sternal v. abdominal) and peri-operative practices. Specialized approaches to catheter placement in clinical practice include use of extended catheters and embedded catheters. Marked variations in patient lifestyle preferences and comorbidities, specifically in high acuity patient populations (polycystic kidney disease, obesity, cirrhosis) necessitate individualized approaches to catheter placement and care. Current consensus guidelines recommend local procedural expertise, consideration of patient characteristics and appropriate resources to support catheter placement and long-term functioning. This review focuses on an overview of approaches to catheter placement with emphasis on a patient-centered approach.

KEYWORDS

dialysis (ESKD), peritoneal, dialysis catheter complications, outcomes - health care, long term optimal planning

Introduction: current placement of PD catheters and issues

It is reported that approximately 424,000 patients worldwide utilize peritoneal dialysis (PD) as a method of kidney replacement therapy (1). A well- functioning PD access is essential to PD technique success, empowering patients to perform a therapy associated with reduced cost and increased patient autonomy (2, 3). There is currently marked heterogeneity in the types of PD catheter used, insertion techniques, location of placement, timing of catheter insertion and peri-operative practices. Commonly reported complications include catheter flow restriction, exit site leaks, pain and infections with resulting termination of PD, delays or interruptions in treatment, emergency department visits or hospitalizations, and need for corrective procedures. Studies have reported 13-17%

of PD technique failure are due to mechanical catheter complications (4–6). Additionally, there is variability in the definitions, reporting methods, choice of outcomes, and analysis of PD access outcomes which hampers the determination of best practices for PD catheter placement (7).

What is optimal PD catheter placement: patient-centered approach

Knowledge of best practices in catheter insertion can minimize the risk of catheter complications leading to early PD failure. Guideline committees under the sponsorship of the International Society for Peritoneal Dialysis (ISPD) recommend optimal PD catheter implantation be based on individualized patient factors, facility resources and operator expertise (8). Currently, most PD catheters for chronic use are made of silicone rubber. There is a marked variability in the types of PD catheters available for use, and include the most common type of double cuff, straight or coiled-tip Tenckhoff catheters with a pre-formed arc bend in the intercuff segment. While single cuff catheters are available, double cuff catheter are thought to be superior in preventing peritonitis caused by periluminal entry of organisms (especially given variable compliance with prophylactic antibiotic ointment used to lessen the risk of exit site infections), and for firm tissue fixation of the catheter (9). There is no significant difference in functionality between straight- and coiled-tip catheters, with or without preformed arc bend (10–12). While coiled-tip catheters are theorized to have less incidence of inflow discomfort and better dialysate dispersion, these effects have not been studied specifically, hence catheter selection is determined largely by availability of local inventory.

Recent PD catheter registries have reported a marked variation in PD catheter insertion techniques that include open surgical dissection, laparoscopic insertion with advanced techniques, blind insertion *via* trocar and blind insertion *via* Seldinger technique (13, 14). An optimal patient centered approach balances local procedural expertise along with patient specific factors and local resource availability. A laparoscopic approach is utilized in patients generally considered safe for general anesthesia with a history of prior abdominal surgeries in addition to having flexibility of waiting for an operating room time (8). Moreover, the laparoscopic approach allows the performance of advanced surgical techniques including rectus sheath tunneling (which reduces risk of pericatheter leaks and prevents tip migration), prophylactic omentopexy and adhesiolysis (which can improve inflow and outflow of dialysate fluid). The ability to perform these proactive adjunctive techniques are thought to improve catheter outcomes (15–17). A recent metanalysis observed a significant reduction in flow obstruction and tip migration when advanced laparoscopic techniques were utilized (18). Additionally, the laparoscopic approach allows for concomitant repair of abdominal wall hernias. Percutaneous catheter insertions by radiologists or nephrologists have been utilized in patients needing PD access in an accelerated timeline (more timely than awaiting operating room time), no major prior abdominal surgeries, and it precludes the need for general anesthesia. However, the percutaneous technique obviates the ability to visualize adhesions, and perform advanced adjunctive techniques. An open surgical dissection method (under local or general anesthesia) has also been utilized for timely placement of PD catheters, both by nephrologists as well as surgeons. Similar to the percutaneous technique, advanced adjunctive techniques cannot be performed *via* open surgical technique (9, 19, 20).

Another tailored approach to optimizing outcomes is consideration of the timing of PD catheter insertion. There is a marked variation in estimated glomerular filtration rates (5- 8 ml/min) at the time of catheter placement (21, 22). Early planning and placement offers larger flexibility to resolve early insertion related problems. A well- organized urgent start PD initiation program with rapid access to catheter insertion allows for new dialysis patients to initiate and establish on PD rather than hemodialysis. However, a caution is that PD catheter use within 7 days of insertion has been showed to increase the risk of exit site leaks and infections, compared to standard initiation (28 days) (23). Specific catheter insertion related interventions to mitigate early complications include utilization of fibrin glue, and additional purse-string sutures at the level of deep cuff as well as near peritoneal membrane (24, 25).

Another strategy for timely initiation of PD is the embedded catheter technique, with the external limb of catheter embedded in subcutaneous tissue until the need for dialysis initiation. This allows for early patient commitment to PD, more predictable operating room scheduling, and immediate utilization of the catheter after exteriorization. However, there is a risk of non-usage of catheters, in addition to catheter dysfunction rates secondary to fibrin accumulation (26–28).

No specific catheter placement approach has been proven to produce superior outcomes. Comparison of percutaneous placement, open surgical dissection and basic surgical laparoscopy have shown equivalent patient outcomes (21, 29–31). However, studies investigating outcomes in advanced laparoscopic studies demonstrate superior outcomes compared to other approaches (18). Patient factors aside, optimal PD catheter placement involves operator expertise, and the ability to provide peritoneal access in a timely fashion. While seemingly simple, PD catheter placement is a critical life-sustaining procedure and patients benefit from experienced operators who are able to identify and rectify problems with catheter placement in a timely manner. When access to an operating room is rate-limiting, percutaneous insertion by a nephrologist for an appropriate patient is a reasonable option, and also provides ongoing continuity of care, patient satisfaction and high rates of peritoneal dialysis utilization (32).

Approaches to PD catheter placement

The goals of PD catheter placement involve a balance between pelvic position of catheter tip to facilitate inflow and outflow of dialysate along with an easily visible and accessible exit site.

Operator expertise and experience necessitates selection of appropriate available catheter type suited to patient specific conditions. Placement includes the consideration of body habitus, belt-line, skin creases, prior scars, stomas, gastrostomy tubes, recreational habits and occupation. An ideal exit site is either above or below the beltline, with a lateral and inferior directed exit site (Figures 1A, B). However, based upon patient-specific criteria, other positions for the catheter exit site may be more appropriate. The catheter insertion site and length of intraperitoneal tubing determines the pelvic position of the catheter tip. While a catheter tip in the pelvis is preferred for optimal hydraulic function, excessively deep placement, or a catheter tip between the rectum and bladder can result in extrinsic catheter compression, flow impairment and pain with draining of the dialysate (33). In the pre-operative planning, the patient is examined while both supine and sitting, using the pubic symphysis as a guide to catheter tip location. Examination in the sitting position allows for visualization of an appropriate exit site (34).

Several patient factors necessitate utilization of an extended-length catheter system. Patients with excessive skin folds, stomas, incontinence, necessity for bath tub or other factors would benefit from an upper abdominal or pre-sternal exit site (Figures 1C, D). This can be achieved *via* a 2- piece extended catheter system, with a long subcutaneous section, while maintaining optimal catheter tip position. Alternatively, single piece catheters with long intercuff segments are also utilized in certain centers (35, 36).

Regardless of a standard vs extended approach, best practices in patient preparation catheter placement have been detailed in multiple publications and include appropriate selection of catheter type and exit site location, pre-op bowel preparation, utilization of a paramedian incision, deep cuff placement within or below the rectus muscle, lateral and downward directed exit site (8).

Catheter placement in special populations

Several high acuity patient conditions (obesity, polycystic kidney disease, cirrhosis/ascites) necessitate a specialized approach for successfully conducting PD as a dialysis modality. This includes not only optimal exit site and catheter tip position,

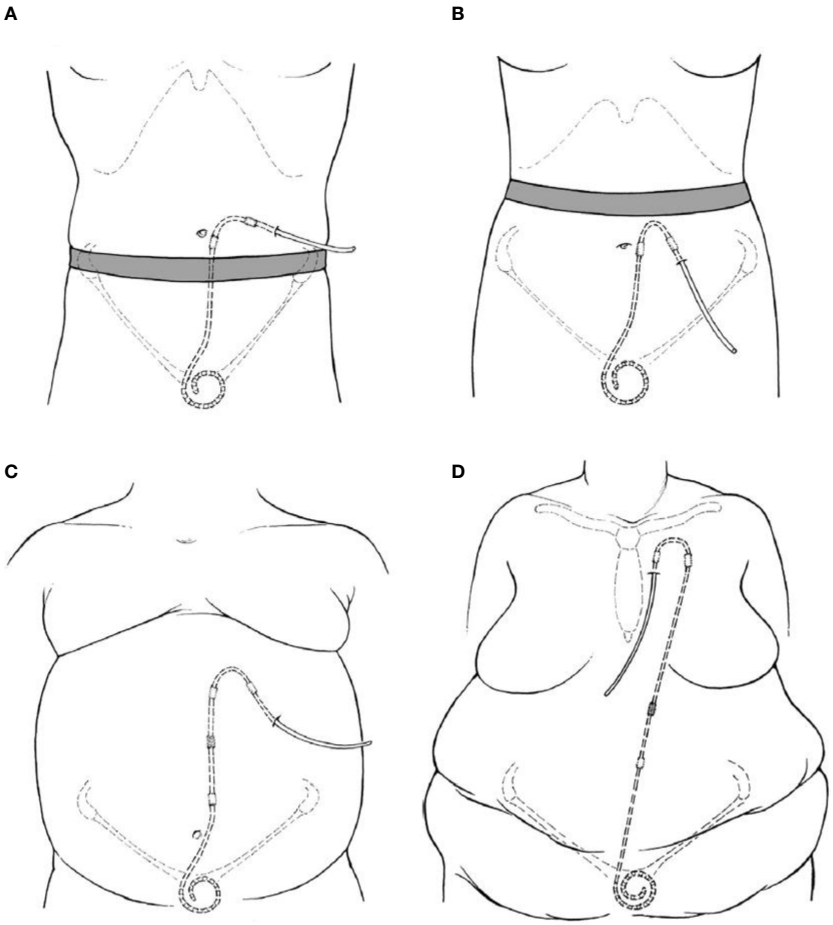

FIGURE 1
Illustrations of PD catheter positions with regards to exit site position **(A)** Laterally directed exit site emerging above the beltline. **(B)** Downward directed exit site below a high beltline. **(C)** Extended catheter system with an upper abdominal exit site. **(D)** Extended catheter system with a presternal exit site (9).

but utilization of focused interventions to ensure ideal long term function. Patients with obesity require creation of an easily visible upper abdomen/presternal exit site requiring an extended catheter approach. The catheter should be allowed to heal completely for several weeks prior to PD initiation. Ideally, a laparoscopic approach is recommended, utilizing selective omentopexy along with resection of epiploic appendices of sigmoid colon if needed. The upper abdominal and chest exit sites are located in areas with relatively thin subcutaneous layer, minimizing tubing stresses from mobility of the subcutaneous fat layer with postural changes. Data suggests longer time to first exit site infections in patients with extended catheters (37). Moreover, extended catheters enable peritoneal access in a subgroup of patients in whom conventional catheter placement would not be possible.

Patients with autosomal dominant polycystic kidney disease (ADPKD) present a unique set of concerns regarding limited peritoneal space, peritonitis risk and hernias. Several studies have reported the feasibility of PD in ADPKD patients (38–40). With regards to long term mechanical complications, these patients are at increased risk of abdominal wall hernias. The cause of these hernias is possibly multifactorial given increased intraperitoneal pressure in addition to possible collagen defects (41, 42). Simultaneous hernia repair and catheter insertion can safely be performed, and a tension-free hernia repair with prosthetic mesh is essential to minimize the risk of recurrence (43, 44).To prevent visceral injury to enlarged abdominal organs, laparoscopic ports, trocars and needles must be inserted and manipulated with increased caution. Ultrasound-guided percutaneous insertion of trocars is a feasible option for prevention of iatrogenic injury (45).

Patients with cirrhosis present their own unique challenges with regards to potential bacterial peritonitis, nutritional challenges, and concerns for leaks (46–49). Several centers have published their experiences regarding perioperative management of ascites. One center has reported catheter placement followed by 5-6 liters of large volume paracentesis. Thereafter, peritoneal drainage volume is allowed to exceed infused volume by 200 ml, allowing for a gradual and controlled drainage (47).Other centers have reported initiating low volume PD exchanges immediately following catheter placement. The drain volumes have been permitted to exceed infused volumes by 20% in certain reports, whereas others have reported an increase in 400-600 ml of effluent over the first few days. This allows for a safe and slow pattern of decompression, allowing for gradual ascites removal prior to training commencement (47–49).

Conclusion

Safe and effective placement of PD access is critical to the ultimate outcomes of PD as a home dialysis modality. Table 1 provides a guideline of potential PD catheter placement measures that home programs should consider monitoring to ensure continuous quality improvement. Ultimately, an effective PD catheter can serve the patient for many years and provide a life-sustaining therapy but this relies on an experienced team that carefully assesses each patient, identifies patient-specific issues that may impede optimal outcomes and addresses these issue through careful planning and monitoring.

TABLE 1 Factors to consider monitoring to ensure optimal pd catheter function and longevity.

Factor	Comments
• Identify patient-specific factors that may impeded catheter function or longevity: o Underlying medical conditions such as diabetes, obesity, ADPKD, cirrhosis/ascites o Hygienic issues o Specific activities that may jeopardize the catheter	• Utilization of patient-specific factors will determine: o Catheter placement technique and particular choice of catheters o Timing of catheter placement (urgent start, training period anticipated, potential issues for delayed wound healing) o Location of catheter exit site o Use of extended catheters o Specific training countermeasures to address risk of catheter malfunction
• Assess early catheter inflow and outflow of dialysate	• Dialysate should readily flow into and out of the peritoneal cavity with minimal to no pain
• Assess position of the PD catheter tip	• Catheter tip should in the lower, deep pelvis. This ensures optimal hydraulic function of the catheter and minimizes the risk for omental entrapment
• Assess position and integrity of exit site	• Location on the abdominal wall (away from belt-line, skin creases and folds • Should be easily visible by the patient • Direction of catheter exit: downward, lateral, or upward pointing • Location of superficial cuff in relation to exit site • Consideration of any risks for impaired wound healing or heightened risk of infections (immunocompromised)

NA, Not Applicable; Quant, Quantitative; Qual, Qualitative.

Author contributions

SK and MR were responsible for preparation, writing and editing of this manuscript. Both authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Yuri Battaglia,
University of Verona, Italy

REVIEWED BY
Francesco Bellocchio,
Fresenius Medical Care, Germany
Michael Kammer,
Medical University of Vienna, Austria

*CORRESPONDENCE
Marina Wainstein
m.wainstein@uq.edu.au
Sally Shrapnel
s.shrapnel@uq.edu.au

†These authors have contributed equally to this work

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Systematic review of externally validated machine learning models for predicting acute kidney injury in general hospital patients

Marina Wainstein[1,2*†], Emily Flanagan[3†], David W. Johnson[4,5,6] and Sally Shrapnel[7,8*]

[1]Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia, [2]Department of Medicine, West Moreton Kidney Health Service, Ipswich Hospital, Brisbane, QLD, Australia, [3]Faculty of Science, University of Queensland, Brisbane, QLD, Australia, [4]Metro South Kidney and Transplant Services (MSKATS), Princess Alexandra Hospital, Brisbane, QLD, Australia, [5]Centre for Kidney Disease Research, University of Queensland at Princess Alexandra Hospital, Brisbane, QLD, Australia, [6]Centre for Kidney Disease Research, Translational Research Institute, Brisbane, QLD, Australia, [7]Centre for Health Services Research, University of Queensland, Brisbane, QLD, Australia, [8]Australian Research Council (ARC) Centre of Excellence for Engineered Quantum Systems, School of Mathematics and Physics, University of Queensland, Brisbane, QLD, Australia

Acute kidney injury (AKI) is one of the most common and consequential complications among hospitalized patients. Timely AKI risk prediction may allow simple interventions that can minimize or avoid the harm associated with its development. Given the multifactorial and complex etiology of AKI, machine learning (ML) models may be best placed to process the available health data to generate accurate and timely predictions. Accordingly, we searched the literature for externally validated ML models developed from general hospital populations using the current definition of AKI. Of 889 studies screened, only three were retrieved that fit these criteria. While most models performed well and had a sound methodological approach, the main concerns relate to their development and validation in populations with limited diversity, comparable digital ecosystems, use of a vast number of predictor variables and over-reliance on an easily accessible biomarker of kidney injury. These are potentially critical limitations to their applicability in diverse socioeconomic and cultural settings, prompting a need for simpler, more transportable prediction models which can offer a competitive advantage over the current tools used to predict and diagnose AKI.

KEYWORDS

systematic review, acute kidney injury, AKI, machine learning, prediction, risk score, models

Introduction

An estimated one in five adults admitted to hospital develop acute kidney injury (AKI) (1). Acute kidney injury is associated with an increased risk of in-hospital death and long-term development of chronic kidney disease (CDK) and other non-kidney complications, such as HTN, cardiovascular disease and stroke (2).

Multiple prediction models and risk scores have been developed over the years to predict the occurrence of hospital-acquired AKI (HA-AKI) in order to improve short- and long-term management (3). In patients presenting to the emergency department (ED) these interventions may be as simple as performing a fluid assessment to optimize hydration status and avoiding nephrotoxic medications. AKI prediction models or risk scores have been developed for various populations, from undifferentiated general hospital patients to critically ill or post-operative patients. Accordingly, predictors used have ranged from general admission observations to laboratory data and specific procedural interventions. Acute kidney injury is most commonly defined using the Kidney Disease Improving Global Outcomes (KDIGO) criteria which uses the rise in serum creatinine or decrease in urine output (4), however, other definitions - such RIFLE, AKIN - have been used in AKI models.

Over the past decade as larger and more complex patient databases have become available, development of machine learning (ML) models for risk prediction has become increasingly popular. Compared to traditional regression models, ML models have the advantage of not being constrained by assumptions between variables and outcomes allowing more subtle relationships in the data to be explored. Additionally, their computational power means that a greater number of input variables and data points can be processed to make more accurate and individualized forecasts.

Past systematic reviews of prediction models in AKI have identified a high risk of bias in most studies resulting from variability in the use of performance measures (in particular calibration reporting), sparse interpretability considerations, possibility of overfitting, narrow scope for reproducibility and a lack of external validation limiting the generalizability and applicability of the models (3, 5). Moreover, while AKI risk prediction is useful in sub-specialized patient populations, the majority of AKI occurs in the general wards, placing a premium on flexible risk prediction models that can perform well in these settings (6).

Hence, the research question of this systematic review is: what are the available machine learning models which can assist a health professional to quantify the risk of KDIGO-defined AKI during a hospital stay in patients admitted to a general hospital or clinic? Accordingly, the aim of this systematic review was to evaluate and critically appraise studies of models developed from general hospital populations, using the current KDIGO definition of AKI, and which have been externally validated.

Methods

This review was designed and conducted according to Preferred Reporting Items and Systematic Review and Meta-Analyses (PRISMA) Protocol guideline (7) and the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) (8).

Study identification

We used PubMed (pubmed.ncbi.nlm.nih.gov) and the Institute of Electrical and Electronic Engineers (IEEE) *Xplore* Digital library (https://ieeexplore.ieee.org/Xplore/home.jsp) for our search. In PubMed we searched titles or abstract with a combination of string and Mesh terms (Table S1). The search was conducted on July 13th, 2022 and was limited to studies published in the last five years (up to July 13th 2017).

Study inclusion and selection

We included studies that validated machine learning models, with or without initially developing those models, for the prediction of AKI (stage 1, 2, 3 or dialysis) in a general hospital population. We excluded studies using the following criteria:

(i) studies in patients under 18 years of age;
(ii) studies which used an outcome definition of AKI other than KDIGO;
(iii) studies presenting models based on regression, such as linear, logistic or penalized regression, or those which are well understood theoretically and by clinicians, such as Naïve Bayes;
(iv) studies presenting models with no external validation;
(v) any comments or editorials or meta-analysis or systematic reviews.

We considered external validation to exist if the developed model was applied to new individuals, either from the same institution but a different time period (temporal validation), from a different institution or country (geographic validation) or on very different individuals (domain validation) (9).

Titles and abstracts were screened by two reviewers (MW and EE), and full articles were reviewed if they were eligible or if reviewers disagreed in the screening process. Disagreements were resolved by a third reviewer (SS).

Data extraction and critical appraisal

A data extraction form was created based on the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist (8) and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) (10). Items extracted included study type, number and location of centers recruited from, patient characteristics (AKI incidence, staging and mortality), model characteristics including prediction windows, predictors used, types of models evaluated, type of external

validation performed, method used to calculate baseline serum creatinine and metrics used to evaluate the models among others. Risk of bias was assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST), which includes four domains and 20 signaling questions (11). Domains were rated as high risk, low risk or unclear risk. Models would need be low risk on all domains to be evaluated overall as low risk. It should be noted that this tool was created for traditional regression models and is currently being updated to include newer model methodology. Data extraction and appraisal were done by EE and MW. Disagreements were resolved through discussion with SS.

Results

Our search returned 889 studies. A majority of studies were excluded initially either because they did not present or validate a prediction model (this included commentaries, editorial letters, narrative reviews and systematic reviews), the subject was irrelevant and/or the population studied was not comprised of general hospital patients (Figure 1). Forty-three were selected for full text review either because they fit the inclusion criteria or because insufficient information was given in the title or abstract to decide on eligibility. A further 40 studies were excluded following full text review of which 16 were excluded for not having external validation. Of the remaining three studies, two developed and validated a model (1 and 3) and one validated a previously developed model (12) (study 2). A list of the types of models excluded based on criteria (iii) can be seen in Table S2.

General study characteristics

Data source and population characteristics

All studies were from urban or suburban tertiary, referral centers in high income countries, two from the United States and one from South Korea (Table 1). Data was sourced either from the individual hospital electronic health records (EHR) (studies 1 and 2) or from clinical research networks, such as the Greater Plains Collaborative (GPC) (study 3). Studies included hospitalized patients with at least two documented serum creatinine measures and/or a minimum of 48 hours of admission (studies 1 and 3) Patients with severe forms of AKI or on kidney replacement therapy (KRT) were uniformly excluded (Data Sheet 1). Patient data was variably collected between 2006 and 2018.

The experimental design used to develop and/or validate model predictions varied between studies. Study 1 split the population of one hospital into training and internal validation cohorts, and the population of the second hospital, from the same city, was used for external validation. Study 2 was based on a previously developed model which was internally validated in the original hospital population and externally validated in a four-hospital health care

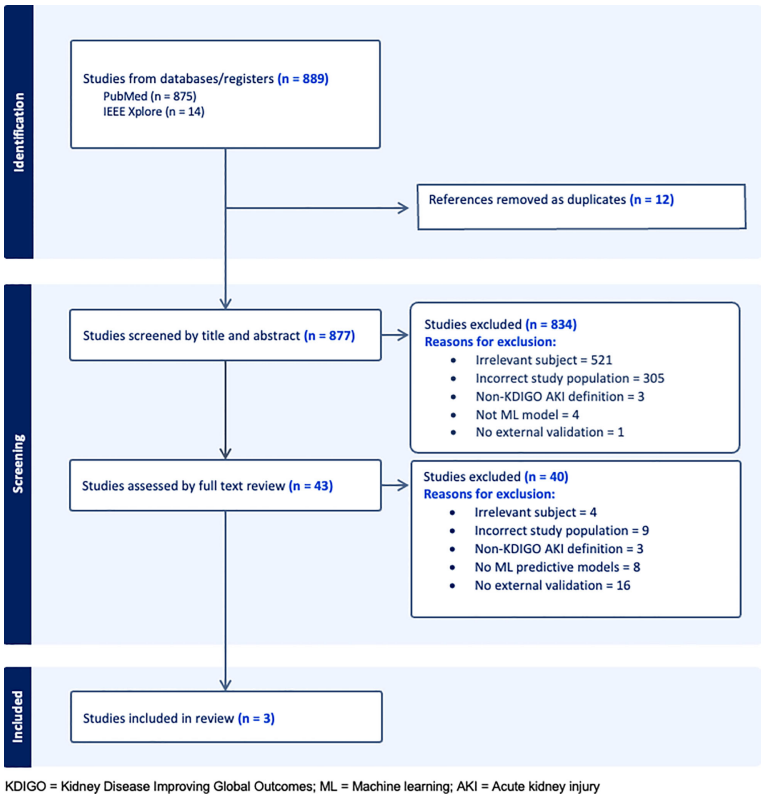

FIGURE 1
PRISMA flow diagram.

TABLE 1 Study population characteristics.

	Study 1 (13)	Study 2 (14)	Study 3 (15)
Number & type of sites	SNUBH: tertiary hospital SNUH: tertiary hospital	UC: urban, tertiary hospital LUMC: suburban tertiary hospital NUS: suburban, 4-hospital health care network	6 GPC sites from 5 US states (all tertiary, referral centers)
Country of sites	Korea	USA	USA
Type of data & collection	EHR/Retrospective	EHR/Retrospective	EHR/Retrospective
Population setting	General inpatients	ED, wards and ICU	Inpatients
Participant eligibility	Age > 18 yo Hospitalized for more than 48 hrs	Age > 18 yo	Patients aged 18 - 90 years old Hospitalized for more than 48 hrs At least 2 sCr
Population size	SNUBH = 76,756 SNUH = 72,352	UC = 48,463 LUMC = 200,613 NUS = 246,895	Site 1: 153,821 encounters Site 2: 100,819 encounters Site 3: 86,264 encounters Site 4: 57,286 encounters Site 5: 19,542 encounters Site 6: 88,865 encounters
Time period data collection	2013-2017	UC = 2008 – 2016 LUMC = 2007 – 2017 NUS = 2006 - 2015	Jan 1st 2010 to 31st December 2018
Experimental design	SNUBH = 90% T, 10% IV SNUH = EV	UC = IV LUMC & NUS = EV	Site 1: Encounters from 2010 to 31st Dec 2016 = 70% T, 15% C, 15% IV. Encounters Jan 2017 onwards: EV Sites 2 – 6: EV
Female (%)	SNUBH = 46.5% SNUH = 48.3%	UC = 53.5% NUS = 56.7% LUMC = 50.3%	All sites: 44 – 52.5%
Age (median/mean)	SNUBH = 59.6 SNUH = 57.1	UC = 56.6 LUMC = 58.6 NUS = 67.4	% of patients ≥ 66 yo: 21 – 60.2%
Minority representation	Not reported	African American UC = 50% LUMC 22.7% NUS = 7.3%	All sites Black = 0.4 – 21% Asian = 0.5 – 1.9% Native American = 0 – 1% Hispanic = 0.4 – 11.5%
AKI incidence	SNUBH = 4536 (5.91%) SNUH = 2626 (3.63%)	Any AKI = 8.3 – 14.3% AKI ≥ Stage 2 UC = 1664 (3.4%) LUMC = 5722 (2.8%) NUS = 3499 (1.4%)	All sites: Any AKI: 10.1 – 16% Stage ≥ 2 AKI: 1.6 – 3.2% Stage 3 AKI: 0.6 – 1.9%

AKI, Acute kidney injury; EHR, Electronic health records; ED, Emergency department; GPC, Greater Plains Collaborative; ICU, Intensive Care Unit; sCr, serum creatinine; eGFR, estimate glomerular filtration rate; RRT, renal replacement therapy; SNUBH, Seoul National University Bundang Hospital; SNUH, Seoul National University Hospital; UC, University of Chicago; LUMC, Loyola University Medical Center; NUS, Northshore University Health System; T, training; C, calibration; IV, internal validation; EV, external validation.

network and a fifth hospital from the same state. Study 3 used the encounters from site 1 from 2010 to 2016 for training, calibration and internal validation. It then used the encounters from 2017 to 2018 and the population of five other GPC sites for external validation.

All validation cohorts had close or over 50,000 patients, except for site 5 in study 3 which had 19,542. Gender distribution was even in all studies. The median or average age was close to 60 in most cohorts with study 3 exhibiting wider variability between the six sites. Black or African American patients comprised 50% of the internal validation cohort of study 2 and up to 20% in the remaining US study. Only study 3 reported the prevalence of Hispanic, Native American and Asian patients, who accounted for no more than 10% of all patients. Incidence of AKI was lowest in study 1 (3-6%), followed by study 2 (8.3 – 14.3%), and study 3 (15.1%).

Outcome

Acute kidney injury was defined by the serum creatinine criteria of the KDIGO definition in all studies. Studies 1 and 3 used AKI of any grade as the primary outcome while study 2 predicted AKI stage 2 or higher (Table 2). All studies used a 48-hr prediction window except for study 1 that predicted AKI within seven days of the present. Prediction was continuous throughout a patient's admission in all studies with data binned into time windows between 6 to 24 hrs. Two of three studies (1 and 3) prioritized a pre-admission serum creatinine to represent the baseline value,

followed by admission measurements (study 2) or imputation using the Modification of Diet in Renal Disease (MDRD).

General model characteristics

Predictor data

The lowest number of predictor variables was 59 (study 2) and the highest was 1933 (study 3) (Table 2). Study 3 used all available variables in their health system or network EHR, while study 1 selected those known to be associated with AKI risk and study 2 did not specify the variable selection process. Most variable categories included demographic information, vital signs, laboratory and diagnostic data, comorbidities, medications, clinical conditions (usually labelled by ICD 9 or 10 codes) procedures or interventions as well as nursing documentation (study 2) and length of stay. All studies included sCr and blood urea nitrogen (BUN) as predictors but only study 3 evaluated model performance with and without the inclusion of

TABLE 2 Prediction model characteristics and results.

	Study 1 (13)	Study 2 (14)	Study 3 (15)
Primary prediction outcome	AKI within 7 days	AKI Stage ≥ 2 within 48 hrs	AKI within 48 hrs
Method used to calculate baseline sCr	1) Min sCr within 2 weeks pre-admission, or 2) Min sCr within 90-180 days pre-admission, or 3) Admission sCr	Admission sCr	1) Most recent sCr pre-admission, or 2) First sCr on admission
Static vs Continuous prediction	Continuous	Continuous	Continuous
Number of predictors in final model	107	59	1933
Predictor categories in final model	Demographic, vital signs, comorbidities, medications, laboratory values and clinical conditions (e.g., ICU admission)	Demographic, absolute values and trend information for vital signs and laboratory values, interventions, medications, procedures, LOS, nursing documentation (e.g., Braden score).	Demographic, diagnoses, procedures, lab tests, medications, vital signs
Method for predictor variable selection	Features considered as risk factors of AKI from the literature or correlated with AKI development.	Not mentioned	All variables in the PCORnet CDM schema shared across the 6 GPC sites
Best performing model type	RNN	DS-GBM	DS-GBM
Comparison model	GBM	–	1) LASSO model 2) Model (GBM & LASSO) without sCr and BUN data
External validation performance AUROC 1 = Any AKI 2 = Stage ≥ 2 AKI	SNUH = 1) 0.84, 2) 0.90	LUMC = 2) 0.85 NUS = 2) 0.86	Site 1: 1) 0.76, 2) 0.81 Site 2: 1) 0.75, 2) 0.79 Site 3: 1) 0.63, 2) 0.73 Site 4: 1) 0.6, 2) 0.68 Site 5: 1) 0.71, 2) 0.8 Site 6: 1) 0.62, 2) 0.71
Other performance measures	Sensitivity, specificity, PPV, NPV, F1 score, MSE	Calibration using visual plots Sensitivity, specificity, PPV, NPV	AUPRC Calibration using Hosmer-Lemeshow score
Type of external validation	Geographic: SNUH	Geographic: LUMC & NUS	Temporal: site 1 Geographic: sites 2-6
Interpretability	1) Shapley Additive Explanations, partial Dependence Plots (PDP) and accumulated local effects plots 2) Instance-wise interpretation with individual conditional expectation (ICE) plots	Variable importance plot	Shapley Additive Explanations
Top predictive variables	1) Baseline eGFR 2) Baseline sCr	1) Change in sCr 2) Length of stay 3) SF ratio	1) sCr and its change 2) Vancomycin exposure 3) Minimal value & hourly change in BP value

(Continued)

TABLE 2 Continued

	Study 1 (13)	Study 2 (14)	Study 3 (15)
Handling of missing information	Carry-forward imputation	Median (for continuous data) or mode (for categorical data) by location being imputed for missing predictor values that remained after carry-forward imputation	Carry-forward imputation
Proportion of missing data	Not reported	Not reported	Not reported
Code availability	Not provided	Not provided	Available on GitHub

sCr, serum creatinine; MDRD, Modification of Diet in Renal Disease; RNN, Recurrent neural network; DS-GBM, Gradient Boosting Model with discrete time survival framework; ML, machine learning; AUROC, area under the receiver operating curve; AUPRC, area under the precision receiver curve; PPV, positive predictive value, NPV, negative predictive value, MSW, mean squared error; SNUH, Seoul National University Hospital; SNUH, Seoul National University Hospital; UC, University of Chicago, LUMC, Loyola University Medical Center; NUS, Northshore University Health System; LASSO, Least absolute shrinkage and Selection Operator; CDM, common data model; SF ratio, ratio of oxygen saturation in arterial blood to the % of oxygen in inspired air.

these variables. All studies used carry-forward imputation for missing data but none of them reported the actual proportion of missing data.

Type of prediction models and performance

In the external validation cohorts and for the prediction of stage 2 or higher AKI within 48 hrs, Study 2, which used a Gradient Boosting Model with discrete time survival framework (DS-GBM) had the best performing model (AUROC 0.85-0.86) followed by study 3 (AUROC 0.68 – 0.81), which also used DS-GBM. Study 1, which used a Recurrent Neural Network (RNN) to predict AKI within 7 days had excellent performance (AUROC all AKI 0.84 and stage ≥ 2 AKI 0.90). Performance was compared to a GBM in study 1 and to a Least Absolute Shrinkage and Selection Operator (LASSO) model in study 3.

Beyond discrimination, studies evaluated models using calibration (1 and 2), sensitivity, specificity, positive and negative predictive value (1-3), area under the precision receiver curve (3) and F1 score (1). All studies performed some form of interpretability analysis to contextualize predictions which showed that serum creatinine – either as a baseline absolute value, in the form of change over time or integrated within an eGFR equation - was consistently the strongest predictor of future AKI risk. Further study and model information can be found in Data Sheet 1 of the Supplemental Material.

Type of external model validation

All three studies performed geographic external validation and study 3 also performed temporal validation using the later encounters from the source population.

Critical appraisal

Assessment of bias, applicability and reproducibility

All except for study 3 were found to have a high risk of bias in the participant and outcome domains. The former resulting from the use of retrospective EHRs as primary data source and the latter to the incorporation bias inherent in the inclusion of serum creatinine in the outcome definition. We considered the development of a second model without serum creatinine and BUN information in Study 3, as an attempt to mitigate this bias. The predictors and analysis domains were uniformly deemed as having low risk of bias (Table 3). Applicability was a concern for studies 1 and 3 that used more than 100 predictor variables. With regards to reproducibility, only study 3 shared code in a publicly accessible domain. Individual study PROBAST assessment forms can be found in the Supplemental Material.

Discussion

We screened 889 studies from the last five years in search of externally validated ML prediction models of AKI based on general hospital patients. Only three studies were retrieved that fit these criteria. While most performed well and had a sound methodological approach, the main concerns relate to their development and validation in populations with limited diversity, comparable digital ecosystems and use of large number of predictor variables. These are potentially critical limitations to their applicability in diverse socioeconomic and cultural settings, prompting a need for simpler and more transportable prediction models. In addition, all models rely heavily on serum creatinine, which questions their added utility and advantage over the current tools used to predict and diagnose AKI.

Of the 886 studies not included, a majority were excluded due to lack of external validation, use of sub-populations (mainly ICU and surgical cohorts) or predictions based on standard regression, parametric models. The finding of a growing number of prediction models generated on clinical sub-populations, often from publicly available datasets, without any external validation has been noted by previous systematic reviews (3, 5).

Most models performed well, especially when predicting stage 2 or higher AKI, which is often regarded as the more meaningful outcome in the acute setting (16). Discrimination remained high between internal and external validation sites in studies 1 and 2 but varied widely across the 6 sites of study 3 which had the highest diversity in demographic profiles and EHR structures. The main barriers to independent validation of a prediction model include patient heterogeneity, clinical process variability, EHR configuration and data warehouse heterogeneity leading to non-interoperable databases across hospitals (15). Models should be ideally trained and validated on diverse populations from healthcare sites with a spectrum of maturity and sophistication in their digital ecosystems. There is little point in training a model with thousands of variables that it is unlikely to ever encounter when applied to a

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TABLE 3 Traffic light plot of risk of bias assessment.

		Study 1	Study 2	Study 3
ROB	Participants	high	high	?
	Predictors	low	low	low
	Outcome	high	high	low
	Analysis	low	low	low
Applicability	Participants	low	low	low
	Predictors	high	low	high
	Outcome	low	low	low
Overall	ROB	high	high	low
	Applicability	high	low	low

ROB, risk of bias; ?, unclear risk.
Red = high risk, Green = low risk, Yellow = Unclear risk.

different healthcare system. Hence, the concerns of applicability in most of the presented studies. To address this, Song et al. (study 3) explored the source of performance variability between the original and target sites and proposed a metric for model transportability. Interestingly, the study brings to light how differences in data representation and format between individual EHRs can have a significant impact on what a model learns and how it performs (15). Overall, this would suggest that a model which uses fewer and more commonly available clinical variables, like the one from study 2, is likely to have better uptake and be more easily validated.

From applicability to implementation, there is a growing concern that much of the attention in the field of machine learning risk prediction has centered around model development and not on the transition to implementation and deployment (17). Providing a framework on the lifecycle management of a model is critical to its success as a clinical decision support tool. This includes information on how often a model should be re-validated, potentially re-trained and fine-tuned as well as how it should be integrated into clinical workflows (18, 19). While this information may be available in the coming years, at present none of the studies specifically addressed this. It should also be said that the reluctance of most groups to share their development code, hinders efforts to make the models more reproducible and transportable.

The use of serum creatinine as a predictor and as part of the outcome definition is problematic. The latter results in incorporation bias whereby the association between the predictor and the outcome is overestimated rendering model performance evaluations optimistic (11). In reality, however, any model that uses the current serum creatinine based KDIGO definition of AKI and has access to repeated measures of serum creatinine, will suffer from this bias. With regards to the use of creatinine as a predictor, the interpretability analyses of all studies revealed that either the baseline serum creatinine and eGFR (which includes serum creatinine in its calculation) or the change in serum creatinine over time were among the top three heaviest contributors to the prediction. The question then becomes: *what can these models offer that a single or trend in serum creatinine readings cannot?* Study 3 trained a model without any information on serum creatinine or BUN which performed competitively with an AUROC of 0.75 for any AKI and 0.82 for stage 2 or higher AKI. The main predictors of AKI in this model were vancomycin exposure, blood pressure change, age, BMI, height, having a chest x-ray and receiving Tazosin antibiotic. It should be noted, however, that this model used almost 2000 predictor variables to arrive at this prediction.

Perhaps the real advantage of these models lies not in their capacity to process large and complex health data in order make timely predictions but in their potential for integration within clinical workflows. A health professional must know to order a serum creatinine test on a particular at-risk patient, they must then remember to check it once it has been reported and to act on it using evidence-based guidelines. A disruption to this process, which is time-consuming and often falls to the most junior medical staff in the hospital, may result in a missed opportunity to avoid or minimize the severity and consequences of AKI. Automating this process with a prediction algorithm that can seamlessly aggregate the relevant historical and admission information and present the clinician with a real-time risk profile for each patient on any given day, may go a long way towards decreasing the incidence of hospital-acquired AKI. It remains to be seen, however, whether the same can be achieved with more comprehensive education of junior doctors and clearer accountability structures within healthcare teams.

The main limitation of our study is the narrow search and selection criteria. In wanting to explore only machine learning as a novel technology in AKI risk prediction we have not compared or evaluated the more traditional regression models and risk scores, such as linear and logistic regression or Naïve Bayes classifier. It would be prudent to say that, at this stage, the benefits of ML in AKI are not clear. Relying on more explainable, less complex statistical models while this technology matures, may be the wiser approach. In addition, by selecting only models that had been externally validated we may have missed studies with sound methodology that were in the early stages of validation.

The use of ML models for AKI prediction requires large and complex data structures to support them, have potentially limited applicability beyond the health systems they were trained on and, at

present, rely heavily on a cheap and readily accessible biomarker of kidney injury with little apparent benefit from the other predictors. In the future, simpler and more transportable models that offer a significant predictive advantage to using serum creatinine measurements may find greater clinical utility and acceptance within the healthcare community.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

MW and SS were responsible for the conception and design of this systematic review. EF and MW performed in equal parts the acquisition, analysis, interpretation and presentation of the data. MW drafted the manuscript. DJ and SS revised each draft critically for important intellectual content. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Supplementary material

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EDITED BY
Motonobu Nakamura,
The University of Tokyo, Japan

REVIEWED BY
Yoshifumi Hamasaki,
The University of Tokyo Hospital, Japan
Daisuke Katagiri,
National Center for Global Health and Medicine, Japan

*CORRESPONDENCE
Farrukh M. Koraishy
Farrukh.Koraishy@stonybrookmedicine.edu

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Dialysis resource allocation in critical care: the impact of the COVID-19 pandemic and the promise of big data analytics

Farrukh M. Koraishy* and Sandeep K. Mallipattu

Division of Nephrology, Department of Medicine, Stony Brook University Hospital, , Stony Brook, NY, United States

The COVID-19 pandemic resulted in an unprecedented burden on intensive care units (ICUs). With increased demands and limited supply, critical care resources, including dialysis machines, became scarce, leading to the undertaking of value-based cost-effectiveness analyses and the rationing of resources to deliver patient care of the highest quality. A high proportion of COVID-19 patients admitted to the ICU required dialysis, resulting in a major burden on resources such as dialysis machines, nursing staff, technicians, and consumables such as dialysis filters and solutions and anticoagulation medications. Artificial intelligence (AI)-based big data analytics are now being utilized in multiple data-driven healthcare services, including the optimization of healthcare system utilization. Numerous factors can impact dialysis resource allocation to critically ill patients, especially during public health emergencies, but currently, resource allocation is determined using a small number of traditional factors. Smart analytics that take into account all the relevant healthcare information in the hospital system and patient outcomes can lead to improved resource allocation, cost-effectiveness, and quality of care. In this review, we discuss dialysis resource utilization in critical care, the impact of the COVID-19 pandemic, and how AI can improve resource utilization in future public health emergencies. Research in this area should be an important priority.

KEYWORDS

critical care, resource deployment, dialysis, COVID-19, big data, artificial intelligence, machine learning

1 Introduction

In the United States, the cost of an intensive care unit (ICU) stay is approximately $4,300 per day, and the total annual critical care cost is estimated to be approximately $108 billion, which is 13.2% of total hospital costs and 4.1% of the national health expenditure (1). The past decade has seen an increasing demand for critical care due to longer life expectancy, greater comorbidity burden, and better survival rates in the ICU (1–4). "Access to critical care" is defined based on the patient's capacity to benefit from the available

resources (5). Often the sickest patients admitted to the ICU have the highest capacity to benefit in terms of reduction in mortality risk, making admissions of these patients more cost-effective (measured by the cost per life-year saved) than those of patients with a lower risk of death (6). Due to the increasing demands and limited resources and budgets, critical care has become a scarce resource, leading to the undertaking of value-based cost-effectiveness analysis (CEA) and resource rationing to achieve the most efficient and effective patient care (2).

The resource utilization policies in the ICU should be guided not just by resources, but also by the goals of equity of access and prevention of both short- and long-term morbidity and mortality (2). Although clinician judgment can be effective at identifying the patients who would benefit most, very large volumes of valuable real-time ICU data are underutilized. Artificial intelligence (AI)-based data analytics are being utilized in multiple data-driven healthcare services such as decision support (7–9), prediction of disease trends and outcomes (10), and long-term health (11). AI also has tremendous potential to improve the optimization of healthcare system utilization (12) through the analysis of extremely large datasets. In this review, we will discuss how AI can improve the utilization of scarce critical care resources, using the lessons learned from dialysis utilization during the COVID-19 pandemic.

2 Dialysis resource management in critical care

2.1 Utilization of dialysis in critically ill patients

Dialysis is one of the most common procedures utilized in the ICU (13). Although neither of the two most commonly used modalities—continuous kidney replacement therapy (CKRT) and intermittent hemodialysis (IHD)—offers a significant survival advantage over the other (14), IHD is the more common modality of choice, and CKRT is typically recommended for patients with hemodynamic instability and those with high levels of intracranial pressure (15, 16). CKRT is also used in fluid management (especially when the obligate intake is large), burns, sepsis, and heart and liver failure patients (17). The choice of modality has been variable and is based on local ICU practices and the availability of resources (18). CKRT is more costly than IHD. In a base-case analysis, CKRT was found to cost $3,679 more than IHD per patient (19). In addition to machine cost, there is a significant cost associated with the large volume of dialysis and replacement fluids involved in CKRT (20). In addition, whereas CKRT is typically conducted by the ICU nurse taking care of the patient, IHD requires dialysis nurses, which adds to the personnel cost (21). Several studies have looked at the cost-effectiveness of CKRT compared with IHD (20, 22–24). In a *post-hoc* analysis of the BEST Kidney Study, using data from 53 centers across 23 countries, Srisawat et al. reported that the median cost per day was $289.60 (IQR $830.8–$116.8) greater for CKRT than for IHD, and that reducing the replacement fluid volumes increased the cost savings (20). In another study of critically ill patients with AKI, despite the greater initial cost of CKRT in the ICU, the 5-year total cost, including the cost of dialysis dependence, was lower for CKRT than for IHD (24). In a recent systemic review of seven published CEAs of CKRT vs. IHD, Singh et al. reported a marginal quality-adjusted life year (QALY) gain for CKRT, and that the cost-effectiveness of CKRT was mainly due to the long-term dialysis dependence rates (23).

2.2 Cost estimation for dialysis utilization in the ICU

Cost estimation in critical care is confounded by other factors such as pre- and post-ICU healthcare and the clinical diversity of patients, making the average daily ICU cost variable from one patient to another (2). Minimizing ICU costs can potentially be plagued by "cost shifting", that is, greater costs incurred in the provision of non-ICU health services for the same patient. Unfortunately, most of the earlier published CEAs in critical care have focused on short-term outcomes such as ICU mortality and length of stay. However, the estimation of long-term outcomes, such as Health-Related Quality of Life (HRQOL) (25), socioeconomic impact of critical illness (26), and measures of longer-term morbidity and mortality in ICU survivors are crucial to more accurately determining cost-effectiveness and guiding decision-making on resource utilization (2). Patient-centered outcomes and societal perspectives are very important to improving the quality of CEA (27–29). In a study of 959 patients with AKI who were treated with dialysis in the ICU and followed up for 3 years, the main factors found to be associated with major adverse kidney events (death, incomplete kidney recovery, or development of end-stage kidney disease [ESKD]) were severity of illness and use of CKRT (vs. IHD) during the ICU admission (30). In another study looking at ICU survivors, the QOL, although lower at 3 months post-discharge, was similar at the 1- and 4-year follow-ups among those admitted to the ICU with acute kidney injury (AKI) requiring dialysis and those without AKI (31). Therefore, both short- and long-term healthcare expenditure and outcomes in critically ill patients with AKI should be analyzed for robust cost estimation. The factors traditionally used in the allocation of dialysis are summarized in Table 1.

3 Impact of the COVID-19 pandemic on dialysis allocation

3.1 Critical care resource allocation during the COVID-19 pandemic

Healthcare emergencies such as natural disasters and infectious disease pandemics exert a severe impact on critical care resources and require the creation of comprehensive policies on resource allocation (32). The influenza pandemics at the start of the 21st

TABLE 1 Factors traditionally linked to the cost of dialysis in the ICU.

Dialysis-related costs	Staff-related costs	Hospital-related costs	Patient-related costs
Dialysis machines	ICU nurse vs. dialysis nurse	ICU beds	Dialysis access placement
Dialysis solutions	Nursing time	Patient monitoring devices	Need for large dialysis volumes and adequate clearance
Dialysis filters (type and life span) and dialysis tubing	Technician time	Patient and machine transport	Hypercoagulable state
Anticoagulation medications	Clinician time		Need for vasopressors during dialysis-related hypotension
Other intravenous solutions such as calcium and saline			

ICU, intensive care unit.

century, such as the H5N1 ("bird flu") and H1N1 ("swine flu") pandemics, resulted in acutely limited availability of mechanical ventilators (33), and triage protocols for resource deployment based on the Sequential Organ Failure Assessment (SOFA) score (34) were created to allocate access to critical care resources (35, 36). However, critical care triage during pandemics simply based on physiological scores such as SOFA has its limitations, and protocols should be modified based on other data, such as those related to outcomes, as they emerge in real-time (36).

The coronavirus disease 2019 (COVID-19) (37) pandemic resulted in an unprecedented burden on critical care units, leading to the reassessment of the existing pandemic utilization and allocation policies to better prepare ICUs for the unique challenges posed by COVID-19 (38). At the start of the pandemic in the United States, an Expert Panel Report of the Task Force for Mass Critical Care and the American College of Chest Physicians recommended a triage system to guide critical care resource management toward the patients who were most likely to benefit while maintaining the standard of care (32). Over the last 3 years, the emergence of new variants, variable isolation protocols, mass vaccination policies across nations and regions, and evolving therapies have led to difficulties in enforcing resource allocation policies that need to be constantly adapted in line with the changing face of the COVID-19 pandemic (39). This has led to the recognition of the importance of utilizing large real-time datasets for institutional planning and resource allocation to ensure standards of care under crisis and to meet the egalitarian and utilitarian principles of clinical practice.

3.2 Allocation of dialysis during the COVID-19 pandemic

AKI is common in patients with COVID-19 (40, 41) and is associated with in-hospital complications and mortality (41–47). A high proportion of COVID-19 patients admitted to the ICU, especially in the first year of the pandemic, required CKRT (48–50), resulting in a major burden on critical care resources. Assessing the risk of respiratory failure and the need for ventilators were not immediately recognized as priorities when treating patients with COVID-19, and similarly, the impact of dialysis-requiring AKI was not fully understood until later in the pandemic (51, 52). In addition to dialysis machines, there was a major increase in demand for all components of hospital dialysis programs, including nursing staff, technicians, and consumables such as dialysis filters and solutions and anticoagulation medications (53). In addition to patients who developed AKI, dialysis requirements also increased for patients with ESKD, who also had significantly increased rates of ICU admission (53).

This crisis led to the development of resource management policies in acute dialysis units across hospitals (53). The shortage of CKRT machines led to the creation of regional and institutional policies on increasing supply and developing stockpiles of CKRT machines (54, 55). Some academic centers adopted crisis protocols of prolonged intermittent kidney replacement therapy (56) or accelerated venovenous hemofiltration (57), and CKRT devices could be shared between patients. This novel strategy entailing the sharing of tools among patients undergoing CKRT in ICUs in close geographical proximity reduced nursing workloads and the need for machine transportation (58). However, the sharing protocols increased the demands of dialysis fluids due to the increased flow rates required for effective clearance. To address this demand, some centers adopted the policy of "fixed hours" on CKRT (51). Alternate dialysis strategies such as sustained low efficiency dialysis (SLED) that utilize the hospital water supply, hence minimizing the need for consumable dialysis solutions, were adopted in some centers (59). However, the drawback with SLED was the requirement of a dialysis nurse since most ICU nurses are not trained in this modality. To address the issue of nursing staff shortage, at our institute we adopted the remote telemonitoring of dialysis treatments, which was found to be safe, reliable, and minimized the risk of staff exposure (60). Some hospitals also employed acute peritoneal dialysis (APD) to expand their capacity and to tackle the shortage of hemodialysis machines (61). However, the role of APD in critically ill patients with COVID-19-related respiratory failure is limited by the risks of ventilatory compromise, especially in patients with requirements for high levels of oxygen, positive end-expiratory pressures, or proning (61, 62). The increased hypercoagulability seen in COVID-19 patients posed another challenge, due to the reduced filter life span and constant need to change filters, leading to increased costs and nursing workload (63). This led to the enforcement of anticoagulation protocols to minimize filter clotting. There is a dearth of data on CEAs in critical care dialysis allocation during the COVID-19 pandemic. One study of patients with ESKD comparing dialysis modality found that IHD was associated with a greater cost than PD during the COVID-19 pandemic (64). Finally, another challenge was the arrangement of outpatient dialysis centers, especially for new patients who required long-term dialysis. The development of isolation protocols and the arrangement of isolation rooms in chronic dialysis units with

limited resources did not occur at a rate equal to the rapid increase in demand. This led to prolonged hospitalizations.

In summary, a large number of factors are involved in dialysis resource allocation to critically ill patients, especially during public health emergencies (Table 2). Using large datasets and smart analytics that can take into account all the relevant healthcare information in the hospital system could lead to efficient and cost-effective dialysis resource allocation in future public health emergencies.

TABLE 2 Non-traditional data can be utilized for AI-based dialysis resource allocation and CEAs in critically ill patients during healthcare emergencies.

Dialysis/ staff	Hospital/ administration	Patient	Outcomes (short- and long-term)
Hemodynamic data	ICU budget	Primary diagnosis	ICU mortality
Ultrafiltration data	Geolocalization of dialysis services	Demographics and zip codes	Hospital mortality
Blood pressure medications	Back-up resource generation	Comorbid medical/mental conditions and pain	Long-term mortality
Stockpiles and inventory of dialysis machines and dialysis catheters	Emergency policy committees	Severity of illness scores	Length of ICU stay
Backup dialysis staff	Redeployment protocols	Medications (outpatient and inpatient)	Length of hospital stay
Backup ICU staff	ICU rooms	Laboratory and other tests (outpatient and inpatient)	Hospital readmission rates
Staff training	Weekend coverage	Baseline ESKD and years on dialysis	Duration of acute dialysis requirement
Social distancing and contact tracking	Isolation rooms	Ventilator and vasopressor data	Days to recovery from AKI
Return-to-work policies	Telemedicine services	Nutritional and functional status	Inpatient nephrology follow-up
PPE	Crisis teams	Long-term dialysis access	Post-AKI CKD
Utilization of APD and SLED	Daily census	Infections, antibiotics, and vaccination data	Post-AKI ESKD
Data on machine sharing and reduced dialysis flow rates/ frequency/time	Inventory and shipment tracking	Transplant status	HRQOL
Anticoagulant dosing	Pharmacy, radiology, and vascular surgery services	Residence location, education level, employment, and socioeconomic status	Outpatient nephrology follow-up
Dialysis prescription		Substance abuse	

(Continued)

4 The role of big data and AI in optimizing utilization and allocation of dialysis resources

4.1 Overview of big data and AI in healthcare

The use of advanced information technologies to improve healthcare has seen a rapid advancement since the turn of the millennium owing to the rapid progress made in computer science and information technology (65). Modern health data analytics is focused on high-quality, efficient, and cost-effective care delivery and personalized medicine (66–70). This requires the ability to capture, integrate, and analyze heterogeneous unstructured and structured data in real-time from healthcare systems (71). Healthcare systems such as ICUs generate very large volumes of data constantly. The rapidly evolving AI techniques such as machine learning (ML) have the ability to analyze extremely large datasets, learn patterns, and identify non-linear associations and causal relationships (72, 73).

Healthcare data analytics include "data-driven" methods that include ML and pattern recognition algorithms and are categorized as supervised (classification) and unsupervised (clustering) learning models (74). "Knowledge-driven" methods include logic-based knowledge modeling and reasoning algorithms based on clinical data (75) and can be more readily applied to clinical decision-making (72). The applications of these models include "decision analytics" (e.g., the diagnosis and treatment of diseases), "predictive analytics" (e.g., using real-time data to predict health outcomes), "prescriptive analytics" (e.g., the simulation of future outcomes), "comparative analytics" (e.g., using data to compare impact of two different interventions on an outcome), and "semantic analytics" (e.g., using large datasets to understand complex relationships between the variables for hypothesis generation and testing) (72).

As the volume of data provided by ICUs and complexity of healthcare data have increased tremendously, there is an increasing need to develop general-purpose frameworks that allow non-experts to be able to easily apply complex AI algorithms to health management (72). It is important that non-AI experts understand the various facets of healthcare data, such as "variety" (multiple novel data sources such as biometrics and "omics" data), "veracity" (source and accuracy of data), "volume" (amount of data),

TABLE 2 Continued

Dialysis/ staff	Hospital/ administration	Patient	Outcomes (short- and long-term)
Missed and/or incomplete dialysis sessions		Imaging data	
Dialysis refusal/ withdrawal		Resuscitation data	
Staff feedback		Patient feedback	
		Wearable devices	
		Health literacy	
		Health insurance	
		Research data	

ICU, intensive care unit; AKI, acute kidney injury; ESKD, end-stage kidney disease; HRQOL, health-related quality of life; PPE, personal protective equipment; SLED, slow low-efficiency dialysis; APD, acute peritoneal dialysis.

"velocity" (the rate at which new data are generated), and, finally, "value" (knowledge gained and potential for clinical application) (76). All these data features are typically high in the ICU, making it an ideal setting for intelligent data analytics. However, to apply the correct analytical methods and to properly interpret the analysis, a proper understanding of each of these facets of healthcare data is critical.

4.2 The use of big data and AI in critical care resource allocation

Data mining and AI technology are now being increasingly used for human resource management systems and to improve workflows and cost–benefit ratios in healthcare systems (77–79). Previous studies have shown the utility of AI in the efficient scheduling of operating rooms (80), improvement of patient waiting times and staff workflow (81–84), reduction of hospital discharge time and length of stay (85), efficient hospital bed allocation (86), and the reduction of response time and hospital costs (87).

AI and big data analytics have great applications in mobile ("m")-health (88) and in the recent pandemic, the use of tele-ICU in care delivery has greatly increased, especially by hospitals in remote, underserved settings (89). An intelligent remote monitoring system with innovative data analytics has been developed for the post-ICU monitoring of patients with COVID-19, which has the potential to reduce the length of ICU stays (90).

The unprecedented challenge created by the COVID-19 pandemic and the constant emergence of new data has further highlighted the importance of the integration of smart advanced information technologies in healthcare (91). Sottile et al. recently reported the use of smart analytics to predict mortality in patients hospitalized with COVID-19 using electronic health record (EHR) data (92). Cheng et al. reported the use of AI-based tools to predict the risk of ICU transfer in patients admitted for COVID-19 (93).

Therefore, the use of big data and AI-based technology has great potential to improve the management and allocation of resources in critical care.

4.3 The use of big data and AI in the allocation of dialysis

There are many factors to consider in the management of resources related to dialysis utilization. In one study conducted among hospitalized patients requiring dialysis, factors such as health insurance, ischemic heart disease, late referral to the nephrologist, and the use of temporary vascular access for the first dialysis were identified as the major factors contributing to an increased length of hospital stay (94). Other studies have identified that poorly controlled anemia, depression, and pain were factors associated with the increased utilization of hospital dialysis resources (95, 96). Limited health literacy was shown to significantly increase the risk of hospitalization among patients on chronic dialysis (97). As mentioned, the allocation of dialysis resources was a major challenge during the COVID-19 pandemic that required the development of emergency programs (98). The shortage of resources also resulted in ethical challenges for patients, families, clinicians, and policymakers for resource prioritization (99, 100).

To ensure equity and justice, there is a critical need to harness big data to maximize the cost-effective utilization of dialysis resources while maintaining the standard of care in critically ill patients. Although previous studies have identified important factors that can be addressed to improve the management of dialysis resources (51, 54–59, 61–63, 94–100), the availability of large volumes of EHR data in dialysis patients is a prime resource for the application of AI-based smart analytic tools for resource management (Table 2). The use of AI-based data analytics is rapidly increasing in the field of nephrology, and its application has increased our understanding of disease pathogenesis, outcome prediction, and the personalization of medicine (101). ML-based analytic models have been shown to outperform clinician-based predictions related to AKI (102–104). We have previously shown the use of X-Boost-based machine learning algorithms to predict the severity of AKI, the need for dialysis, and renal recovery in patients with COVID-19 (105). Data from existing repositories such as the EHR can help clinicians and administrators better triage existing dialysis resources to the hospitals that are and the patients who are predicted to need them most. Future research in this area should be an important priority.

4.4 Knowledge gaps and challenges in the use of big data and AI

As with any innovative technology, the hype and expectations surrounding intelligent data analytics have to be modified based on their limitations and drawbacks. The incorrect selection of datasets or analytic tools, erroneous processing of data, and incorrect interpretations of the results are major challenges that will need

TABLE 3 Key factors in the application of AI-based analytics of EHR data for dialysis resource allocation.

Correct selection of datasets or analytic tools
Correct data processing
Rigorous data quality checks
Harmonization of data from different EHR systems
Data security
Correct interpretations of the results
Minimize bias
External validation of tools
Output data needs to be easily understood by clinicians (XAI)
Patient education
Patient privacy and confidentiality
Resource supply and demand monitoring
Incorporation of evolving disease management guidelines, especially during new health emergencies such as epidemics/pandemics
Cyber security
Development of regulations and guidelines for the use of AI-based smart analytics in patient care

AI artificial intelligence; XAI, explainable artificial intelligence; EHR, electronic health record.

to be overcome in a field such as healthcare where the health of patients is at stake (Table 3). In a systemic review of 46 studies of the use of ML models to predict AKI, a high risk of bias and lack of external validation of the models was observed (102).

To develop the trust of the healthcare community in this technology, the output data need to be clinically explainable and the processes transparent (106). In addition to clinicians, it will also be important to develop patient trust; hence, patient education will be crucial. Explainable artificial intelligence (XAI) is the next frontier in AI-based healthcare analytics (107). As with all aspects of healthcare delivery, patient privacy and confidentiality are paramount (108) and the privacy risks should be communicated to the patients and their consent obtained (109). Several regulatory compliance steps for data security might limit the use the AI systems until transparency and understanding improve (110). Patient characteristics, the nature of diseases, and the types of diagnostic tests and treatments can change with time, and this needs to be accounted for when updating existing AI tools and developing new ones. Rigorous checks on data quality must be carried out, and the harmonization of data across different EHRs in different health systems should be conducted before their application for analysis. In our recent study on characterizing AKI in patients with COVID-19, we leveraged EHR data in patients with COVID-19 from 53 healthcare systems across the United States (41). State-of-the-art data cleaning, quality control, and harmonization processes were undertaken before the analytical steps (41). Finally, the vulnerabilities of AI models to "adversarial attacks" should be routinely monitored and appropriate precautionary and corrective measures should be applied (111).

The development of laws, regulations, and guidelines for the use of healthcare data and AI-based smart analytics needs to be developed for use in all aspects of healthcare, including resource allocation (112). Improved accuracy of the data and understanding of AI tools would strengthen the healthcare community's trust in them (113).

5 Conclusions

The COVID-19 pandemic resulted in an unprecedented burden on critical care units worldwide. Dialysis machines became scarce, leading to value-based CEA and the rationing of resources to deliver patient care of the best quality. AI-based big data analytics are now being utilized in multiple data-driven healthcare services, including the optimization of healthcare system utilization. Data from existing repositories such as the EHR can help clinicians and administrators to better triage existing dialysis resources to the hospitals and patients who are predicted to need them most. Although the application of AI-based big data analytics for dialysis allocation in critical care holds a lot of promise, several challenges need to be taken into consideration. Future research in this area should be an important priority.

Author contributions

FK: Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing. SM: Conceptualization, Funding acquisition, Resources, Validation, Visualization, Writing - review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Sayna Norouzi,
Loma Linda University Medical Center (LLUMC), United States

REVIEWED BY
Augusto Ministro,
CHUL, Portugal
Khaled Boubes,
The Ohio State University, United States

*CORRESPONDENCE
Gift Echefu
Gechefu@uthsc.edu

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Central vein stenosis in hemodialysis vascular access: clinical manifestations and contemporary management strategies

Gift Echefu[1]*, Ifeoluwa Stowe[2], Abdulkareem Lukan[3], Gaurav Sharma[4], Indranill Basu-Ray[5,6], London Guidry[7], Jon Schellack[7] and Damodar Kumbala[7,8]

[1]Division of Cardiovascular Medicine, The University of Tennessee Health Science Center, Memphis, TN, United States, [2]Department of Internal Medicine, Baton Rouge General Medical Center, Baton Rouge, LA, United States, [3]Department of Internal Medicine, Advocate Illinois Masonic Medical Center, Chicago, IL, United States, [4]Department of Nephrology, AIIMS Rishikesh, Rishikesh, India, [5]Department of Cardiology, AIIMS Rishikesh, Rishikesh, India, [6]Department of Cardiovascular Disease, Memphis Veterans Affairs Medical Center, Memphis, TN, United States, [7]Vascular Clinic of Baton Rouge, Baton Rouge, LA, United States, [8]Renal Associates of Baton Rouge, Baton Rouge, LA, United States

Central venous stenosis is a significant and frequently encountered problem in managing hemodialysis (HD) patients. Venous hypertension, often accompanied by severe symptoms, undermines the integrity of the hemodialysis access circuit. In central venous stenosis, dialysis through an arteriovenous fistula is usually inefficient, with high recirculation rates and prolonged bleeding after dialysis. Central vein stenosis is a known complication of indwelling intravascular and cardiac devices, such as peripherally inserted central catheters, long-term cuffed hemodialysis catheters, and pacemaker wires. Hence, preventing this challenging condition requires minimization of central venous catheter use. Endovascular interventions are the primary approach for treating central vein stenosis. Percutaneous angioplasty and stent placement may reestablish vascular function in cases of elastic and recurrent lesions. Currently, there is no consensus on the optimal treatment, as existing management approaches have a wide range of patency rates.

KEYWORDS

central vein stenosis and obstruction, hemodialysis vascular access dysfunction, percutaneous angioplasty (PTA), indwelling catheter complications, endoluminal obstruction, Hemodialysis Reliable Outflow (HeRO) graft

Introduction

Hemodialysis patients with end-stage renal disease need optimal vascular access to promote survival. The type of hemodialysis access and its maintenance significantly impact their mortality and quality of life. Functioning access is essential for the provision of appropriate hemodialysis (HD). In cases where an arteriovenous fistula cannot be placed,

an arteriovenous graft is an alternative access. The tunneled, cuffed HD catheter is the least favored. Cuffed HD catheters are usually placed for the initiation of HD in patients with immature AV access or as a last resort in patients with no other vascular access alternatives (1–3). According to the Kidney Disease Outcome Quality Initiative (KDOQI), a CVC is acceptable for dialysis in the short term if an AV access has been created but is not ready for use, in patients with acute transplant rejection, or other complications requiring dialysis, peritoneal dialysis patients with complications that require short-term HD due to time-limited peritoneal rest or AV access complications that result in temporary non-use and patient scheduled for a living donor transplant in <90 days. Furthermore, it is acceptable for long-term use if the patient has had multiple failed prior AV accesses with no available options, limited life expectancy, or valid patient preference (4).

Although central venous stenosis and occlusion are common, they are often underdiagnosed, resulting in significant long-term effects, such as venous hypertension leading to inadequate dialysis delivery due to recirculation, reduced AVF maturation, and lower long-term patency rates, and superior vena cava syndrome. CVS increases with stiff non-cuffed catheters primarily if used for an extended period (1, 5, 6). Therefore, KDOQI guidelines recommend their use for periods not exceeding seven days (7). Nevertheless, central venous stenosis has been observed in patients with neither a central vein catheter nor a history of thrombogenic procedures (8). Once this condition develops, management becomes a challenge. Despite percutaneous intravascular intervention being regarded as the initial therapy of choice, the best management approach to achieve the highest patency still needs to be determined. This review aims to present current information regarding the pathophysiological mechanisms and risk factors that contribute to the development of central venous stenosis/occlusion. Additionally, the management strategies and the evidence regarding patency rates are discussed.

Anatomy

The present review focuses primarily on obstruction of the thoracic central venous system, including the intrathoracic segments of the subclavian, brachiocephalic, internal jugular veins, and the superior vena cava. The standard definition for thoracic central veins refers to those located inferior to the thoracic outlet, central to the inner margin of the first rib, and superior to the diaphragmatic hiatus (9). Central veins are larger, with fewer valves and high flow rates compared to peripheral veins. They have unidirectional blood flow routes, but collaterals may develop in diseased states. Understanding the path of the central veins and their course through surrounding structures is crucial to comprehending why CVS occurs at these sites. The brachial and basilic veins unite at the inferior border of the teres major muscle to form the axillary vein. It then courses anterior to the subscapularis muscle, posterior to the pectoralis minor, and projects to the lateral border of the first rib, continuing as the subclavian vein. The subclavian vein enters the thoracic inlet just posterior to the clavicle, anterior to the first rib and costoclavicular space, where it unites with the internal jugular vein (from the head and neck) to become the brachiocephalic vein (BCV). The BCV on both sides then merges to form the superior vena cava (10). Central venous catheters may terminate in the superior vena cava (SVC), inferior vena cava (IVC), or right atrium. This review does not address several morphological variants of the central thoracic veins rarely associated with reduced function or CVS.

McCrae et al. detailed the anatomic distribution of CVS based on the study of 133 HD patients with venogram-confirmed CVS (11). According to the authors, most CVS lesions are located at the junction of the subclavian and cephalic veins (38%), followed by the brachiocephalic vein (29%), and then the superior vena cava (24%). The free segment of the subclavian vein is the least involved (Figure 1) (11).

Epidemiology

In 2019, over 130,000 individuals in the United States were newly diagnosed with end-stage renal disease (ESRD) with an adjusted incidence of 386 parts per million, and 85% of these individuals initiated in-center hemodialysis (HD) (12). The prevalence of CVS varies, ranging from 4.3-41% depending on the population studied. The true prevalence may be underestimated since patients without suggestive symptoms are not routinely screened (1, 11, 13–15).

In a study to determine the prevalence of CVS among HD patients who underwent venography for access-related complaints, 41% of these patients exhibited significant CVS on venogram in contrast, when the study population consisted of stage 4 &5 pre-dialysis chronic kidney disease (CKD) and ESRD patients on HD who underwent venographic vein mapping, the prevalence of central vein stenosis was 10% for the whole group, 13% among patients with tunneled central venous dialysis catheters and 2% among the pre-dialysis patients (11, 14).

A retrospective study of ESRD patients on HD reported CVS in 4.3% (120) of 2811 patients at a median dialysis vintage of 2.9 years (1). Further study analysis to identify the rates of CVC-associated CVS revealed that in a subset review of 500 patients with such history, CVS was noted in about 34 (6.8%), at the rate of 2.2 per 100 patient-years. In addition, the frequency of central venous stenosis

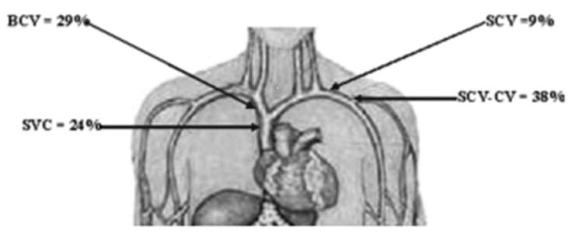

FIGURE 1
Anatomic distribution of CVS. CVS, central vein stenosis; SCV, subclavian vein; BCV, brachiocephalic vein; SVC, superior vena cava; SCV-CV, SCV, and subclavian-cephalic vein junction. Image is derived from MacRae et al. (11).

increased with the number of previous catheters (RR, 2.2; 95% CI, 1.6 to 2.9), pacemaker implantation RR 3.9; 95% CI, 1.7 to 8.9) and decreased with age (RR, 0.7 per decade; 95% CI, 0.6 to 0.8) (1).

Risk factors

Factors that have been independently associated with CVS include the use of tunneled hemodialysis catheters, duration of CVC dependence, the number of CVC placements, presence of cardiac devices, younger age at dialysis initiation, previous history of fistula or graft, and history of prior kidney transplant (11, 14–16). Increased risk for the development of CVS is directly related to the placement of intravascular catheters and devices. Insertion of CVC at the time of HD initiation is a common practice. Based on the report from the United States Renal Data System (USRDS), the percentage of patients initiating HD with a catheter (with or without a maturing graft or fistula) in 2019 was 81.8%, while the percentage of patients initiating HD with a catheter alone was 67.8% (12). The incidence of CVS associated with HD catheters varies relative to the type of catheter, duration of use, and location of the vessel accessed (16). The lifetime number of CVC placements is independently associated with a high risk of CVS (11, 16). A single-center study of 106 HD patients found a prevalence of 28.3% (17) of CVS cases.

The prevalence of CVS was 3.4%, 29.4%, and 53.8% among patients with a history of 0-1 vs. 2-3 vs 4 or more central venous catheter placements, respectively. Furthermore, CVS was more prevalent in patients with one prior or current subclavian vein catheterization than in patients without catheter placement in this vein (respectively 47.8% vs. 22.0%, p = 0.02). No similar trend was observed in patients with previous or current jugular or femoral venous catheterizations (16). The right internal jugular vein is the preferred site for hemodialysis catheter placement due to the relatively lower incidence of CVS associated with this site. This is attributable to the straight course of the catheter as it goes through the right internal jugular vein into the right brachiocephalic vein and then the superior vena cava (18–21). Despite the lower incidence of CVS associated with IJ catheters, they are associated with CVS as high as 25-40%, according to study reports (18–21). The subclavian vein has the highest incidence of CVS compared to other vessels due to the mechanical effect of the catheter relative to vascular anatomy (16, 22). Catheter placement for a longer duration increases the risk for CVS. Therefore, shorter terms are usually recommended (11, 22). A prospective study investigating the impact of short-term hemodialysis catheter placement on central veins reported a 14% (in 8 patients) incidence of CVS at a mean dwell time of 21 days (21). MacRae et al. also noted dialysis vintage and previous HD catheter use as associated risks for CVS (11).

Peripherally inserted central catheters are associated with a high incidence of venous stenosis in the peripheral (cephalic thrombus) and central veins (23). In a review analysis of angiographic studies performed pre- and post-PICC placement in 150 patients, 4.8% had central vein stenosis, and 2.7% had central venous occlusion (24). Considering the high incidence of thrombosis associated with PICC placement in established or prospective patients for HD, an alternative means of access should be explored to preserve vascular longevity. Furthermore, there may be merits in pursuing upper extremity venography before placing permanent HD access in patients with a history of PICC line placement. Similarly, placement of cardiac implantable devices (such as cardiac pacemakers and implantable cardioverter defibrillator devices) through the transvenous approach is associated with high rates of (25-64%) CVS in the general population (23–27).

Pathomechanisms of central venous stenosis

CV stenosis could develop from thoracic inlet syndrome, extrinsic compression, and previous clavicle or pacemaker wire fracture. Among patients with a history of CVC, it is thought to be a consequence of endothelial injury with changes in the vessel wall that result in microthrombi, smooth muscle proliferation, and, ultimately, stenosis.3-5 Thus, the three primary mechanisms contributing to central venous obstruction include venous wall thickening, endoluminal obstruction, and extrinsic compression (Figure 2). It is common for these mechanisms to overlap to result in clinically significant CV occlusions.

Venous wall thickening

Wall thickening is the most common mechanism for CVS. It could result from injury due to indwelling venous catheters or devices, organized mural thrombus or fibrosis, and *de novo* smooth muscle hyperplasia with no antecedent injury (28). Tunneled hemodialysis catheter and the presence of cardiac rhythm devices are independently associated with CVS. The pathogenesis of venous wall disease in vessels with CVC is a multi-step process. Firstly, there is consequent damage to the vessel at the CVC insertion site. This, combined with micro-injuries to the endothelium resulting from movement of the indwelling catheter, induces an inflammatory response and activation of the coagulation cascade leading to platelet activation and aggregation (17, 29–31). In a swine model, researchers identified cells in the venous neointima that were positive for alpha-smooth muscle actin, CD68, Ki67, smoothelin, and vimentin (32). Clots may develop along the thrombogenic catheter and form a sheath-like encasement to which fibrin attaches, the infiltration of smooth muscles ensues and, ultimately, the formation of vascularized connective tissue with smooth muscle cells, collagen, and endothelial cells (17, 29–31). These venous wall changes have been reported to occur hours to days after CVC insertion and are often progressive (31).

High blood flow rates through the central veins, often encountered in hemodialysis accesses, promote endothelial injury and, ultimately, stenosis (31). In addition, turbulent flow incites an inflammatory response and intimal hyperplasia culminating in venous wall remodeling. *De novo* CVS due to high blood flow rates were reported among six (10%) patients (out of 57 participants) in a study investigating the incidence of *de novo* CVS among HD patients. The average blood flow volume in four

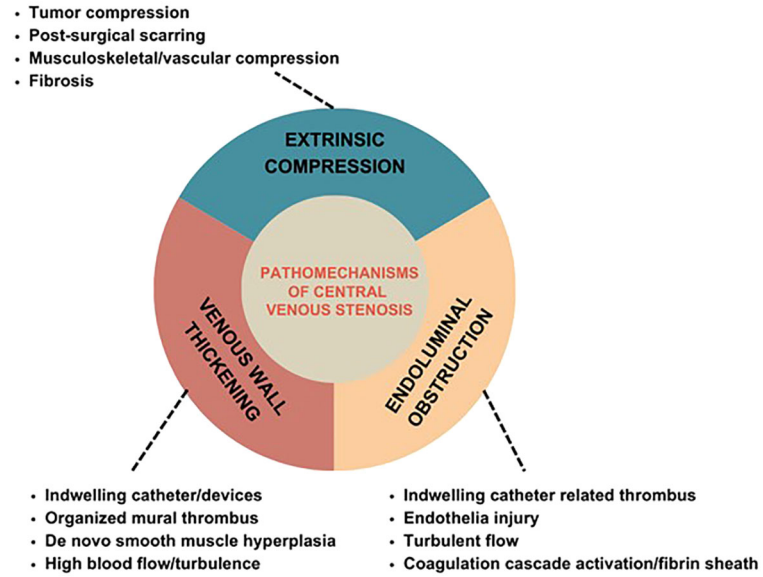

FIGURE 2
Pathomechanisms of Central Venous Stenosis.

patients with measured access blood flow volume was 2347 mL/min (21). Similarly, two studies reviewed 69 and 103 patients for CVS and reported *de novo* cases among 14 and 64 patients, respectively (33, 34). Some of these incident cases may have had unreported central vein catheter placements or interventions, considering that CKD patients likely have high comorbid conditions that could predispose them to these interventions.

Endoluminal obstruction

Thrombus associated with indwelling catheters can form within the vessel, obstructing blood flow or extraluminally. They arise from endothelial injury, flow turbulence, activation of the coagulation cascade, and fibrin sheath formation (35). Extraluminal thrombus, including right atrial or mural thrombus, can produce extrinsic catheter compression, resulting in insufficient blood flow and hemodialysis (35). Endoluminal obstruction may result from thrombosis, especially as a complication of the acute non-tunneled catheter relative to the chronic hemodialysis catheter. Most cases are subclinical and undetected, often diagnosed incidentally or in aggressive forms. As aforementioned, the presence of a foreign object in the vessel lumen precipitates thrombus formation, especially with prolonged indwelling. Without early treatment, the thrombus may become attached to the wall and organize to obstruct the lumen permanently (36).

Extrinsic compression

Extrinsic compression is precipitated by tumor compression, post-surgical scarring, musculoskeletal compression, vascular compression, and fibrosis. The most frequent location of extrinsic mechanical compression of central veins is where the subclavian vein crosses between the clavicle and the first rib. In this instance, the thoracic outlet is relatively small; hence repetitive arm movement during exertion leads to progressive trauma to the endothelium and the wall of the subclavian vein inducing intraluminal thrombosis and causing stenosis (37).

Clinical manifestations

Central vein stenosis symptoms stem from venous hypertension behind the occlusion (Figure 3). Central venous stenosis can be asymptomatic. Signs are generally insidious in patients on HD but mostly become prominent in the presence of an ipsilateral arteriovenous graft or fistula draining into the affected central veins (38). CVS related to grafts and upper arm access are more likely to be symptomatic when compared to fistulas and forearm access (39). In functional HD access sites, asymptomatic CVS has been reported in up to 29% of cases (40). CVS may cause ipsilateral arm swelling, leading to severe venous dilatation, worsening upper extremity edema with pain and discomfort, skin ulceration, and recurrent infection if left untreated. The patient may also develop dilated and tortuous collateral veins over the ipsilateral arm, neck, and chest because the high venous blood flow and pressure via the fistula may overwhelm the collateral lymphatic and venous drainage (13, 41). Dialysis access sites become increasingly challenging to cannulate in clinically significant lesions due to vascular access thrombosis. Compromised blood flow, increased venous pressure during dialysis, excessive bleeding from the access site, and inadequate dialysis delivery due to access recirculation that eventually render the access inoperative are dreaded complications (38).

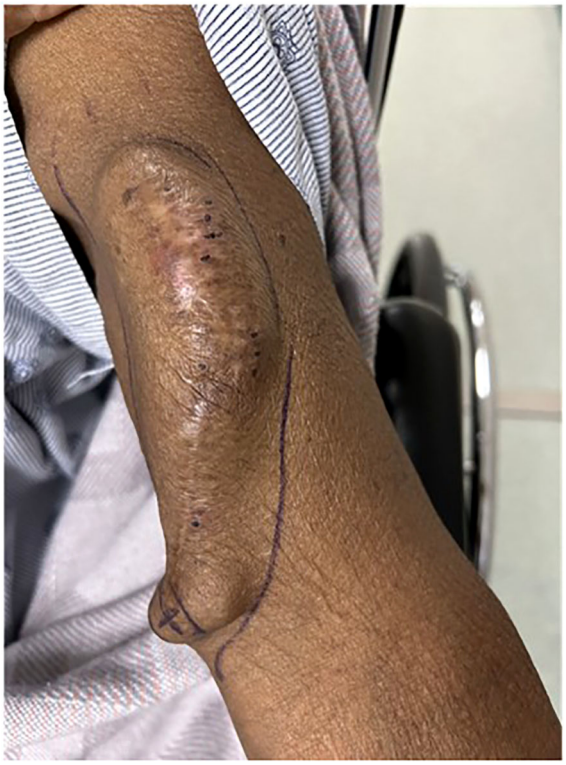

FIGURE 3
Left atrioventricular fistula HD access hypertension in a patient with central venous stenosis.

Diagnosis

The diagnosis of CVS is suspected based on history and examination findings and confirmed by imaging. Important pointers in the history include risk factors such as a history of previous CVC placement and cardiac devices, complaints of arm swelling, pain or discomfort, skin ulceration, and access problems during dialysis (37, 42). Examination findings include ipsilateral arm edema and dilated collaterals in the neck or chest (37, 42). The clinical picture of SVC syndrome with facial edema can also be seen in bilateral SVC-related CVS (13). Multiple imaging techniques may be utilized to establish the diagnosis. Conventional venography is considered the gold standard for diagnosis but is invasive (40). Therefore, non-invasive imaging methods such as magnetic resonance (MR) angiography, computed tomography (CT) venography, and duplex ultrasound [DU] are often initially employed. KDOQI recommends central venous imaging before the creation of permanent vascular access in patients with ESRD suspected to have CVS or who have had prior CVC placement. It is required that venography be performed before treatment initiation (4, 13, 41).

Duplex ultrasound is cost-effective, non-invasive, can be used in patients with contrast allergy, and is easily reproducible. CVS is diagnosed on DU if the affected vessel fails to exhibit normal respiratory variation in vascular diameter and lacks polyphasic atrial waves (28). Limitations include the inability to fully visualize the proximal third of the subclavian or innominate vein; it also performs poorly in obese patients or those with significant muscle mass. DU is sensitive enough to identify clinically significant vein stenosis and in the presence of a pressure gradient of 3mmHg, a peak vein velocity ratio of >2.5 across the stenosis is the proposed best criterion (43). DU may also help select patients for intervention and monitor treatment success during follow-up (43). Stenosis severity is often determined by vascular diameter, with significant stenosis determined at >50 decreases in luminal diameter on ultrasonography. When utilized alone, the DU modality could present the risk of poorly estimating the lesion's severity. Calcified vascular lesions, cross-section, and inappropriately high gain present technical limitations contributing to these estimation issues.1 Measures of peak velocity ratio, blood flow, and the residual diameter of 2 mm in grafts are additional criteria proposed to improve the diagnostic accuracy in determining the severity of central venous stenosis lesions (7, 44–46).

Conventional catheter venography, either via digital subtraction or fluoroscopy, gives an exact outline of the central veins and reveals the presence of stenosis with localization of the lesion; a stenotic lesion greater than 50 percent is considered significant (Figure 4). The gold standard for CVS diagnosis is digital subtraction venography, which is more sensitive than DU (40, 47). MR venography is an alternative to conventional venography. It was initially discouraged in hemodialysis patients due to the risk of developing nephrogenic systemic fibrosis associated with administering gadolinium contrast (48). Recent studies utilizing ferumoxytol as an alternative report its safety in patients with renal impairment, making the use of MR venography feasible, with a sensitivity of 99% and specificity of 98% (49).

Management strategies for symptomatic CVS associated with hemodialysis access

CVS management aims to relieve symptoms and morbidity and maintain vascular access longevity. Therapeutic intervention is only indicated in patients with clinically confirmed stenosis and associated symptoms (50). Stenotic lesions with a greater than 50 percent decrease in the luminal diameter are considered clinically significant (50). The presence of anatomic lesions without hemodynamic, functional, and clinical symptoms does not warrant prophylactic management and should only be observed (51). A retrospective study investigated the natural history of incidentally diagnosed high-grade CVS (>50%) among asymptomatic patients (52). This study treated 64 central venous stenosis lesions with percutaneous transluminal angioplasty, and 24 were left untreated. The authors observed an accelerated progression and *de novo* CVS lesions among the treatment population. In the study period, none of the patients in the untreated group exhibited clinical symptoms, *de novo* CVS, or progression of their CVS lesion, and none required intervention (52). The optimal management option depends on the nature and location of the lesion. There are no standardized trials comparing the techniques and outcomes of the various interventions.

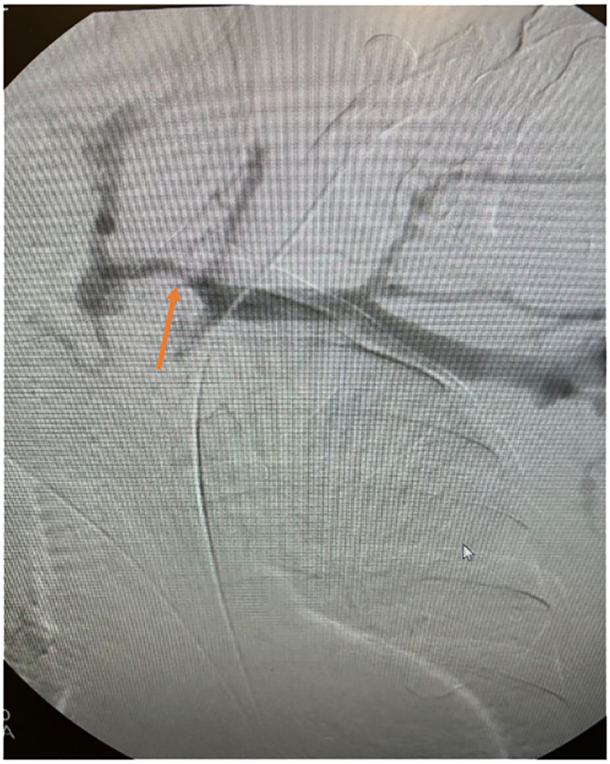

FIGURE 4
Angiographic representation of subclavian vein occlusion prior to revascularization.

Endovascular interventions

KDOQI recommends PTA with or without stent placement as the preferred therapeutic approach for symptomatic CVS (53). Endovascular intervention for CVS has shown variable results but remains the recommended initial treatment in this patient population. Treatment options include percutaneous transluminal angioplasty with or without stents.

Percutaneous transluminal angioplasty

Angioplasty is the preferred treatment for symptomatic central vein stenosis (53) (Figure 5). The initial success rates, technical success, and complication rates are acceptable for PTA. No large, randomized trials have investigated PTA for the management of CVS. Based on the data from several studies, the reported technical success rate ranged from 70 to 90% (53–59). Unassisted patency rates following PTA ranged from 23% - 63% at 6 months, with cumulative patency rates ranging from 29%-100%. At 12 months, the unassisted patency rates were between 12% - 50% and 13-100% for cumulative patency (10, 54–59). However, these investigations employed different criteria to describe lesions, severity, and outcomes and were conducted in different demographics using diverse techniques resulting in substantial outcome heterogeneity (10, 54–59). Maintaining long-term patency and preventing occlusion necessitates repeated interventions due to a high recurrence rate. The high recurrence rate has partly been attributed to endothelial and vascular wall elasticity. Restenosis is not uncommon after endovascular interventions due to neointimal hyperplasia and often occurs at the same site (60). Angioplasty techniques require cracking and fissuring of the vessel intima, which can induce the recurrence of venous stenosis (61).

Davidson et al. presented the histologic characteristics of stenotic lesions seen in CVS (62). The authors employed catheter-based intravascular ultrasonography (IVUS) with contrast cine angiography. IVUS pictures were acquired during 38 successive percutaneous balloon angioplasties to manage hemodialysis fistula-related stenoses. Quantitative and qualitative evaluations were conducted on images of the vessels, including 11 central veins. Plaque dissection was observed in 16 (42%) lesions, and both vascular stretch and elastic recoil were seen in 19 (50%) patients. The combination of vascular stretch and dissection was reported in 7 (18%) cases, and elastic recoil and dissection occurred in nine (24%) patients. Central veins exhibited the most prevalence of elastic recoil, and this property accounts for high recurrence and inadequacy of initial PTA in maintaining patency (62). An immunohistochemistry study revealed a high proliferative index in the vessel wall (intima and media) among patients with re-stenotic lesions compared to those with primary stenosis ($P<0.001$). Diabetes was associated with an even greater risk of restenosis. Restenosis rates may be expedited by high blood flow rates and turbulence (60, 61). Following initial angioplasty, failure has been reported to exceed 30% residual stenosis (61). Patency rates have also been reported for angioplasty in managing cardiac pacemaker-induced CVS in HD patients. The primary patency rates were 18% and 9% at 6 and 12 months, respectively. At 6, 12, and 24 months, the secondary patency rates were 95%, 86%, and 73%, respectively. Secondary patency required an average of 2.1 procedures per year (63).

Angioplasty with stents: bare metal stents and stent-grafts

The indications for stent placement in CVS remain the same for peripheral venous lesions. The guideline recommendation for stent deployment in managing CVS is for recurrent symptomatic lesions after PTA, especially within three months and those exhibiting elastic recoil (64, 65). (Figure 5) Stents resolve kinked stenotic lesions, prevent elastic rebound following balloon angioplasty, secure flow-limiting dissection, and maintain vein patency (53). It improves short- and long-term outcomes and HD access longevity. Self-expanding stents have shown superior success in managing elastic lesions than angioplasty alone (66). The inherent severity and nature of resistant lesions make comparing these populations challenging. Stent placement is not recommended in the device-related CVS due to a tendency for stent wire trapping in these cases. If stenting is indicated, the device should be removed and then replaced following placement (63).

Rajan et al. conducted a retrospective study of HD patients with autologous fistulas and synthetic grafts treated with angioplasties (83 angioplasty vs. 6 PTA with stents) for CVS to determine if

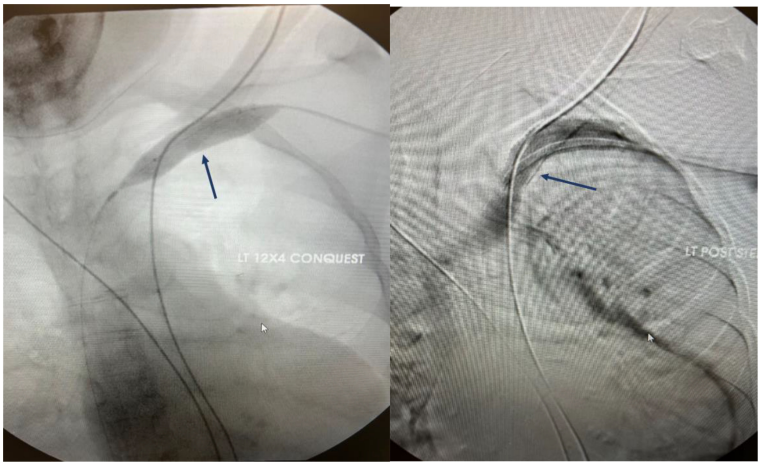

FIGURE 5
Angiographic representation of subclavian vein stenosis. The lesion was crossed with a sharp needle recanalization, then sequential a 10 x 8cm Conquest balloon was deployed followed by the 12x 4 cm Atlas balloon. A 13.5 x 10 cm Viabahn was ultimately deployed to maintain patency.

primary patency rates differed across groups (67). Patients shared similar demographic characteristics with similar technical and clinical success. Previous ipsilateral central venous catheter placement was reported in about 76% of the patients. Primary patency rates ± standard errors at 3, 6, and 9 months were 88.5% ± 4.8, 59.4% ± 7.6, and 46% ± 7.9 rates in the fistula arm and 78.1% ± 7.3, 40.7% ± 9, and 16% ± 7.3, respectively. Overall, primary patency lasted longer for AV fistulas (p=0.014) and those with no prior history of CVC placement (p=0.001). Overall, endovascular interventions require repeat interventions to maintain patency and longevity of ipsilateral HD access sites.

In a retrospective study, Quaretti et al. compared the patency rates of various endovascular treatments for symptomatic central venous stenosis in 70 dialysis patients (68). A comparative analysis was conducted on three cohorts, including angioplasty alone (n=22), a bare metal stent (n=28), and stent graft (n=20). The stent graft demonstrated primary patency rates of 100%, 100%, 100%, and 84% at 3, 6, 12, and 24 months respectively, while angioplasty exhibited rates of 90%, 79%, 58%, and 43% (P = .014), and bare-metal stent showed rates of 84%, 80%, 75%, and 46% (P = .062). When the lesions' sites were matched, the stent graft demonstrated a more favorable overall comparison (P = .020). There was no significant difference in angioplasty and bare-metal stent patencies (P = .141). The stent graft was associated with a lower risk of restenosis (hazard rate [HR] 0.20, confidence interval [CI] 0.06-0.7) and fewer reinterventions (P <.01). However, overall survival was influenced by age (HR 1.04, CI 1.001-1.08) and cardiovascular disease (HR 2.26, CI 1.06-4.84). No significant disparity was observed in the assisted primary patency. A prospective study compared the outcomes of CVS lesions treated with either PTA alone or with endovascular bare metal stent placement in patients undergoing hemodialysis. Eighty-seven patients were enrolled, 40 (46%) underwent PTA with stent placement, and 47 (54%) were treated with PTA alone. Primary patency rates with PTA were reported at 81%, 23%, and 12% at 60, 180, and 360 days, respectively, whereas the stent group achieved rates of 67%, 11%, and 11% at the same intervals (P =.4595). Secondary patency rates for PTA were 100% at 60, 180, and 360 days, respectively, whereas secondary patency rates for stents were 100%, 89%, and 78% (P =.5408) (59). There was no difference in the patency rates across the two interventions. High-pressure balloons are associated with about 60% and 30% primary patency rates at 6 and 12 months, better than previously reported (69). Primary patency rates at two years have been reported as low as 0% (55). Bakken et al. conducted a retrospective study comparing outcomes between HD patients with CVS who underwent high-pressure balloon angioplasty alone and PTA with stent group, primary, assisted primary patency, and ipsilateral HD survival were equal. The authors surmised that both techniques are safe and adoptable but were associated with high failure rates requiring repeat interventions.

Haage et al. reviewed the technical success, patency rates, and complications associated with stent placement in the primary management of central venous obstruction in hemodialysis patients (70). Fifty patients with symptoms of central venous obstruction underwent wall stent placement. There were no complications during stent deployment in any of the patients. One patient (2%) experienced an early re-thrombosis within one week. There were 73 cases of re-obstruction, of which 54 (74%) were treated percutaneously. Twenty-nine (26% of the cases) required additional stent placements. The primary patency rates were 92%, 84%, 56%, and 28% at 3, 6, and 12 months, respectively. Patency rates for the stents were 97% after 6 and 12 months, 89% after 24 months, and 81% after 36 and 48 months. Multiple interventions were required to maintain patency despite acceptable technical results from stent placement.

Similarly, a long-term study investigated the outcomes and effectiveness of stent-graft placement in managing CVS refractory to PTA in HD patients with functioning AV fistulas (71). Primary patency rates were 97%, 81%, 67%, and 45% at 3, 6, 12, and 24 months.

At 3, 6, 12, and 24 months, the primary assisted patency rates were 100%, 100%, 80%, and 75%, respectively. Patients who had not undergone PTA or bare metal stent placement had significantly

shorter intervals to repeat intervention (P.018) than those who had previously undergone PTA or bare metal stent deployment. The primary patency interval was substantially shorter in patients with occlusive lesions (P.05) than in those with stenoses. Occluded veins were more likely to need additional stent grafts (P.02). Twelve patients needed additional stent grafts to preserve patency. In the case of covered stents, endothelialization is primarily facilitated by the graft material, which serves as an inert scaffold to prevent restenosis (71, 72). Despite this, the utilization of stent grafts should be individualized.

Drug-eluting stents

To mitigate the high rates of post-intervention restenosis associated with PTA and bare metal stents, investigations are underway into specialized covered stents and drug-eluting stents (73). Paclitaxel-coated balloons (PCBs) have been evaluated for their effectiveness and safety in managing malfunctioning HD access in a few randomized studies and retrospective case reviews with promising results. Notably, many of these studies excluded patients with central venous stenosis, limiting the application of the results to this population (74–78). Kitrou et al. compared the clinically assessed intervention-free period of a paclitaxel-coated balloon with conventional balloon angioplasty to manage symptomatic CVS. A total of 40 patients were enrolled (with a mix of AVG and AVF HD access) into the balloon angioplasty group (N=20) vs. the PCB (N=20) group. Patients were followed for an average of 180 days. The median intervention-free period (IFP) was significantly better in the PCB group (PCB group: 179 days, vs. CBA group: 124.5 days, P= .026). Outcomes were similar in the two types of HD access, management of *de novo* or stenotic lesions, and those with prior CVC placement. Across the re-stenotic lesions in the PCB group, longitudinal comparison between treatments showed better outcomes in this group (median IFP in PCB group 177 vs. 91 days in CBA group; P= .01). Massmann et al. reported similar success with PCBA providing significant longevity from the need for revascularization compared to conventional balloon angioplasty (79, 80). Farber et al. compared outcomes between PTA and Dacron-covered nitinol stents in managing access-related venous occlusions (73). The authors noted a secondary patency rate of 60% at 3 and 6 months among the CVS (subclavian vein stenosis) cohort. This study is notably underpowered, and patients with peripheral venous lesions were included. A similar study reported cumulative patency rates of 67.7% and 55.4% at 6 and 12 months, respectively, for implantation of Dacron-covered stents (72).

Access flow reduction with banding techniques

High-flow volumes across HD vascular accesses are linked to a high recurrence rate after initial interventional therapy. Patients may be asymptomatic and only experience severe symptoms when the overall cross-sectional area of draining collaterals is inadequate to manage the arterial flow. In this instance, some patients may require ligation of an otherwise well-functioning vascular access. Access inflow restriction techniques aimed at restoring flow balance can limit excess access blood flow and pressure to preserve the access function. Successful recurrence and symptom resolution prevention have been reported in patients with recalcitrant CVS lesions following angioplasty and stent placement by flow reduction via balloon-assisted banding of the inflow (21, 81). Patients with access to blood flow volume below 700-800 mL/minute may not have successful outcomes (81). Unsurprisingly, banded graft accesses' reported primary patency rates are lower relative to AVF (82). Grafts with significantly occluded central venous outflow with no established collaterals are prone to recurrent thrombosis and imminent failure and should not be banded.

Hemodialysis reliable outflow dialysis catheter

In patients with central vein occlusion but no conventional upper arm HD access alternatives, inserting a lower extremity graft or hybrid catheter-graft device is usually the next step. The HeRO graft is a composite graft that comprises a central venous silicon and nitinol outflow segment, which is inserted into the right atrium and connected to a polytetrafluoroethylene (PTFE) arteriovenous graft (83). An industry-funded randomized trial evaluated the safety and efficacy of the HeRO graft relative to the upper limb grafts. The study enrolled 72 patients, 20 in the graft and 52 in the HeRO cohorts. Quite notably, the investigators excluded patients with significant central venous stenosis. In addition, there was no significant difference in the 12-month primary and secondary patency rates in the HeRO and graft groups, 35% versus 31% and 68% versus 58%, respectively (84).

Particularly for CVS, Sur et al. conducted a retrospective investigation comparing the outcomes of HeRO graft and stent placement (85). The HeRO group included 29 patients, while 14 patients underwent stent placement. At follow-up of >500 days, primary patency among patients in the HeRO group was 16/28 (57%) and 4/14 (28%) in the stent cohort. The average number of interventions per patient year for the HeRo and stent groups were 1.4 and 2.3, respectively. There was no significant difference in the outcomes across both groups. The authors concluded that the HeRO graft is an alternative for HD patients with refractory CVS lesions who are poor surgical candidates. The HeRO graft may be an option in carefully selected patients in the right clinical setting, but many require at least two interventions per year to maintain patency and function.

Surgical interventions

Open surgical techniques to treat central venous stenosis and occlusion are highly morbid, necessitating a median sternotomy to access deeply located central veins and the right atrium. These procedures often utilize autogenous veins or the

polytetrafluoroethylene (PFTE) graft (86). Reported primary patency rates are high, approaching 80-85% at one year (87). Despite this high success rate, it has gained little enthusiasm due to its invasiveness and associated complications. The deep location of the central veins and the poor health status of these patients make it highly morbid (88, 89). It is regarded as a last resort in patients with failed endovascular interventions, young patients with minimal comorbidities, and refractory clinical symptoms (90).

Identifying the precise location of the lesion is critical to determining the best reconstruction technique. A central venogram is a necessary preoperative step to comprehensively map out the patient's venous anatomy before open surgical intervention. The primary objective of surgical intervention is to establish venous outflow into the right atrium. Open surgical intervention can be achieved through central reconstruction, which involves connecting the central veins directly to the right atrium or via extra-anatomic graft bypass to the right atrium (89). The use of prosthetic grafts and spiraled great saphenous vein have been reported. In addition, open venous patch angioplasty has been documented as a viable approach for addressing stenotic central veins (91). The reported outcomes of these surgical options are positive. However, sternotomy-associated complications have led to their infrequent performance (88, 89). Doty et al. performed the first surgical intervention to manage HD-related CVS in a patient with superior vena cava syndrome by placing a spiral vein graft constructed from an autogenous vein. The patient had clinical relief and graft patency up to 6 months following the procedure (92).

Extra-anatomic bypass entails connecting the ipsilateral HD access to a peripheral vein draining into the right atrium. This avoids the morbidity and complications associated with a sternotomy. The saphenous, femoral, ipsilateral, and contralateral jugular veins have all been utilized as venous bypasses for access output (93, 94). However, in circumstances where the complete obstruction occurs, particularly at the osseous costoclavicular junction, the range of available endovascular interventions and open venous reconstructions are limited, necessitating the adoption of bypass grafting (95). Glass et al. presented the substernal tunneled subclavian to right atrial appendage bypass approach. This was performed in patients with occluded central veins, including the subclavian, innominate, and caval veins. These patients had occluded central veins with good fistula or symptomatic fistula malfunction, patent subclavian and axillary veins to the costoclavicular junction, and no alternative way to achieve HD access in the contralateral upper extremity. Intrathoracic access was gained by claviculectomy and "mini pericardiotomy" through the 3rd intercostal space exposing the right atrium. Three bypasses were performed with autogenous vein grafts (two femoral and one saphenous), while eight were performed with PTFE. The immediate postoperative complications were sepsis and acute pericardial effusion. The average follow-up duration was 16 months, and primary patency at 6 and 10 months were 67% and 33%, respectively. Notably, central bypass stenosis or occlusion rates appeared to be high at 36%, and postoperative infection rates were relatively high at 18%. Overall, there were significantly high failure and recurrence rates. Therefore, it could be pursued with extreme caution in very select patients with no other alternatives for HD access (86).

Obstructions affecting the innominate veins or the superior vena cava (SVC) are addressed by expanded polytetrafluoroethylene (ePTFE) grafts to create a bypass from either the axillary or subclavian veins to the jugular veins or right atrium (Figure 3). In addition, isolated subclavian vein occlusion can be treated with internal jugular vein turn-down or bypass graft. In IJV turn-down or transposition, the ipsilateral IJV is anastomosed to the distal subclavian or the axillary vein (94). The downside is that this procedure prevents IJVs from being used for hemodynamic monitoring, venous outflow for AV fistulas, or even temporary access in the future.

El-Sabrout et al. reported on right atrial bypass grafting outcomes for central venous occlusion among patients with previous bilateral temporary subclavian dialysis catheters (89). In their technique, a large diameter (10-16mm) externally reinforced PTFE graft bypassed the obstruction and was then anastomosed to the right atrial appendage. Clinical relief was recorded in 8 out of 9 patients following the procedure. However, grafts remained patent at an average of 15.4 (1.5-52) months. Although this study presented right atrial bypass grafting as a viable option in patients with central venous stenosis, the process of patient and technique selection was questioned (89).

Bhatia et al. compared the outcomes and patency rates between stent placement and surgical bypass graft. They reported similar symptom-free intervals in both groups at six and twelve months, with no significant difference in periprocedural complications and one-year mortality (87). This indicates that bypass graft should only be recommended for the minority of patients with no alternative access sites and lesions refractory to percutaneous angioplasty intervention (89).

Ayarragaray presented venous decompression as a novel surgical alternative for managing HD patients with central venous stenosis with PTFE graft malfunction (96). This procedure was performed on 3 HD patients. A 6 mm expanded and reinforced PTFE graft was connected to the brachiocephalic graft proximally, and the distal graft was connected to the femoral vein. There were no reported perioperative complications. Patients had clinical symptom improvement within the first 48-72 hours and had functional access to dialysis. At a follow-up of 16.3 months, one patient had clinically detectable AV graft dysfunction. The two other patients maintained graft patency till death. This procedure could be an option for patients with many vascular access points and significant central vein stenosis or blockage.

Alternative renal replacement therapy strategies in CVS

In the event of bilateral recalcitrant thoracic CVS precluding installation of AV access in the upper limb, several options may be pursued for HD delivery in patients needing access. Complete or tight SVC stenosis often has high recurrence rates despite repeated and adequate endovascular interventions precluding future upper limb AVF or graft. Peritoneal dialysis should be considered when feasible. Upper thigh AVF or graft are also viable options. It is common for patients with high dialysis vintage to exhaust all viable

definitive access options. In these instances, tunneled cuffed HD catheters and hemodialysis reliable outflow (HERO device) may be the alternatives (97). In the event of treatment failure, the only option is to occlude the AV access via balloon, manual, or surgical approaches. Occlusion leads to the resolution of symptoms associated with venous hypertension and precludes using the ipsilateral limb for access.

Cardiac implantable electronic devices in hemodialysis

Evidently, cardiovascular complications abound among HD patients including arrhythmia and sudden cardiac death oftentimes requiring cardiac implantable electronic devices (CIED) such as pacemakers, loop recorders, and defibrillators (98). Patent central venous access is paramount for the creation of viable A-V HD access impacting survival. In instances where a patient has a CIED on one arm and no suitable veins for creating an arteriovenous fistula on the other arm, the process of creating permanent vascular access can become complicated. This is particularly challenging when hemodialysis is the only available option for renal replacement therapy. The risks associated with creating arteriovenous access on the side with the CIED include venous hypertension resulting from central vein stenosis related to the leads and the potential for systemic infection, including lead-associated endocarditis (99). In some instances, placement of CIED can be precluded by pre-existing stenosis stemming from HD vascular access complications. Consequently, the various clinical scenarios of CIED placement in HD patients require individualized management demanding a multidisciplinary collaboration between the nephrologist and cardiologist. Innovations in the CIED realm have provided alternative device options to standard pre-pectoral in this patient population (99). Alternative routes of placement such as endovascularly placed leadless pacemakers, subcutaneous implantable cardioverter defibrillators, and endocardial left ventricular pacing options are available to patients with CV stenosis or those in whom vascular preservation for future AV hemodialysis access is anticipated (99). Likewise, in HD patients with bilateral subclavian vein occlusion/superior vena syndrome, the femoral or iliac pacing system could be considered.

Conclusion

Hemodialysis patients with a history of indwelling central venous catheter or intravascular device placement are at risk for central venous stenosis. Patients are often asymptomatic, but appropriate diagnostic investigations should be pursued in those with clinical indications. A complex vascular dilemma may result from coexisting cardiac implantable devices and arteriovenous fistulae, grafts, and tunneled catheters in hemodialysis patients. Perhaps the use of leadless pacemakers, epicardial leads, and subcutaneous defibrillators will lead to a reduction in the incidence of central venous stenosis in patients with ESRD. Treatment is reserved for clinically significant lesions, and percutaneous angioplasty is the preferred initial form of therapy. Recurrence and recalcitrant lesions abound, requiring multiple interventions to maintain patency and functioning HD access. In these cases, surgical bypass of the obstruction site may be required. Further prospective, randomized controlled studies with extended follow-up of currently available therapeutic options are needed to develop superior management protocols.

Author contributions

IS: Writing – original draft, Writing – review & editing. GE: Conceptualization, Writing – original draft, Writing – review & editing. AL: Writing – review & editing. GS: Writing – review & editing. IB-R: Writing – review & editing. LG: Writing – review & editing. JS: Writing – review & editing. DK: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Sayna Norouzi,
Loma Linda University Medical Center (LLUMC), United States

REVIEWED BY
Enrique Morales,
CSUR Complex Glomerular Pathology, Spain
Melin Narayan,
Loma Linda University, United States

*CORRESPONDENCE
Erietta Polychronopoulou
Erietta.Polychronopoulou@chuv.ch
Daniel Teta
daniel.teta@hopitalvs.ch

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SGLT2 inhibitors in diabetic and non-diabetic kidney transplant recipients: current knowledge and expectations

Erietta Polychronopoulou[1,2]*, Fanny Bourdon[1] and Daniel Teta[1]*

[1]Service of Nephrology, Hôpital du Valais, Sion, Switzerland, [2]Transplantation Center, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

The beneficial effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown recently in numerous randomized controlled trials (RCT) and systematic reviews. According to KDIGO guidelines, SGLT2i currently represent a first choice for diabetic patients with chronic kidney disease (CKD). In addition, a recent meta-analysis of 13 large led by the 'SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium' (SMART-C) provided solid evidence of SGLT2i beneficial effects in CKD or in patients with heart failure, with and without diabetes. Collectively, the patients treated with SGLT2i had a decreased risk of CKD progression, acute kidney injury (AKI), end-stage kidney disease (ESKD) or death from heart failure. Whether these cardio-renal benefits should be extrapolated to kidney transplant recipients (KTR) needs to be assessed in further studies. In this article, we report recent data accumulated so far in the literature, looking at the efficacy and safety of SGLT2i in diabetic and non-diabetic KTR. We found encouraging data regarding the use of SGLT2i in KTR with diabetes. These agents appeared to be safe, and they reduced body weight and blood pressure in this group of patients. Potential effects on kidney graft function and survival are yet to be investigated.

KEYWORDS

SGLT2 inhibitor, kidney transplantation, diabetic kidney disease, post transplantation diabetes mellitus, diabetic kidney transplant recipients, CKD - chronic kidney disease

Introduction

SGLT2 inhibitors (SGLT2i), also called gliflozins, inhibit the activity of the Sodium Glucose Cotransporter 2 (SGLT2) in renal tubules, ultimately leading to glucosuria. They were originally thought to only have an effect on glucose control; however large clinical trials have displayed numerous additional advantages, dramatically outperforming initial expectations (1). There are three different gliflozins available in the pharmaceutical market, i.e., empagliflozin, dapagliflozin, and canagliflozin. They all induce glucosuria and thus reduce levels of blood glucose and HbA_{1c} by inhibiting glucose reabsorption in the

proximal tubules. SGLT2i also induce sodium excretion which in turn counteracts the tubulo-glomerular feedback (TGF) and to decrease intraglomerular pressure, a crucial mechanism known to foster protective effects on kidney function. As a consequence, SGLT2i reduce albuminuria significantly in diabetic and non-diabetic patients with CKD. This impact on albuminuria is additive to the action of the renin-angiotensin-aldosterone system (RAAS) blockade. With the use of SGLT2i, multiple mechanisms are contributing to the reduction of albuminuria. The most important one is vasoconstriction of the afferent arteriole of the glomeruli, which results in a decrease of the intraglomerular pressure and hyperfiltration (1). Additional effects of the SGLT2i include reduction of inflammatory marker levels of IL-6, TNF-alpha, IFNγ, NF-κβ, TLR-4, and TGF-β and improvement of mitochondrial function (2). These mechanisms may contribute to limit inflammation, fibrosis, and oxidative stress in heart and kidneys tissues. It is important to note that all these modifications seem to result from consequences of metabolic and hemodynamic effects of SGLT2 co-transporter inhibition (2–5).

Hyperfiltration pathophysiology in renal transplantation

Kidney transplantation is characterized by glomerular hyperfiltration, which is also observed in various clinical settings associated with nephron reduction. Hyperfiltration results from afferent arteriolar vasodilation, and/or by efferent arteriolar vasoconstriction secondary to the activation of the RAAS, consequently leading to glomerular hypertension and thus glomerular injury in the remaining nephrons (4, 6). In KTR, hyperfiltration is clearly an adverse factor leading to unfavorable long-term kidney outcomes in this group of patients already subjected to injuries through immunological and non-immunological mechanisms (7). Since SGLT2i are efficiently reducing glomerular hyperfiltration, it is anticipated that these agents may prove instrumental to improve kidney allograft outcomes.

SGLT2i and CKD recommendations

Recent RCT in native CKD have shown a large range of clinical benefits of SGLT2i, especially cardio renal protective effects in patients with and without type 2 diabetes mellitus (8). In addition, the EMPEROR-Reduced randomized placebo-controlled trial, which aimed to explore the impact of empagliflozin in patients with reduced ejection fraction across a broad range of different kidney functions, has demonstrated a significant decrease in cardiovascular deaths and heart failure hospitalizations, in favor of the empagliflozin versus the placebo group (9). According to the above evidence, SGLT2i now constitute a first-line treatment for diabetic patients with CKD, together with metformin, RAAS blockade and statins, as recommended in the KDIGO guidelines 2022 (10). For all patients, lifestyle adaptation and control of risk factors are the basis of this approach, including diet, physical activity, smoking cessation, and body weight control. In addition to these basic measures, there is a range of proven drug treatments, depending on the patient's comorbidities, including SGLT2i. For patients with diabetes and CKD, a combination of metformin, if estimated glomerular filtration rate (e GFR) > 30ml/min/1.73m^2 and SGLT2i (introduced if eGFR > 20ml/min/1.73m^2 and continued until dialysis or transplantation), is recommended. Statin therapy is also recommended. Depending on other comorbidities, the addition of RAAS inhibitors is a first-line treatment for patients with hypertension or albuminuria. If glycemic control is unsatisfactory despite SGLT2i and metformin, or if their use is contraindicated, glucagon-like peptide-1 (GLP-1) receptor agonists may be used. Non-steroidal mineralocorticoid receptor antagonists (ns-MRA) can be added to first-line treatments in diabetic patients with a high risk of CKD progression, such as persistent albuminuria > 3g/mol.

What is more astonishing is that SGLT2i have been proven to retard the decline of eGFR in non-diabetic individuals with proteinuria (6). However, according to initial studies in CKD, there were safety concerns regarding severe urinary tract infections (UTI) and vaginal infections in women. This is why the extension of these clinicals benefits to the KTR population needs to be assessed in further studies.

Efficacy and safety of SGLT2i in diabetic kidney transplant recipients

The use of SGLT2i in KTR could be of great advantage, especially because the characteristics of this group of patients, with significant cardiovascular risk, and chronic kidney allograft disease. These patients especially suffer from prevailing long-term kidney allograft lesions usually associated with hyperfiltration, such as arteriolar hyalinosis and focal segmental glomerulosclerosis (1, 11). Halden et al. (12), carried out a first prospective placebo controlled RCT evaluating the efficacy and the safety of empagliflozin 10 mg, once a day, in KTR with post-transplant diabetes mellitus (PTDM). There were no significant differences between empagliflozin and placebo regarding adverse events, immunosuppressive drug levels, and eGFR decline. The group of empagliflozin-treated patients showed a statistically significant reduction in HbA1C and body weight, compared with the placebo group (-0.2% vs. +0.1%, p=0.025 and -2.5 kg vs. +1.0 kg, respectively, p=0.014). There was no significant difference between the two groups, concerning incident UTI (12). This study was however limited by the small number of participants (n=44) and the short follow-up of 24 weeks. In addition, several observational studies (Table 1) also looked at SGLT2i in KTR with type 2 diabetes (T2DM) or PTDM (24). These studies demonstrated that patients with SGLT2i presented a lower glucose level and lower body weight and blood pressure. No difference in adverse events was noted when KTR were compared with native CKD patients.

There are actually six ongoing RCT (Table 2) looking at the use of SGLT2i in KTR. First, the CREST-KT (25), which is a single center double-blind RCT in 72 patients, with a follow-up of 18 months. A second study from the University of Toronto is a

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TABLE 1 Observational studies so far and ongoing (1, 13).

Study	Population	Intervention	Results with SGLT2i
Fructuoso et al., 2023 (14).	Observational, n= 339 KTR with T2DM or PTDM		Significant reductions in body weight, BP, fasting glycaemia, HbA1c, UPCR. The most frequent adverse event was UTI in 14%.
Rajasekeran et al., 2017 (15)	Case series (4 SPKT, 6 KTR) KTR or SPKT on canagliflozin	Canagliflozin	Reduction of HbA1c −0.84% Reduction of body weight −2.14 kg Reduction of BP −6.4mmHg No UTI or mycotic infection
AlKindi et al., 2020 (16).	Case series (8 KTR) KTR on SGLT2i (T2DM or PTDM)	Empagliflozin (6 patients), dapagliflozine (2 patients)	-6 months follow-up: Decrease in body weight -4kg -12 months follow-up: Decrease of HbA1c Stable eGFR Stable BP One episode of UTI
Attallah and Yassine 2019 (17)	Case series (8 KTR) KTR on empagliflozin (T2DM or PTDM)	Empagliflozin	-12 months follow-up: Reduction of HbA1c Slight reduction in eGFR, then stabilized Reduction of proteinuria (UPCR) of 0.6 g/day. Reduction of body weight - 2.4 kg. Two cases of UTI
Schwaiger et al., 2019 (18)	Prospective interventional study (14 KTR) KTR with insulin	Empagliflozin	-4 weeks follow-up: Reduction of eGFR by 7.5 ml/min/1.73 m2. Three cases of UTI and one case of uncomplicated balanitis. -12 months follow-up: Stable HbA1c. Reduction of body weight -1.6 kg
Mahling et al., 2019 (19)	Prospective case series (10 KTR) Stable KTR	Empagliflozin	-12 months follow-up: No change in eGFR Reduction of body weight −1.9 kg Low rate of UTI and other side effects
Shah et al., 2019 (20)	Prospective descriptive study (24 KTR) Stable KTR with T2DM or PTDM	Canagliflozin	-6 months follow-up: Decrease of body weight -2.5kg Decrease of: SBP -8mmHg, DBP -2mmHg HbA1c reduction -0.9% No UTI increase
Song et al., 2020 (21)	Observational retrospective (50 KTR)	Empagliflozin (n = 43), canagliflozin (n = 6) or dapagliflozin (n = 1)	-6 months follow-up: Decrease of body weight −2.95 kg No increase of UTI Stable renal function
Lim et al., 2022 (22)	Observational retrospective (226 KTR) KTR with T2DM on SGLT2i		Lower risk for all-cause mortality, death-censored graft failure and serum creatinine doubling eGFR stable
Lemke et al., 2022 (23)	Observational retrospective (39 KTR) KTR on SGLT2i (T2DM or PTDM)	Canagliflozin (n = 12), dapagliflozin (n = 3), empagliflozin (n = 24)	-12 months follow-up: Stable renal function UTI was the most common adverse event HbA1c reduction -1%

AKI, acute kidney injury; BP, Blood Pressure; DBP, diastolic blood pressure; eGFR, estimated Glomerular Filtration Rate; RCT, Randomized Control Trial; KTR, kidney transplant recipient; SBP, systolic blood pressure; PTDM, Post Transplant Diabetes Mellitus; SPKT, Simultaneous pancreas-kidney transplantation; UPCR, Urine Protein Creatinine Ratio; UACR, Urine Albumin creatinine Ratio; UTI, Urinary Tract infection.

randomized double-blind study, dapagliflozin versus placebo, looking at blood pressure as a primary outcome in patients with preexisting diabetes (26). A third large randomized, placebo-controlled trial study including 330 patients during 3 years of follow-up from Oslo University Hospital is investigating the effect of SGLT2i in KTR looking at preservation of eGFR, reduction of interstitial fibrosis in the kidney transplant, and metabolic risk factors for graft failure such as visceral obesity, glucose intolerance and blood pressure (27). Another ongoing study also from the University of Toronto plans to determine the short-term efficacy, mechanisms, and safety of a combination between dapagliflozin and semaglutide (GLP-1 receptor agonist) over 12 weeks in 20 KTR, with and without T2DM, i.e. the HALLMARK study (28). Another, randomized single-blinded controlled trial from the University of Sao Paulo General Hospital, aims to evaluate the effect of dapagliflozin on the renal functional deterioration of KTR with or without diabetes (29). The authors intend to enroll 220 KTR, in order to evaluate mean eGFR differences, between baseline and one year after randomization. Studies are also anticipated in non-diabetic KTR. Finally, the RENAL LIFECYCLE Trial, a multicenter RCT from the University Medical Center Groningen, which has as an objective to establish the reno- and cardioprotective efficacy and safety of dapagliflozin in patients with severe CKD, including KTR patients (30).

Risks and concerns

Urinary tract infections

The main concern with SGLT2i in the kidney transplant community is the potential increased risk for UTI. Data

TABLE 2 Randomised clinical trials so far and ongoing.

Study	Population	Intervention	Results with SGLT2i
Halden et al., 2019. (12)	*n* = 44 (22 patients on empagliflozin) PTDM with KTR >1 year, eGFR >30 ml/min/1.73 m^2	Empagliflozin versus placebo	• Reduction of HbA1c: −0.2% • Reduction of body weight • No changes in BP or eGFR • No interactions observed with immunosuppressive drugs • One case of urosepsis and one mycotic infection
CREST-KT ongoing (25)	72 KTR with (n=36) and without (n=36) T2DM	Empagliflozin versus placebo	Primary outcomes: •Change in kidney function as measured by albuminuria •Change in cardiac structure •Change in blood insulin level •Change in fasting blood sugar •Number of UTI and genital infections
INFINITI 2019 ongoing (26)	52 KTR with T2DM or PTDM	Dapagliflozin versus Placebo	Primary outcome: determine if dapagliflozin is superior to placebo in reduction of BP in KTR.
Can Dapagliflozin Preserve Structure and Function in KT? Ongoing (27)	330 KTR	Dapagliflozin versus Placebo	Primary outcome: •Effect of Dapagliflozin on the GFR slope in KTR. • Difference in eGFR slope between groups
The Efficacy, Mechanism & Safety of Sodium Glucose Co-Transporter-2 Inhibitor & GLP-1 Receptor Agonist Combination Therapy in Kidney Transplant Recipients (HALLMARK) Ongoing (28)	20 KTR, with and without T2DM	Dapagliflozin Semaglutide	Primary outcome: • Mechanisms and safety of 12 weeks of dapagliflozin and semaglutide combination therapy.
Effect of adding dapagliflozin to allograft dysfunction of	220 KTR, with and without T2DM	Dapagliflozin versus Placebo	Primary outcome: •Estimate the mean delta difference of the eGFR, between baseline and one

(Continued)

TABLE 2 Continued

Study	Population	Intervention	Results with SGLT2i
renal transplanted patients Ongoing (29)			year after randomization.
The RENAL LIFECYCLE Trial: A RCT to Assess the Effect of Dapagliflozin on Renal and Cardiovascular Outcomes in Patients with Severe CKD (30)	1500 patients -with advanced CKD, i.e. an eGFR ≤25mL/min*1.73m2 -on dialysis with a residual diuresis >500 mL/24h (at least 3 months after start of dialysis) -KTR and an eGFR ≤45mL/min/1.73m2 (at least 6 months after transplantation)	Dapagliflozin 10 mg/day or matching placebo	Combined endpoint of all-cause mortality, kidney failure, and hospitalization for heart failure in the overall study population

accumulated so far, do not show a significant difference in the occurrence of UTI in patients using SGLT2i versus those with no SGLT2i. In most studies, patients selected for the use of SGLT2i were started after more than 1-year post-transplantation, due to clinician's main concern regarding a possible decline in eGFR and the incidence of UTI during the first year after kidney transplantation (24).

Acute kidney injury

SGLT2i might result in AKI by multiple mechanisms, such as depletion of effective volume because of excessive diuresis, or because of significant decrease in trans-glomerular pressure, especially in patients on RAAS blockade. Another possible mechanism is the hypoxic injury, associated to elevated distal tubular transport, particularly with the simultaneous use of agents already known to impair oxygen transport to the kidney medulla, such as non-steroidal anti-inflammatory drugs or radiographic iodine contrast agents. Thus, in KTR, clinicians must be careful on the importance of maintaining blood volume; in particular, patients must be informed that, in case of volume-depletion situations, for instance vomiting, diarrhea, SGLT2i should be discontinued (31).

Increased risk for amputations

The Canagliflozin Cardiovascular Assessment Study (CANVAS) and the Canagliflozin Cardiovascular Assessment Study-Renal (CANVAS-R) demonstrated that canagliflozin increased leg and foot amputations in research participants

compared with placebo (6.3 vs 3.4 per 1,000 patient-years) (32). Data from studies in KTR until now, have not shown an increase in the incidence of amputations, although studies were underpowered to look at this outcome (12).

Ketoacidosis

SGLT2i, may cause euglycemic ketoacidosis; however, this risk is extremely low.

It is not advised to use SGLT2i in patients who have predisposing factors such acute gastroenteritis or insulin pump failure (33). No episode of ketoacidosis was reported in the study conducted by Halden et al. (12). For type1 diabetes (T1D) patients, SGLT2i potentially address some of the unmet needs associated with T1D. They improve glycaemic control and induce weight loss, increasing hypoglycemia. However, because of side effects, the european recommendation for the use of SGLT2i on T1D was withdrawn. Further studies are needed to determineSGLT2i safety in T1D and to define the type of patient who can benefit most from these medications (34).

Discussion

Most of the existing evidence concerning the application of SGLT2i in kidney transplantation is accumulated mostly from observational studies and only one small RCT. Ongoing RCT in this population are in progress. Although the evidence remains insufficient, these data, mostly observational, encourage physicians to use SGLT2i in diabetic KTR. The evidence shows encouraging data regarding the incidence of UTI and the decrease of body weight and blood pressure (1). Long-term outcomes regarding renal graft function and survival are still awaited. The data show that the use of SGLT2i in diabetic KTR results in lower levels of HbA1c without an increased risk for UTI or euglycemic ketoacidosis. The absence of significant drug-drug interaction with the immunosuppressive treatment and the advantageous impact of SGLT2i including weight loss, make SGLT2i an appealing treatment option for KTR (24). Two recent systematic review and meta-analysis also indicate that although studies with extensive follow-up are required in KTR with or without PTDM receiving SGLT2i so as to evaluate their potential benefits in prevention of allograft dysfunction, it is still reassuring that no clinically significant acute falls in the eGFR were detected (35, 36).

The studies in KTR, appear to show similar results than in the native CKD population. SGLT2i in KTR may cause an acute temporary decline of eGFR, which is thought to be associated with SGLT2i induced afferent arteriolar vasoconstriction. There is evidence that even in the denervated kidney allograft, SGLT2i have the same impact in natriuresis that eventually results to increased tubulo-glomerular feedback and afferent arteriolar vasoconstriction (24). Further research is required to explore the potential impact of reducing intraglomerular hypertension and hyperfiltration on proteinuria/albuminuria and on preservation of eGFR in KTR. The studies so far, offer valuable insights which may stimulate to the development of additional studies focused on establishing the safety and effectiveness of these medications, along with their potential benefits in terms of cardiac and renal protection for KTR, in diabetic and non-diabetic patients. Although the evidence remains insufficient, these data, mostly observational, should encourage renal transplant physicians to use SGLT2i in diabetic KTR, after the first 12 months of follow-up since kidney transplant surgery, mainly for the effect on blood pressure and weight. We recommend using SGLT2i in this setting. Patients should be instructed to maintain sufficient, if not overhydration, in order to prevent eGFR to suffer from hemodynamic effects of SGLT2i. In addition, patients should be counseled regarding perineal hygiene measures to prevent UTI. We do not recommend using SGLT2i in recipients who underwent repeated UTI. In non-diabetic KTR, data are yet insufficient to recommend the use of these drugs, although their great potential may see the light in the near future. Novel and ongoing RCT in this population are expected to provide positive hard clinical outcomes, especially renal allograft survival in the near future.

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EDITED BY
Vikram Sabapathy,
University of Virginia, United States

REVIEWED BY
Mara Medeiros,
Federico Gómez Children's Hospital, Mexico
Murat Dogan,
University of Tennessee Health Science Center (UTHSC), United States
Nikhil Raisinghani,
Icahn School of Medicine at Mount Sinai, United States
Srivatsa Angraje,
Sapthagiri Institute of Medical Sciences and Research Centre, India

*CORRESPONDENCE
Shyam Bihari Bansal
drshyambansal@gmail.com

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Gender and kidney transplantation

Arushi Nautiyal[1], Soumita Bagchi[2] and Shyam Bihari Bansal[3]*

[1]Department of Nephrology, Jaipur Golden Hospital, New Delhi, India, [2]Department of Nephrology, All India Institute of Medical Sciences, New Delhi, India, [3]Department of Nephrology, Medanta - Medicity, Gurugram, India

Kidney transplantation provides the best form of kidney replacement therapy with improvement in quality of life and longevity. However, disparity exists in its availability, utilisation and outcomes, not only due to donor availability or financial constraints but also arising from the influence of biological sex and its sociocultural attribute i.e., Gender. Women make up the majority of kidney donors but are less likely to be counselled regarding transpantation, be waitlisted or receive living/deceased donor kidney. Biological differences also contribute to differences in kidney transplantation among the sexes. Women are more likely to be sensitised owing to pregnancy, especially in multiparous individuals, complicating donor compatibility. A heightened immune system in women, evidenced by more autoimmune illnesses, increases the risk of allograft rejection and loss. Differences in the pharmacokinetics of transplant drugs owing to biological variances could also contribute to variability in outcomes. Transgender medicine is also increasingly becoming a relevant topic of study, providing greater challenges in the form of hormonal manipulations and anatomic changes. It is thus important to determine and study transplantation and its nuances in this backdrop to be able to provide relevant sex and gender-specific interventions and design better practices for optimum kidney transplant utilisation and outcomes.

KEYWORDS

gender, kidney, transplantation, sex, women, India

1 Introduction

The world is becoming increasingly inclusive and plural with pushback on discrimination of any kind. However, a basic sex and gender-based disparity remains everywhere including in healthcare. This exists at all levels encompassing access to healthcare, its utilisation and outcomes as well as research. Some of this disparity arises

Abbreviations: CKD, chronic kidney disease; KT, kidney transplantation; KRT, kidney replacement therapy; ESKD, end stage kidney disease; HLA, human leucocyte antigen; MHC, major histocompatibility complex; CNI, calcineurin inhibitors; MPA, mycophenolic acid; SRTR, Scientific registry of transplant recipients; NGOs, Non governmental organisations; LMICs, Low and middle income countries.

from the biological differences related to sex, whereas the rest stems from its behavioural and sociocultural attributes i.e., gender (1). Biological variances between the sexes at the genetic, hormonal and anatomic levels may alter disease phenotypes; similarly, behavioural traits and cultural factors relating to gender can modify disease perception, treatment-seeking behaviour and coping mechanisms. Therefore, the epidemiology, course, response to treatment and outcome of many diseases may vary depending on sex and gender.

Previously, human and animal model-based research would pool data or extrapolate from the commonly male majority towards the rest of the population (1, 2). Steinberg et al, in a cross-sectional analysis of 20,000 plus studies over recent two decades, were able to identify increased reporting of sex-based data, but also found a sex-based bias in research enrolment in various disciplines, often determined by the primary purpose of the study; the female sex was found to be under-represented in nephrology and genitourinary studies (3). Research governing bodies and scientific journals are now increasingly mandating sex and gender-based analysis in both clinical and pre-clinical settings. Adoption of such practices would allow for the discovery of clinically relevant dissimilarities to allow targeted therapeutic interventions (1).

In the realm of kidney disorders, chronic kidney disease (CKD) is a growing public concern associated with notable morbidity and mortality, especially with the projection rates of diabetes set to rise significantly; as diabetes is the most common cause of kidney dysfunction (4, 5). Worldwide, the majority of population studies report pre-dialysis CKD prevalence rates to be higher in women than men except for a few populations (6). However, in India, women have been consistently under-represented in population data studies focussing on CKD; in some large studies, they only comprised one-third of the study population (5, 7, 8). The authors do comment on possible sociocultural factors affecting health-seeking behaviour in females in low and middle-income countries like India (5).

The prevalence of common causes of CKD like diabetes, hypertension, and chronic interstitial nephritis are similar in men and women (5). However, autoimmune diseases like systemic lupus nephritis are more common in women. Pregnancy is another situation, exposing women to hypertensive disorders, acute kidney injury (AKI), complement dysfunction, and worsening of CKD if present antenatally (6, 9, 10).

Despite higher numbers in the prevalent CKD population, various studies have shown a lesser number of women progress to end-stage kidney disease (ESKD) in comparison to men. Multiple hypotheses have emerged to explain the lower rate of CKD progression among women including incorrect eGFR-based calibration, kidney protective effects of the female hormonal milieu and deleterious effect of testosterone demonstrated in experimental studies (11) and higher prevalence of unhealthy lifestyles among men. There is also a gender-based discrepancy in dialysis initiation rates. A knowledge gap exists among women about their disease and treatment options and they more often tend to opt for conservative management or defer dialysis, especially when elderly (11, 12). There is also a disparity in the access to chronic disease care and kidney replacement therapies(KRT) among men and women and this bias may vary across geographies being more prominent in low and middle-income countries(LMICs) like India compared to high-income countries in the West.

1.1 Gender and access to kidney transplantation

Kidney transplantation (KT) provides the best modality of kidney replacement therapy (KRT), it is associated with a survival benefit and lesser morbidity than dialysis in any form (13). It also allows for a close to normal resumption of day-to-day living, thus improving quality of life and is cost-effective in the long term as compared to dialysis (14).

However, a disparity exists in kidney transplantation too. In USRDS data, the rates of waitlisting and subsequent transplantation for women continue to be lower than men, in both deceased donor as well as living donor transplantation. In 2020, rates for kidney transplants among women were 3.5 compared to 4 per 100 person-years for men in the US (15). In low and -middle-income countries like India, data is often difficult to come by, often represented by single-centre or regional studies (16, 17). In a single centre report from north India, only 11.1% transplant recipients were women. 66.1% kidney donors were women with 90.7% of spousal donors being wives (16). In a large public sector transplant hospital in Gujarat, India, KT rates in women were close to one-fifth of those of men (17).

Women are less likely to be counselled regarding kidney transplantation by their healthcare providers (18, 19), though cardiovascular morbidities are more common in men than women in the ESKD population (12, 20, 21). Segev et al, conducted a USRDS-based registry data study spanning 5 years, they were able to identify that with increasing age and co-morbidities, women had less access to transplants compared to men with similar profiles; though the survival benefit of transplants was similar. This disparity was attributed to perceived frailness by physicians, patients or family members (19). A recent multi-regional cohort study from USA observed interaction between gender, age and race with regard to kidney transplant referral, found that older non-Hispanic black and white women were less likely to be referred for a transplant compared to men (22),.

In a multicentric, cross-sectional survey of outpatients at dialysis centres, Salter and colleagues, found that older adults and women of all ages had fewer discussions with both healthcare providers and their social groups regarding KT (23). A lack of information and awareness regarding treatment options is the first hurdle in identifying an optimum therapeutic plan for oneself, and thus the role of healthcare providers in educating their patients, especially women is paramount. In a retrospective analysis, Monson et al, found white and black women to have slower rates of completion of pre-transplant medical evaluation in comparison to white and Hispanic men (24).

It is imperative to have social support in navigating KT, in identifying a living donor if possible as well as completing the investigation process and follow-up. Women are often the primary caregivers in a family unit (25). Studies have shown a differential

level of care received by older women suffering from disability than men (18, 26), such experiences may lead to apprehensions among women regarding social support available for their care in the peri-operative period.

In a situation with multiple co-morbidities, self-advocacy and patient enthusiasm are often a catalyst for transplant consideration; however, in studies on access to transplant information, women are less inclined to accept counselling regarding KT (27, 28), expressing more health-related and psychological concerns regarding transplantation than their male counterparts (21, 29). Frailty and personal perceptions regarding the same can lead to concerns regarding the ability to withstand surgical stress and immunosuppression, perhaps leading to hesitation in contemplating transplantation both by the patient and their healthcare provider. Adoption of objective measures of frailty by healthcare providers, such as the Fried physical frailty phenotype, as opposed to subjective screening and targeted interventions where possible, could help improve access to transplants for women and the elderly (30). This is especially important as studies have shown an improvement in frailty scores (31) and survival benefit post-transplantation in all groups (19). Educational programmes and the involvement of social support groups may help women address their apprehensions about transplantation. Depression and behavioural disorders are more prevalent in women in the ESKD population (12, 21), involvement of mental health specialists, counselling and therapy could further help in the acceptance of transplantation as a preferred modality for KRT among women. Factors affecting access to transplantation and suggestions to improve outcomes are listed in Table 1.

TABLE 1 Factors affecting renal transplant access and measures to improve outcomes.

Factors Affecting Transplant Access	Suggested Measures to improve outcomes
Community awareness of kidney disease and treatment options	Improved Government policies, NGOs, training of local healthcare workers, skits and educational programmes in local languages
Economic constraints	State based health schemes, rural and urban-poor insurance schemes, NGOs
Change in Gender based attitudes and norms/Familial roles	Increasing literacy rates and skill development especially for females; increasing share of females in workforce, community sensitisation, Advocacy groups
Medical issues impeding KT	Patient education campaigns regarding diet, exercise, avoidance of smoking, blood pressure and blood glucose management; improving frailty indices; optimising medications; educational information leaflets; patient help groups
Gender disparities in kidney donation	Empowering women, financial independence, increasing literacy in women, Donor advocacy
Health worker bias	Review local and state wise data. Introspection of practises. Independent donor advocate. Encourage shared decision making. Measures to increase community awareness
Improving transplant outcomes	Counselling regarding need for medication adherence especially among adolescents, follow up visits. Education regarding and ensuring clean water supply, maintenance of sanitation. Navigating contraception and pregnancy. Research into optimising individual immunosuppression, precision medicine. Emphasising on sex and gender based analysis in research.

NG0, non-government organization; KT, kidney transplantation.

1.2 Gender and access to pediatric transplantation

Studies in pediatric KT have also shown a gender disparity; A European study involving 35 countries found that although overall transplant rates were similar among boys and girls, pre-emptive transplants were lower in girls by 23% in comparison to boys, leading to longer times spent on dialysis (32). This was not explained by medical factors alone and parental and healthcare provider attitudes or bias was considered as probable cause. Girls were also found to be waitlisted less than boys for deceased donor transplants (33).

1.3 Social, economic factors generating gender bias in access to healthcare and kidney transplantation

The financial burden of transplantation is an important consideration as KT is associated with high initial costs (direct and indirect) but the overall cost is less in long-term as compared to those on dialysis (34). Even in countries with universal healthcare like the United Kingdom, lower transplantation rates have been reported in socially deprived subgroups (defined by unemployment, car ownership, home ownership, and overcrowding) (35). Couchoud et al, also found older, non-working women in France to be less likely to be waitlisted for KT (21).

As the majority of healthcare expenditure in India tends to be out of pocket, chronic medical illness often places severe financial constraints on families. Gender disparity in all aspects of healthcare expenditure has been widely documented in India (36), which may play a huge role in inequity in kidney transplantation. Men are usually the primary breadwinner in the family and are therefore more likely to be prioritized for financial and social support for KRT than women. Women are often unemployed and financially dependent, assuming non-paying household work and caregiving duties (37). Women in India have lower health literacy with lesser access to communication media (37). In patriarchal societies, such as India, women also tend to have less agency for themselves, even in aspects about healthcare and lack independence to take treatment decisions which are often made by their male family members. Similar gender based inequalities have been noted among other LMICs (38). Even in high income countries where health awareness among women is considered to be greater, with studies even reporting higher primary care utilisation by women perceived unmet health needs were found to be higher among women than

men (39), gender differences in critical care have also been described with women receiving less invasive therapeutic interventions (40).

Depression and anxiety disorders are also more common in women, often fuelled by poverty (41), making them susceptible to defer initiation of KRT, let alone transplantation; mortality in such patients is often unaccounted for (12). A qualitative study exploring nephrologists' perspectives highlighted gender stereotyping, stigma and prejudice with men being vested with decision making powers and educational and financial handicaps being the major factors contributing to the gender disparities in access to KT (42). These social factors were considered to be significant even though most of the nephrologists interviewed were from high income developed countries(Australia, USA and Austria) and likely to be of greater concern in traditional societies and LMICs.

Increasing education and awareness in the general population and challenging traditional gender roles in communities could bring improvement in access to healthcare. Recognising and changing restrictive gender norms as well as impugning practises that maintain them in communities at the grass root level is required through social and economic policies. Similarly a change in gender-based attitudes among healthcare providers is required to remove biases and improve both primary and specialty care and community health.

Significant barriers in transplantation and CKD outcomes are also seen based on a rural-urban divide, which may also add to gender based disparity. Pertinent factors such as distance from available healthcare facilities, quality of nearest facilities, laboratory and imaging services available weigh appreciably on community health and KT (43, 44). Considerable distance from adequate healthcare facilities and poor transport infrastructure affects health seeking behaviour (44, 45) and may make medication availability a considerable challenge. Linguistic barriers, inability or frustration in navigating healthcare systems, need for geographic relocation and ensuing economic costs add to the challenges for kidney replacement therapies including transplant for rural communities, Ensuring clean water supply and ability to maintain sanitation and hygiene can be a task in underserved rural and urban poor dwellings, increasing risks of infections.

Policies for rural healthcare, transport and clean water access need to be strengthened and regularly reassessed by local governments and stakeholders, increasing use of telehealth and remote monitoring can allow for better follow up, local health auxiliary workers can help co-ordinate such communication with specialists and overcome language barriers.

1.4 Medical issues, gender and access to kidney transplantation

Even following waitlisting, women are less likely to receive deceased donor transplants (6, 20). Various studies including donors from any source, have found a higher body mass index (46), type 2 diabetes mellitus causing CKD (20), and higher panel reactive antibodies (18) among others as reasons for such disparity. Obesity predisposes to more surgical risk; women have greater body fat percentage than men which may lead to physician-centred bias in proceeding with transplantation (46). In a retrospective analysis of USRDS data, focussing on differential deceased donor transplantation rates among the sexes, based on the cause of CKD, Ahearn and colleagues found that women with type 2 diabetes mellitus, were less likely to receive KT, despite having lesser cardiovascular comorbidity than their male counterparts with diabetes (20). Pregnancy and subsequent sensitisation, leading to HLA incompatibilities, especially with spouses and children as potential donors creates barriers for women in living donor transplantation. Studies have also reported the differential sensitisation to be largely contributed by pregnancy more than other sensitising events such as blood transfusion or previous transplant (47, 48).

2 Gender and kidney donation

The majority of living kidney donors tend to be female. In India, living kidney donation constitutes the bulk of kidney transplantation in the country (17, 49–51). These trends have also been reported in other countries like China (52) and Turkey (53). Kurnikowski et al, conducted an analysis of sex distribution of donors based on varying sources of data from multiple countries; it found that in the majority of the sampled countries, female donors outnumbered males and the donation rates were disproportionate to their representation in the general population. Similarly, females were less likely to be transplant recipients than males. The authors hypothesised that reduced tobacco use among women and overall lower employment rate among females increase their availability as donors (54). A study in a single large public transplant centre in India found female predominance among kidney donors in all categories, whether parental, spousal or sibling (17). In recent decades, spousal donation rates have been increasing steadily; shrinking family units may be responsible for such trends and these include predominantly female donors (49). Zimmermann et al., in an analysis of potential donor pools for transplant recipients in Canada, also found greater female predominance among donors, fuelled mostly by spousal donation (55). However a change in such trends in recent times has been noted (56). Biological factors responsible for lesser donation among men include an immunological barrier in husband to wife donation, unhealthy lifestyle choices or population-based, evidence of greater hypertension, and heart disease among men (54, 57). In a registry-based analysis of donor safety, though absolute numbers were low, men also had significantly greater perioperative mortality than women (58). However, social factors have been considered to contribute more towards the lesser number of male donors (59).

A gender difference in attitudes towards organ donation has been seen in community studies. Women are traditionally perceived as caregivers and hence more forthcoming for donation, based on greater empathy and altruistic tendencies. Almeida et al, in a general population-based survey, found females to have a more positive attitude towards kidney donation in comparison to men (60). Similarly, in a survey of adults in the United States, Yee and colleagues found that women were more willing to donate organs to family members and strangers than men (61). An improved

quality of life of the partner and lesser caregiving requirements in opting for kidney transplants over other forms of kidney replacement therapy for spousal donors are also frequent considerations, especially for women who tend to shoulder the bulk of caregiving duties (62). Living kidney transplantation can often put an emotional and economic strain in the family (63); fears about adverse consequences and lost income underlies an unwillingness to involve family members with more earning potential in the donation process, more likely to be male. Coercion and manipulation from family members also influence decisions for donation, especially in the case of female donors who are often uneducated and unemployed (37, 60), and there should be safeguards to prevent this during the donor review process.

2.1 A survey on gender discrimination and kidney transplantation in India:

We recently conducted a survey among Indian Nephrologists regarding access to kidney transplants based on gender (Unpublished). There were 267 respondents, and 80% answered that in their practice women comprise < 25% of recipients and > 75% of donors. Women were less likely to receive KRT or KT as compared to males. About the reasons for this disparity in getting KT: 16.5% cited the misconception about transplant, 36% financial reason, 44% said that women were reluctant to take a kidney from a family member and 64% responded that the family members were unwilling to donate due to female gender. The survey also found out that in the case of women being recipients, 85% of donors were parents, however, if a male was a recipient, then approximately 70% of donors were spouses (Figure 1).

3 Gender and transplant outcomes:

Kidney transplant outcomes are affected by various factors including immune activity, medication compliance, donor characteristics, and dialysis vintage among others, some of which are influenced by sex and gender aspects. When assessing for differences in transplant outcomes according to sex, various studies have shown conflicting data with some showing poorer results for female recipients while others have revealed no long-term differences (63–66). Females are also more likely to react to the sex- dependant H-Y minor histocompatibility antigens found in male donor kidneys (67).

In a retrospective analysis of deceased donor recipients using the Scientific Registry of Transplant Recipients (SRTR) database, Lepetyre et al, studied the interaction between donor sex, recipient age and recipient sex with graft outcomes; they found that females of all ages had poorer graft outcomes when receiving male kidneys, whereas only females between the ages of 15-24 years did poorly even with female donors compared to male recipients (68). In comparison, Vinson et al, in a multinational analysis using SRTR, Australia and New Zealand Dialysis and Transplant Registry, and Collaborative Transplant Study registry data, which included countries providing universal healthcare, identified higher graft loss in young females receiving male kidneys (likely from H-Y antigen effect), they also found lower graft survival in older males recipients than females receiving female kidney, which was considered to be associated with better medication adherence in females (69). Mortality risk is often linked intricately with the risk of graft loss in transplant patients. In an analysis of sex differences in excess mortality (greater than general population mortality rates for that sex) among recipients of a first deceased donor kidney transplant belonging to three large international transplant databases. Excess mortality in female recipients (except ages 45-59 years) was identified, more in the younger than older members of the cohorts, being statistically significant only if the donor was male. Mortality in younger women was more due to loss of graft function, whereas in older women more deaths with functioning grafts were reported (70). Some of the important studies regarding gender and Transplant are shown in Table 2.

Innate and adaptive immunity differs by sex and age. Post pubertal effect of sex steroids on immunity leads to a more robust response in women under the influence of estrogen, whereas androgens have been found to have immunosuppressive effects. This dimorphism predisposes men to infections and women to enhanced immune reactivity which may be harmful in certain

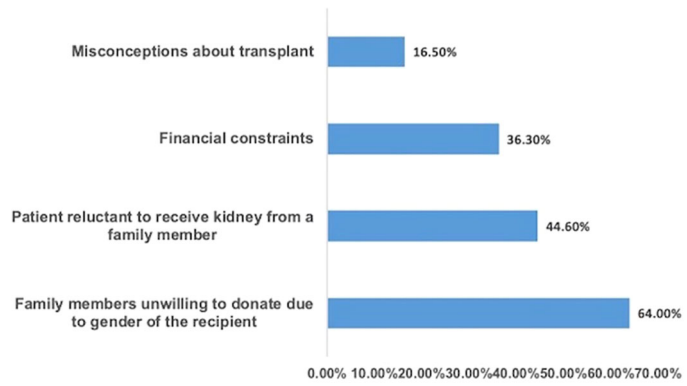

FIGURE 1
Reasons attributed by nephrologists for gender disparity in access to transplantation.

TABLE 2 The important studies on gender disparity in transplantation.

Authors (Country)	Type of Study	Alms	Results
Bal (16) **(Kerela, India)**	Single centre, Retrospective analysis of LDKT, 2001-2005	To study the gender disparity in LDKT	682 LDKT recipients 88.9% male, 11.1% female, Donors- 66.1%- female 33.9% male
Segev (19) **(United States)**	National Cohort study, USRDS, 2000-2005	Study points- Gender disparities- • Access to transplant (ATT) • Survival benefit after Transplant (SBT)	Multivariate analysis - Overall women had 11% less ATT Increasing significantly for age and comorbidities - more than 75 yr olds- 59% less ATT- likely perception of frailty No difference in SBT between men and women of all ages, irrespective of co-morbidities
Gill (46) (2014)	Retrospective, USRDS, Incident ESKD pts (1995-2007)	Aim- determine association of BMI with access to KT (deceased and living donor) in men and women	Females- BMI>25 kg/m2 -lower likelihood of transplantation from any donor source (HR, 0.75; [95% CI], 0.73 to 0.77) Male- BMI >40kg/m^2 – lower likelihood of living donor BMI>35kg/m^2 – lower deceased donor Tx
Bromberger (47) (2017)	Single centre, intention to treat analysis, Prospective cohort study, Pennsylvania, US 2587 LDKT candidates 62% male, 38% female	To identify sex specific points of attrition in LDKT process	-Similar referrals -Similar rates of crossmatch -Among crossmatched candidates- 50% men vs 35% women received LDKT (p-0.01) -31% potential donor loss in females vs 9% for males - cPRA men =7% ± 22% versus women =24% ± 35%; *P*<0.001) - living donor incompatibility -significantly higher than predicted by cPRA among weakly sensitized candidates with a history of pregnancy
Vinson (69) **(2022)**	Retrospective cohort study • American SRTR • Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry • International Collaborative Transplant Study (CTS) database	Aim- compare graft loss rates between male and female recipients accounting for the modifying effects of recipient age and donor sex	**Male donor-** More graft loss in young females • 0–12 y: adjusted hazard ratio [aHR] 1.42, (95% [CI], 1.17-1.73) • 13–24 y: 1.24 (1.17-1.32) • 25–44 y: 1.09 (1.06-1.13) (likely HY effect) **Female donor-** More graft loss in older males in comparison to older females • aHR 0.93 (0.89–0.98) in 45–59 y-old • 0.89 (0.86–0.93) in ≥ 60 y-old recipients (likely better medication adherence in females)
Vinson (70) **(2023)**	Retrospective cohort study of first deceased donor KT • American SRTR • ANZDATA • CTS	Aim- compare **excess risk of mortality** by recipient sex (excess in comparison to sex and age matched general population)	**Male donor-** Female recipients 0–12 years (Relative Excess Risk 1.54, 95% CI 1.20–1.99) 13–24 years (1.17, 1.01–1.34) 25–44 years (1.11, 1.05–1.18) > 60 years (1.05, 1.02– 1.08) showed higher excess mortality risks than male recipients of the same age except for 45-60 years (only for male donors) Younger females mortality associated with graft loss Older females more death with functioning grafts

LDKT, Lliving donor kidney transplantation; USRDS, United states renal data system; ESKD, End stage kidney disease; BMI, Body mass index; KT, Kidney transplantation; cPRA, Calculated panel reactive antibody; SRTR, Scientific registry of transplant recipients.

situations and be responsible for a greater amount of autoimmune diseases in women as well. In the post-menopausal state, women tend to experience a rapid decline in sex hormone effect which may diminish immune responses (66, 71). This difference may explain the greater likelihood of graft failure in younger women (68, 69). Greater reactivity to male donor kidneys in female recipients likely stems from differences in sexually determined alloantigens such as H-Y minor histocompatibility antigens. The immunosenescence that develops with age, may reduce the reactivity in older female recipients to H-Y antigens. These antigens, expressed by the Y chromosome, are present in all male tissues (65, 68). Their expression varies in different tissues and is prognostically found to be most important in stem cell transplants. However, even in the setting of KT, they have been found to have a significant influence, especially in the short term; Tan et al, demonstrated antibodies to H-Y antigens in female recipients of male kidneys which showed a strong association with acute rejection in multivariate analysis (67).

Medication adherence has been frequently reported to be greater in females (72, 73). Donor recipient weight mismatch (74) with women usually weighing less, leading to nephron underdosing and sex-related differences in metabolic demand on the graft which tend to be higher in men (75) have also been considered as non-immunological factors responsible for graft dysfunction.

Cancer risk in kidney transplant recipients has been greater than in the general population, increasing with transplant vintage (76). Studies looking at gender differences in cancer incidences have found conflicting data, with some observing greater risk in males (77) whereas others reported higher risk in females (76). Webster et al, assessed cancer risk among the sexes stratified by age and found greater risk in younger women than men transplanted at the same age, similar rates in middle-aged recipients and greater rates in older men (78).

4 Effect of gender on transplant immunosuppression

Immunosuppression is the backbone of organ transplantation, the most commonly used medications for maintenance immunosuppression in KT include- Calcineurin inhibitors (CNI) i.e. Cyclosporine and the more commonly used drug Tacrolimus (TAC), antimetabolites- such as Mycophenolate mofetil (MMF) and Azathioprine, and steroids. Lifelong intake of these medications is necessary for the long-term survival of graft, however, these drugs are associated with many adverse effects including increased risk of infections due to lowered immunity, drug and food interactions and long-term consequences such as malignancy. CNIs are drugs of a narrow therapeutic index, necessitating drug-level monitoring, thus ascertaining the optimum dose for any individual is of utmost importance. Sex and gender-related variations in drug metabolism have been noted and a greater understanding of the differing pharmacokinetics and pharmacodynamics would help in individualising immunosuppressive regimens.

CNIs are metabolised by the CYP3A4/5 subfamily of enzymes and are substrates of efflux transporter p-glycoprotein; polymorphisms in genes encoding these proteins and other factors such as diarrhoea and drug and food interactions are responsible for the great amount of inter and intra-individual variability in CNI drug levels (79). Tornatore et al. found greater cumulative, neurological and aesthetic adverse effects from tacrolimus in women than men, especially black women (80). Gender and race-related differences have been found in various studies assessing the pharmacokinetics and pharmacodynamics CNIs, but the results have not been conclusive and thus sex specified doses are as yet not recommended (79).

In a pharmacokinetic study of MPA, Morissette et al, found significantly higher ratios of MPA metabolite to MPA in men than women, showing higher clearance in men (81). Sex hormones have been documented to modulate the metabolism of MPA (79). Azathioprine is another antimetabolite which is often used in situations where mycophenolate is not tolerated or in pregnancy. Its converted to its active metabolite- 6-mercaptopurine, which is metabolised by thiopurine S-methyl transferase enzyme (TPMT). The inactivating enzyme expression has been found to be higher in men and influenced by testosterone, however, the clinical implications of this difference are still not clear (82).

Glucocorticoids are a common part of triple-drug immunosuppression regimens for kidney transplantation. Prednisolone has been found to have reduced rates of clearance in women in comparison to men, and thus increased systemic exposure. However, Magee et al. also found that in addition to reduced clearance rates, women have a greater volume of distribution of prednisolone which leads to similar half-lives in both sexes (83). Clearance of unbound prednisolone has also been found to be lower in post-menopausal women as opposed to premenopausal women with no effect of hormone replacement therapies (84). Glucocorticoids are associated with significant adverse effects and thus efforts to streamline optimal doses to reduce steroid exposure could be helpful and need further study.

MTOR inhibitors such as Sirolimus and its derivative Everolimus are also used in alternate immunosuppression regimens. They are also substrates of CYP3A and p-glycoprotein. Sirolimus clearance has been found to be higher in females by 20% (sirolimus), however, no major pharmacokinetic differences by sex have been documented with everolimus (79).

5 Kidney transplantation in the transgender population

Transgender refers to individuals whose gender identity does not conform to the sex they were assigned at birth. A substantial proportion of such persons express a desire to transition to the gender they identify with, involving hormonal manipulations and often gender-affirming surgeries. Kidney transplantation in such populations is associated with some unique challenges involving use of hormonal therapy, anatomic changes from gender-affirming surgeries, and psychosocial issues among others (18).

Some trans-individuals opt for gender-affirming surgeries, which may include mastectomy, breast augmentation, facial

surgery or urogenital surgeries such as phalloplasty or vaginoplasty. Gender-affirming surgeries have been shown to reduce gender dysphoria. This is a newly advancing field with implications in kidney transplantation as urogenital surgeries with manipulation of urethra can result in strictures, and fistulas or lead to recurrent urinary tract infections (85, 86). Thus medical providers should inquire about and discuss intentions for gender-affirming surgery with transgender patients both prior to and after kidney transplantation (85).

Hormonal therapy can have medical and surgical implications in KT. Feminising medications often include estrogen as oral, transdermal gel or intramuscular preparations. Ethinyl estradiol has been known to increase the risk of venous thromboembolism and is generally held for 2-4 weeks before and after the operative procedure, though such discontinuation may lead to dysphoria (18, 85). Estrogen has also been found to increase tacrolimus levels which may necessitate dose reductions (87), but it requires more studies. Antiandrogens like spironolactone may lead to hyperkalemia which can interact with concomitant transplant drugs like Calcineurin inhibitors or trimethoprim-sulphamethoxazole 86). Testosterone given for masculinising therapy can contribute to alopecia associated with tacrolimus, can cause acne which can be exacerbated with steroids and predispose to infectious vaginitis in individuals who have undergone female-to-male gender affirmation surgery. Testosterone can also increase erythropoiesis and contribute to the development of post-transplant erythrocytosis (18).

Transgender individuals have a high risk of psychiatric illnesses including anxiety, depression or substance abuse (85, 88). Mental health issues may contribute to medication non-adherence or declining appropriate therapy which may affect transplant outcomes. Thus involvement of mental health professionals in the transplant team is essential. Such illnesses can also be aggravated during periods of increased steroid dosages such as antirejection therapy. Changes in physical appearance with transplant medications may also lead to medication non-adherence such as the development of cushingoid body habitus with chronic steroid use, alopecia with tacrolimus or hirsutism with cyclosporine (89). Transgender kidney transplant patients require close psychosocial monitoring and social support alongside usual care for good transplant outcomes. A greater sensitivity and discretion on the part of the healthcare providers is required in managing their kidney disease.

6 Pregnancy and fertility after kidney transplantation

Fertility in CKD is low, owing to factors such as the dysfunctional interplay of gonadotropins and hypothalamic-pituitary axis and reduced renal clearance of prolactin among others (90). Hormonal changes often reverse with kidney transplantation and improve fertility (18). Metanalysis and systematic reviews have identified a higher live birth rate among transplant recipients but also noted a higher caesarean section rate, gestational diabetes, hypertension, pre-eclampsia, low birth weight and fetal loss (91, 92). Kidney transplant recipients may have pre-existing diabetes, hypertension and cardiovascular disease, or have advanced maternal age which may contribute to increased risk of complications (91). Certain transplant medications such as MMF are also teratogenic which can lead to increased spontaneous abortions and ear and facial fetal deformities and thus need substitution to azathioprine prior to planning pregnancy (92). Deshpande et al. reported an acute rejection rate of 4.2% during pregnancy among 2412 pregnant recipients (91). Studies assessing graft outcomes in pregnancy have been inconclusive and suffer from bias, with some showing greater acute and chronic graft loss in the first two years post-pregnancy (93) and others observing a comparable graft function with nulliparous controls, and no long-term effects on graft function, with a marginal higher impairment noticed in two years post-partum (94). Transplant recipients are usually counselled to avoid pregnancy in the first 2 years after transplant, and plan pregnancy only in the presence of stable graft function (serum creatinine <1.5mgdl) with an absence of significant proteinuria on stable pregnancy safe immunosuppression with no recent rejection event (18, 94). Safer methods of contraception in transplant recipients include progesterone-only pill or intramuscular depot injections, and intrauterine devices. Physical barrier methods such as condoms are useful in avoiding sexually transmitted diseases, however, are not very effective when used alone for contraception. Estrogen-containing oral contraceptive pills are associated with risks of venous thromboembolism or hypertension and are better avoided (92).

Men also have poor fertility in CKD, with low sperm counts and testosterone which improves following transplantation, with restoration of fertility. A significant proportion of men with CKD have erectile dysfunction, which often improves with kidney transplantation but may persist in 20-50% of patients, likely from medication effect, altered endocrine milieu, polyneuropathy, diffuse vascular disease and psychosocial problems which may impair quality of life (95).

7 Limitations of current evidence

The current information is based mainly on single-centre studies limited by small sample size, incomplete data about relevant variables and the influence of local centre practices. They may be biased by local social structure leading to gender disparity in access to healthcare and family support. There is a paucity of data from LMICs like India where most of the information comes from single-centre retrospective studies (16, 17). However, considering the findings are similar from different parts of the country, gender disparity seems to be widely prevalent.

The large multi-centric studies based on registry data (12, 19, 22, 46, 47, 69, 70) should also be interpreted with caution due to their retrospective design. At best, they report associations but cannot establish causation. There may be residual confounding as details of certain vital parameters like severity of comorbidities, cognitive function, dementia, medication compliance which may influence decisions regarding transplantation as well as socio-economic cultural factors which play an important role in gender

inequality were not examined. Certain variables like obesity were captured at the time of diagnosis of ESRD (46) and not when the patient is waitlisted which may have led to misclassification. The gender is often assigned by the healthcare provider which may differ from the gender perception of the individual (22). The majority of these large, multi-centric or registry studies are from Western, high-income countries and the findings cannot be generalized to other regions, especially LMICs where women face significantly more social and financial barriers when seeking treatment. There is limited information on patient and healthcare providers' perspectives about gender bias in transplantation (25, 29, 42) with the possibility of selection bias and lack of transferability of conclusions to other countries and regions. We need prospective studies with adequate global representation exploring socio-cultural, financial and psychological issues as well as medical factors contributing to gender inequality in access to transplantation.

Lastly the role of transgender and other gender identities has not been addressed in these studies.

Conclusions

Sex and gender differences affect all aspects of kidney transplantation and need due consideration for improving patient and graft outcomes. Equitable access to Kidney Transplantation with gender neutrality should be the goal and LMICs should not be lagging behind the rest. More research is needed on differential aspects including access to transplants, immunosuppression protocols, genetic and hormonal influences. A greater sensitisation is required in the medical community regarding gender disparity in transplantation and efforts to dispel conscious or unconscious bias based on sex and gender should be made. Regular analysis of gender-specific national and regional data regarding kidney transplantation can help in increasing awareness and introspection. Social support groups can help in navigating the transplant process and help in removing psychosocial barriers to transplantation. Healthcare policies should be geared towards improving deceased organ donation, establishing regional and national paired kidney exchange programs and transplant registries. National and state-sponsored schemes for financial support and increasing community awareness would allow for equitable access to kidney transplantation among all sexes and genders. In the future, the development of precision medicine with the help of genomics and proteomics may help in optimising immunosuppression and follow-up protocols for all groups based on individual differences.

Author contributions

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Conflict of interest

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EDITED BY
Piergiorgio Messa,
University of Milan, Italy

REVIEWED BY
Francesco Forfori,
University of Pisa, Italy
Keiko Greenberg,
MedStar Georgetown University Hospital,
United States

*CORRESPONDENCE
Rogério da Hora Passos
rogerio.passos@einstein.br

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The utility of point-of-care ultrasound in critical care nephrology

Rogério da Hora Passos[1]*, Uri Adrian Prync Flato[1,2], Paula Rodrigues Sanches[1], Carolina Moraes Pellegrino[1], Ricardo Luiz Cordioli[1], Bruno Caldin Silva[1], Felipe Galdino Campos[1], Dalton de Souza Barros[3], Fernanda Oliveira Coelho[4], Bruno de Arruda Bravim[1] and Thiago Domingos Corrêa[1,2]

[1]Critical Care Department, Hospital Israelita Albert Einstein, São Paulo, Brazil, [2]Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, Brazil, [3]Critical Care Unit, Hospital CardioPulmonar, Salvador, Bahia, Brazil, [4]Critical Care Unit, Davita Tratamento Renal, Salvador, Bahia, Brazil

Point-of-care ultrasonography (POCUS) is gaining heightened significance in critical care settings as it allows for quick decision-making at the bedside. While computerized tomography is still considered the standard imaging modality for many diseases, the risks and delays associated with transferring a critically ill patient out of the intensive care unit (ICU) have prompted physicians to explore alternative tools. Ultrasound guidance has increased the safety of invasive procedures in the ICU, such as the placement of vascular catheters and drainage of collections. Ultrasonography is now seen as an extension of the clinical examination, providing quick answers for rapidly deteriorating patients in the ICU. The field of nephrology is increasingly acknowledging the value of diagnostic point-of-care ultrasound (POCUS). By employing multi-organ POCUS, nephrologists can address specific queries that arise during the diagnosis and treatment of patients with acute kidney injury. This approach aids in ruling out hydronephrosis and offers immediate information on hemodynamics, thereby consolidating patient data and facilitating the development of personalized treatment strategies.

KEYWORDS

point-of-care ultrasound, intensive care, acute kidney injury, nephrologist, VExUS, renal resistance index (RRI), AV fistula, nephrology

1 Introduction

The incidence of acute kidney injury (AKI) requiring renal replacement therapy (RRT) has significantly increased over the years, affecting up to 15% of critically ill patients (1–3). Intradialytic hypotension (IDH) has been found to complicate 10%–70% of intermittent hemodialysis sessions, approximately 40%–60% of sustained, low-efficiency dialysis

sessions, and 19%–43% of continuous renal replacement therapy treatments. While the association between intradialytic hypotension and adverse outcomes is unclear, studies on critically ill patients have shown a higher mortality rate and impaired renal recovery in those who experience IDH (4–6). Additionally, critically ill patients treated with vasopressors for shock often experience significant and prolonged relative hypotension, which is associated with poor kidney-related outcomes (7). There is no definitive evidence supporting the routine use of any specific intervention to prevent IDH, as its causes are multifactorial and include both the dialysis process itself and factors related to critically ill patients (8). The combination of decreased blood volume and impaired vascular resistance, along with reduced cardiovascular reserve, can lead to hemodynamic instability. Furthermore, the dialysis process has the potential to disrupt compensatory mechanisms, increasing the risk of hypotension. Point-of-care ultrasonography (POCUS) is now used in many clinical settings to enhance patients' management. An assessment of predialytic cardiopulmonary profiles, defined based on sonographic findings, could facilitate IDH prediction and is an emerging part of critically ill patients' bedside evaluation. Additionally, several other patient-related factors, such as baseline cardiac dysfunction, vascular tone, and impaired compensatory responses, can contribute to IDH. Therefore, bedside ultrasound for cardiovascular performance assessment serves as a valuable tool for conducting a comprehensive evaluation of patients requiring renal replacement therapy. In this review, we discuss the rationale behind nephrologists performing POCUS, explain the fundamental principles of focused ultrasonography, and provide our expert perspective on its effectiveness for delineating and comprehending the mechanisms of hypotension in patients undergoing RRT. We also discuss how POCUS can contribute to personalized resuscitation and improve patient outcomes.

2 The use of point-of-care ultrasound in the field of acute care nephrology

Caring for acutely ill patients with AKI who are undergoing RRT can be extremely difficult. The nephrologist is tasked not only with managing the kidney disease and dialysis procedure itself but also with addressing all the consequences that arise from the disrupted balance within the body. The use of POCUS has expanded significantly (Figure 1), and it has become an effective tool in diagnosing the cause of renal dysfunction, identifying pulmonary infiltrates, and assessing volume and acute circulatory failure in these patients (14, 15). Despite its clear benefits and acceptance in other medical fields, POCUS is still not widely used by nephrologists (16). The reasons for this are not clear, but it may be due to a lack of exposure and expertise acquired during training, time constraints for busy nephrologists, and a lack of standardized protocols for using POCUS. However, there has been a recent increase in interest among nephrologists, and POCUS training is now being incorporated into fellowship programs (17). The adoption of POCUS by nephrologists will provide them with a valuable tool that can greatly impact the management of AKI patients (18).

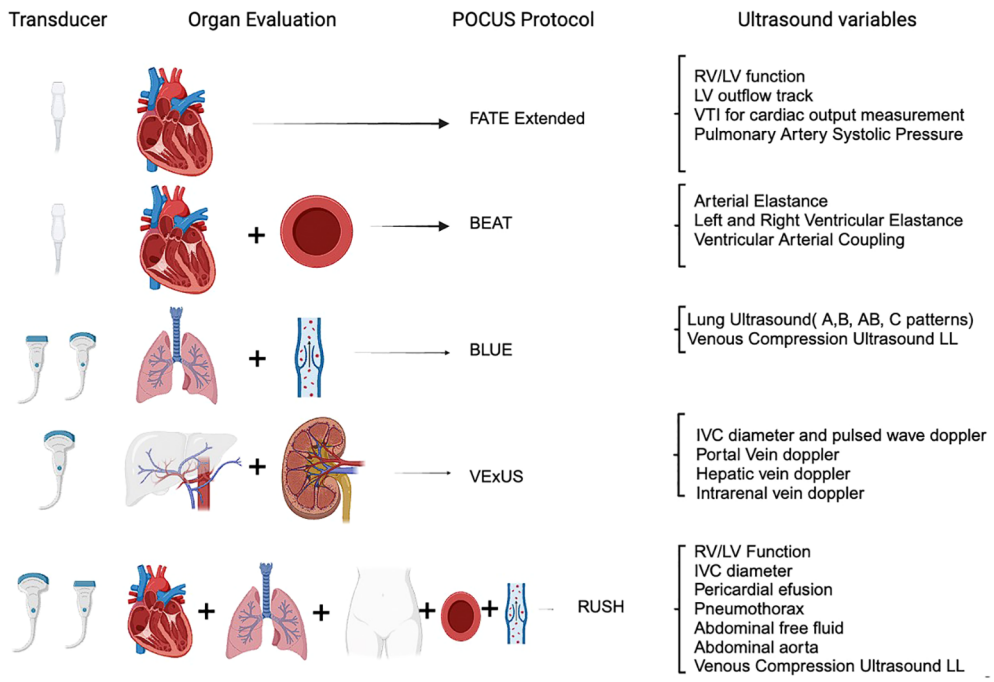

FIGURE 1
Point-of-care ultrasound protocols for acute care nephrology. RV, right ventricle; LV, left ventricle; VTI, velocity time integral; IVC, inferior vena cava; LL, lower limb; FATE extended (9), focus-assessed transthoracic echocardiography; BEAT (10), Browse the heart, Elastances, Assess volume status and Treat; BLUE (11), bedside lung ultrasound in emergency; RUSH (12), rapid ultrasound in shock examination; VExUS (13), venous excess ultrasound.

Point-of-care ultrasound (POCUS) is increasingly recognized as a vital tool in managing unstable medical conditions, offering rapid diagnostic insights that can significantly impact patient care outcomes. However, proficiency in performing ultrasound across various anatomical regions involves a notable learning curve that affects its effective utilization. Achieving competence in POCUS requires comprehensive training and continual practice to master image acquisition, interpretation, and integration into clinical decision-making (19, 20).

The learning curve for ultrasound proficiency varies depending on the body district being examined. For example, abdominal ultrasound necessitates expertise in visualizing organs through different acoustic windows while navigating challenges such as bowel gas interference (21). In contrast, mastering cardiac ultrasound requires precise probe positioning and advanced interpretation skills to assess cardiac chamber dimensions, valve function, and hemodynamics accurately (22).

Training programs tailored to POCUS encompass diverse educational approaches, including didactic sessions, hands-on workshops, simulation-based training, and supervised clinical practice. These programs are essential to ensure that clinicians acquire and maintain proficiency in ultrasound techniques across varied clinical scenarios (23). Competency assessments and quality improvement measures, such as peer review and proficiency evaluations, further enhance the reliability and clinical impact of POCUS in acute and critical care settings (24).

In conclusion, while POCUS enhances diagnostic capabilities in unstable conditions, addressing the learning curve across different body districts is essential for optimizing its clinical utility. Continuous training and proficiency assessments are crucial to ensure accurate and effective use of ultrasound, thereby improving patient outcomes in diverse clinical contexts.

3 Lung ultrasonography for nephrologists

Nephrologists and AKI patients struggle to control volume overload and its complications. Traditional signs of volume overload in physical examination, such as rales and edema, are not reliable indicators of pulmonary congestion (25). The reliable detection of pulmonary congestion holds the potential to predict the need for additional ultrafiltration (26). From a technical perspective, the appearance of a normal lung structure is hindered by reverberation artifacts caused by the difference in density between skin and soft tissue (water density) and the alveolar sac (air density) in ultrasound images (27). In healthy individuals, the lung exhibits a pattern of horizontal reflections called the A-line pattern. As pulmonary congestion increases, this pattern shifts to a vertically oriented B-line pattern. B-lines manifest as hyperechoic lines extending to the ultrasound field's edge, moving synchronously with respiration. Quantifying pulmonary congestion involves counting B-lines across multiple intercostal spaces, with the eight-zone anterior lung ultrasound being the most validated method for research (28). The more B-lines are counted, the greater the pulmonary congestion, which correlates with extravascular lung water (29). Quantitative lung ultrasound has shown good reliability and agreement compared to ultrasound transducers. The optimal images are obtained by setting the focal depth at the pleural line, increasing gain in the far field, and turning off harmonics. Lung ultrasound surpasses physical examination and chest X-ray in predicting acute cardiogenic pulmonary edema (30). It is also sensitive in detecting pleural effusions, which appear as anechoic structures between the lung and diaphragm. Lung ultrasound can easily be taught using a remote web-based application.

The lung ultrasound score (LUS) is a tool that has gained traction among nephrologists due to its utility in assessing and managing patients with kidney diseases. This scoring system is based on the quantification of B-lines using a quick eight-zone protocol (Figure 2) that can be completed in under 2 min (31). In practice, the lung is divided into eight zones, and each zone is scored based on the number and intensity of B-lines that are observed. The cumulative score provides a semiquantitative assessment of lung water, which correlates with the degree of pulmonary congestion. This method offers a more nuanced and precise approach to fluid management compared to traditional methods like physical examination or chest X-ray, particularly in dialysis patients, where an accurate assessment of dry weight is crucial. It is non-invasive and radiation-free and can be performed at the bedside with portable ultrasound machines. This makes it an ideal tool for real-time monitoring and decision-making in acute care settings. However, the accuracy of LUS depends on the operator's skill and experience, highlighting the need for adequate training and standardization in its application.

When discussing lung ultrasound, it is crucial to elucidate the relationship between extravascular lung water (EVLW) and B-lines, particularly for optimizing dialysis sessions. Nephrologists have effectively utilized B-line assessments to enhance dialysis treatment, as evidenced by several key studies. For instance, Mallamaci et al. demonstrated the detection of pulmonary congestion via chest ultrasound in dialysis patients, highlighting the clinical utility of this method (32). Moreover, Noble et al. provided significant insights into the time course for the resolution of EVLW in patients undergoing hemodialysis, emphasizing the role of ultrasound in effectively monitoring and managing fluid status (33).

Lung ultrasound offers several advantages, particularly when compared to cardiac ultrasound. First, it is non-invasive, making it safer and more comfortable for patients. The method allows for frequent repetitions, enabling continuous monitoring of a patient's condition without the risks associated with radiation exposure. Lung ultrasound also provides real-time results, facilitating immediate clinical decision-making, which is crucial in managing fluid status in dialysis patients (28). Furthermore, it is relatively low cost and can be performed at the bedside, making it accessible in various healthcare settings (29).

However, lung ultrasound does have limitations. The accuracy of the results is highly dependent on the operator's skill and experience, necessitating thorough training and proficiency in interpreting ultrasound images (11). Variability between operators can lead to inconsistencies in diagnosis and assessment. Additionally, while lung ultrasound is excellent for detecting B-lines and assessing EVLW, it may be less effective in differentiating

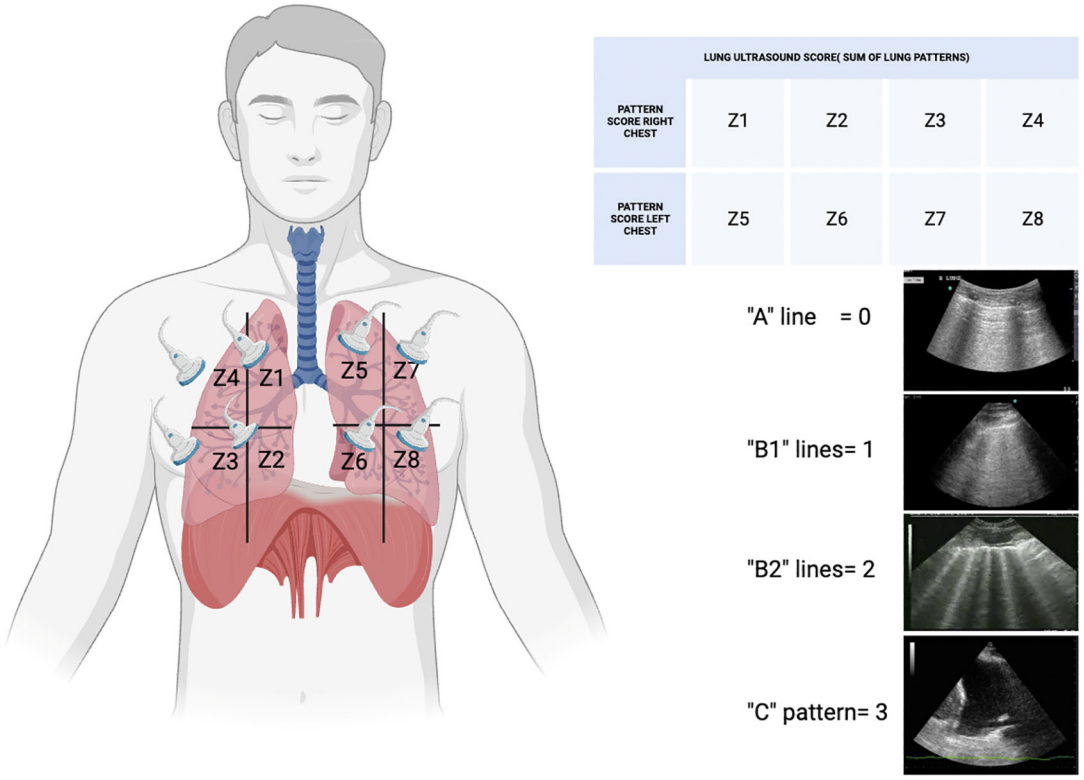

FIGURE 2
Diagram of the lung ultrasound score (LUS) adapted from Volpiceli et al. (28). Score grade from 0 to 24; the higher the score, the more severe the lung disease. LUS is a useful diagnostic tool in monitoring treatment and prognostic factors. Z, zone. The "B-lines" observed in lung ultrasonography are reverberation artifacts that indicate the presence of alveolar interstitial syndrome. The lines can be classified into various profiles according to the therapeutic context. For example, a "B1" profile could indicate a certain quantity and arrangement of B-lines that imply a specific pathological condition, while a "B2" profile could indicate a more severe or extensive interstitial disease. A "C" profile may indicate the existence of consolidation, indicating an alternative underlying condition such as pneumonia or atelectasis.

between various causes of pulmonary congestion, thus requiring supplementary diagnostic methods (34).

Despite these challenges, the application of chest ultrasound in dialysis patients offers substantial benefits. It provides a practical, effective, and accessible approach to the assessment and management of pulmonary congestion, ultimately improving patient outcomes and optimizing dialysis sessions. By integrating lung ultrasound into routine practice, clinicians can enhance their ability to monitor fluid status and tailor dialysis treatments more precisely, thereby enhancing overall patient care.

4 Cardiovascular ultrasonography for nephrologists

The main goal of basic cardiac ultrasonography is to provide succinct and targeted qualitative assessments that aid in guiding management decisions. This non-invasive imaging technique is particularly valuable in assessing left ventricular hypertrophy, cardiac chamber sizes, valvular heart disease, and systolic and diastolic function. It also plays a crucial role in evaluating fluid status and cardiac output, which are essential in managing fluid overload, a frequent challenge in dialysis patients. Moreover, regular cardiac ultrasonography can help in the early detection of cardiovascular diseases, allowing for timely intervention. The cognitive skills needed include assessing the overall size and function of the left ventricle, distinguishing between segmental and global wall motion abnormalities, evaluating the size and function of the right ventricle, and identifying severe valvular dysfunction using color Doppler (35). Basic cardiac ultrasonography helps in accurately categorizing shock and identifying the potential life-threatening causes of shock; shock is not uncommon in critically ill patients evaluated by nephrologists (36). Cardiac ultrasonography can quickly determine if there is evidence of hypovolemia, a pericardial effusion, or cardiac tamponade. The presence of an enlarged right ventricle may indicate acute cor pulmonale and impending right ventricular failure (37).

5 POCUS in hemodynamic instability during acute kidney injury and acute renal replacement therapy

Hemodynamic instability is a prevalent condition in critical illness and can have a significant impact on patient outcomes in the ICU. This instability can interfere with tissue perfusion and oxygen

delivery, leading to multi-organ dysfunction. AKI is also frequently observed in critically ill patients and can further aggravate patient outcomes. Hypotension and AKI (38) are often associated, through direct and indirect mechanisms, with both conditions potentially stemming from a single underlying cause of organ damage. Approximately 10%–20% of ICU patients with AKI require acute RRT, and their expected mortality rate is nearly 50% (38). The epidemiological and pathophysiological correlation between hypotension and RRT is acknowledged although a clear definition of hemodynamic instability during RRT remains elusive (39). Reports on critically ill patients indicate that IDH is linked to increased mortality and compromised renal recovery. POCUS assessment can provide nephrologists with hemodynamic parameters that can be targeted and integrated into organ perfusion surrogates to potentially yield the best results (39–43). The utilization of POCUS in revealing these mechanisms holds significant implications for the management of patients, as reducing ultrafiltration may not always be the optimal course of action, particularly in instances of substantial fluid overload (44).

5.1 Preload dependence and POCUS

Ultrasound has emerged as a crucial tool for assessing volume status and response to volume resuscitation in critically ill patients. Its non-invasive nature and low cost make it an attractive option, and clinicians can perform repeat ultrasounds at the patient's bedside as needed. Extensive research has focused on the elasticity of large veins, including the IVC and internal jugular vein, to determine standardized parameters for fluid responsiveness, such as the collapsibility index (45). These parameters are linked to traditional predictors of fluid responsiveness, such as central venous pressure (46). Recent studies have shown that large arteries, such as the common carotid artery, are also dynamically compliant and can predict fluid responsiveness (47). However, it is important to note that ultrasound interpretation is operator-dependent. To address this issue, standardized parameters like angulation probe and corrected flow time can be calculated using ultrasound, potentially minimizing discrepancies in image interpretation among providers (48).

5.2 Ventricular–arterial coupling and POCUS

The idea that optimal cardiovascular performance is achieved when the heart and arterial system are coupled has been well-established through various studies (49). When the heart pumps blood into the vascular tree at a rate and volume that matches the arterial system's ability to receive it, both cardiovascular performance and its associated cardiac energetics are optimized. Deviations from this optimal state, such as high or low contractility or arterial tone, can lead to cardiac failure, independent of other disease processes. Ventricular–arterial coupling (VAC) analysis quantifies the optimal matching of the left ventricular workload and the arterial system, with minimal changes in left ventricular (LV) pressure and the complete transfer of mechanical energy from the ventricle to the arterial system (50). The role of VAC in managing critically ill patients with severe hemodynamic instability and shock is increasingly being recognized. VAC is calculated as the ratio of arterial elastance (E_a) to ventricular elastance (E_{es}), proposed by Suga (51) as a measure of cardiovascular mechanical efficiency and the interaction between cardiac performance and vascular function. The E_a/E_{es} ratio is a reliable and effective measure of cardiovascular performance, with optimal efficiency achieved when the ratio is near 1. VAC is an effective index of LV's mechanical performance and dynamic modulation of the cardiovascular system (52) and reflects cardiac energetics. The balance between myocardial oxygen consumption and mechanical energy required for cardiac work is optimal when the heart and peripheral vascular system are coupled. The area of the LV pressure–volume (P–V) loop during a single cardiac cycle represents the total mechanical energy of the heart during that beat and correlates linearly with myocardial oxygen consumption. Understanding VAC requires knowledge of the determinants E_a and E_{es} and their bedside measurement in critically ill patients. LV contractile function can be evaluated using the relationship between end-systolic pressure (ESP) and end-systolic volume (Figure 3). Non-invasive measurement approaches for measuring VAC have been developed (53), with the modified single-beat method being validated against the invasive measurement of E_{es}. This method utilizes echocardiographic measures of LV end-diastolic and end-systolic areas, LVEF, stroke volume, pre-ejection time, and systolic time interval, coupled with systolic and diastolic arterial pressure measurements. E_a is calculated as ESP/stroke volume or 0.9 × systolic arterial pressure/stroke volume. If the patient experiences hypotension during hemodialysis despite volumetric resuscitation, assessing parameters for VAC (vascular access compression) becomes crucial for guiding further interventions like inotropes or additional volume or vasopressors. These bedside measures are essential in evaluating VAC in critically ill patients. The resuscitation algorithm for patients on RRT is dynamic, mandating ongoing reassessment and adjustment based on the patient's changing clinical condition. This highlights the need for a balanced approach to fluid management and hemodynamic support to enhance patient outcomes.

5.3 Myocardial function and POCUS

Several studies have been conducted to evaluate the accuracy of left ventricular assessment by non-cardiologists in detecting left ventricular systolic dysfunction after various training programs (54–56). These studies (57) have demonstrated good sensitivity in determining left ventricular function at the extreme ends, such as assessing a left ventricular ejection fraction (LVEF) above or below 50% (sensitivity 74%–95%) and an LVEF above or below 30% (sensitivity 100%). This indicates that even with limited training, physicians, residents, and medical students can accurately differentiate between normal and abnormal and severely and non-severely impaired left ventricular systolic function and determine the specific degree of left ventricular dysfunction (Figure 4). It has

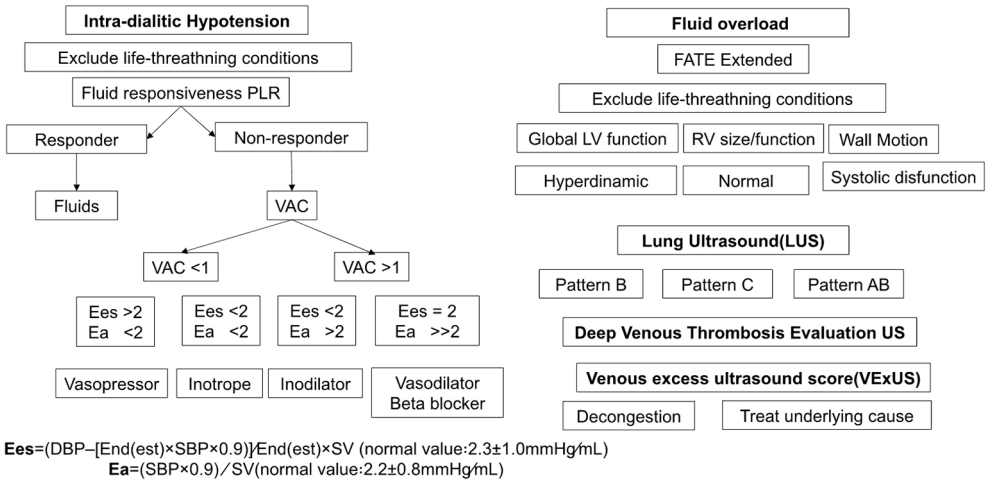

FIGURE 3
Resuscitation algorithm based on optimizing intradialytic hypotension and fluid overload in critically ill patients undergoing renal replacement therapy. PLR, passive leg raising; VAC, left ventricular–arterial coupling; E_a, effective arterial elastance; E_{es}, left ventricular effective end-systolic elastance; FATE, focus-assessed transthoracic echocardiography; LV, left ventricle; RV, right ventricle; US, ultrasound.

been demonstrated that focused cardiac ultrasound (58), even in the hands of novice users, is superior to clinical examination by experts in identifying cardiac abnormalities.

5.4 Systemic venous congestion and renal resistive index

Traditional methods of assessing fluid status and cardiac function often fall short when attempting to accurately identify venous congestion, a condition that can lead to organ dysfunction and worsened prognosis in critically ill patients (59). The venous excess ultrasound (VExUS) score emerges as a promising tool in this context. VExUS is an ultrasound-based scoring system that assesses venous congestion by examining the IVC, hepatic vein (HV), portal vein (PV), and intrarenal venous (IRV) Doppler waveforms (Figure 5). This approach provides a more comprehensive understanding of the patient's resuscitation strategy, incorporating the concept of fluid tolerance (FT) (60). VExUS can guide clinicians in making more informed decisions regarding fluid administration, deresuscitation, and potentially preventing the progression of kidney dysfunction. Recent studies incorporating VExUS into critical care protocols have shown that patients with reduced scores over 48 h and higher doses of diuretics had significantly more RRT-free days over a 28-day period (61). The ability of VExUS to non-invasively and dynamically assess venous congestion offers a significant advantage over traditional hemodynamic monitoring techniques, which often fail to detect subtle changes in venous return and congestion. The application of VExUS has been associated with the prognostication of AKI in patients with cardiorenal syndrome, aiding in the clinical decision for the patient to undergo fluid removal (62). Furthermore, VExUS-guided fluid management has the potential to personalize and optimize fluid therapy, moving beyond the "one-size-fits-all" approach (63). This personalized management is particularly beneficial in the heterogeneous population of critically ill patients, where the physiological responses to illness and therapy can vary markedly.

The renal resistive index (RRI), assessed via Doppler ultrasound, plays a pivotal role in nephrology, particularly in critically ill patients for the early detection and management of AKI and hepatorenal syndrome (HRS). RRI reflects renal vascular resistance by measuring the ratio of (peak systolic velocity–end diastolic velocity) to peak systolic velocity within the renal arteries. Elevated RRI values signify increased vascular resistance and reduced renal perfusion, which are early indicators of renal dysfunction in conditions such as sepsis, shock, or other critical illnesses.

In the context of AKI, RRI monitoring allows for preemptive intervention before changes in traditional biomarkers like serum creatinine are evident. This capability is crucial in guiding therapeutic strategies to optimize renal perfusion and mitigate further renal damage. For instance, in septic shock, elevated RRI values prompt adjustments in fluid resuscitation and vasopressor therapy to maintain adequate renal blood flow, potentially preventing AKI progression (64).

In hepatorenal syndrome, where renal impairment occurs secondary to severe liver disease and circulatory dysfunction, RRI serves as a vital tool in assessing renal vascular resistance changes. In HRS, elevated RRI values often indicate decreased renal perfusion due to systemic vasodilation and renal vasoconstriction. Monitoring RRI guides therapeutic decisions such as albumin infusions, vasoconstrictor therapy (e.g., terlipressin), or consideration of liver transplantation to improve renal function (65).

The continuous assessment of RRI offers dynamic insights into renal hemodynamics, crucial for managing critically ill patients prone to renal complications. Its integration into clinical practice enhances diagnostic precision, facilitates early intervention, and optimizes patient outcomes by tailoring therapeutic approaches to individual renal perfusion dynamics.

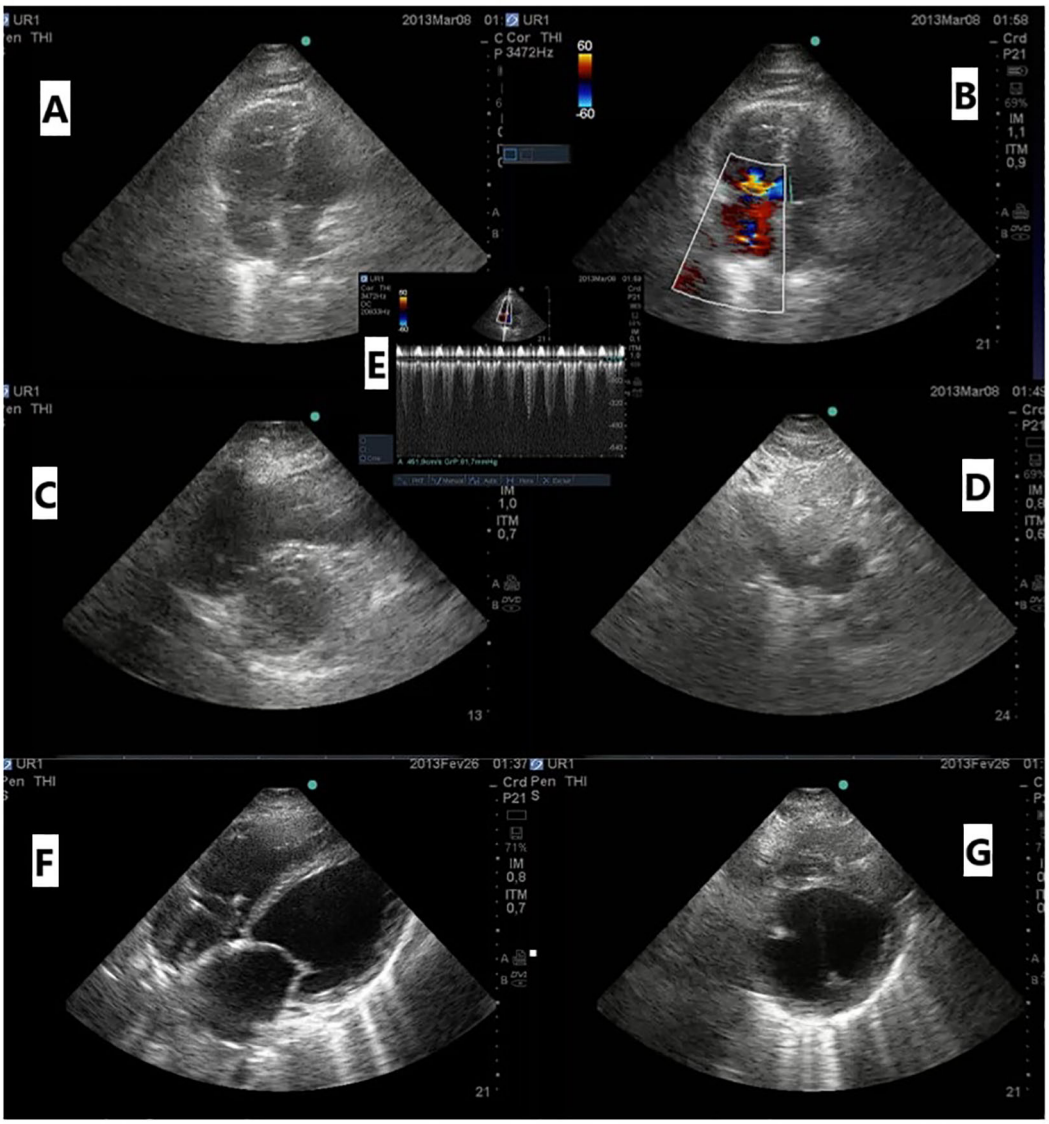

FIGURE 4
(A) Apical four-chamber (A4C) view with a dilated right ventricle (RV); **(B)** color Doppler of tricuspid regurgitation A4C; **(C)** parasternal short-axis view (PSA) showing an enlarged RV with a flattened interventricular septum; **(D)** dilated inferior vena cava; **(E)** continuous wave Doppler of tricuspid regurgitation showing estimated pulmonary systolic pressure of 96 mmHg in a patient with acute pulmonary embolism; **(F)** subcostal view with dilated left chambers; **(G)** PSA showing an enlarged left ventricle with severe systolic dysfunction related to myocarditis.

6 Abdominal ultrasonography for nephrologists

In AKI, the use of abdominal ultrasound helps in differentiating pre-renal, renal, and post-renal causes. It can identify obstructions in the urinary tract, such as stones or clots, and can also detect conditions like hydronephrosis. It can also guide percutaneous procedures, like kidney biopsies or the placement of dialysis catheters, reducing the risk of complications. Furthermore, abdominal ultrasonography is beneficial in screening for renal malignancies and in the follow-up of renal transplant patients. It can monitor graft size, detect complications like collections or obstruction, and assess vascular anastomoses.

The contribution of venous congestion to kidney dysfunction is increasingly being acknowledged, as unresolved congestion is linked to unfavorable kidney outcomes in patients with heart failure (66). Similarly, any condition that results in elevated central venous pressure, such as pulmonary hypertension, can lead to impaired kidney perfusion by increasing cardiac afterload. POCUS allows for clinicians to objectively evaluate hemodynamics at the bedside, thereby guiding patient management. Although inferior vena cava (IVC) POCUS is employed to estimate right atrial pressure, it cannot demonstrate organ congestion and bears several limitations, including the influence of ventilation settings, the patient's inspiratory efforts, coexisting cardiac conditions, and intra-abdominal hypertension (67). Recently, venous excess Doppler ultrasound has emerged as a real-time tool to assess

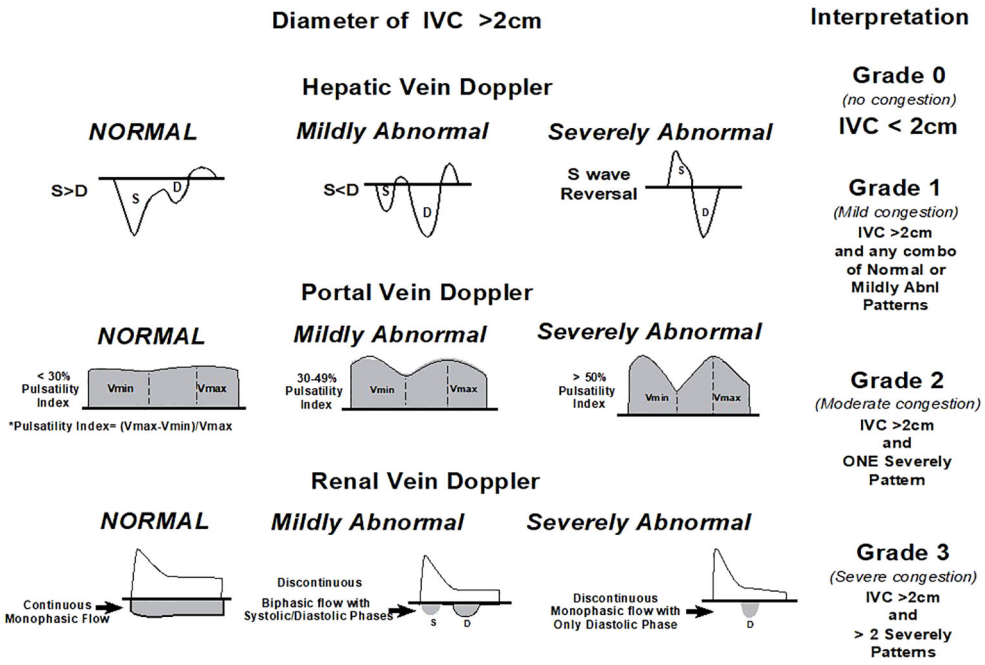

FIGURE 5
Venous excess Doppler ultrasound grading. Based on the degree of anomalies on the hepatic, portal, and intrarenal venous Doppler, three degrees of congestion are identified when the diameter of the IVC is greater than 2 cm. When the S wave on a hepatic vein Doppler is smaller than the D wave but remains below the baseline, it is classified as mildly abnormal; when the S wave is inverted, it is classified as seriously abnormal. When the pulsatility is between 30% and 50%, the portal vein Doppler is deemed slightly abnormal; when it is ≥50%, it is deemed seriously abnormal.
* Pulsatility measurement points. When an intrarenal vein Doppler has a distinct D and S component and is pulsatile, it is considered mildly aberrant; when it shows a monophasic D-only pattern, it is considered highly abnormal. With permission, this figure was modified from NephroPOCUS.com.
VExUS, venous excess Doppler ultrasonography; IVC, inferior vena cava.

venous congestion at the organ level (68). Severe flow abnormalities in hepatic, portal, and kidney parenchymal veins have been shown to predict the risk of congestive kidney injury and aid in monitoring the efficacy of decongestive therapy (69). Herein, we provide a brief overview of the various components of venous excess Doppler ultrasound and share our perspective on incorporating this innovative tool in nephrology practice.

7 Ultrasound assessment of arteriovenous fistulas in nephrology practice

Assessing the patency and functionality of arteriovenous (AV) fistulas is critical for nephrologists managing patients with end-stage renal disease reliant on hemodialysis. Ultrasound has become indispensable in this regard, offering a non-invasive and real-time method to evaluate AV fistulas. Using Doppler ultrasound, nephrologists can assess important hemodynamic parameters such as flow velocity and resistance indices and detect abnormalities such as stenosis or thrombosis (70).

Regular ultrasound surveillance plays a pivotal role in the early detection of complications like aneurysm formation or pseudoaneurysms, which could compromise the patency of AV fistulas. This proactive approach allows for timely intervention to maintain vascular access integrity, ensuring effective hemodialysis delivery (71).

In clinical practice, nephrologists rely on ultrasound-guided assessments to optimize dialysis efficacy and minimize access-related complications, thereby improving overall patient outcomes and quality of life.

8 Limitations of multi-organ POCUS

Patient-specific variables, including adiposity, subcutaneous edema, and the presence of inserted devices, which are prevalent in critically ill patients, can substantially impede the precision and practicality of POCUS. These circumstances can diminish the quality of ultrasound images, making it difficult to acquire dependable evaluations. Moreover, the assessment of POCUS results necessitates a considerable degree of expertise and proficiency, which may not be evenly accessible in all clinical environments, resulting in inconsistencies in the precision of diagnoses and treatment choices. Furthermore, within the framework of RRT, the dynamic alterations in fluid distribution and fluctuations in cardiovascular function present additional obstacles to the reliable analysis and verification of ultrasound images over a period of time. We must combine the data and acknowledge that they are not a substitute for the comprehensive information obtained from a meticulous clinical examination and

other diagnostic modalities. Though POCUS is a useful and quickly deployable tool that does not require invasive procedures, its limits highlight the importance of thorough training, establishing standardized protocols, and incorporating other clinical data to enhance patient care.

9 Conclusions

Hemodynamic instability is a frequent condition in critically ill patients undergoing RRT and is associated with increased mortality rates and the potential impairment of renal recovery. While excessive ultrafiltration is a known cause of hypotension, it may not always constitute the primary underlying mechanism. Multiple other RRT-related factors can contribute to a decreased cardiac output, decreased peripheral resistance, or both. In the management of patients requiring RRT, POCUS plays a crucial role in the initial diagnostic assessment of hemodynamically unstable patients, as well as in monitoring the outcomes of therapeutic interventions. We strongly advocate the incorporation of POCUS into the standard of care for all nephrologists and urge hospitals to provide the necessary resources to support a successful program.

Author contributions

RP: Writing – original draft, Writing – review & editing. UF: Writing – original draft, Writing – review & editing. PS: Writing – original draft, Writing – review & editing. CP: Writing – original draft, Writing – review & editing. RC: Writing – original draft, Writing – review & editing. BS: Writing – original draft, Writing – review & editing. FGC: Writing – original draft, Writing – review & editing. DB: Writing – original draft, Writing – review & editing. FOC: Writing – original draft, Writing – review & editing. BB: Writing – original draft, Writing – review & editing. TC: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Vikram Sabapathy,
University of Virginia, United States

REVIEWED BY
Bassam G. Abu Jawdeh,
Mayo Clinic Arizona, United States
Jeroen Peter Kooman,
Maastricht University Medical Centre, Netherlands
Marc Hilhorst,
Academic Medical Center, Netherlands

*CORRESPONDENCE
Géssica Sabrine Braga Barbosa
sabrinebraga@usp.br

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Vascular injury in glomerulopathies: the role of the endothelium

Géssica Sabrine Braga Barbosa[1]*, Niels Olsen Saraiva Câmara[2], Felipe Lourenço Ledesma[3], Amaro Nunes Duarte Neto[3] and Cristiane Bitencourt Dias[1]

[1]Renal Pathophysiology Laboratory, Hospital das Clínicas, University of São Paulo School of Medicine, São Paulo, Brazil, [2]Discipline of Immunology, University of São Paulo School of Medicine, São Paulo, Brazil, [3]Department of Pathology, University of São Paulo School of Medicine, São Paulo, Brazil

In glomerulopathies, endothelial dysfunction and the presence of histological vascular lesions such as thrombotic microangiopathy, arteriolar hyalinosis, and arteriosclerosis are related to a severe clinical course and worse renal prognosis. The endothelial cell, which naturally has anti-inflammatory and anti-thrombotic regulatory mechanisms, is particularly susceptible to damage caused by various etiologies and can become dysfunctional due to direct/indirect injury or a deficiency of protective factors. In addition, endothelial regulation and protection involve participation of the complement system, factors related to angiogenesis, the renin–angiotensin system (RAS), endothelin, the glycocalyx, the coagulation cascade, interaction between these pathways, interactions between glomerular structures (the endothelium, mesangium, podocyte, and basement membrane) and interstitial structures (tubules, arterioles and small vessels). Dysregulation of those components is also associated with the progression of renal fibrosis, since endothelial cell damage promotes endothelial-to-mesenchymal transition. Although the potential mechanisms of vascular injury have been widely described in diabetic kidney disease, hypertensive nephrosclerosis, and hemolytic uremic syndrome, they require further elucidation in other glomerulopathies. A better understanding of the pathogenesis of vascular injury in patients with glomerular diseases could contribute to the development of specific treatments for such injury.

KEYWORDS

arteriolar hyalinosis, arteriosclerosis, glomerular endothelial cell, glomerulopathy, thrombotic microangiopathy

1 Introduction

Vascular lesions are important findings in renal histology of glomerular diseases. The presence of thrombotic microangiopathy, arteriolar hyalinosis and arteriosclerosis can guide differential diagnoses, therapeutic options and prognosis. The pathogenesis of vascular injury can be multifactorial, but the initial process seems to be related to endothelial dysfunction resulting from endothelial injury (1).

Damage to the endothelial cells of the glomeruli, renal arterioles, and renal arteries can occur in various etiologies, such as autoimmune diseases, complement system dysregulation, preeclampsia, diabetic kidney disease and hypertensive nephrosclerosis. In primary glomerulopathies such as immunoglobulin A nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy, vascular injury is less common, but when present they confer a worse renal prognosis (2–6). In diseases in which the mechanism of endothelial injury is better elucidated, guided therapy provides significant clinical benefit. Atypical hemolytic uremic syndrome (aHUS) provides an example of how the discovery of a dysregulation in the complement system, as the initial mechanism for the occurrence of thrombotic microangiopathy (TMA), led to the development of treatments that block components of the complement system, which have modified the trajectory of the disease (7). Other glomerular diseases dependent on complement activation, including primary membranoproliferative glomerulonephritis and C3 glomerulopathy (C3G), can also present with vascular injury, and therapies involving complement inhibition have been tested in these conditions (8–10). In preeclampsia, the discovery of an imbalance between angiogenic factors, as a central mechanism of systemic endothelial dysfunction and vascular damage, has allowed for better clarification of the diagnosis and better monitoring of pregnant women at high risk for developing that complication (11). Beyond these conditions, the mechanisms of vascular injury have been widely described mainly in diabetic kidney disease, hypertensive nephrosclerosis, and ANCA-associated vasculitis (12–14). More recently, some studies have addressed vascular injury related to lupus nephritis (LN) and IgAN, although the exact mechanisms have not yet been fully elucidated (15, 16). The presence and pathogenesis of endothelial involvement in other glomerular diseases merit further analysis.

Understanding the mechanisms of endothelial dysfunction in glomerular disease can be complex, because endothelial regulation and protection involve participation of the complement system, factors related to angiogenesis, the renin–angiotensin system (RAS), endothelin, the glycocalyx, the coagulation cascade, interaction between these pathways, interactions between glomerular structures (the endothelium, mesangium, podocyte, and basement membrane) and interstitial structures (tubules, arterioles and small vessels) (1).

The aim of this review is to describe the potential mechanisms of endothelial dysfunction and discuss the occurrence of vascular lesions in glomerulopathies.

2 The glomerular endothelium

Renal endothelial cells have specific characteristics highlighting the glomerular endothelium, which is highly fenestrated and covered by the rich structure of the glycocalyx. The glomerular endothelium is part of the glomerular filtration barrier, influences vascular permeability, and helps maintain podocyte morphology. The glycocalyx is a thin layer with a negative charge, composed of proteoglycans (mainly heparan sulfate and chondroitin) and glycosaminoglycans (mainly hyaluronic acid), and is essential for regulating the glomerular filtration barrier (1). The glomerular endothelium, in addition to presenting anti-inflammatory and anti-thrombotic regulatory mechanisms, including components of the complement system, also expresses (17): vasoactive factors, such as endothelin-1 (ET-1), prostacyclin, nitric oxide, and the vascular endothelial growth factor (VEGF) receptor; intercellular adhesion molecules, such as platelet endothelial cell adhesion molecule-1, intercellular adhesion molecule-1, intercellular adhesion molecule-2, and vascular adhesion cell molecule-1; and thrombotic regulators, such as von Willebrand factor, tissue factor, plasminogen activator, and plasminogen activator inhibitor-1. All these components contribute to the integrity of the endothelial cell.

3 Glomerular endothelial dysfunction

In glomerular diseases, endothelial damage triggered by immune system dysfunction, cytokines, toxins, ischemia or deficiency of endothelial protective factors (the glycocalyx, angiogenic factors, or complement regulators) can lead to the loss of endothelial integrity and consequently endothelial dysfunction (1). This process begins with an initial activation/inflammation phase and culminates in fibrosis, which is associated with the progression of kidney disease (17), as illustrated in Figure 1.

4 Markers of endothelial dysfunction

The main markers of endothelial injury that can be the target of research to understand the pathogenesis and treatment of some glomerular diseases are described below.

Abbreviations: ADAMTS13, a disintegrin and metalloprotease with thrombospondin type one repeats, member 13; aHUS, atypical hemolytic uremic syndrome; ANCA, antineutrophil cytoplasmic antibody; AngII, angiotensin II; AT_1-AA, angiotensin II type 1 receptor autoantibody; AT_1R, angiotensin type 1 receptor; C3G, C3 glomerulopathy; CECs, circulating endothelial cells; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; EM, electronic microscopic; EMPs, endothelial cell-derived microparticles; eNOS, endothelial nitric oxide synthase; EPCs, endothelial progenitor cells; ET-1, endothelin-1; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; IgAN, IgA nephropathy; LN, lupus nephritis; MCP, membrane cofactor protein; RAS, renin–angiotensin system; SGLT2, sodium-glucose cotransporter 2; THBD, thrombomodulin; TMA, thrombotic microangiopathy; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

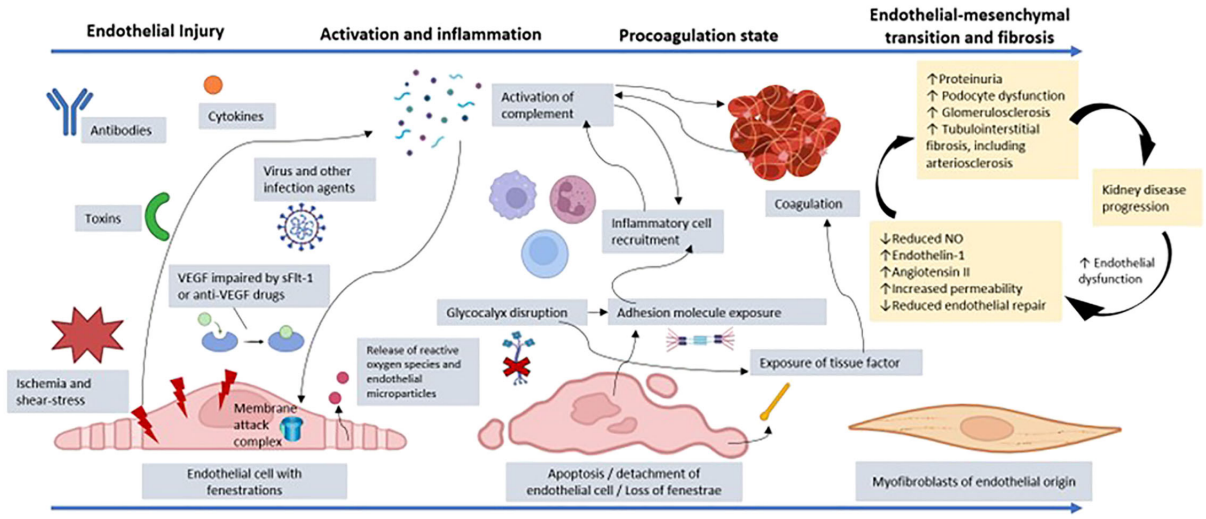

FIGURE 1
Representation of the process of endothelial dysfunction resulting from injury to a glomerular endothelial cell by toxins, cytokines, antibodies, infectious agents, VEGF depletion, ischemia, or another factor. Cellular injury promotes the release of reactive oxygen species and endothelial microparticles. There is activation of the complement system, which can culminate in the production of the membrane attack complex and endothelial lysis. In addition, anaphylatoxins from the complement system, such as C3a and C5a, promote recruitment of inflammatory cells, amplifying the inflammatory state. The disruption of the glycocalyx and the endothelial injury itself promote exposure of adhesion molecules, which increases the connection with other inflammatory mediators. There is also exposure of tissue factor with activation of prothrombotic mechanisms, which favors microthrombi affecting the microcirculation. The coagulation system is also activated through dysregulation of the complement system, which favors platelet aggregation via cytokines. Given that the insult persists, and endothelial repair is impaired, there can be loss of fenestrations and endothelial cell detachment, with reduced vascular permeability. The persistent dysfunction evolves with a change from the endothelial to the mesenchymal phenotype, contributing to renal fibrosis. Furthermore, there is increased expression of the angiotensin II and endothelin-1 receptors, which act by promoting vasoconstriction by decreasing nitric oxide (NO) production, thus increasing inflammation and fibrosis. The interaction between the endothelium, podocyte, and tubulointerstitium is dysregulated, increasing proteinuria and contributing to glomerulosclerosis and tubulointerstitial fibrosis, including impairment of arterioles and small vessels. Finally, there is accelerated progression to chronic kidney disease because uremic toxins perpetuate the state of endothelial dysfunction. VEGF, vascular endothelial growth factor; sFlt-1, soluble fms-like tyrosine kinase-1. (Created with BioRender.com).

4.1 Plasma markers

Adhesion molecules (soluble vascular adhesion cell molecule-1, soluble intercellular adhesion molecule-1, and soluble E-selectin) are found at high levels during endothelial dysfunction, as are pro-inflammatory markers (inflammatory cytokines and endocan), thrombotic mediators (thrombomodulin, von Willebrand factor, and tissue factor), markers of nitric oxide dysregulation highlighting dimethylarginine and markers of glycocalyx disruption, such as heparan sulfate (1).

Below, we explore other plasma markers of endothelial damage considered relevant for understanding the pathogenesis of glomerular diseases, vascular lesions and as targets for treatment.

4.1.1 Vascular endothelial growth factor

The most important pro-angiogenic factor is VEGF. It also regulates endothelial cell function through the induction of nitric oxide, promoting vasodilation, decreased vascular tone, and reduced blood pressure. In the kidney, VEGF is located mainly in the podocyte, playing an important role in the maintenance and stability of the glomerular filtration barrier (18, 19). Situations that cause a reduction in VEGF expression are associated with endothelial and podocyte damage, leading to proteinuria, hypertension, and the TMA as a more severe presentation (18). The main scenarios associated with reduced VEGF expression are the use of anti-VEGF drugs, such as for the treatment of neoplasms, and preeclampsia, caused by a disproportionate increase in soluble fms-like tyrosine kinase-1 (produced in the process of inadequate placentation), which binds to circulating VEGF and placental growth factor, thus preventing them from interacting with their endothelial receptors (18). In recent years, many studies have also demonstrated the involvement of VEGF in the progression of chronic kidney disease and as a prognostic marker in glomerulopathies, including lupus nephritis and membranous nephropathy (19–22).

4.1.2 Angiotensin II

Angiotensin II (AngII) is the main effector of the RAS, being responsible for activating several mechanisms involved in vasoconstriction, as well as pro-oxidant and inflammatory pathways that affect endothelial cell function (23). The effects of AngII activity occur through the action of AngII receptors, mainly the angiotensin type 1 receptor (AT_1R). After binding to AT_1R, AngII exerts vasoconstrictive effects (from the release of Ca^{2+}, leading to an increase in vascular tone), together with prothrombotic, pro-oxidant, and antifibrinolytic effects, as well as stimulating the expression of pro-inflammatory, atherogenic, and fibrogenic factors (24, 25).

It is known that AT_1R is present in various cells of the body, especially in the smooth muscle of arteries and arterioles. In the kidney, it is expressed not only in arteries and the endothelium but also in the medulla, proximal tubular epithelium (where it plays a role in sodium reabsorption), podocytes, and glomerular mesangial cells (26). Vasoconstriction of the efferent arteriole, caused by AngII, leads to increased intraglomerular pressure, resulting in proteinuria and glomerular sclerosis. In addition to the hemodynamic effect, the inflammatory stimulus is associated with progression to fibrosis and progression of kidney disease. There is increased expression of AngII and AT_1R in the renal interstitial cells of patients with progressive glomerulopathies, mainly in those with interstitial fibrosis (27). It is known that atrophy and tubulointerstitial fibrosis are important markers of the progression of kidney disease in many glomerulopathies. The use of AngII receptor blockers and AngII-converting enzyme inhibitors has proven benefits in effectively and safely reducing the progression of renal fibrosis, improving blood pressure control, as well as cardiovascular and renal outcomes (28–30).

The association between vascular injury and interstitial fibrosis could explain the fact that glomerulopathies with ischemic vascular lesions, such as IgAN, membranous glomerulopathy, FSGS, and LN, have worse prognoses than glomerulopathies without such lesions. Increased AT_1R expression plays a fundamental role in renal fibrogenesis, which also involves the participation of ET-1, another potent vasoconstrictor present in progressive glomerulopathies, the blockade of which reveals a renoprotective effect (31). Studies have shown that AngII acts to increase ET-1–induced vasoconstriction by increasing the expression of the ET-1 receptor and the binding between ET-1 and its receptor (32).

In addition, AngII regulates and increases the expression of transient receptor potential channel C6, a calcium-dependent channel associated with the slit diaphragm. In animal models, it has been shown that this increased activity through AT_1R leads to cytoskeletal disruption, podocyte damage, and glomerulosclerosis (33).

4.1.3 Agonist angiotensin II type 1 receptor autoantibody

In 1999, Wallukat et al. identified the previously unknown agonist angiotensin II type 1 receptor autoantibody (AT1-AA) in the circulation of pregnant women with preeclampsia (34). It is primarily a member of the immunoglobulin G_3 antibody subclass that has an agonistic action in the AT_1R, thus exerting vasoconstrictive effects similar to those of AngII (25). Depending on the clinical scenario, it can present as one of the other immunoglobulin G subclasses. This antibody binds with high affinity to AT_1R, promoting permanent stimulation. It is known that renin, angiotensin, and aldosterone levels are reduced in pregnant women with preeclampsia. Activation of AT_1R by AT_1-AA would therefore explain the occurrence of systemic vasoconstriction and hypertension in preeclampsia, even with low levels of RAS components (25), as represented in Figure 2.

Various studies have corroborated the correlation between AT_1-AA positivity and the occurrence of preeclampsia. Experimental animal models of pregnancy have shown that AT_1-AA injection triggers the manifestation of maternal preeclampsia syndrome, with

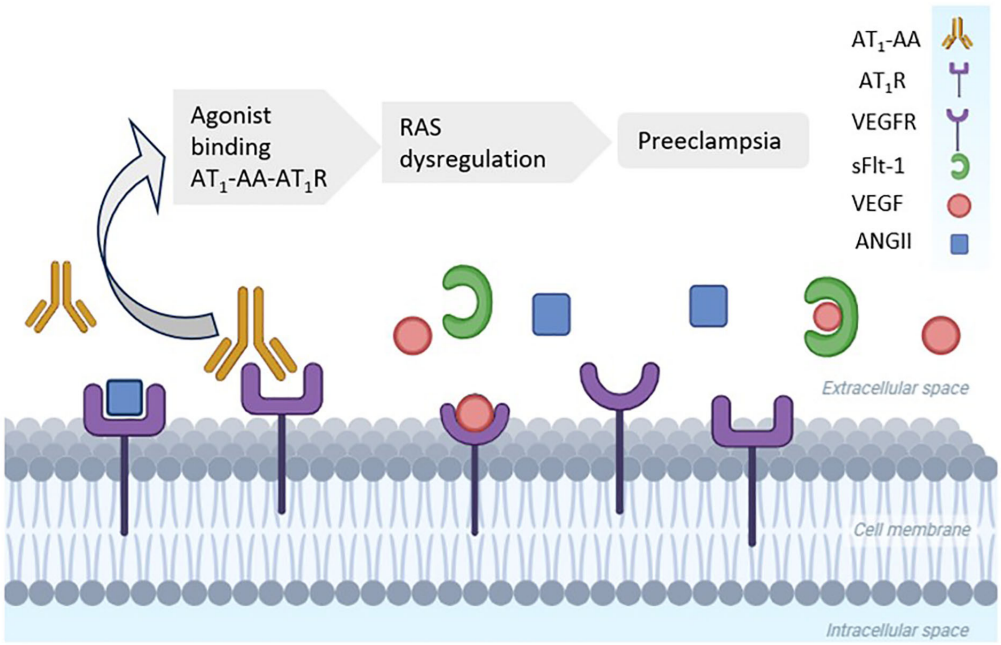

FIGURE 2
High levels of agonist angiotensin II (AngII) type 1 receptor autoantibody (AT_1-AA) in women with preeclampsia. AT_1-AA binds to the angiotensin type 1 receptor (AT_1R), whereas soluble fms-like tyrosine kinase-1 (sFlt-1) blocks the vascular endothelial growth factor receptor (VEGFR). Both processes promote a hypertensive status in preeclampsia. RAS, renin–angiotensin system. (Created with BioRender.com).

hypertension, proteinuria, and glomerular endotheliosis, the main renal histopathological finding of endothelial injury in preeclampsia (35). Subsequent studies implicated AT_1-AA in vascular transplant rejection, malignant hypertension, glomerulopathies, scleroderma and other scenarios, as well as showing that it is associated with accelerated vascular senescence (34, 36–38).

Some studies have analyzed the role of AT_1-AA in glomerulopathies. In a study of patients with LN, the AT_1-AA positivity rate was 66% (39). In that study, AT_1-AA levels were higher among the patients without immunosuppression and with other signs of disease activity such as complement consumption and high anti-DNA titers. In a subsequent study (40), the association between AT_1-AA and vascular damage was analyzed in patients with LN. In that study, renal biopsies showed that medial layer hypertrophy and subintimal fibrosis were greater in the vessels of AT_1-AA–positive patients than in those of AT_1-AA–negative patients. One report described the case of an AT_1-AA–positive patient with LN who underwent kidney transplantation and developed non-human leukocyte antigen antibody-mediated rejection, together with collapsing FSGS (41). The authors reported that the patient presented a good response to treatment with plasmapheresis, immunoglobulin, and AT_1R blockade. It has been demonstrated that the levels of AT_1-AA are significantly higher in patients with LN than in those with other primary glomerulopathies, such as membranous glomerulonephritis, IgAN, and FSGS (38), although no significant differences have been detected in comparison with patients with cytoplasmic or perinuclear antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. It is known that severe vascular injury, such as that provoked by TMA, is associated with worse outcomes in LN. The incidence of TMA is greater in LN with higher levels of activity, which somehow provides an immunological stimulus for vascular damage (42). The presence of AT_1-AA is correlated with higher levels of immunological activity in patients with LN (38). Therefore, AT_1-AA might play a central role in intense immunological stimulation and vascular damage.

4.1.4 Endothelin

Although it was originally described as an endothelium-derived vasoconstrictor, ET-1 is now known to play a role in cell proliferation, water–sodium balance, acid–base balance, tissue injury, fibrosis, and the progression of kidney disease, depending on which receptor is activated (43). The two main receptors are endothelin receptor type A (through which ET-1 promotes vasoconstriction, cell proliferation, and matrix accumulation) and endothelin receptor type B (through which ET-1 promotes antiproliferative, antifibrotic, and vasodilatory effects), being the type A expressed predominantly in vascular smooth muscle cells and the type B in vascular smooth muscle cells and endothelial cells, but both of which are also found in the mesangium, podocytes and tubules (44). Plasma ET-1 is increased in conditions of inflammation and vascular damage, correlating with albuminuria, and a high plasma ET-1 level is also an independent predictor of vascular dysfunction in chronic kidney disease (43). Treatment with selective endothelin A receptor blockers has been shown to provide a significant reduction in proteinuria, making it a useful tool in the treatment of FSGS, IgAN, and chronic kidney disease, mainly in combination with an AT_1R antagonist (45–48).

4.1.5 Complement system

The complement system is a crucial part of the innate immune response, being responsible for clearing microorganisms, damaged cells, and immune complexes, as well as promoting inflammation and attacking the cell membranes of pathogens (49). The complement system can be activated through the lectin, classical, and alternative pathways leading to the generation of the C5b9, known as the membrane attack complex, as reviewed by Yoshida Y et al. (50). On the endothelial cell surface, C5b9 stimulates the secretion of von Willebrand factor, stimulates endothelial prothrombinase activity, and induces tissue factor expression. This process can involve nuclear factor kappa B, inflammatory cytokines, and culminates in an intense state of inflammation and microvascular coagulation (51).

Various proteins act as complement system regulators to prevent exacerbated activation of the complement system and protect autologous tissues, such as glomerular endothelial cells, against attack by the complement system. The main ones are membrane cofactor protein (MCP/CD46), Complement Factor H (CFH), Complement Factor I (CFI), C4b-binding protein, CR1, decay accelerating factor (DAF/CD55), and CD59 (50).

In aHUS, the dysfunction of regulatory or activating factors is associated with the pathogenesis of vascular damage, and the dosage of some components can show the complement system activation, although only genetics tests can define the constitutive complement system dysregulation (52). CFH is a fluid-phase protein, but it is also found on the cell surface, binding to glycosaminoglycans and sialic acid. In fact, CFH dysfunction is detected in aHUS and C3G, suggesting that it plays an important role in the pathogenesis of TMA in these glomerular disease (50). In some glomerulopathies, the serum level of many factors can be associated with active disease, such as C3a and C5a in ANCA-vasculitis, and soluble C5b-9 in C3G (52). MCP, CR1, CD55, and CD59 are expressed in the glomerulus and can be altered in several glomerular disorders, such as IgAN, lupus nephritis, membranous nephropathy, and primary membranoproliferative glomerulonephritis (53). More details on the mechanisms of complement-endothelial interactions in glomerulopathies are described in section 5.

4.1.6 Coagulation system

Under physiological conditions, the endothelium maintains the environment in a more anticoagulant state by producing regulatory factors and through the action of the undamaged glycocalyx. The glycocalyx disruption exposes tissue factor, which triggers the coagulation cascade (1).

The coagulation system works together with platelets, leukocytes, and the complement system when endothelial cells are damaged. The coagulation and complement systems share common proteolytic pathways that enable an inflammatory response. In

endothelial cells and neutrophils, C5a and C5b-9 induce tissue factor expression, initiating the extrinsic coagulation cascade. In addition, C5a induces secretion of von Willebrand factor and P-selectin, as well as increasing neutrophil adhesion in endothelial cells in culture. In addition, coagulation factors can activate the complement system at different levels (50). This interaction can be observed clinically in glomerular diseases associated with intense manifestations of TMA and antiphospholipid syndrome, including some with thrombomodulin and plasminogen variants (54).

4.1.7 Circulating cells within the endothelial compartment

The endothelial compartment comprises circulating endothelial cells (CECs), endothelial cell-derived microparticles (EMPs), and endothelial progenitor cells (EPCs). After endothelial injury, it is crucial that there is a balance between CECs and EMPs (released into the bloodstream after endothelial injury)—and the capacity for endothelial repair by EPCs. The activation of EMPs is also closely related to the activation of the alternative complement pathway, which can favor the development of TMA (55). The EPCs promote angiogenesis and microvascular repair through the production of VEGF, fibroblast growth factor 2, and angiopoietin (1).

In the setting of vascular injury with endothelial dysfunction, regardless of the etiology, markers of injury/activation (circulating endothelial cells and EMPs) are at high levels, while endothelial repair markers (endothelial progenitor cells and circulating angiogenic cells) are at low levels (1).

4.2 Genetic markers

The endothelial response to injury also involves genetic influence. The presence or absence of adequate expression of certain genes can contribute to the occurrence of vascular lesions secondary to severe endothelial damage. In TMA, especially in aHUS, and C3 glomerulopathy, genetic sequencing studies have contributed to the identification of genetic variants involved in the complement pathways, such as: CFH, CFI, MCP/CD46, complement factor B (CFB), thrombomodulin (THBD), C3 and others (56, 57). Variants in complement genes have also been described in TMA associated with glomerular diseases including LN (58). Local CFH seems to protect the renal endothelial cell, and its absence is associated with altered cytoskeleton, altered cell metabolism, and increased proliferation (59). In addition to the complement system, variants in genes of pathways involving the renin-angiotensin system, angiogenic factors, endothelial nitric oxide synthase (eNOS) have also been reported in many studies in association with TMA lesions (60, 61). Mutations related to hereditary thrombophilia have been reported as causes of renal vascular lesions in patients without diabetes, hypertension, or a history of smoking (62). A transcriptomic analysis revealed molecular alterations in pathways related to cell adhesion, the actin cytoskeleton, angiogenesis and apoptosis of glomerular endothelial cell after podocyte injury, demonstrating that glomerular endothelial dysfunction may be a secondary event to podocyte damage, with the involvement of p53, transforming growth factor-beta 1 (TGF-β1) and TGF-α as important mediators of this process (63).

4.3 Histological markers

The presence of endothelial damage can be expressed by the finding of vascular lesions on renal biopsy histology. The main vascular lesions are: microangiopathy (with or without the presence of fibrin thrombi in capillaries or small vessels), arteriosclerosis, fibrosis and/or intimal thickening and arteriolar hyalinosis.

In addition to the anatomical expression of vascular involvement, it is possible to detect endothelial injury through immunohistochemistry. In individuals with such injury, there is a detectable expression of a series of factors (64–67): proteins related to the endothelial-to-mesenchymal transition (e.g., fascin-1, vimentin, and heat shock protein 47); glycocalyx-related proteins (heparan sulfate domains); endothelial adhesion molecules (e.g., vascular adhesion cell molecule-1 and platelet endothelial cell adhesion molecule-1); and angiogenic factors (e.g., VEGF receptors and AngII receptors).

4.3.1 TMA in renal histology

Classically, TMA is defined as a pathological lesion characterized by endothelial damage and the formation of microthrombi in small vessels (68). It can manifest clinically as microangiopathic hemolytic anemia, thrombocytopenia and ischemia (68). In the kidney, the acute finding of fibrin thrombus (often accompanied by fragmented red blood cells) is not always present. However, the presence of other morphological changes constitutes the aspect of microangiopathy. For example, in the active/acute phase the following lesions can be present: in glomeruli—endothelial edema, mesangiolysis (Figure 3A), and microaneurysms; in arterioles—endothelial/intimal edema, intramural fibrin, and myocyte necrosis; and in arteries—myxoid intimal edema and intramural fibrin. Electron microscopy (EM) shows glomerular endothelial cells with loss of fenestrations, fibrin tactoids with fragmented red blood cells and platelets, and expansion of the inner lamina. In the chronic phase, the main findings on light microscopy are as follows (68–70): double-contour sign in the glomerular capillary basement membrane (Figure 3B) - which appears in the EM as interposed cells with deposition of new matrix material; arteriolar hyalinosis; and thickening/fibrosis of the arterial intima, with an "onion-skin" appearance (Figure 3C). In the absence of a fibrin thrombus and of clinical signs of a TMA syndrome, there is still no consensus regarding how many of these other lesions must be present to confirm TMA or whether they would serve only to describe microangiopathy alone with or without thrombus. In such a situation, the diagnosis of TMA would be presumptive because other lesions are typically present in the classic form.

4.3.1.1 TMA in glomerulopathies

Historically, the initial classification of TMA was based on clinical manifestation, with two main spectra: thrombotic thrombocytopenic purpura, in which there is greater neurological

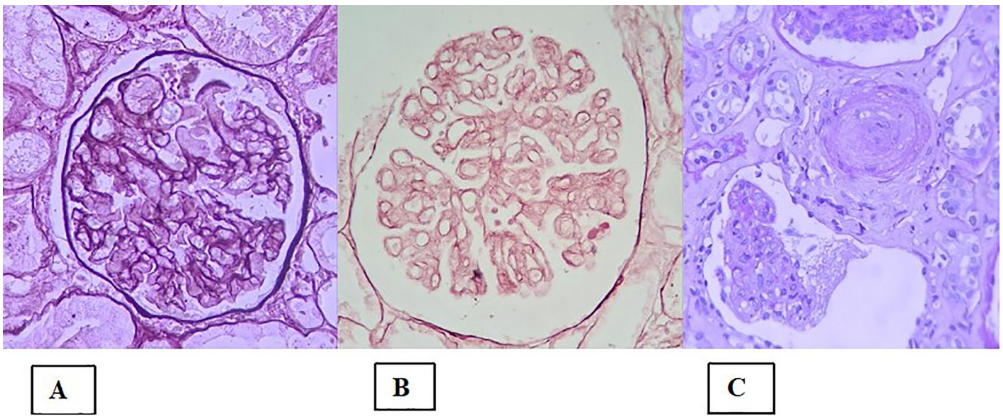

FIGURE 3
Histological lesions in the presentation of thrombotic microangiopathy. **(A)** Global mesangiolysis; **(B)** Extensive double contours of the glomerular basement membrane (two-layer appearance); **(C)** Concentric myointimal proliferation in an "onion-skin" pattern, with mucoid edema and lumen obliteration. There is also a glomerular tuft with a retracted appearance and a wrinkled basement membrane (lower portion of the image).

involvement; and HUS, in which there is greater renal involvement. Subsequently, the classification evolved toward a molecular basis of the disease (68): a disintegrin and metalloprotease with thrombospondin type one repeats, member 13 (ADAMTS13) deficiency is associated with thrombotic thrombocytopenic purpura; and HUS is classified as typical or atypical depending on whether shiga toxin is present or absent (HUS and aHUS, respectively). The discovery of dysregulation of the complement system in a significant proportion of patients with aHUS led to the classification of this subcategory as complement-mediated aHUS and contributed to the development of drugs that act to block components of the complement system (such as the C5 blocker eculizumab), leading to major improvements in the clinical outcomes in such patients (7). Concomitant with those discoveries, there have been numerous reports of TMA associated with other factors, such as autoimmune diseases, malignancy, drug use, pregnancy, malignant hypertension, glomerulopathies, and transplantation. Those cases were classified as secondary TMA, whereas those involving complement dysregulation due to genetic or acquired factors would be classified as primary TMA (68). However, in many secondary causes, including glomerulopathies, the intrinsic amplification/dysregulation of the complement pathway has been observed, which has even led to the use of complement system blockers, with a satisfactory therapeutic response in glomerular diseases, such as ANCA-associated vasculitis, in C3 glomerulopathy, in LN, and in IgAN, although it has not been specifically studied in those glomerulopathies expressing or associating with TMA (71).

The occurrence of TMA in glomerulopathies confers greater severity and a worse prognosis, with many cases quickly progressing to renal failure and the need for dialysis or kidney transplantation (68). The main autoimmune etiologies of TMA are LN, antiphospholipid syndrome, systemic sclerosis and Sjögren's syndrome (72). Systemic lupus erythematosus is an autoimmune disease historically related to activation of the complement system, mainly from the classical pathway due to the presence of immune complexes. The occurrence of TMA in LN increases severity, lowers the therapeutic response, worsens the prognosis, and might be related to deficiency of regulatory factors in the complement pathway, leading to amplification of the pathway, culminating in the formation of a membrane attack complex, endothelial injury, and platelet aggregation (fibrin microthrombi) in the lumen of small vessels (42, 68). In IgAN, the pathogenesis of TMA is not well defined, although there is growing evidence of involvement of the complement system, based on the identification of deficiency of regulatory factors or complement activation by IgA immune complexes (71). In IgAN, TMA is associated with an unfavorable clinical outcome (2). In ANCA-associated vasculitis, endothelial injury arises mainly from products toxic to the endothelium released by neutrophils that are activated by autoantibodies (ANCAs). Several studies have demonstrated the involvement of the complement mediators, especially anaphylatoxin C5a, through activation from the initial process itself (1, 71, 73). In fact, treatment for ANCA-associated vasculitis aimed at blocking the complement system has shown good efficacy (74). Dysregulation of the complement pathway—by genetic defects, mainly related to CFH or by autoimmune diseases, mainly related to autoantibodies (such as C3, C4, and C5 nephritic factors) against components of the pathway —results in C3 glomerulopathy. Amplification of the pathway ultimately culminates in endothelial injury (71). The occurrence of TMA in patients with FSGS or minimal change disease is characterized by steroid-resistant nephrotic syndrome. Factor H deficiency has been reported in some cases (5, 75). In addition, TMA is a common finding in collapsing glomerulopathy, suggesting that endothelial injury is involved in its pathogenesis (76). There have been reports of cases of membranous nephropathy in combination with thrombotic thrombocytopenic purpura, even in patients testing positive for anti-phospholipase A2 receptor antibodies, probably due to the presence or stimulation of the development of antibodies against ADAMTS13 (6, 77). In many cases of glomerulopathy, the occurrence of TMA is not accompanied by systemic involvement with thrombocytopenia and hemolytic anemia, being a histopathological finding, which raises the hypothesis of local activation of the complement system involving regulatory factors on the endothelial surface or in other glomerular structures (42).

4.3.2 Arteriolar hyalinosis in renal histology

Arteriolar hyalinosis, also known as hyaline arteriolosclerosis, is the deposition of proteinaceous material with a hyaline appearance in the subendothelial region of arterioles (78). That deposition results in thickening of the vessel wall and narrowing of the lumen, leading to ischemia (Figure 4A). Arteriolar hyalinosis can be observed in healthy individuals as they age. However, it occurs earlier in patients with hypertension or diabetes mellitus.

4.3.2.1 Arteriolar hyalinosis in glomerulopathies

Arteriolar hyalinosis is well described as a predictor of renal outcome in kidney transplant recipients, diabetes, and hypertension patients (79, 80). In patients with glomerulopathies, arteriolar hyalinosis can be associated with hypertension concomitant with glomerular disease, although its clinical significance and role in the pathogenesis of glomerular disease, especially in the presence of other vascular lesions such as TMA, still need to be clarified. In IgAN, for example, arteriolar hyalinosis is an independent risk factor for an unfavorable renal prognosis (81). Arteriolar deposition of C4d in biopsies of patients with IgAN is associated with glomerular C4d deposition and both are associated with the progression of kidney disease (82). In steroid-resistant FSGS, arteriolar hyalinosis can hinder the treatment, because the use of cyclosporine can worsen renal function in such cases (83). In renal biopsy studies, a finding of arteriolar hyalinosis is a risk factor for the progression of renal disease (84).

4.3.3 Arteriosclerosis in renal histology

Arteriosclerosis is characterized by thickening of the intimal layer by smooth muscle fibers or fibroblasts, collagen fibers and the fundamental connective tissue that causes narrowing of the vessel lumen (Figure 4B). It does not have the homogeneous appearance characteristic of arteriolar hyalinosis, with which it should not be confused (78). It is also commonly found in elderly individuals, individuals with hypertension, and individuals with diabetes.

4.3.3.1 Arteriosclerosis in glomerulopathies

Arteriosclerosis has been well characterized in patients with arterial hypertension or diabetes mellitus (85, 86). In the context of kidney transplantation, a finding of arteriosclerosis is correlated with shorter graft survival in all cases, including those in which the donor kidney is from a donor with uncontrolled hypertension, representing a relevant variable in the Banff classification criteria (87, 88). In patients with LN, the use of the Banff score to evaluate vascular lesions showed that the prevalence of renal arteriosclerosis is accelerated by two decades in such patients, which constitutes an early cardiovascular risk factor (89). Severe arteriosclerosis is associated with shorter renal survival in patients with crescentic glomerulonephritis (90). In other glomerulopathies, the meaning of a finding of arteriosclerosis on renal histology is poorly understood.

5 Endothelial dysfunction in glomerular diseases

There are some glomerular diseases in which the pathogenesis of vascular lesions is partially understood, such as diabetic kidney disease and hypertensive nephrosclerosis. In other situations, especially in primary glomerulopathies, the pathogenesis of vascular lesions is not yet well defined, with potential mechanisms being the activation of the complement system and dysregulation of pathways involving podocyte–endothelium and tubule/interstitium–endothelium interactions.

5.1 Potential mechanisms of endothelial involvement in glomerulopathies

The mechanisms of endothelial dysfunction in glomerular diseases can involve direct or indirect damage with endothelial cell activation or deficiency of factors that regulate or protect the endothelium. Table 1 summarizes the potential mechanisms.

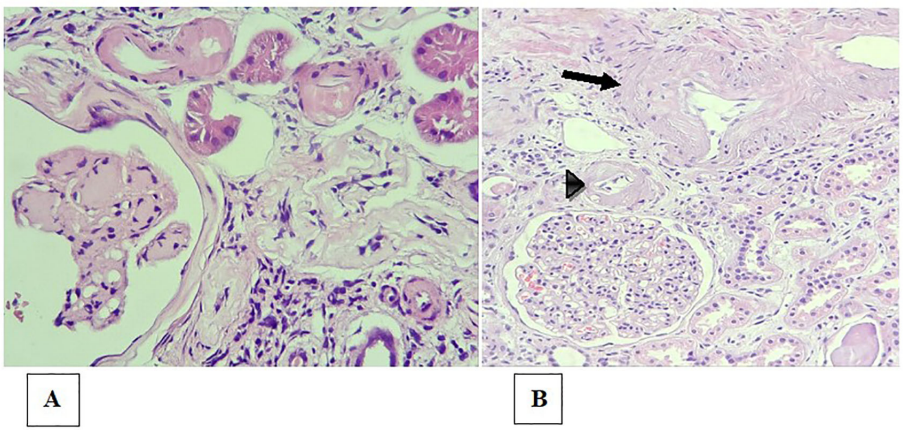

FIGURE 4
Arteriolosclerosis and renal arteriosclerosis. **(A)** Bulky, circumferential mural hyaline deposits in the arteriole walls (upper portion of the image), in a patient with diabetes and nodular glomerulosclerosis (lower left corner of the image); **(B)** Moderate intimal fibrosis in the interlobular arterial branch (arrow) and intense arteriolar hyalinosis (arrowhead).

TABLE 1 Potential mechanisms of endothelial dysfunction in glomerulopathies.

Glomerular disease	Potential mechanisms of endothelial dysfunction
Lupus nephritis	Immune complex deposition causes endothelial cell damage. There is increased expression of adhesion molecules; increased secretion of interleukins (IL-6 and IL-8); increased levels of tumor necrosis factor alpha, chemokine CCL2, and nitric oxide; inhibition of angiogenesis; activation of complement pathways with direct and indirect endothelial injury; and imbalance of regulatory and activating factors of endothelial cells due to a functional defect mediated by interferon I, making them susceptible to apoptosis. There can be production of specific antibodies that act on the endothelial cell surface (1, 15, 91).
ANCA-associated vasculitis	Neutrophils activated by antineutrophil cytoplasmic antibodies adhere to the endothelial cell, leading to activation of the endothelium and increased vascular permeability. Activated neutrophils release toxic granules, causing direct endothelial cell injury and fibrinoid necrosis through an increase in reactive oxygen species, proteases, and neutrophil extracellular traps. There is activation of the alternative complement pathway with amplification of inflammation through the recruitment of anaphylatoxins, especially C5a, leading to greater endothelial dysfunction (14, 73, 92).
IgA nephropathy	Deposition of IgA1 in the mesangium increases the local inflammatory response, leading to endothelial damage due to mesangium–endothelium interaction with increased nitric oxide synthase. The high affinity of IgA1 for the glomerular endothelium, especially in endocapillary proliferative forms with complex immune deposits, leads to the production of cytokines and adhesion molecules, as well as endothelial barrier dysfunction and loss of glycocalyx. There is activation of the complement system through the lectin pathway and deficiencies in complement regulatory factors, with consequent endothelial damage. There is also activation of the coagulation cascade from endothelial damage favoring local microangiopathy. Elevation of soluble fms-like tyrosine kinase-1 and inhibition of VEGF cause endothelial injury, a reduction in angiogenesis, and the development of anti-endothelial cell antibodies (16, 93, 94).
Focal segmental glomerulosclerosis	Podocyte injury promotes dysregulation in the podocyte–glomerular endothelium interaction mainly by reducing VEGF production, which results in endothelial damage and impaired angiogenesis. There is increased expression of the endothelin type A receptor in the endothelial cell, which induces endothelial oxidative stress (95, 96).
Membranous nephropathy	Probable endothelial cell apoptosis results from deposition of immune complexes in the glomerular capillary wall. There are low levels of plasma VEGF and urinary VEGF excretion, representing a defect in endothelial function, compromising angiogenesis (21, 67).
Membranoproliferative glomerulonephritis and C3 glomerulopathy	Dysregulation of the alternative complement pathway by antibodies, immunoglobulins, toxins or acquired intrinsic defects, among others. The change can occur more as a result of the activation of C3b receptors in the glomerular endothelium than as a result of activation of the membrane attack complex (10, 97)..
Diabetic kidney disease	Hyperglycemia induces glomerular endothelial cell apoptosis, alteration of the glycocalyx, with reduced heparan sulfate synthesis. It also interferes with VEGF receptors expressed by the podocyte, contributing to endothelial cell dysfunction and dysfunctional endothelium–podocyte interaction, as well as stimulating the change from the endothelial to the mesenchymal phenotype, thus promoting renal fibrosis (1, 12, 98).
Hypertensive nephrosclerosis	Increased blood pressure induces mechanical stress on the vessel wall, causing vascular injury and activation of the intimal thickening process, with or without hyalinosis of the arterioles and small vessels, including the glomerular capillaries. Activation of the renin–angiotensin system with increased angiotensin II promotes vasoconstriction, inflammation, and fibrosis. There is also a loss of renal autoregulation, resulting from vascular injury, and narrowing of the vessel lumen. Arteriosclerosis induces ischemia, which amplifies endothelial damage. Complement activation with endothelial dysregulation culminating in thrombotic microangiopathy occurs mainly in cases of accelerated malignant hypertension (13, 99, 100).

IgA, immunoglobulin A; VEGF, vascular endothelial growth factor.

In glomerulopathies, the pathogenesis of vascular injury is described as being mainly related to damage to the glomerular endothelium, although the approach to the involvement of arterioles and small vessels has not been well elucidated. TMA, regardless of etiology, has been linked to dysregulation of the complement system (local or systemic). However, in some glomerulopathies, even with dysregulation of the pathway, TMA does not develop, whereas it does develop in other glomerulopathies without clear evidence of complement system dysregulation. Further studies are needed in order to understand whether there are specific pathways or endothelial regulatory factor deficiencies that are related to the development of TMA in glomerular diseases. Regarding arteriosclerosis and arteriolar hyalinosis, the hypothesis that arterial hypertension and age are involved has been raised. However, some studies have shown that these types of vascular injury occur in some glomerulopathies even in the absence of hypertension and of advanced age (13, 101). The potential mechanisms involved in this situation are not clear and might be related to initial damage to the glomerular endothelium or podocyte, with consequent interaction between the tubules and the interstitium, together with a defect in renal autoregulation, as well as to factors such as hyperuricemia, elevated cholesterol, and dysregulation of complement factors (81, 102).

5.2 The endothelium as a therapeutic target in glomerulopathies

The endothelial cell and its mediators have always been a target of study for the development of treatments for chronic kidney disease, including glomerulopathy. The use of a renin–angiotensin–aldosterone system blocker was perhaps the first treatment for which there was robust evidence of an ability to control the progression of kidney disease and proteinuria, which made it the standard treatment for many glomerulopathies, such as IgA nephropathy and diabetic nephropathy, and for chronic kidney disease itself (103, 104). Concomitant to the discoveries related to angiotensin in numerous studies, the effects of ET-1 and the benefits

of selective endothelin A receptor blockade were also described, mainly in the reduction of renal progression (105). Recently, the recovery and refinement of knowledge regarding these mechanisms has led to the development of new, more selective drugs for blocking the receptors of angiotensin, endothelin, and aldosterone, alone or in combination (46, 47, 106). In addition, the combination of these drugs with a sodium-glucose cotransporter 2 (SGLT2) inhibitor has shown clinical benefit, which also demonstrates a role for SGLT2 inhibitors in endothelial activity (48, 107). After the advent of SGLT2 inhibitors, which have provided great benefit in reducing proteinuria and progression of kidney disease, many studies have focused on the mechanisms of those effects. In fact, recent evidence shows that SGLT2 inhibitors achieve their antioxidant and anti-inflammatory effects by reducing the expression of endothelial adhesion molecules, thus preventing endothelium–leukocyte interaction (108). In relation to TMA, most studies have focused on blocking the complement system, taking into account the change in clinical evolution in patients with aHUS treated with C5 blockade. The finding of complement protein deposits, either alone or in combination with immune complexes and local inflammation, has led to the study of complement blockers as treatments for glomerulopathies. In C3 glomerulopathy with or without microangiopathy, the fact that the pathogenesis involves dysregulation of the alternative pathway makes the indication for blockade more specific (103). In other glomerular diseases, complement blockade appears to play a role in reducing inflammation. In ANCA-associated vasculitis, for example, treatment with complement blockade has been shown to provide a clinical benefit, especially in controlling the action of anaphylatoxin, through blockade of the C5a receptor (74). In the presence of microangiopathy accompanying glomerulopathies, despite the reference to TMA mechanisms in aHUS, there is little evidence to support the use of complement blocking drugs, although some studies and case reports have shown therapeutic potential in certain situations. Table 2 summarizes the studies that have associated complement blockade as a specific treatment for TMA in glomerulopathies.

Most case reports of glomerular disease with TMA and treatment with complement blockade include LN, ANCA vasculitis, IgAN and C3 glomerulopathy. With regard to FSGS and membranous nephropathy, published case reports on the use of complement blockers mainly involve the occurrence of TMA after

TABLE 2 Complement blockade in glomerulopathies with TMA.

Glomerulopathy with TMA	Genetic Variant	Complement Blocker	Renal Clinical Response
LN			
de Holanda MI, et al., 2017 (2 cases) (109)	CFHR1/CFHR3	Eculizumab	Improvement
Raufi AG, et al., 2016 (110)	Absent	Eculizumab	Improvement
El-Husseini A, et al., 2015 (111)	Not performed	Eculizumab	Improvement
Coppo R, et al., 2015 (112)	Absent	Eculizumab	Improvement
Bermea RS, et al., 2016 (113)	Not performed	Eculizumab	No improvement
Torres EA, et al., 2021 (114)	CFHR1-3	Eculizumab	Partial improvement (incremental dialysis).
Kim MJ, et al., 2021 (115)	C3 mutation	Eculizumab	Improvement
Kello N, et al., 2019 (116) (considering 3 cases of LN without APS)	Not performed	Eculizumab	1 case: improvement 2 cases: no improvement
Park MH, et al., 2018 (54) (considering 7 cases of LN without APS and renal transplant)	CFH in patient A Absent in patients B, C, and D Not performed in patient E Thrombomodulin, Plasminogen and CFH in patient F CFHR1-CFHR3, Plasminogen, and MCP in patient G	Eculizumab	Improvement in A, B, D, and G No improvement in C, E, and F
Ono M, et al., 2018 (117)	Not performed	Eculizumab	No improvement
Cavero T, et al., 2017 (118) (considering 3 cases)	Absent in 2 cases/Not performed in 1 case	Eculizumab	No improvement in 2 cases and partial improvement in 1 case
Smith J, et al., 2024 (119)	CFH	Eculizumab	Improvement
ANCA vasculitis			
Cao M, et al., 2017 (120)	CFH;	Eculizumab	Improvement
Cavero T, et al., 2017 (118) (considering 2 cases)	Absent/CFHR1	Eculizumab	Partial improvement/No improvement

(Continued)

TABLE 2 Continued

Glomerulopathy with TMA	Genetic Variant	Complement Blocker	Renal Clinical Response
IgAN			
Patel DM, et al., 2021 (121)	Not performed	Eculizumab	Improvement
Matsumura D, et al., 2016 (122)	Not performed	Eculizumab	No improvement
Nakamura H, et al., 2018 (123)	CFH	Eculizumab	Partial improvement
C3G			
Chabannes M, et al., 2023 (124) (Considering 10 cases)	CFH (3 cases)/Absent (5 cases)/Not performed (2 cases)	Eculizumab	Improvement in 6 cases (2 cases with CFH mutation)
Ravindran A, et al., 2022 (125) (Considering 1 case treated with eculizumab)	Absent	Eculizumab	No improvement
Osawa K, et al., 2023 (126)	CFI	Eculizumab/ Ravulizumab	Improvement

LN, Lupus Nephritis; ANCA, Antineutrophilic cytoplasmic antibody; IgAN, IgA Nephropathy; C3G, C3 Glomerulopathy; APS, antiphospholipid syndrome.

kidney transplantation (127, 128). Minimal Change Disease with TMA has, to date, no published case of specific treatment with complement blockade.

In LN with TMA, a systematic review suggests that the use of eculizumab may be beneficial, especially in refractory situations, but some of the included studies showed an association of SLE with antiphospholipid syndrome (APS), which represents another aspect of the disease (129). Tables 2 show cases of LN with TMA and without APS, which demonstrate great variability in the response to eculizumab, some without testing for genetic variants, which makes it difficult to define a clinical decision on the use of complement blockade in this condition. In situations where ADAMTS13 activity is normal and antiphospholipid antibody is negative, complement system analysis is recommended, since many cases are related to complement-mediated TMA that is resistant to conventional treatment, with eculizumab being a considerable therapeutic option, although dosage and duration are not well defined (130).

In TMA-ANCA vasculitis and in the TMA-IgAN, Table 2 shows cases with variable results, and it is not possible to conclude recommendations due to the lack of evidence considering TMA association, although for ANCA-vasculitis, in general, C5a receptor blockade has shown good efficacy (74).

In C3G with TMA, a case series revealed that renal survival was significantly improved in patients treated with eculizumab, and it is reasonable to consider the complement blocker in this situation if no response is observed after conventional treatment (124).

In hypertensive nephrosclerosis, the occurrence of TMA is more common in situations of malignant hypertension. Recently, the discovery of a higher proportion of pathogenic genetic variants in these cases has raised the suspicion that many are complement-mediated TMA presenting with severe hypertension (131). A registry analysis evaluated the use of eculizumab in patients with TMA/aHUS and malignant hypertension, suggesting that it may be an effective alternative (132). The decision to treat with complement blockers depends on classifying the condition as complement-mediated TMA with severe hypertension, rather than TMA secondary to hypertension, which is quite difficult in clinical practice. Some authors suggest considering cardiac hypertrophy and the predominance of arteriolar lesions as characteristics more related to hypertension-associated TMA, while increased glomerular involvement and the lack of response to aggressive antihypertensive therapy are more related to complement-mediated TMA with severe hypertension (133).

Diabetic kidney disease with TMA has, to date, no published case of specific treatment with complement blockade.

It is known that the mechanisms of involvement of the complement system vary between diseases, sometimes being non-specific and in others playing a central role in the pathogenesis, justifying the difference in therapeutic response. Unfortunately, there is no exact test and no solid evidence that would justify the widespread use of complement blockade in glomerulopathy with TMA (134). Low levels of complement proteins, such as C3, may not be present in many cases of system dysregulation (135). Although the involvement of complement can be evaluated with detection of autoantibodies to complement factors and by functional assays, such as soluble C5b-9 and tissue deposition of C5b-9, so far only genetic tests have been able to distinguish complement dysregulation from overactivation/amplification (135, 136). However, it is known that the genetic test is not available to everyone, the absence of detectable genetic mutation does not rule out complement-mediated TMA and that the cost of the drug is high. On the other hand, the worsening clinical evolution despite conventional treatment of the glomerulopathy has become increasingly worrying, which makes it urgent to define the situations in which the use of complement blockers can be beneficial. Some authors advocate the use of complement blockade in secondary TMA to control transient overactivation of the complement system and reduce endothelial damage when there is no response to standard treatment and, once the initial condition has resolved, the complement blocker can be discontinued (137). Some studies have shown that in the absence of pathogenic variants in complement genes, the risk of relapse after discontinuation is low, although glomerulopathies has low representative in these

studies (118). Conversely, if pathogenic variants are detected, the case may be primary TMA and the glomerulopathy may have occurred as a trigger. In this situation, the use of complement blockers should be extended (137). It seems reasonable to use complement blockers when dysregulation of the complement system is detected by the presence of a genetic variant as a determining factor in pathogenesis and when this is documented by accumulated scientific evidence, as is the case with C3G.

Therefore, the decision to start a complement blocker in glomerulopathies with TMA should be based on clinical evolution, response to conventional treatment, evidence of complement involvement and the results of genetic tests. More importantly, inclusion in randomized clinical trials will allow for a more precise response to this controversy. In addition, microangiopathy lesions in glomerular diseases may be related to defects in endothelial cell regulators, dysregulation of the local coagulation system, angiogenesis defects and other pathways besides the complement system, as already mentioned in this article. For example, there are some studies that show a better clinical response with the use of anticoagulation in cases of TMA and LN + APS, which is a recommendation of the latest KDIGO update (130, 138). With regard to endothelial cell regulators, there is emerging evidence that glycocalyx could be a therapeutic target in TMA (139).

In conclusion, glomerular disease can cause damage to the glomerular endothelial cell in many structures and pathways (complement system; angiogenesis-related factors; renin-angiotensin system; endothelin complex; coagulation cascade; interaction between these pathways; interactions between glomerular structures and interstitial structures), which may represent different potential therapeutic targets to explore in the case of vascular damage associated with glomerular diseases, in particular TMA.

6 Conclusion

Endothelial dysfunction and the presence of vascular disorders such as TMA, arteriolar hyalinosis, and arteriosclerosis are associated with a more severe clinical course and a worse renal prognosis in glomerulopathies. In glomerular diseases, the mechanisms of endothelial dysfunction can involve direct or indirect damage with endothelial cell activation or deficiencies of factors that regulate or protect the endothelium. Blocking the RAS and endothelin are therapeutic strategies that act on mechanisms related to endothelial cells and have provided clinical benefit in reducing proteinuria and slowing the progression of kidney disease. The use of complement blockade has increased in diseases with clear evidence of impairment of the complement system and consequent endothelial damage, such as TMA. However, not all glomerular diseases present concomitant vascular damage, even in the presence of endothelial dysfunction. That raises the hypothesis that a potential intrinsic defect in endothelial regulation/protection is involved. A greater understanding of the pathogenesis of vascular injury could lead to specific therapeutic advances in this most severe manifestation of glomerular disease.

Author contributions

GB: Conceptualization, Data curation, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. NC: Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing. FL: Data curation, Writing – review & editing. AD: Data curation, Writing – review & editing. CD: Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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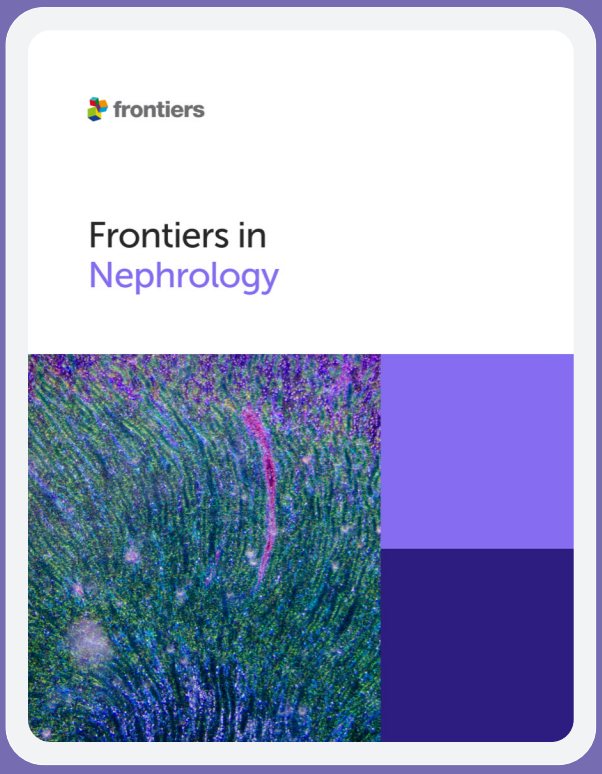

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