NUTRITIONAL ASPECTS OF KIDNEY DISEASE

EDITED BY: Alice Sabatino and Carla Maria Avesani
PUBLISHED IN: Frontiers in Nutrition

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88974-005-5
DOI 10.3389/978-2-88974-005-5

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

NUTRITIONAL ASPECTS OF KIDNEY DISEASE

Topic Editors:
Alice Sabatino, University of Parma, Italy
Carla Maria Avesani, Karolinska Institutet, Sweden

Citation: Sabatino, A., Avesani, C. M., eds. (2021). Nutritional Aspects of Kidney Disease. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-005-5

Table of Contents

frontiers in Nutrition

EDITORIAL
published: 17 November 2021
doi: 10.3389/fnut.2021.803351

Editorial: Nutritional Aspects of Kidney Disease

Alice Sabatino[1]* *and Carla Maria Avesani*[2]

[1] *Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy,* [2] *Medical Unit Clinical Nutrition, Division of Renal Medicine and Baxter Novum, Department of Clinical Science, Technology and Intervention, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden*

Keywords: kidney disease, nutrition, chronic kidney disease, acute kidney injury, body composition, end-stage kidney disease, dialysis

Editorial on the Research Topic

Nutritional Aspects of Kidney Disease

The kidneys are homeostatic organs that remove waste products from the metabolism and regulate the concentration of mineral, ions and the volume of body fluids. In the presence of kidney disease (KD) this function is compromised, leading to accumulation of water, minerals and waste products in the body. A close nutritional follow-up which comprises periodical nutritional assessment and supervised dietary modification is key for the management of KD (1, 2), playing an important role in reducing the risk for cardiovascular disease and managing the clinical effects of the reduced glomerular filtration rate, while keeping an optimal nutritional status (3).

This recent Research Topic on "Nutritional aspects of kidney disease" represents a collection of 11 articles, including 8 original research articles, ranging from pathophysiological-related mechanisms to body composition assessment, dietary patterns, and clinical counseling in the field of chronic kidney disease (CKD) and acute kidney injury (AKI). A common theme across the Research Topic is the assessment of nutritional status and body composition of patients with KD. This is an important topic for investigation since protein energy wasting (PEW) and sarcopenia are common in patients with KD, and are associated with adverse clinical outcomes (4, 5). In the current issue Macedo et al. showed that older adults on hemodialysis can concomitantly have malnutrition and sarcopenia, and that both conditions can be independently present in this patient group even if overweight is present. In addition, the authors also demonstrated that malnutrition and sarcopenia together have a worse quality of life and survival.

Many are the factors involved in the worsening of nutritional status of patients with CKD, including unsupervised dietary modifications, which in conjunction with the loss of appetite often observed in this patient group, may lead to spontaneous reduction in energy and nutrient intake (6). Moreover, the catabolic effects of kidney replacement therapy (KRT), metabolic and hormonal derangements, the presence of systemic inflammation and comorbid conditions, and also reduced physical activity contribute to a state of negative energy and protein balance both in patients with AKI and patients with CKD/ESKD (6, 7). A recent hypothesis is that patients undergoing dialysis are more "anabolic resistant," characterized by blunted stimulation of muscle protein synthesis to common anabolic stimuli such as food intake and physical activity. Garibotto et al. thoroughly discuss this hypothesis in a very interesting and in-depth review, bringing awareness to a problem that is far from being solved.

Unique aspects of KD, such as fluid overload and consequent body weight fluctuations, hinder a reliable assessment of nutritional status, and consequently, the management of these conditions. This topic gathers much interest and most papers from this special collection discuss or investigate different tools to assess body composition in patients with KD. Sabatino et al. presented the

OPEN ACCESS

Edited and reviewed by:
Maurizio Muscaritoli, Sapienza Università di Roma, Italy

***Correspondence:**
Alice Sabatino
alice.sabatino86@gmail.com

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *27 October 2021*
Accepted: *29 October 2021*
Published: *17 November 2021*

Citation:
Sabatino A and Avesani CM (2021) Editorial: Nutritional Aspects of Kidney Disease. Front. Nutr. 8:803351. doi: 10.3389/fnut.2021.803351

results of an observational study that investigated the role of ultrasound (US) in the monitoring of quadriceps muscle mass of patients with AKI. They observed an important reduction in quadriceps muscle mass in the first 5 days in the ICU stay, which is expected given the strong catabolic stimuli present in this clinical setting. Overall, this paper provides evidence that US is emerging as a sensitive alternative for the body composition assessment of patients with KD. Aligned with this idea, Reis et al. investigated the role of electrical bioimpedance (BIA) in patients on peritoneal dialysis, showing how single frequency BIA seems to be more accurate than multi-frequency BIA in this clinical setting. Finally, Bellafronte et al. showed that predictive equations applied to estimate skeletal muscle mass from BIA parameters can be useful for the identification of patients with low muscle mass. In addition, Sabatino et al. discuss in a narrative review the usefulness of different bedside tools currently studied and/or applied in the clinical practice for patients on hemodialysis. An emphasis is given to simplified creatinine index [SCI], bioimpedance spectroscopy (BIS) and muscle US, all suitable for clinical practice use. From these, US is the only method that measures muscle in different dimensions, while BIS and SCI are dependent on either theoretical assumptions or on the use of population specific regression equations, which may lead to errors when fluid alteration (over or dehydration) is present, a condition often observed in patients with KD.

A decline in physical function is also of much concern in this clinical setting, being related with increased mortality, falls, fractures, disability and low quality of life (8). Although malnutrition, sarcopenia and low physical function partially overlap, they do not develop in the same rate nor necessarily at the same time (4). In this regard, Mota Silva et al. demonstrated how low lean mass as assessed by phase angle from BIA, but not inflammation and overhydration, has a moderate but statistically significant correlation with worse physical function in patients on peritoneal dialysis.

Another important challenge in the current nutritional management of patients with end stage kidney disease (ESKD) on hemodialysis is the achievement of a good dietary quality pattern (9). The fear of hyperkalemia often precludes clinicians from recommending patients to eat fruits and vegetables, which results in poor fiber intake. A low-fiber dietary intake seems to associate with the development of low grade systemic inflammation through the promotion of intestinal dysbiosis and should not be overlooked (10). Other unwanted consequences, especially in this clinical setting, may arise from a pro-inflammatory dietary habit. Qin et al. show how pro-inflammatory dietary patterns, as assessed by the dietary inflammatory index (DII), positively correlated with parathyroid hormone (PTH) and increased the risk of hyperparathyroidism in patients with early stages of CKD. Although it is a challenge to improve diet quality; tabus, pre-conceptions and non-evidence based dietary counseling regarding the role of fruits and vegetables in the development of hyperkalemia must be resolved, and dietitians should be called into action. That is the theme of a very interesting article published in the current Research Topic. Chan et al. evaluates the impact of individualized nutritional counseling in improving diet quality in patients with CKD, showing encouraging results.

Finally, complementing this special collection, Wang et al. describe the risk factors for renal impairment in adult patients with short bowel syndrome; and Graidis et al. discuss the role of vitamin D in the development and prognosis of AKI as well as a therapeutic adjuvant.

To summarize, we understand that this volume brings a conjunction of papers that makes up a translational point of view for the medical nutritional therapy of kidney diseases—all aligned with the unanswered questions pointed as topics requiring investigation by the KDOQI 2020 Clinical Practice Guideline for Nutrition in Chronic Kidney Disease (1). We are certain that this reading will add new information for clinicians and researchers in the field of nutrition and kidney diseases.

AUTHOR CONTRIBUTIONS

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

REFERENCES

1. Ikizler T, Burrowes J, Byham-Gray L, Campbell K, Carrero J, Chan W, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis.* (2020) 76(3 Suppl 1):S1–S10. doi: 10.1053/j.ajkd.2020.05.006
2. Fiaccadori E, Sabatino A, Barazzoni R, Carrero J, Cupisti A, De Waele E, et al. ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. *Clin Nutr.* (2021) 40:1644–68. doi: 10.1016/j.clnu.2021.01.028
3. Rhee C, Ahmadi S, Kovesdy C, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. *J Cachexia Sarcopenia Muscle.* (2018) 9:235–45. doi: 10.1002/jcsm.12264
4. Sabatino A, Cuppari L, Stenvinkel P, Lindholm B, Avesani C. Sarcopenia in chronic kidney disease: what have we learned so far? *J Nephrol.* (2020) 34:1347–72. doi: 10.1007/s40620-020-00840-y
5. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* (2008) 73:391–8. doi: 10.1038/sj.ki.5002585
6. Sabatino A, Regolisti G, Karupaiah T, Sahathevan S, Sadu Singh BK, Khor BH, et al. Protein-energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis. *Clin Nutr.* (2017) 36:663–71. doi: 10.1016/j.clnu.2016.06.007
7. Fiaccadori E, Regolisti G, Maggiore U. Specialized nutritional support interventions in critically ill patients on renal replacement therapy. *Curr Opin Clin Nutr Metab Care.* (2013) 16:217–24. doi: 10.1097/MCO.0b013e32835c20b0
8. Stenvinkel P, Carrero J, von Walden F, Ikizler T, Nader G. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. *Nephrol Dial Transplant.* (2016) 31:1070–7. doi: 10.1093/ndt/gfv122
9. Campbell K, Carrero J. Diet for the management of patients with chronic kidney disease; it is not the quantity, but the quality that matters. *J Ren Nutr.* (2016) 26:279–81. doi: 10.1053/j.jrn.2016.07.004

10. Sabatino A, Regolisti G, Brusasco I, Cabassi A, Morabito S, Fiaccadori E. Alterations of intestinal barrier and microbiota in chronic kidney disease. *Nephrol Dial Transplant.* (2015) 30:924–33. doi: 10.1093/ndt/gfu287

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 18 January 2021
doi: 10.3389/fnut.2020.618758

Risk Factors for Renal Impairment in Adult Patients With Short Bowel Syndrome

Peng Wang[1†], *Jianbo Yang*[2†], *Yupeng Zhang*[1], *Li Zhang*[1], *Xuejin Gao*[1] *and Xinying Wang*[1*]

[1] Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, China, [2] Department of General Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

OPEN ACCESS

Edited by:
Carla Maria Avesani,
Karolinska Institutet, Sweden

Reviewed by:
Christiane Ramos,
Federal University of Sao Paulo, Brazil
Ailema González-Ortiz,
National Autonomous University of Mexico, Mexico
Maria Ines Barreto Silva,
Rio de Janeiro State Federal University, Brazil

***Correspondence:**
Xinying Wang
wangxinying@nju.edu.cn

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: 18 October 2020
Accepted: 14 December 2020
Published: 18 January 2021

Citation:
Wang P, Yang J, Zhang Y, Zhang L, Gao X and Wang X (2021) Risk Factors for Renal Impairment in Adult Patients With Short Bowel Syndrome. Front. Nutr. 7:618758. doi: 10.3389/fnut.2020.618758

Renal impairment is a common complication in patients with intestinal failure that is mostly caused by short bowel syndrome (SBS) and is associated with adverse outcomes that severely affect the quality of life or even survival. The prevalence and risk factors for renal impairment in patients with SBS remain unclarified. Therefore, we aimed to determine the prevalence of renal impairment and identify potential risk factors for renal impairment in adult patients with SBS. We retrospectively identified 199 patients diagnosed with SBS admitted to the Department of General Surgery between January 1, 2012 and January 1, 2019, from a prospectively maintained database. Overall, 56 patients (28.1%) with decreased renal function (eGFR < 90 mL/min/1.73 m^2). The median duration of SBS was 7 months (IQR, 3–31 months) and the mean eGFR was 103.1 ± 39.4 mL/min/1.73 m^2. Logistic regression modeling indicated that older age [odds ratio (OR), 1.074; 95% CI, 1.037–1.112, $P < 0.001$], kidney stones (OR, 4.887; 95% CI, 1.753–13.626; $P = 0.002$), decreased length of the small intestine (OR, 0.988; 95% CI, 0.979–0.998; $P = 0.019$), and prolonged duration of SBS (OR, 1.007; 95% CI, 1.001–1.013; $P = 0.046$) were significant risk factors for renal impairment. This is the largest study that has specifically explored the risk factors for renal impairment in a large cohort of adults with SBS. The present study showed that renal function should be closely monitored during treatment, and patients should be given prophylactic interventions if necessary. This retrospective study is a part of clinical study NCT03277014, registered in ClinicalTrials.gov PRS. And the PRS URL is http://register.clinicaltrials.gov.

Keywords: short bowel syndrome, selective digestive decontamination, risk factors, intestinal failure, renal impairment

INTRODUCTION

Short bowel syndrome (SBS) is a rare disease usually caused by the removal of the small intestine due to a variety of underlying diseases, and it accounts for 74.4% of chronic intestinal failure (1). In patients with intestinal failure who are treated with long-term parenteral nutrition (PN) support therapy, impaired kidney function has also been reported (2–5).

Renal injury is a serious life-threatening complication that beginning with renal impairment. Worldwide, increasing numbers of patients are affected by chronic kidney disease (6–8). Two factors that have been reported are important for end-stage renal disease (ESRD): aging and type 2 diabetes mellitus (8). The gold standard for evaluating renal function involves inulin or radiolabeled markers to measure the glomerular filtration rate (GFR) (9, 10). However, considering the cost and complexities of measuring GFR, estimated GFR (eGFR) is widely used in clinical work.

In patients with SBS, studies showed that chronic renal failure (CRF) was related to intestinal failure and long-term PN (3, 11). Infections, dehydration, hypovolemic state, and age are also reported were risk factors for renal impairment in patients with SBS; however, these results were not consistent among studies (2–4). In summary, the risk factors of renal impairment (eGFR $<$ 90 mL/min/1.73 m^2) in adult patients with SBS remain uncharacterized.

Small intestinal bacterial overgrowth (SIBO) occurs commonly in SBS. A study found that among patients with SBS 63% (27 of 43) of patients had SIBO (12). This means that the gut microbiota was disrupted in patients with SBS. A study showed that in patients with SBS, both fecal and colonic biopsy samples were found to have a high prevalence of Lactobacillus, with an associated depletion of Clostridia and Bacteroidetes (13). The crosstalk between the gut microbiota and the host has attracted considerable attention owing to its involvement in various diseases. Many papers report that chronic kidney disease (CKD) is associated with gut dysbiosis and altered host-microbiota crosstalk (14–16). One paper also suggested that the overgrown bacteria translocated from the gut to the blood, where they contributed to the development of CKD (16). Selective digestive decontamination (SDD) is a treatment for SIBO and the principal method that uses broad-spectrum and other antibiotics including those that cover anaerobic bacteria and antifungals (17–19). However, whether there is a crosstalk between gut flora and renal function in patients with SBS remains unclear.

This study aimed to determine the prevalence of renal impairment in clinical practice and to identify potential risk factors for renal impairment in adult patients with SBS.

MATERIALS AND METHODS

Participants

We retrospectively identified consecutive SBS patients from a prospectively maintained database at the Clinical Nutrition therapy center, Jinling Hospital, from January 1, 2012, to January 1, 2019. The prospective database was maintained to enable the guidance of patients' home nutritional support. We included patients who underwent small bowel resection with the length of remaining small bowel $<$200 cm and were diagnosed with SBS. Patients were excluded if (1) eGFR $<$ 90 mL/min/m^2 before SBS diagnosed; (2) their serum creatinine and cystatin C level increased significantly in the last 3 months; (3) their remaining intestinal length and the anatomical structure was not clear; (4) the patients were at the acute stage of SBS ($<$4 weeks after intestinal resection surgery); (5) age $<$ 18 years. The present study was approved by the Ethics Committee of Jingling Hospital. The ethics committee registration number was 2015ZFYJ-010.

Demographic data at admission were collected from the database, including age, sex, body mass index (BMI), nutritional risk screening 2002 (NRS-2002) score ($\geq$3.0 means nutritional risk) (20), subjective global assessment (SGA) score (A means well-nourished; B means moderately malnourished; C means severely malnourished) (21), diabetes mellitus, hypertension, and serum concentrations of albumin, pre-albumin, creatinine, cystatin C, hemoglobin, and C-reactive protein. Unintentional weight loss in recent months (3–6 months), and underlying diseases were recorded. The intestinal anatomy (including small bowel length, anatomy type, presence of an intact ileocecal valve, and colon-in-continuity) were also recorded. Parenteral nutrition (PN) dependence, whether patients received SDD treatment, presence of nosocomial catheter-related bloodstream infections (CRBSIs) were evaluated in hospitalization for intestinal rehabilitation after SBS diagnosis in our center.

Definitions

The diagnosis of SBS was made in our clinical nutrition center by two gastroenterologists, three surgeons, and one dietitian. The anatomy of the remaining small bowel was used to classify SBS into type 1 (end-jejunostomy with no colon-in-continuity), type 2 (jejuno-colic anastomosis with partial colon-in-continuity), and type 3 (jejuno-ileal anastomosis with an intact colon). The *duration of SBS* was defined as the time interval between the diagnosis of SBS and the previous hospital visit. *Malnutrition* was retrospectively diagnosed by two clinical nutritional physicians, according to the ESPEN diagnostic criteria of 2015 (22). *Kidney stones* were diagnosed based on abdominal imaging (CT, MRI, or ultrasound).

Creatinine and cystatin C were used to calculate the eGFR, using the CKD-EPI equation (23, 24). According to the KIDGO Guideline for the evaluation and management of chronic kidney disease (CKD) which published in 2012, the prognosis of CKD graded by eGFR categories was divided into five grades (G1, normal or high; G2, mildly decreased; G3a, mildly to moderate decreased; G3b, moderate to severe decreased; G4, severely decreased; G5, kidney failure). Hence, we defined the *Renal impairment* as an eGFR of $<$90 mL/min/1.73 m^2 (11, 25). The diagnosis of SIBO in patients with SBS mainly depends on two methods; the culture of duodenal fluid was widely used and was considered the gold standard (26), and the other is the hydrogen breath test (27). Nevertheless, both tests raise several issues regarding repeatability, accuracy, and optimal cut-off values (28–30). For these reasons, there is no consensus regarding the optimal test for SIBO. The management of patients with SIBO should consider gastroenterological, surgical, microbiologic, pharmacologic, nutritional, and metabolic factors (31). So, we developed an SDD treatment process combining the etiology, symptomology, and the results of the fecal smear test to determine whether SIBO was present in patients with SBS. We empirically diagnosed patients with SIBO according to (1) the pathogenesis [proton pump inhibitors used for more than 3 weeks; intestinal motility impaired; intestinal anatomy changed (32, 33)], (2) symptoms reported in the literature [diarrhea/stool

smelly, abdominal pain, bloating, weight loss, unexpected plateau during the weaning of PN (12, 34, 35)], and (3) the results of the smear test of fecal bacteria (proportion of bacteria was abnormal, and the appearance of other abnormal bacteria). Patients diagnosed with SIBO were then treated with SDD (oral amikacin/vancomycin/gentamicin with metronidazole and fluconazole three times per day for 3 days).

Statistical Analysis

Numerical data that were normally distributed were expressed as mean ± standard deviation (SD); others were expressed as median (first-to-third interquartile range). Categorical variables were expressed as numbers and percentages. Binary data were presented as 0 (no) or 1 (yes). Data between groups were compared using Student's *t*-test for normally distributed values and the Mann-Whitney *U*-test was used to compare median values, while Pearson's chi-square test was used for categorical variables. Potential risk factors for renal impairment were evaluated by univariate analysis, and risk factors with $P < 0.1$ were included in multivariate binary logistic stepwise regression analysis. In the multivariate analysis statistical significance was set at two-sided $P < 0.05$. Statistical analyses were performed using SPSS software (version 20.0 Win; SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

A total of 239 patients were diagnosed with SBS in our center during 2012–2019. However, according to our exclusion criteria, data from 40 patients were not used in the present study because they were either in the acute stage of the SBS (20 patients) or eGFR < 90 mL/min/1.73 m^2 before SBS diagnosed (6 patients) or age<18 years old (14 patients). Eventually, we identified 199 patients for the study (**Figure 1**). The mean age was 48.8 ± 17.3 years, and 138 (69.3%) were male. The mean BMI was 18.1 ± 4.6 kg/m^2. Regarding the SGA score, there were 12 patients in level A (well nourished), 113 patients in level B(moderately malnourished), and 74 patients in level C(severely malnourished), as for the NRS2002 score there are 96 (48.5%) patients with nutritional risk (NRS2002 ≥3). The median duration of SBS was 7 months (interquartile range 3–31). There were 118 (59.2%) patients requiring PN at admission; 141 (71.4%) patients were malnourished according to ESPEN diagnostic criteria of 2015. There were 34 (17.1%) patients with kidney stones; 56 (28.1%) patients with bowel symptoms who received SDD treatment, while 34 (17.1%) contracted nosocomial CRBSIs. The characteristics of the study population at admission are outlined in **Table 1**.

The mean small bowel length of the patients was 85.6 ± 45.5 cm; the median was 80.0 cm; 53 (26.6%) patients had type 1, 69 (34.7%) had type 2, and 77 (38.7%) had type 3 SBS. A total of 146 (73.4%) patients had continuity of the colon. The ileocecal valve had been removed in 77 (38.7%) patients (**Table 2**). The most common underlying diseases were mesenteric ischemia (41.7%), volvulus (23.6%), surgical complications (19.6%), radiation enteritis (6.0%), and others (9.0%) (**Table 3**).

The mean eGFR of patients with SBS was 103.1 ± 39.4 mL/min/1.73 m^2. There were 56 (28.1%) patients decreased the eGFR. According KDIGO guideline, in the 56 patients with renal impairment, 25 (44.6%) of them were classified as G2 (eGFR 60–89 mL/min/1.73 m^2), 10 (17.9%) of them were classified as G3a (eGFR 45–59 mL/min/1.73 m^2), 6 (10.7%) of them were classified as G3b (eGFR 30–44 mL/min/1.73 m^2), 6 (10.7%) of them were classified as G4 (eGFR 15–29 mL/min/1.73 m^2) and 9 (16.1%) of them were classified as G5 (eGFR < 15 mL/min/1.73 m^2) and four of them required dialysis therapy. The incidence of renal impairment was 23.2% in type 1 SBS, 41.1% in type 2 SBS, and 35.7% in type 3 SBS ($P = 0.962$).

Patients were divided into a renal impairment group (decreased eGFR, eGFR < 90 mL/min/1.73 m^2) and a normal renal function group (eGFR ≥ 90 mL/min/1.73 m^2). Compared with patients in the normal renal function group, patients with renal impairment tend to be older (58.6 ± 12.5 years vs. 44.9 ± 17.4 years, $P < 0.001$), having longer duration of SBS (12.0 vs. 5.0 months, $P = 0.051$), and lower hemoglobin concentration (97.8 ± 27.6 vs 107.2 ± 20.1 g/L, $P = 0.031$) and albumin concentration (34.7 ± 7.3 vs 36.9 ± 6.6 g/L, $P = 0.046$). Compared with patients in the normal renal function group, in the renal impairment group there were more patients with kidney stones (28.6 vs. 12.6%, $P = 0.008$), receiving SDD treatment (53.5 vs. 18.1%, $P < 0.001$), with nosocomial CRBSIs (25.0 vs. 13.9%, $P = 0.067$) and hypertensive (23.2 vs. 6.9%, $P = 0.001$). Regarding small bowel length, the renal impairment group was shorter than the other group (75.8 ± 41.2 vs. 89.4 ± 46.6 cm, $P = 0.068$). The two groups were similar regarding sex, BMI, NRS-2002 score, diabetes, PN dependence, and the biochemical indicators of nutritional status (all $P > 0.1$).

Independent Risk Factors for Renal Impairment in Patients With Short Bowel Syndrome

We incorporated potential variables with $P < 0.1$ in the univariate analysis into a multivariate logistic regression analysis. The results indicated that the age ($P < 0.001$), SBS duration ($P = 0.046$), small bowel length ($P = 0.019$), and existing kidney stones ($P = 0.002$) were independent risk factors for reduced eGFR. SBS duration had an OR of 1.007 per month resulting in a 10-year cumulative risk of 2.3 folds (1.007^{120}) (**Table 4**).

DISCUSSION

To the best of our knowledge, this is the largest study that has specifically explored the risk factors for renal impairment in a large cohort of adults with SBS ($n = 199$). The incidence of renal impairment in adults with SBS was 28.1%, and the median duration from SBS diagnosis to the development of renal impairment was 12 months. Renal impairment in adults with SBS was influenced by age, shorter length of the small bowel, kidney stones, and prolonged duration of SBS.

Renal impairment has been widely reported in patients with SBS. To date, Buchman et al. (3) reported decreased GFR >20%

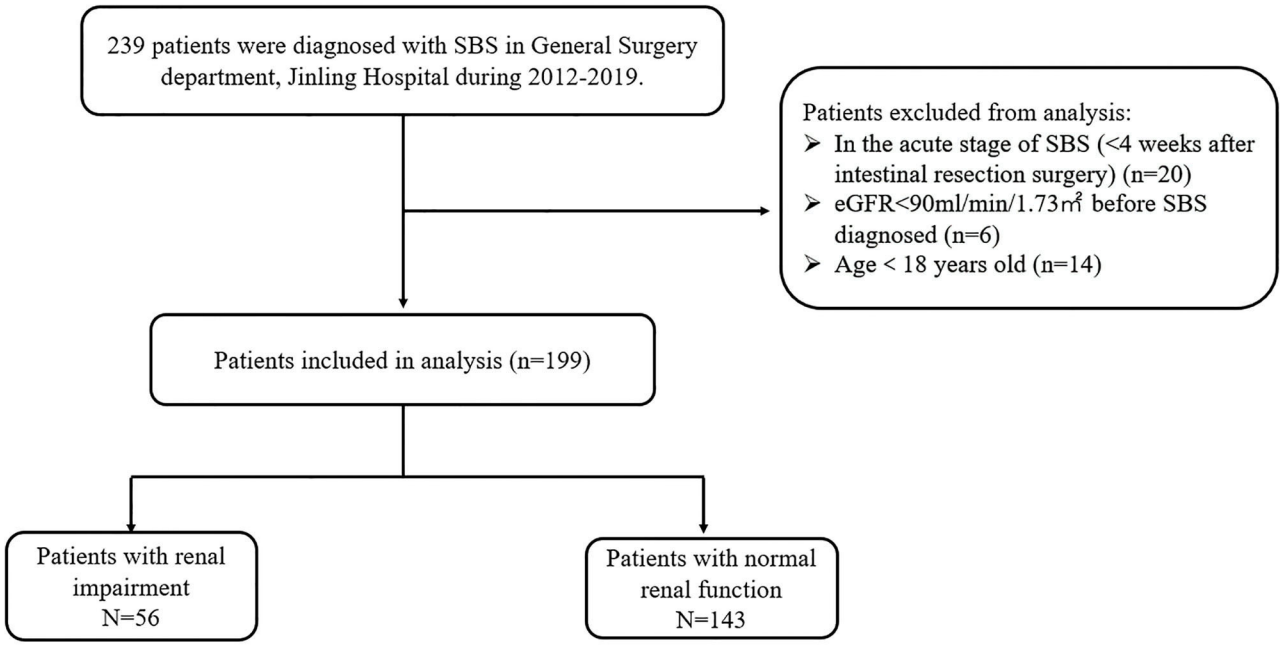

FIGURE 1 | The flow chart demonstrates the selection process of the patients.

in 52.5% of patients, and 3.5% decline per year of creatinine clearance and a reduced kidney function in ∼50% of patients was observed; Lauverjat et al. (4) reported that decreased GFR was found in 9 of 16 patients with SBS also receiving home parenteral nutrition (HPN). Some risk factors have been reported, including infections, dehydration, hypovolemic state, duration of HPN, and patient age; however, these results were not consistent among studies (2–4). Both studies had results similar to ours. Ylinen et al. (11) found that small bowel length was a risk factor for renal impairment in children. Agostini et al. (36) found that age, urologic disease, sepsis, and SBS significantly influenced the development of CKD in patients with HPN, and that eGFR comparable with the median decreased −2.4 to −7.3% per year. Because our study absorbed all patients either receiving PN support therapy, or weaned off PN, and receiving enteral nutrition support therapy, the incidence of renal impairment only was 28.1%.

Patients with SBS need long-term PN. However, with the progress of treatment the amount of fluid and basal metabolism required by patients changed significantly. Most patients do not adjust their PN support plan timeously, resulting in them becoming chronically dehydrated for long periods. A retrospective study of 33 patients with long-term PN found that the GFR decreased by 3.5% ± 6.3% per year (3). Similarly, in our study, we found that the cumulative risk of eGFR was 2.3 fold (1.007^{120}) after 10 years. A decrease in renal function with aging is a natural phenomenon.

In patients with SBS, renal impairment is mainly due to systemic fluid imbalance caused by excessive loss of ostomy fluid, CRBSIs, chronic dehydration, and electrolyte imbalance (37). The small bowel length is an important factor that can affect nutrients and electrolyte absorption, as well as renal function (11). Similar to the results of previous reports, the length of the small intestine in our study was an important factor for determining renal impairment. In the present study, nosocomial CRBSIs are not considered independent risk factors for renal impairment because we did not analyze the occurrence of CRBSIs during HPN, and CRBSIs are well-controlled during hospitalization. However, in the renal impairment group, a higher percentage of patients suffered CRBSIs (25.0 vs. 13.9%).

The ileocecal valve plays an important role in the alimentary canal since it can influence nutrients absorbed and keep electrolytes balanced. Although in the present study the renal dysfunction has no difference in patients with or without the ileocecal valve, we found that the eGFR of SBS in various types were significantly different (type 1 SBS was 107 ± 33.5 mL/min/1.73 m^2, type 2 SBS was 94.1 ± 43.7 mL/min/1.73 m^2 and type 3 SBS was 108.4 ± 38.1 mL/min/1.73 m^2, type 2 vs. type 3, $P = 0.037$). The eGFR was significantly lower in patients with type 2 SBS than in type 3 SBS. Although type 1 SBS includes patients with stomas who are prone to water and electrolyte loss, no significant reduction in eGFR was found. This phenomenon may be related to the acute phase of the disease, since most of the acute phase occurs during the hospitalization period when doctors pay more attention to water and electrolyte balance.

Kidney stones have been reported in patients with SBS, resulting in adverse clinical sequelae (38, 39). The prevalence of kidney stones is increased in patients who have undergone intestinal surgery, especially in patients with jejunostomy or ileostomy, with an occurrence of 5–15% (40–42). Patients

TABLE 1 | Characteristics of adult patients with SBS with and without renal impairment.

Variables	All patients	Patients with renal impairment*	Patients with normal renal function	*P*-value
No. of patients	199	56	143	
Age, year	48.8 ± 17.3	58.6 ± 12.5	44.9 ± 17.4	***<0.001***
Male, *n* (%)	138 (69.3)	43 (76.8)	95 (66.4)	0.154
Diabetes mellitus, *n* (%)	7 (3.5)	1 (1.8)	6 (4.2)	0.682
Hypertension, *n* (%)	23 (11.6)	13 (23.2)	10 (6.9)	***0.001***
Kidney stones, *n* (%)	34 (17.1)	16 (28.6)	18 (12.6)	***0.008***
BMI, kg/m^2	18.1 ± 4.6	18.0 ± 4.7	18.1 ± 4.6	0.889
Malnutrition, *n* (%)	141 (71.4)	42 (76.8)	99 (69.9)	0.291
NRS2002 ≥ 3, *n* (%)	96 (48.5)	26 (46.4)	70 (49.0)	0.832
<3, *n* (%)	103 (51.5)	30 (53.6)	73 (51.0)	
SGA class (A; B; C)	12/113/74	4/27/25	8/86/49	0.311
Hemoglobin (g/L)	104.5 ± 23.5	97.8 ± 29.6	107.2 ± 20.1	***0.031***
Albumin (g/L)	36.3 ± 6.8	34.7 ± 7.3	36.9 ± 6.6	***0.046***
Serum creatinine (μmol/L)	56.1 (43.0–76.0)	116.0 (89.7–185.5)	50.0 (38.5–61.0)	***<0.001***
Cystatin c (mg/L)	0.8 (0.6–1.0)	1.3 (1.1–1.9)	0.7 (0.6–0.8)	***0.010***
eGFR (mL/min/1.73 m^2)	103.1 ± 39.4	51.8 ± 27.8	123.2 ± 20.4	***<0.001***
≥ 90, *n* (%)	143 (71.9)	–	143 (100)	
60–89, *n* (%)	25 (12.5)	25 (44.6)	–	
45–59, *n* (%)	10 (5.0)	10 (17.9)	–	
30–44, *n* (%)	6 (3.0)	6 (10.7)	–	
15–29, *n* (%)	6 (3.0)	6 (10.7)	–	
<15, *n* (%)	9 (4.5)	9 (16.1)	–	
ALT (U/L)	33.0 (18.8–58.3)	31.5 (15.8–58)	33.0 (19.0–58.8)	0.547
AST (U/L)	28.5 (18.0–43.0)	25.0 (17.3–59.5)	29.0 (18.0–41.5)	0.124
CRP (mg/L)	3.9 (0.9–19.6)	8.8 (2.0–30.0)	3.0 (0.8–10.9)	0.191
PN requirement, *n* (%)				0.947
Yes	118 (59.2)	33 (58.9)	85 (59.4)	
Weaned	81 (40.7)	23 (41.1)	58 (40.6)	
Duration of SBS, (months)	7.0 (3.0–31.0)	12.0 (5.3–46.0)	5.0 (2.0–16.0)	0.051
SDD, *n* (%)	56 (28.1)	30 (53.5)	26 (18.1)	***<0.001***
Nosocomial CRBSIs, *n* (%)	34 (17.1)	14 (25.0)	20 (13.9)	0.067

Values were presented as n (%), or mean ± SD, or median (first–to-third interquartile range).

BMI, body mass index; NRS2002, Nutrition Risk Screening 2002; Scr, Serum creatinine; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reaction protein; PN, Parenteral Nutrition; SBS, Short Bowel Syndrome; SDD, Selective decontamination of the digestive tract; CRBSIs, catheter-related blood stream infections. Duration of SBS: the time interval between the diagnosis of SBS and the previous hospital visit.

**Renal impairment was defined as eGFR < 90 mL/min/1.73 m^2 calculated by the CKD-EPI equation. P-value < 0.05 were bolded and italicized.*

with kidney stones have significantly increased incidences of adverse renal outcomes, including chronic renal failure (43). Our previous studies also found that patients with kidney stones have lower eGFR than patients without kidney stones (44). In the present study, we found that patients with kidney stones may be prone to renal impairment. Nevertheless, the mechanisms linking nephrolithiasis to impairment of renal function remain unclear. The intestinal surgery alters the anatomy of intestinal results in malabsorption of bile acids and fatty acids (45). Normally, the oxalate in dietary binds to calcium in luminal forming calcium oxalate which cannot be absorbed. At the same time, unabsorbed fatty acids bind to luminal calcium and form insoluble calcium soaps which inhibit the binding of luminal oxalate to calcium and increase its absorption. Besides these, the bile acids enrichment in colon and increases the absorption of oxalate, results in hyperoxalatemia and increase the formation of oxalate stones (38). There is also a study found that the plasma oxalaye increase at lower GFR levels even among those without entric or primary hyperoxaluria and established the relationships between plasma oxalate, GFR and urine oxalate among patients with routine urinary stone disease. In present study, we found that the patients with kidney stones may be prone to renal dysfunction, may be the decreased of GFR resulted the kidney stones (46).

SDD is an infection preventive measure for ICU patients that was proposed more than 30 years ago (47). It has been reported to have a favorable effect on mortality in adult patients in general intensive care units (48). In patients with SBS, a review showed that cyclical use (1 week per month) of broad-spectrum antibiotics was the mainstay of therapy for small-intestinal bacterial overgrowth (49).

TABLE 2 | The intestinal anatomy of adult patients with SBS with and without renal impairment.

Variables	All patients	Patients with renal impairment*	Patients with normal renal function	*P*-value
No. of patients, *n*	199	56	143	
Small bowel length (cm)	85.6 ± 45.5	75.8 ± 41.2	89.4 ± 46.6	0.068
Median (cm)	80.0 (57.5–117.5)	77.5 (50.0–100.0)	90 (60.0–120.0)	
Anatomy type, *n* (%)				0.962
I	53 (26.6)	13 (23.2)	40 (28.0)	
II	69 (34.7)	23 (41.1)	46 (32.2)	
III	77 (38.7)	20 (35.7)	57 (39.9)	
Ileocecal valve intact, *n* (%)	77 (38.7)	20 (35.7)	57 (39.9)	0.591
Colon in continuity, *n* (%)	146 (73.4)	43 (76.8)	103 (72.0)	0.495

Values were presented as n (%), or mean ± SD, or median (first-to-third interquartile range).
Type I:end-jejunostomy with no colon-in-continuity.
Type II: jejuno-colic anastomosis with partial colon-in-continuity.
Type III: jejuno-ileal anastomosis with an intact colon.
**Renal impairment was defined as eGFR < 90 mL/min/1.73 m^2 calculated by the CKD-EPI equation.*

TABLE 3 | The underlying diseases in adult patients with SBS with and without renal impairment.

Variables	All patients	Patients with renal impairment*	Patients with normal renal function	*P*-value
No. of patients, n	199	56	143	
Mesenteric ischemia	83 (41.7)	30 (53.5)	53 (37.1)	0.266
Radiation enteritis	12 (6.0)	3 (5.4)	9 (6.3)	1.000
Surgical complications	39 (19.6)	9 (16.1)	30 (20.1)	1.000
Volvulus	47 (23.6)	8 (14.3)	39 (27.3)	0.269
Others	18 (9.0)	6 (10.7)	12 (8.4)	1.000

Values were presented as n (%).
**Renal impairment was defined as eGFR < 90 mL/min/1.73 m^2 calculated by the CKD-EPI equation.*

TABLE 4 | Multivariate analysis of the factors associated with renal impairment in adults with SBS.

Variables	β	OR	95%CI	*P*-value
Age	0.071	1.074	1.037–1.112	***<0.001***
Kidney stones	1.587	4.887	1.753–13.626	***0.002***
Length of SI	−0.012	0.988	0.979–0.998	***0.019***
Duration of SBS	0.007	1.007	1.001–1.013	***0.046***
Hypertension	0.140	1.150	0.338–3.910	0.823
Hemoglobin	−0.016	0.984	0.961–1.008	0.183
Albumin	0.041	1.042	0.955–1.136	0.441
SDD	0.820	2.272	0.897–5.755	0.356
CRBSIs	−0.088	0.916	0.313–2.679	0.837

SBS, Short bowel syndrome; SI, Small intestine; SDD, Selective decontamination of the digestive tract.
Duration of SBS: the time interval between the diagnosis of SBS and the previous hospital visit. P-value < 0.05 were bolded and italicized.

We diagnosed patients with SIBO using our SDD management scheme. Many papers reported that disordered gut flora could influence the renal function of the host. Vaziri et al. (50) found that there were 190 bacterial OTUs in the stool, with marked differences in abundance between patients with ESRD and normal controls. In addition, Wang et al. performed a clinical trial that showed that bacterial DNA was detected in the blood of six (20%) patients with ERSD. The bacterial genera found in the blood that were overgrown in the intestines were mainly *Klebsiella* spp., *Proteus spp, Escherichia* spp., *Enterobacter* spp., and *Pseudomonas* spp. (16). This paper suggests that the overgrown bacteria translocated from the gut to the blood, where they contributed to the development of CKD. Hence, SIBO may be an independent risk factor for renal impairment in patients with SBS. However in the present study, 56 (28.1%) patients received SDD treatment (may with SIBO), less than the previously reported value (63%) (12). The reason for our low result is that we can only rely on symptoms and experience to

diagnose SIBO. And SIBO is not an independent risk factor for renal impairment in patients with SBS. The relationship between intestinal flora disorder and SBS-related kidney damage needs further study.

The present study had several limitations. First, it was a retrospective single-institution study performed at a tertiary-care referral center. Second, the dietary habits, home PN formulation, and total time that patients required PN support therapy were not available. Third, the incidence of CRBSIs during HPN could not be recorded. Fourth, because most patients with SBS in our center were adults, we only evaluated the risk factors for renal impairment in adults. Fifth, it was a retrospective study performed at a tertiary-care referral center, the data of urine test (hematuresis and proteinuria) was lacking. Therefore, the incidence of renal impairment may have been underestimated. Large, multicenter, prospective studies focusing on the reason for renal impairment in both pediatric and adult patients with SBS should be conducted in the future.

The strengths of the present study. Firstly, it is the largest study that has specifically explored the risk factors for renal dysfunction in a large cohort of adults with SBS ($n = 199$). In addition, we found that the duration of SBS, kidney stones, old age, and the length of the small bowel are the independent risk factors for renal dysfunction in adult patients with SBS. And, SBS duration had an OR of 1.007 per month resulting in a 10-year cumulative risk of 2.3 fold (1.007^{120}). Given that patients with SBS have increased risk for renal impairment and associated adverse outcomes, close monitoring of renal function and prophylactic interventions should be conducted routinely in clinical practice.

CONCLUSION

Renal function impairment is common in adults with SBS and can results in adverse clinical consequences. In our study, 56 (28.1%) in 199 patients developed renal function impairment with eGFR $<$ 90 mL/min/1.73 m^2, 34 (17.1%) developed nephrolithiasis. The risk of renal impairment is increased in patients with older age, kidney stones, shorter length of remaining small intestine, and prolonged duration of SBS. In the chronic stage of SBS, renal impairment is primarily related to water and electrolyte loss, kidney stones, old age, and the length of the small bowel. Given that patients with SBS have increased risk for renal impairment and associated adverse outcomes, close monitoring of renal function to avoid dehydration, and prophylactic interventions should be conducted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Jingling Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PW and XW contributed to conception, design of the research, and critically revised the manuscript. PW and JY contributed to acquisition, analysis, and interpretation of the data. XG, LZ, and YZ drafted the manuscript. All authors agreed to be fully accountable for ensuring the integrity and accuracy of the work, read, and approved the final manuscript.

FUNDING

This study was supported by the National Natural Science Foundation of China (81470797 and 81770531), the Science Foundation of Outstanding Youth in Jiangsu Province (BK20170009), Military Medical Innovation Project (18CXZ031), the National Science and Technology Research Funding for Public Welfare Medical Projects (201502022), and The 13th Five-Year Plan Foundation of Jiangsu Province for Medical Key Talents (ZDRCA2016091).

ACKNOWLEDGMENTS

We thank Editage China for editing the English text of a draft of this manuscript.

REFERENCES

1. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. *Clin Nutr.* (2016) 35:247–307. doi: 10.1016/j.clnu.2016.01.020
2. Boncompain-Gerard M, Robert D, Fouque D, Hadj-Aissa A. Renal function and urinary excretion of electrolytes in patients receiving cyclic parenteral nutrition. *JPEN J Parenter Enteral Nutr.* (2000) 24:234–9. doi: 10.1177/0148607100024004234
3. Buchman AL, Moukarzel A, Ament ME, Gornbein J, Goodson B, Carlson C, et al. Serious renal impairment is associated with long-term parenteral nutrition. *JPEN J Parent Enteral Nutr.* (1993) 17:438–44. doi: 10.1177/0148607193017005438
4. Lauverjat M, Hadj Aissa A, Vanhems P, Bouletreau P, Fouque D, Chambrier C. Chronic dehydration may impair renal function in patients with chronic intestinal failure on long-term parenteral nutrition. *Clin Nutr.* (2006) 25:75–81. doi: 10.1016/j.clnu.2005.09.010
5. Pironi L, Lauro A, Soverini V, Zanfi C, Agostini F, Guidetti M, et al. Renal function in patients on long-term home parenteral nutrition and in intestinal transplant recipients. *Nutrition.* (2014) 30:1011–4. doi: 10.1016/j.nut.2014.02.001
6. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. *J Am Soc Nephrol.* (2002) 13(Suppl. 1):S37–40.
7. Bailie GR, Uhlig K, Levey AS. Clinical practice guidelines in nephrology: evaluation, classification, and stratification of chronic kidney disease. *Pharmacotherapy.* (2005) 25:491–502. doi: 10.1592/phco.25.4.491.61034

8. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. *Lancet.* (2005) 365:331–40. doi: 10.1016/s0140-6736(05)17789-7
9. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol.* (2009) 4:1832–43. doi: 10.2215/cjn.01640309
10. Hsu CY, Bansal N. Measured GFR as "gold standard" —all that glitters is not gold? *Clin J Am Soc Nephrol.* (2011) 6:1813–4. doi: 10.2215/cjn.06040611
11. Ylinen E, Merras-Salmio L, Gunnar R, Jahnukainen T, Pakarinen MP. Intestinal failure as a significant risk factor for renal impairment in children. *Nutrition.* (2018) 45:90–3. doi: 10.1016/j.nut.2017.07.011
12. Dibaise JK, Young RJ, Vanderhoof JA. Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. *Clin Gastroenterol Hepatol.* (2006) 4:11–20. doi: 10.1016/j.cgh.2005.10.020
13. Joly F, Mayeur C, Bruneau A, Noordine ML, Meylheuc T, Langella P, et al. Drastic changes in fecal and mucosa-associated microbiota in adult patients with short bowel syndrome. *Biochimie.* (2010) 92:753–61. doi: 10.1016/j.biochi.2010.02.015
14. Ranganathan N, Friedman EA, Tam P, Rao V, Ranganathan P, Dheer R. Probiotic dietary supplementation in patients with stage 3 and 4 chronic kidney disease: a 6-month pilot scale trial in Canada. *Curr Med Res Opin.* (2009) 25:1919-30. doi: 10.1185/03007990903069249
15. Crespo-Salgado J, Vehaskari VM, Stewart T, Ferris M, Zhang Q, Wang G, et al. Intestinal microbiota in pediatric patients with end stage renal disease: a Midwest Pediatric Nephrology Consortium study. *Microbiome.* (2016) 4:50. doi: 10.1186/s40168-016-0195-9
16. Wang F, Jiang H, Shi K, Ren Y, Zhang P, Cheng S. Gut bacterial translocation is associated with microinflammation in end-stage renal disease patients. *Nephrology.* (2012) 17:733–8. doi: 10.1111/j.1440-1797.2012.01647.x
17. Lauritano EC, Gabrielli M, Scarpellini E, Ojetti V, Roccarina D, Villita A, et al. Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. *Eur Rev Med Pharmacol Sci.* (2009) 13:111–6.
18. Esposito I, de Leone A, Di Gregorio G, Giaquinto S, de Magistris L, Ferrieri A, et al. Breath test for differential diagnosis between small intestinal bacterial overgrowth and irritable bowel disease: an observation on non-absorbable antibiotics. *World J Gastroenterol.* (2007) 13:6016–21. doi: 10.3748/wjg.v13.45.6016
19. Madrid AM, Hurtado C, Venegas M, Cumsille F, Defilippi C. Long-Term treatment with cisapride and antibiotics in liver cirrhosis: effect on small intestinal motility, bacterial overgrowth, and liver function. *Ame J Gastroenterol.* (2001) 96:1251–5. doi: 10.1111/j.1572-0241.2001.03636.x
20. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* (2003) 22:415–21. doi: 10.1016/s0261-5614(03)00098-0
21. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? *J Parent Enteral Nutr.* (1987) 11:8–13. doi: 10.1177/014860718701100108
22. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition—an ESPEN Consensus Statement. *Clini Nutr.* (2015) 34:335–40. doi: 10.1016/j.clnu.2015.03.001
23. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *New Engl J Med.* (2012) 367:20–9. doi: 10.1056/NEJMoa1114248
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* (2009) 150:604–12. doi: 10.7326/0003-4819-150-9-200905050-00006
25. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Di.* (2014) 63:713–35. doi: 10.1053/j.ajkd.2014.01.416
26. Khoshini R, Dai SC, Lezcano S, Pimentel M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. *Digest Dis Sci.* (2008) 53:1443–54. doi: 10.1007/s10620-007-0065-1
27. Ghoshal UC, Ghoshal U, Das K, Misra A. Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome and its relationship with oro-cecal transit time. *Indian J Gastroenterol.* (2006) 25:6–10.
28. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *Jama.* (2004) 292:852–8. doi: 10.1001/jama.292.7.852
29. King CE, Toskes PP. Comparison of the 1-gram [14C]xylose, 10-gram lactulose-H_2, and 80-gram glucose-H_2 breath tests in patients with small intestine bacterial overgrowth. *Gastroenterology.* (1986) 91:1447–51. doi: 10.1016/0016-5085(86)90199-x
30. Bauer TM, Schwacha H, Steinbruckner B, Brinkmann FE, Ditzen AK, Kist M, et al. Diagnosis of small intestinal bacterial overgrowth in patients with cirrhosis of the liver: poor performance of the glucose breath hydrogen test. *J Hepatol.* (2000) 33:382–6. doi: 10.1016/s0168-8278(00)80273-1
31. Ponziani FR, Gerardi V, Gasbarrini A. Diagnosis and treatment of small intestinal bacterial overgrowth. *Expert Rev Gastroenterol Hepatol.* (2016) 10:215–27. doi: 10.1586/17474124.2016.1110017
32. Husebye E. The pathogenesis of gastrointestinal bacterial overgrowth. *Chemotherapy.* (2005) 51(Suppl. 1):1–22. doi: 10.1159/000081988
33. Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. *Gastroenterol Hepatol.* (2007) 3:112–22.
34. Wanitschke R, Ammon HV. Effects of dihydroxy bile acids and hydroxy fatty acids on the absorption of oleic acid in the human jejunum. *J Clin Invest.* (1978) 61:178–86. doi: 10.1172/jci108916
35. Grace E, Shaw C, Whelan K, Andreyev HJ. Review article: small intestinal bacterial overgrowth—prevalence, clinical features, current and developing diagnostic tests, and treatment. *Aliment Pharmacol Ther.* (2013) 38:674–88. doi: 10.1111/apt.12456
36. Agostini F, Sasdelli AS, Guidetti M, Comai G, La Manna G, Pironi L. Outcome of kidney function in adults on long-term home parenteral nutrition for chronic intestinal failure. *Nutrition.* (2019) 60:212–6. doi: 10.1016/j.nut.2018.10.005
37. Pironi, Loris. Definitions of intestinal failure and the short bowel syndrome. *Best Pract Res Clin Gastroenterol.* (2016) 30:173–85. doi: 10.1016/j.bpg.2016.02.011
38. Johnson E, Vu L, Matarese LE. Bacteria, bones, and stones: managing complications of short bowel syndrome. *Nutr Clin Pract.* (2018) 33:454–66. doi: 10.1002/ncp.10113
39. Khan SR, Pearle MS, Robertson WG, Gambaro G, Canales BK, Doizi S, et al. Kidney stones. *Nat Rev Dis Primers.* (2016) 2:16008. doi: 10.1038/nrdp.2016.8
40. O'Connor RC, Worcester EM, Evan AP, Meehan S, Kuznetsov D, Laven B, et al. Nephrolithiasis and nephrocalcinosis in rats with small bowel resection. *Urol Res.* (2005) 33:105–15. doi: 10.1007/s00240-004-0460-4
41. McConnell N, Campbell S, Gillanders I, Rolton H, Danesh B. Risk factors for developing renal stones in inflammatory bowel disease. *BJU Int.* (2002) 89:835–41. doi: 10.1046/j.1464-410x.2002.02739.x
42. Clarke AM, McKenzie RG. Ileostomy and the risk of urinary uric acid stones. *Lancet.* (1969) 2:395–7. doi: 10.1016/s0140-6736(69)90108-1
43. Li CC, Chien TM, Wu WJ, Huang CN, Chou YH. Uric acid stones increase the risk of chronic kidney disease. *Urolithiasis.* (2018) 46:543–7. doi: 10.1007/s00240-018-1050-1
44. Yang J, Sun H, Wan S, Mamtawla G, Gao X, Zhang L, et al. Risk factors for nephrolithiasis in adults with short bowel syndrome. *Ann Nutr Metab.* (2019) 75:47–54. doi: 10.1159/000502329
45. Hofmann AF, Poley JR. Role of bile acid malabsorption in pathogenesis of diarrhea and steatorrhea in patients with ileal resection. I. response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglyceride. *Gastroenterology.* (1972) 62:918–34.
46. Perinpam M, Enders FT, Mara KC, Vaughan LE, Mehta RA, Voskoboev N, et al. Plasma oxalate in relation to eGFR in patients with primary hyperoxaluria, enteric hyperoxaluria and urinary stone disease. *Clin Biochem.* (2017) 50:1014–9. doi: 10.1016/j.clinbiochem.2017.07.017
47. Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Intensive Care Med.* (1984) 10:185–92. doi: 10.1007/bf00259435
48. Price R, MacLennan G, Glen J. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ.* (2014) 348:g2197. doi: 10.1136/bmj.g2197
49. Duggan CP, Jaksic T. Pediatric intestinal failure. *N Engl J Med.* (2017) 377:666–75. doi: 10.1056/NEJMra1602650

50. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, DeSantis TZ, et al. Chronic kidney disease alters intestinal microbial flora. *Kidney Int.* (2013) 83:308–15. doi: 10.1038/ki.2012.345

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.

frontiers in Nutrition

SYSTEMATIC REVIEW
published: 04 March 2021
doi: 10.3389/fnut.2020.630951

Vitamin D and Acute Kidney Injury: A Two-Way Causality Relation and a Predictive, Prognostic, and Therapeutic Role of Vitamin D

Spyridon Graidis[1†], *Theodosios S. Papavramidis*[2†] *and Maria Papaioannou*[1*]

[1] *Laboratory of Biological Chemistry, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece,* [2] *1st Propedeutic Department of Surgery, Faculty of Health Sciences, School of Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece*

OPEN ACCESS

Edited by:
Alice Sabatino,
University of Parma, Italy

Reviewed by:
Cassiana Regina de Góes,
Universidade Federal de Lavras, Brazil
Francesca Di Mario,
University Hospital of Parma, Italy

***Correspondence:**
Maria Papaioannou
mpapaioannou@auth.gr
orcid.org/0000-0003-3149-6523

†ORCID:
Spyridon Graidis
orcid.org/0000-0003-0356-850X
Theodosios S. Papavramidis
orcid.org/0000-0002-7097-9889

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *18 November 2020*
Accepted: *31 December 2020*
Published: *04 March 2021*

Citation:
Graidis S, Papavramidis TS and Papaioannou M (2021) Vitamin D and Acute Kidney Injury: A Two-Way Causality Relation and a Predictive, Prognostic, and Therapeutic Role of Vitamin D. Front. Nutr. 7:630951. doi: 10.3389/fnut.2020.630951

Background: Acute kidney injury (AKI) constitutes a multi-factorially caused condition, which significantly affects kidney function and can lead to elevated risk of morbidity and mortality. Given the rising scientific evidence regarding vitamin D's (VitD's) multisystemic role, the connection between AKI and VitD is currently being studied, and the complex relation between them has started to be unraveled.

Methods: A systematic review had been conducted to identify the pathogenetic relation of VitD and AKI and the potential role of VitD as a biomarker and therapeutic–renoprotective factor.

Results: From 792 articles, 74 articles were identified that fulfilled the inclusion criteria. Based on these articles, it has been found that not only can VitD disorders (VitD deficiency or toxicity) cause AKI but, also, AKI can lead to great disruption in the metabolism of VitD. Moreover, it has been found that VitD serves as a novel biomarker for prediction of the risk of developing AKI and for the prognosis of AKI's severity. Finally, animal models showed that VitD can both ameliorate AKI and prevent its onset, suggesting its renoprotective effect.

Conclusion: There is a complex two-way pathogenetic relation between VitD disorders and AKI, while, concomitantly, VitD serves as a potential novel predictive–prognostic biomarker and a treatment agent in AKI therapy.

Keywords: vitamin D, acute kidney injury, pathogenesis, biomarker, prediction, prognosis, therapeutic agent

INTRODUCTION

Acute kidney injury (AKI), acute kidney failure (AKF), or acute renal failure (ARF) is a multi-factorially caused condition, characterized by sudden and rapid loss of kidney function. Acute kidney injury results in further systemic disorders and is related to elevated morbidity and mortality (1). There are many different definitions for AKI, characterized by different biochemical, physiological, and clinical cutoff points. The most preponderant ones are based on serum creatinine (sCr), glomerular filtration rate (GFR), and urine output (UO). According to the Kidney Disease

Improving Global Guidelines (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury definition, there are three stages of AKI. Stage 1 includes one of the following: (a) 1.5–1.9 times baseline sCr, (b) $\geq$ 0.3 mg/dl increase of baseline sCr, or (c) <0.5 ml/kg/h UO for 6–12 h; Stage 2 includes one of the following: (a) 2–2.9 times baseline sCr or (b) <0.5 ml/kg/h for $\geq$12 h; and Stage 3 includes one of the following: (a) 3 times baseline sCr, (b) $\geq$ 4.0 mg/dl increase, (c) initiation of renal replacement therapy (RRT), (d) in patients <18 years old, a decrease of eGFR < 35 ml/min/1.73 m^2, (e) <0.3 ml/kg/h for >24 h, or (f) anuria $\geq$12 h (2).

The pathophysiology of AKI can be classified into: (1) prerenal azotemia (disruption of kidneys' blood inflow, without cellular or structural damage), (2) intrinsic or intrarenal AKI (direct damage to kidney's structure) due to acute tubular necrosis (ATN), vascular damage, and glomerular damage, (3) interstitial AKI (damage of the interstitial tissue), or (4) postrenal AKI (obstruction of urinary tract) (3). Moreover, AKI can be induced by septic shock, cardiogenic shock, pharmaceutical administration, hepatorenal syndrome, obstructive uropathy, and hypovolemia (4).

Due the necessity to specify the causes and the risk factors inducing AKI, many efforts have been made in order to identify sensitive, specific, and cost-efficient biomarkers, which may contribute to early detection and disease prognosis. In this regard, research has been also focused on the relation between AKI and vitamin D (VitD).

Apropos of VitD, it is an important part of the physiological function of various systems. VitD is, mainly, produced in the skin *via* UV radiation–induced transformation of 7-dehydroxycholesterol (7DHC) to cholecalciferol, which then undergoes consecutive hydroxylations in the liver and kidneys, accordingly, which leads to the synthesis of $1,25(OH)_2D$ (5, 6). However, 1,25(OH)2D can be synthesized into many extrarenal tissues, which possess the CYP27B1 enzyme, which is essential for the process (7). VitD's effects are classified into endocrine, paracrine, and autocrine, while the mechanism of action is both genomic [based on the action of VitD receptor (VDR) on VitD response elements (VDREs)] and non-genomic (8, 9). Briefly, VitD affects, significantly, calcium–phosphate homeostasis, leads to bone reabsorption, enhances muscular contraction and proliferation, intensifies myocardial contracture and lowers blood pressure *via* affecting the renin–angiotensin–aldosterone system (RAAS), enhances innate immunity and changes the cytokine and chemokine profile of acquired immunity from proinflammatory to anti-inflammatory, and protects against autoimmune response and cancer (10).

The aim of the present systematic review is to unravel the relationship between AKI and VitD in both patients and experimental models. We assumed that this is a two-way relationship, insinuating that on the one hand, VitD levels may play a role in AKI, and inversely, AKI induces changes in VitD levels. In this perspective, we examined whether hypo- or hypervitaminosis causes AKI and, inversely, whether AKI causes hypo- or hypervitaminosis. It was actually pointless to search for active comparators. Moreover, we examined possible implications of VitD as a predictive and prognostic marker for AKI, as well as its role in AKI treatment.

METHODS

In May 2020, a bibliographic search was conducted in PubMed, Scopus, and Embase regarding the relation between VitD and AKI. The terms employed were "vitamin D AND AKI," "vitamin D AND ARF," and "vitamin D AND acute kidney injury." Additionally, a manual search of the reference lists of other studies had been conducted, to detect subsequent material that could be included in this systemic review.

Then, the articles were screened, based on:

1. Removing duplicates
2. Relativity to the subject
3. Date of publication
4. Validity of methods and conclusions

Articles that did not meet the above criteria were excluded.

RESULTS

There were 756 articles identified in the three databases. Moreover, 36 articles have been included from screening the reference lists of the articles. After the exclusion of 336 duplicates and 340 irrelevant studies, the remaining 117 articles were analyzed based on the eligibility for full access and the inclusion criteria. Finally, 74 articles matched our search criteria (**Figure 1**).

These articles reveal a two-way relation between VitD and AKI. Acute kidney injury can, *via* various mechanisms, lead to either D hypo- or hypervitaminosis. Moreover, both VitD deficiency and VitD toxicity can lead to the development of AKI.

Given the fact that our knowledge concerning the relationship between VitD and AKI comes from small series, cases, and experimental models, extrapolation of our results to the general population may be risky and biased. Moreover, introducing VitD in the treatment of AKI is also questionable on a clinical basis since there are no prospective randomized trials available and our knowledge is a result of animal experiments. Finally, more clinical data are available on the use of VitD levels as biomarkers concerning both the prediction and the prognosis of AKI. However, despite the fact that there are nine clinical studies on this matter, those studies are observational (either prospective or retrospective), and no data coming from randomized controlled trials are available.

DISCUSSION

The Development of AKI Is Associated With VitD Disorders

Acute kidney injury is the significant depletion of renal function, affecting the normal renal enzymatic activity, and consequently disrupts VitD. Usually, the decreased kidney function causes VitD deficiency, but in some cases, VitD toxicity is also observed (**Table 1**).

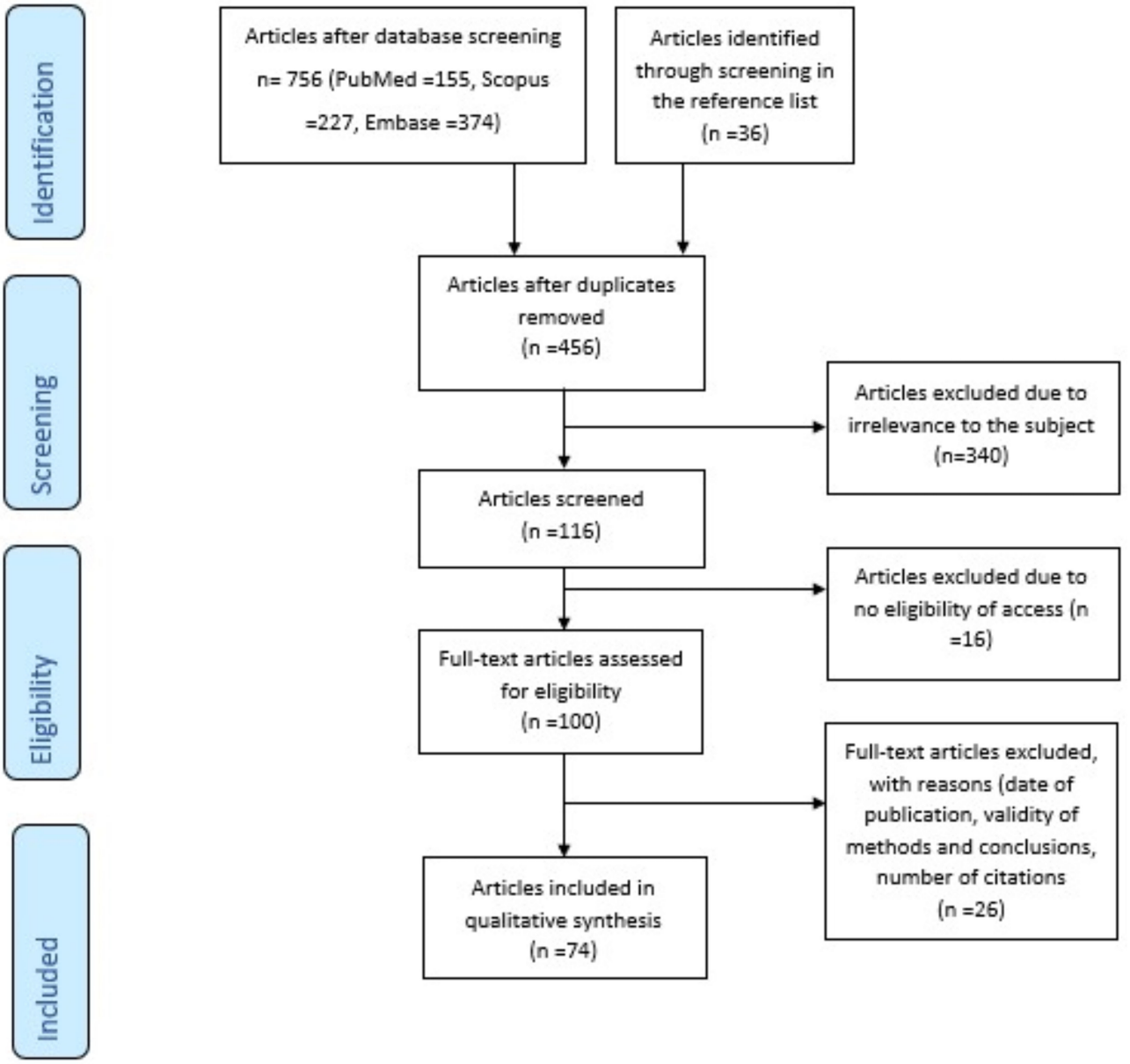

FIGURE 1 | Prisma flow diagram of the systematic review's methodology: This figure clearly depicts the methodology of the identification, screening, and exclusion of articles, in order to reach the final number ($n = 74$) of articles that are relevant to the topic and fulfill the inclusion criteria.

The progressive depletion of renal function during AKI leads to retention and accumulation of phosphate, due to the inability to excrete it. Phosphate acts as a negative regulator of 1-hydroxylase, an enzyme of $1,25(OH)_2D$ synthesis, and therefore negatively contributes to VitD metabolism (11, 12). Moreover, as the final hydroxylation takes place in the kidney's active unit, the gradual loss of active nephrons leads to reduced ability of VitD synthesis (11) and to diminution of calcium's intestinal absorption. However, calcium's concentration depletion contributes to an increase of the parathyroid hormone (PTH). Due to secondary hyperparathyroidism and induction of CYP27B1, the levels of VitD can also be elevated (6, 11).

Fibroblast growth factor-23 (FGF-23), a phosphaturic factor, induces phosphaturia *via* acting on FGF-receptor (FGFR)/Klotho coreceptor complex, by (1) downregulating the luminal sodium/phosphate cotransporter in the proximal convoluted tubules, (2) suppressing kidneys' 1-hydroxylase, and (3) inducing 24-hydroxylase, which catalyzes the first step of VitD catabolism, causing hypophosphatemia and significantly lower levels of active VitD (13, 14). The soluble Klotho (sKl) can also regulate calcium and phosphate metabolism *via* an FGF-23–independent mechanism affecting the renal outer medullary potassium (ROMK) channel and the transient receptor potential vanilloid-5 (TRPV5). Moreover, sKl has a renoprotective effect

TABLE 1 | AKI as a cause of vitamin D (VitD) disruptions: AKI leads to the development of either hypovitaminosis D or hypervitaminosis D through various mechanisms.

Condition	Mechanism	Citation
Hypovitaminosis D	Retention and accumulation of phosphate.	(11, 12)
	Depletion of active nephrons, where the second hydroxylation occurs.	(11)
	Klotho deficiency leads to secondary increase of FGF-23 and deterioration of AKI.	(13, 14)
	Increase of FGF-23.	(13, 15)
Hypervitaminosis D	Due to calcium's diminution, the secondary hyperparathyroidism leads to induction of CYP27B1.	(6, 11)
	Rhabdomyolysis-induced mechanism.	(16)

This table presents the mechanisms via which AKI can lead to either VitD deficiency or VitD toxicity. FGF-23, fibroblast growth factor-23; AKI, acute kidney injury; CYP27B1, cytochrome P450 family 27 subfamily B member 1 or 1α-hydroxylase.

via (1) the transforming growth factor-β1 (TGF-β1)–dependent anti-fibrotic mechanism and (2) the tumor necrosis factor (TNF)/nuclear factor-κB (NFκB)–dependent anti-inflammatory mechanism (14).

VitD deficiency can be caused by increased expression of FGF-23, which has been observed in AKI cases. Leaf et al. presented a case of a 45-year-old male hospitalized due to rhabdomyolysis and with a history of polysubstance abuse. The concurrent AKI was accompanied by elevated levels of FGF-23 and slightly decreased levels of 25(OH)D and $1,25(OH)_2D$ (15). Additionally, FGF-23 can be secondarily elevated due to Klotho deficiency, which is prevalent, mostly, in chronic kidney disease (CKD) but also has been observed in AKI (13). Klotho's deficiency affects VitD levels, not only by upregulating FGF-23 but also through increasing the extent of AKI, due to depleted renoprotection, and leading, consequently, to greater VitD deficiency (14).

Moreover, Akmal et al. presented a study with patients suffering from rhabdomyolysis and AKI. The patients were initially hypocalcemic. However, during the diuretic phase, an elevation of 25(OH)D and $1,25(OH)_2D$ was observed, which was greater in patients who developed hypercalcemia (16). These results suggest that the elevation of serum $1,25(OH)_2D$ plays an important role in the development of hypercalcemia and that this increase may be due to extrarenal production or/and dysregulated renal production.

VitD Deficiency Induces AKI

VitD depletion, VDR knock-out, or disruption of VitD synthesis contributes to AKI development (**Table 2**) by leading to upregulation of RAAS and to elevated mRNA expression of renal-vascular renin. Due to obstruction and increased levels of extracellular matrix proteins (such as collagen I and fibronectin) and proinflammatory and profibrogenic factors [such as TGF-β, connective tissue growth factor, and monocyte chemoattractant protein-1 (MCP-1)], the renal injury becomes more severe. Moreover, epithelial-to-mesenchymal transition (EMT) was observed (17). Upon angiotensin I antagonist administration, there was no difference between wild and $VDR^{-/-}$ mice, suggesting that angiotensin II is responsible for the increased renal damage. Contrarily, when VDR agonists were administrated, proteinuria, podocytes' damage, mesangial dilation, macrophage infiltration, oxidative stress damage, proinflammatory and profibrogenic factors, and extracellular matrix protein and neutral lipid accumulation were reduced, proposing that VDR depletion worsens renal injury (17, 18).

Moreover, VitD deficiency can exacerbate pre-existing AKI [ischemia/reperfusion injury (IRI) induced AKI] by deteriorating the renal vascular condition and it can accelerate the AKI-to-CKD progression, *via* both an increased TGF-β1 signaling and a decreased VDR and Klotho (19–21).

Buttar et al. presented a case of an 86-year-old woman with mild chronic disease and decreased levels of 25(OH)D, who developed rhabdomyolysis and secondary AKI after sitagliptin administration. The patient was on chronic atorvastatin therapy, and a possible interaction between these two drugs is proposed (22).

VitD as a Predictive and Prognostic Biomarker

In current clinical practice, most assays estimate total 25(OH)D, which cannot distinguish the three different forms of 25(OH)D [VitD binding protein (VDBP)–bound 25(OH)D, albumin-bound 25(OH)D, and free 25(OH)D]. This approach has many limitations since there are many variables that are influenced by physiologic and pathophysiologic conditions. The VDBP's affinity is affected by both hyperlipemic conditions and the three common variants of VDBP's gene, GC1F (group-specific component-1f), GC1S, and GC2 (23). Many efforts were made at inventing new assays that can directly, validly, efficiently, affordably, and quickly estimate free 25(OH)D, rather than calculating it using already-existing multi-factorial formulas. Free 25(OH)D measurement is considered to have more benefits than total 25(OH)D. So far, the studies have only proved the benefits of free 25(OH)D (1) in cases with differences in VDBP affinity, (2) in the elderly, (3) in pregnancy to detect VitD deficiency, (4) in liver diseases, (5) in kidney disorders (AKI, CKD), (6) in acromegaly, and (7) in allergies associated with atopy and pulmonary function in asthmatic children (23, 24). However, in many studies, no significant superiority of free 25(OH)D was observed. Still, there were many limitations in some of the studies, due to sample size and due to the use of monoclonal VDBP kits in multiracial/non-Caucasian populations, which affected the outcome (23, 24).

Regarding the predictive and prognostic role of VitD and its metabolites, mostly 25(OH)D but, also, $1,25(OH)_2D$ can act as novel biomarkers of AKI (**Supplementary Table 1**).

Braun et al. found that 25(OH)D could serve as an independent predictor of AKI since serum 25(OH)D deficiency (<15 ng/ml) and insufficiency (15–30 ng/ml) are associated with greater risk of AKI. Moreover, serum 25(OH)D can also act as independent prognostic biomarker of 30-day mortality since its deficiency and insufficiency are linked to elevated risk of 30-day death (25).

TABLE 2 | VitD deficiency induces AKI through various mechanisms.

Condition	Type of model	Mechanism	Citation
VitD deficiency	Wild-type and $VDR^{-/-}$ mice	Upregulation of RAAS *via* lack of obstruction of angiotensin II receptor and mineral-corticoid receptor	(17)
	Diet-induced obesity mice	Elevation of extracellular matrix proteins and of profibrogenic and proinflammatory factors	(18)
	Wistar rats	Deterioration of already-existing renal vascular damage (ischemia/reperfusion injury induced AKI), which leads to accelerated AKI-to-CKD progression *via* increased TGF-β1 signaling and *via* decreased VDR and Klotho expression	(19–21)
	Human case	In rhabdomyolysis-induced AKI, simultaneous administration of atorvastatin and sitagliptin	(22)

This table presents the mechanism through which VitD deficiency can lead to the development of AKI. RAAS, renin–angiotensin–aldosterone system; CKD, chronic kidney disease; TGF-β1, tumor growth factor-β1; VDR, VitD receptor.

Similarly, Zapatero et al. showed that serum 25(OH)D can act as a predictor of AKI, given that patients with serum 25(OH)D < 10.9 ng/ml had greater risk of AKI than VitD-sufficient patients. Moreover, lower levels of serum 25(OH)D were more common in non-survivor patients, and serum 25(OH)D acted as a prognostic biomarker of mortality (best cutoff value = 10.9 ng/ml) (26).

Leaf et al. found by using a two-multivariable-adjustment model that bioavailable 25(OH)D could serve as an independent prognostic biomarker of sepsis severity ($r = -0.45$) and mortality, while 25(OH)D can only correlate with sepsis severity ($r = -0.42$). Also, VDBP, $1,25(OH)_2D$, and FGF-23 are predictive biomarkers of AKI, while FGF-23 served as biomarker of sepsis severity too ($r = 0.35$) (27).

Sahin et al. found that VitD acts as an independent predictive biomarker of contrast-induced nephropathy (CIN)–AKI, even in multivariable models (28).

Chaykovska et al. found that neither urinary VDBP (uVDBP) nor uVDBP/sCr could predict AKI development, but they served as biomarkers of need-of-dialysis, mortality, major adverse renal events (MAREs) (only uVDBP), and non-elective hospitalization. After adjustments, the predictive value of uVDBP was confirmed and was independent of well-known CIN risk factors, such as anemia, already-existing kidney injury, heart failure, and diabetes (29).

Vicente-Vicente et al. found that uVDBP can, potentially, predict the risk of gentamicin-induced AKI, in order to prevent its manifestation, given that increased uVDBP is associated with chronic proclivity to gentamicin nephrotoxicity (30).

Rebholz et al. found that VDBP, free 25(OH)D, bioavailable 25(OH)D, total 25(OH)D, and $1,25(OH)_2D$ (it is the only dependent biomarker) act as independent biomarkers of development of the ESRD stage, even after various multivariable models of adjustments (31).

Lai et al. studied the predictive and prognostic value of $1,25(OH)_2D$, 25(OH)D, and $[1,25(OH)_2D/25(OH)D] \times 1,000$ ratio. As for the prediction of AKI, only $1,25(OH)_2D$ and $[1,25(OH)_2D/25(OH)D] \times 1,000$ ratio were significant, while as for the prognosis, these two biomarkers had been negatively correlated with AKI stage stratification (Risk, Injury, Failure). None of the markers could predict mortality, while 25(OH)D showed neither predictive nor prognostic effect (32).

Leaf et al. studied the prognostic value of human cathelicidin antimicrobial protein-18 (hCAP-18), free 25(OH)D and bioavailable 25(OH)D, and the predictive value of hCAP-18. As for the prognosis, hCAP-18 measured on ICU day 1 is an independent biomarker of sepsis and 90-day mortality, as had been found *via* univariate and multivariate models of adjustments. However, hCAP-18 showed no significant predictive effect regarding AKI. As for the prognostic value of free and bioavailable 25(OH)D, only the former acted as a biomarker of 90-day mortality, while the latter showed no significant prognostic value (33).

Vitamin D in the Treatment of AKI

Many studies have been performed mainly with rats to define the potential use of VitD as treatment for AKI (**Supplementary Table 2**).

A dominant cause of AKI is IRI, induced by the actuation of inflammation and the increased expression of matrix metalloproteinases (MMPs). Ersan et al. studied the effect of paricalcitol on MMPs expression and, subsequently, on IRI progress. Pre-treatment with paricalcitol resulted in amelioration of IRI-AKI *via* an MMP-dependent inflammatory mechanism (34).

Hamzawy et al. studied the effect of pre-treatment with 22-oxacalcitriol (OCT) on IRI-AKI and found that it can ameliorate AKI through: (1) an anti-inflammatory mechanism *via* inhibition of Toll-like receptor-4 (TLR-4) and interferon-γ (IFN-γ), (2) a reduction of Na^+/H^+ exchanger-1 (NHE-1 exchanger), (3) a pro-autophagic action *via* elevating Beclin-1 expression and LC3II/LC3I ratio, (4) an anti-apoptotic action *via* elevating Bax/Bcl-2, cytochrome c and caspase-3 expression, and (5) an inhibitory action on G1 cell cycle arrest *via* reducing insulin-like growth factor-binding protein-7 (IGFBP-7) and tissue inhibitor of matrix metalloproteinases-2 (TIMP-2) expression (35).

In another study, Kapil et al. also investigated the protective role of VitD pre-treatment in IRI-AKI and showed a renoprotective effect in IRI against oxidation and lipid peroxidation mediated by peroxisome proliferator–activated receptor-γ (PPAR-γ)- (36).

Additionally, Arfian et al. studied the impact of VitD on IRI-AKI and found that its administration can mitigate AKI through reducing the inflammation and the production of myofibroblasts, *via* reducing the expression TLR-4 and MCP-1 (37).

Also, Silva Barbosa studied the effect of estrogen sulfotransferase (SULT1E1) inhibition on IRI-AKI and found

that this inhibition attenuates AKI *via* elevating the VDR activation, as shown by the elevated Cyp24α1 and Ccnd1 and by the decreased Fgg expression (38). This effect has been found to be estrogen- and androgen-independent (38). Additionally, only in male mice, the liver expression of Sult1e1 has been found to be necessary for IRI-AKI development, thus proposing a tissue- and sex-specific relation between the expression of Sult1e1 and sensitivity to IRI-AKI (38).

Moreover, Lee et al. examined the effect of paracalcitol on IRI and demonstrated that it can attenuate AKI *via* an anti-inflammatory mechanism mediated by the inhibition of TLR-4 expression and the suppression of NFκB signaling, by increasing IκB in a TNF-α-dependent way (39).

Xu et al. studied the effect of pre-treatment with VitD on liposaccharide (LPS)-induced AKI and found that it can attenuate AKI through: (1) an anti-oxidative mechanism *via* increasing glutathione (GSH), superoxide dismutase (SOD)-1, and SOD-2 and *via* decreasing nitric oxide synthase (iNOS), p47phox, and gp91phox (subunits of renal NADPH oxidase) and (2) an anti-apoptotic mechanism (40).

Du et al. studied the effect of paracalcitol on LPS-AKI and found that its administration ameliorates AKI through: (1) an anti-inflammatory mechanism *via* reduction of TLR-4 and (2) an anti-apoptotic mechanism *via* elevation of Bcl-2 (it is anti-apoptotic) and *via* decrease of caspase-3, PUMA (it is a pro-apoptotic member of the Bcl-2 family), and miR-155 (it targets Bcl-2 and blocks its expression) (41). Regarding the decrease of PUMA and miR-155, it has been found that this is due to the VitD-dependent inhibition of NFκB expression by disrupting the IKK kinase complex or by blocking the p65/p50 nuclear translocation (41).

Park et al. investigated the impact of paricalcitol on cisplatin-induced AKI and found that it ameliorated AKI through: (1) inhibiting EMT, (2) reducing apoptosis *via* increasing Bcl-2 and *via* decreasing P-p53 and p21, p-Bad, Bax, and caspase-3 expression, and (3) increasing the cell proliferation *via* elevating the expression of $p27^{kip1}$ and decreasing that of cyclin-dependent kinase-2 (CDK2) and Cyclin E. The underlying mechanism of these actions includes the inhibition of TGF-β1 and p53 signaling pathways and the elevation of the $p27^{kip1}$ signaling pathway (42).

Another study on the effect of paricalcitol on cisplatin-induced AKI demonstrated that the ameliorated AKI was correlated with reduced lipid peroxidation and ferroptotic cell death due to the direct binding of VDR to the glutathione peroxidase 4 (GPX4) promoter, which induces the expression of GPX4, affecting the induction of ferroptosis (43).

Also, Moneim et al. studied the impact of alfacalcidol and BQ-123, a selective endothelin receptor A blocker (ET_AR blocker), on cisplatin-induced AKI. Their administration led to attenuation of AKI *via* a VDR-, ET-1-, and ET_AR-dependent mechanism, which includes the signaling cascade of Pnf-κBp65, TNF-α, and TGF-β1. The combined administration of both drugs led to an enhanced therapeutic effect. These results propose a merger of VitD and endothelin-1 signaling pathways, which is promising as a therapeutic option for cisplatin-induced AKI (44).

In another study, administration of $1,25(OH)_2D_3$ on gentamicin-induced AKI had no beneficial effect on ameliorating AKI (45). However, there was a decrease of the systolic blood pressure, to some extent, and an increase of the urine volume, probably due to its inhibitory role in RAAS. Also, VitD acted as an antioxidant factor by increasing GSH (45). So, VitD may be a promising therapeutic agent due to its RAAS- and GSH-related action.

Additionally, El-Boshy et al. studied the role of VitD in paracetamol-induced AKI and liver failure. They found that both the therapeutic and the prophylactic use of VitD can ameliorate AKI and liver failure through: (1) an anti-apoptotic mechanism *via* reducing caspase-3 and (2) a decrease of Cyp24α1 and VDBP expression and an increase of Cyp27b1, Cyp2R1, and VDR expression, (3) an anti-oxidative and anti-inflammatory mechanism *via* decreasing IL1-β, IL1R1 (IL-1 receptor 1), IL-6, IL6R (IL-6 receptor), IFN-γ, IFNGR1 (IFN-γ receptor 1), IL17A, and IL17RA (IL-17 receptor A) and *via* elevating GSH, chloramphenicol acetyltransferase (CAT), Gpx, IL10 (and its gene), IL22, and IL22RA (IL-22 receptor A) (46). The effect of the prophylactic use of VitD has been found to be greater than that of its use for treatment (46).

In another study, the administration of 500 and 1,000 IU/kg VitD can ameliorate AKI and liver failure induced by paracetamol. Interestingly, the dose of 500 IU/kg presented a greater protective role (47). The underlying mechanism includes: (1) an anti-oxidative action *via* the reduction of the expression of heme oxygenase 1 (HO-1) and its regulators, NrF2 and BACH1, and (2) an anti-inflammatory action *via* the reduction of NFκB, TNF-α, and IL-10 (47).

Finally, Reis et al. studied the impact of calcitriol on rhabdomyolysis-induced AKI and found that AKI was ameliorated through: (1) an anti-inflammatory mechanism *via* decreasing NFκB and Jun N-terminal kinase (p-JNK), MCP-1, and IL-1β, (2) an anti-oxidative mechanism *via* elevating SOD and *via* decreasing 8-epi-PGF2α and nitrotyrosine, (3) reducing vimentin, proliferating cell nuclear antigen (PCNA), and caspase-3, and (4) elevating CYP24 (48).

Vitamin D Toxicity Induced AKI

Although VitD seems to ameliorate AKI, its administration should be performed with extreme caution. Hypervitaminosis D can significantly afflict kidney function by inducing hypercalcemia and hyperphosphatemia. Specifically, hypercalcemia leads to the development of nephrogenic diabetes insipidus, which affects water homeostasis by causing polyuria and diuresis. Therefore, there is evident loss of water, leading to hypovolemia, which causes AKI and concomitantly deteriorates the hypercalcemia. So, there is a continuous circle of hypercalcemia causing hypovolemia-induced AKI and vice versa (49–51). Moreover, hypercalcemia and hypercalciuria can lead to deposition of calcium, thus causing nephrolithiasis and renal calcification, which can cause the development of AKI (49–51). Also, hypercalcemia can cause renal vasoconstriction, which subsequently leads to severe GFR decrease and AKI (49–51). As for the hyperphosphatemia, it can cause acute phosphate nephropathy due to the tubulointerstitial deposition of phosphate calcium, a condition that concomitantly worsens the already-existing hyperphosphatemia, thus leading to a

vicious circle of deterioration (49–51). As for the acute phosphate nephropathy, it can also be due to significant phosphate intake and the subsequent diarrhea-induced hypovolemia (52). Specifically, the hypovolemia leads to great reabsorption of water and sodium chloride in the proximal tubule and the descending limb of Henle's loop, while calcium and phosphate are not that easily reabsorbed (52). As a result, the greater concentration of these substances in the distal tubule and the collecting duct leads to significant deposition of calcium phosphate in these structures, a deposition that is exacerbated due to surface expression of hyaluronan and osteopontin as a result of hypovolemia-induced tubular injury (52). Among risk factors for the development of acute phosphate nephropathy are: advanced age, hypertension, CKD, drugs (such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and loop- or thiazide-type diuretics), female gender, diabetes mellitus, and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (52). As for the treatment of acute phosphate nephropathy, kidney replacement therapy (KRT) can be used to tackle this condition, and particularly, sustained low efficiency dialysis (SLED) has gained ground in treatment, given that it is a hybrid technique, which combines the advantages of both intermittent and continuous KRT (53).

VitD-mediated hypercalcemia can be due to: (1) excessive $VitD_2$ or D_3 ingestion/supplementation, (2) extravagant calcitriol ingestion or pharmaceutical administration, (3) elevated ectopic production of calcitriol (evident in granulomatous diseases, such as tuberculosis, sarcoidosis, leprosy, fungal infections, and others; in Hodgkin's and non-Hodgkin's lymphomas; in malignant lymphoproliferative diseases), (4) milk-alkali syndrome (MAS), and (5) depleted catabolism of calcitriol due to mutations of CYP24A1 genes (54).

VitD toxicity due to immoderate administration of VitD supplements or overfortified milk is a global phenomenon (55), potentially affecting kidney function. Chowdry et al. presented a study of VitD toxicity incidents in a tertiary care center at the Sher-i-Kashmir Institute of Medical Sciences, in which 16 out of 19 patients where identified with hypervitaminosis D–induced AKI due to extravagant doses of VitD (median cumulative dose of VitD is 6,000,000 IU), in order to correct VitD deficiency. Not all the patients with toxic levels of 25(OH)D (>150 ng/ml) developed symptoms (56). Similarly, 13 patients in Brazil developed AKI due to intramuscular injection of veterinary supplements of vitamins A, D, and E for esthetic purposes (57).

Also, VitD toxicity–induced AKI has been observed due to anabolic steroid and VitD supplement abuse (58), dispensing errors (59), dosage malpractice and overcorrection of VitD deficiency (60), intramuscular injection of VitD after operation (61), overfortification of milk with VitD (62), over-the-counter supplements (63), and topical treatment with calcitriol analog in combination with oral calcium/VitD for psoriasis (64).

Additionally, in another study, 33 patients with osteoporosis treated with 0.75 μg/day eldecalcitol developed hypercalcemia-induced AKI since the discontinuation of eldecalcitol ameliorated the situation (65). Furthermore, 11 patients developed with hypercalcemia-induced AKI, due to alfacalcidol (9 patients) or calcitriol (2 patients) (65).

TABLE 3 | Cases of hypervitaminosis D as cause of AKI.

References	Article type	Sample size	Substance	Concentration
Chowdry et al. (56)	Case series	19 patients	25(OH)D	371 (190–988) ng/ml
Daher et al. (57)	Case series	16 patients	Vitamin D	135 ± 75 ng/ml
Daher et al. (58)	Case series	2 patients	Vitamin D	N/A
Nasri et al. (59)	Case	1 patient	Vitamin D	>400 nmol/L
Kaur et al. (60)	Case series	16 patients	Serum 25(OH)D	371 (175–1,161) ng/ml
Bansal et al. (61)	Case	1 patient	Serum 25(OH)D	150 ng/ml
Jacobus et al. (62)	Case series	8 patients	Serum 25(OH)D	293 ± 174 ng/ml
Koutkia et al. (63)	Case	1 patient	Serum 25(OH)D	487.3 ng/ml
Corden et al. (64)	Case	1 patient	Vitamin D	N/A
Aihara et al. (65)	Case series	43 patients	Eldecalcitol (32 patients) Alfacalcidol (9 patients) Calcitriol (2 patients)	N/A
Tollit et al. (66)	Case	1 patient	Vitamin D	N/A
Lavender et al. (69)	Case	1 patient	$1,25(OH)2D_3$	318 pmol/L
Karmali et al. (70)	Case	1 patient	$1,25(OH)2D_3$	145 pg/ml
Altun et al. (71)	Case	1 patient	Calcitriol	N/A
Jeong et al. (72)	Case	1 patient	Calcitriol	N/A
Asghar et al. (73)	Case	1 patient	Vitamin D	119 ng/ml
Tsao et al. (74)	Case	1 patient	$1,25(OH)2D_3$	268 pmol/L

This table presents the different studies that have been done regarding vitamin D toxicity as a cause of AKI. It depicts information regarding the type of study conducted, the sample size, the vitamin D–related substance that has been calculated, and the concentration of this substance.

Moreover, VitD toxicity–induced AKI is related with granulomatous diseases (especially sarcoidosis), MAS, subclinical hyperparathyroidism, and immune reconstitution syndrome.

Tollitt and Solomon presented a case of a 38-year-old male and two other patients with a history of sarcoidosis. After treatment with high doses of cholecalciferol, the patient developed different symptoms of hypercalcemia, such as vomiting, nausea, muscle cramps, and constipation, and subsequent AKI (66). In these cases, the hypercalcemia is due to the extrarenal synthesis of $1,25(OH)_2D$ by macrophages within the sarcoid granulomas, the process of which is without systemic regulation (67, 68). The sufficient administration of prednisolone inhibits macrophages' 1-α hydroxylase activity and protects against hypercalcemia (66). A similar relation between VitD administration and VitD-induced hypercalcemia has been observed in tuberculosis and Hodgkin's lymphomas (69, 70).

MAS is a result of VitD, calcium carbonate, and bisphosphonate administration for osteoporosis, iatrogenic hypothyroidism, and idiopathic hypothyroidism treatment. Although there is limited knowledge regarding its pathophysiology, it affects patients who absorb more calcium than average. Among the risk factors are old age, medication that reduces GFR, and hypovolemia. MAS consists of hypercalcemia, metabolic alkalosis, and renal function disruption, and, particularly, hypercalcemia leads to AKI *via* renal vasoconstriction, polyuria, and GFR depletion (71, 72).

Asghar et al. presented a case of a 55-year-old female who had slightly elevated calcium and was found to be VitD-deficient. The prescription of VitD led later to the development of a giant cystic parathyroid adenoma and to manifestation of parathyroid crisis, accompanied by severe gastrointestinal symptoms and AKI. This suggests that VitD administration can unveil subclinical hyperparathyroidism (73).

Finally, Tsao et al. described a case of immune reconstitution inflammatory syndrome (IRIS) due to *Mycobacterium tuberculosis* lymphadenitis. It was manifested in a patient with history of silent human immunodeficiency virus-1 (HIV-1) infection, who was in highly active antiretroviral therapy (HAART) because of plasma viral load increase. This 48-year-old male patient, after the initiation of HAART, developed various hypercalcemia symptoms, accompanied by hypervitaminosis D [$1,25(OH)_2D_3$, 268 pmol/L], which progressed to coma and AKI. IRIS can be due to many opportunistic infections, but the most common infection is *M. tuberculosis*, which is incriminated as the cause of VitD-induced hypercalcemia, which leads to AKI (74). All cases of hypervitaminosis D–induced AKI are summarized in **Table 3**.

CONCLUSION

It can be concluded that there is a two-way relation between AKI and VitD. Specifically, disruptions of VitD—both hypovitaminosis and hypervitaminosis—can lead to the development of AKI, while also, AKI can contribute to dysregulation of VitD's homeostasis and function.

On this ground, due to this two-way causality relation, VitD is examined on whether its forms can act as a novel biomarker of AKI. Many studies have confirmed VitD's significant role as a predictive (it can help to determine the risk of developing AKI) and prognostic (it can help determine the stage, progress, clinical outcomes, and mortality risk of AKI) biomarker.

Finally, VitD is found to be a potentially important therapeutic factor for AKI due to its multisystemic functions, which include regulation of many enzymic mechanisms *via* genomic and non-genomic actions.

However, many prospective studies and trials need to be conducted, in order to: (1) fully determine the complex relation between VitD and AKI, (2) find the best cutoff points with the most significant statistic importance, and (3) determine the therapeutic protocols of VitD as treatment of AKI and its potential adverse effects.

Despite the necessity of future studies, VitD is a very promising biomarker and a potential treatment for AKI, which is one the most prominent health problems nowadays.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MP and TP: conceptualization and supervision. SG and MP: data curation and investigation. SG: formal analysis and writing—original draft. All authors methodology and writing—review and editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2020.630951/full#supplementary-material

REFERENCES

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Workgroup A. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. (2004) 8:R204–12. doi: 10.1186/cc2872
2. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. (2012) 120:c179–84. doi: 10.1159/000339789
3. Greenberg A, Cheung AK, Coffman TM, Falk RJ, Jennette JC. Clinical approach to the diagnosis of acute kidney injury. In: Greenberg A, editors. *Primer on Kidney Diseases*. Philadelphia, PA: Elsevier . p. 393–402.

4. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. (2005) 294:813–8. doi: 10.1001/jama.294.7.813
5. Chen TC, Lu Z, Holick MF. Photobiology of vitamin D. In: Holick MF, editor. *Vitamin D*. Totowa, NJ: Humana Press (2010). p. 35–60.
6. Schuster I. Cytochromes P450 are essential players in the vitamin D signaling system. *Biochim Biophys Acta Proteins Proteomics*. (2011) 1814:186–99. doi: 10.1016/j.bbapap.2010.06.022
7. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, et al. Extrarenal expression of 25-hydroxyvitamin D 3−1α-hydroxylase 1. *J Clin Endocrinol Metab*. (2001) 86:888–94. doi: 10.1210/jcem.86.2.7220
8. Prentice A, Goldberg GR, Schoenmakers I. Vitamin D across the lifecycle: physiology and biomarkers. *Am J Clin Nutr*. (2008) 88:500S−6S. doi: 10.1093/ajcn/88.2.500S
9. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *Am J Clin Nutr*. (2008) 88:491S−9S. doi: 10.1093/ajcn/88.2.491S
10. Battault S, Whiting SJ, Peltier SL, Sadrin S, Gerber G, Maixent JM. Vitamin D metabolism, functions and needs: from science to health claims. *Eur J Nutr*. (2013) 52:429–41. doi: 10.1007/s00394-012-0430-5
11. Audran M, Kumar R. The physiology and pathophysiology of vitamin D. *Mayo Clin Proc*. (1985) 60:851–66. doi: 10.1016/S0025-6196(12)64791-0
12. Omdahl JL, Morris HA, May BK. Hydroxylase enzymes of the vitamin D pathway: expression, function, and regulation. *Annu Rev Nutr*. (2002) 22:139–66. doi: 10.1146/annurev.nutr.22.120501.150216
13. Wolf M. Forging forward with 10 burning questions on FGF23 in kidney disease. *J Am Soc Nephrol*. (2010) 21:1427–35. doi: 10.1681/ASN.2009121293
14. Tan S-J, Smith ER, Hewitson TD, Holt SG, Toussaint ND. The importance of klotho in phosphate metabolism and kidney disease. *Nephrology*. (2014) 19:439–49. doi: 10.1111/nep.12268
15. Leaf DE, Wolf M, Stern L. Elevated FGF-23 in a patient with rhabdomyolysis-induced acute kidney injury. *Nephrol Dial Transplant*. (2010) 25:1335–7. doi: 10.1093/ndt/gfp682
16. Akmal M, Bishop JE, Telfer N, Norman AW, Massry SG. Hypocalcemia and hypercalcemia in patients with rhabdomyolysis with and without acute renal failure. *J Clin Endocrinol Metab*. (1986) 63:137–42. doi: 10.1210/jcem-63-1-137
17. Zhang Y, Kong J, Deb DK, Chang A, Li YC. Vitamin D receptor attenuates renal fibrosis by suppressing the renin-angiotensin system. *J Am Soc Nephrol*. (2010) 21:966–73. doi: 10.1681/ASN.2009080872
18. Wang XX, Jiang T, Shen Y, Santamaria H, Solis N, Arbeeny C, et al. Vitamin D receptor agonist doxercalciferol modulates dietary fat-induced renal disease and renal lipid metabolism. *Am J Physiol Physiol*. (2011) 300:F801–10. doi: 10.1152/ajprenal.00338.2010
19. de Bragança AC, Volpini RA, Mehrotra P, Andrade L, Basile DP. Vitamin D deficiency contributes to vascular damage in sustained ischemic acute kidney injury. *Physiol Rep*. (2016) 4:e12829. doi: 10.14814/phy2.12829
20. de Bragança AC, Volpini RA, Canale D, Gonçalves JG, Shimizu MHM, Sanches TR, et al. Vitamin D deficiency aggravates ischemic acute kidney injury in rats. *Physiol Rep*. (2015) 3:e12331. doi: 10.14814/phy2.12331
21. Gonçalves JG, de Bragança AC, Canale D, Shimizu MHM, Sanches TR, Moysés RMA, et al. Vitamin D deficiency aggravates chronic kidney disease progression after ischemic acute kidney injury. *PLoS ONE*. (2014) 9:e107228. doi: 10.1371/journal.pone.0107228
22. Buttar RS, Batra J, Kreimerman J, Aleta M, Melamed ML. Rhabdomyolysis and AKI with atorvastatin and sitagliptin use in the setting of low 25-hydroxyvitamin D levels. *J Gen Intern Med*. (2017) 32:1156–9. doi: 10.1007/s11606-017-4115-x
23. Tsuprykov O, Chen X, Hocher C-F, Skoblo R, Lianghong Yin, Hocher B. Why should we measure free 25(OH) vitamin D? *J Steroid Biochem Mol Biol*. (2018) 180:87–104. doi: 10.1016/j.jsbmb.2017.11.014
24. Bikle D, Thadhani R, Schoenmakers I. Vitamin D metabolites in captivity? Should we measure free or total 25(OH)D to assess vitamin D status? *J Steroid Biochem Mol Biol*. (2017) 173:105–16. doi: 10.1016/j.jsbmb.2017.01.007
25. Braun AB, Litonjua AA, Moromizato T, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill. *Crit Care Med*. (2012) 40:3170–9. doi: 10.1097/CCM.0b013e318260c928
26. Zapatero A, Dot I, Diaz Y, Gracia MP, Pérez-Terán P, Climent C, et al. La hipovitaminosis D grave al ingreso en el paciente crítico se asocia a fracaso renal agudo y mal pronóstico. *Med Intensiva*. (2018) 42:216–24. doi: 10.1016/j.medin.2017.07.004
27. Leaf DE, Waikar SS, Wolf M, Cremers S, Bhan I, Stern L. Dysregulated mineral metabolism in patients with acute kidney injury and risk of adverse outcomes. *Clin Endocrinol (Oxf)*. (2013) 79:491–8. doi: 10.1111/cen.12172
28. Sahin I, Gungor B, Can MM, Avci II, Guler GB, Okuyan E, et al. Lower blood vitamin D levels are associated with an increased incidence of contrast-induced nephropathy in patients undergoing coronary angiography. *Can J Cardiol*. (2014) 30:428–33. doi: 10.1016/j.cjca.2013.12.029
29. Chaykovska L, Heunisch F, Von Einem G, Alter ML, Hocher C-F, Tsuprykov O, et al. *Urinary Vitamin D Binding Protein and KIM-1 Are Potent New Biomarkers of Major Adverse Renal Events in Patients Undergoing Coronary Angiography*. (2016). Available online at: http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0145723&type=printable (accessed August 22, 2018).
30. Vicente-Vicente L, Ferreira L, González-Buitrago JM, López-Hernández FJ, López-Novoa JM, Morales AI. Increased urinary excretion of albumin, hemopexin, transferrin and VDBP correlates with chronic sensitization to gentamicin nephrotoxicity in rats. *Toxicology*. (2013) 304:83–91. doi: 10.1016/j.tox.2012.12.006
31. Rebholz CM, Grams ME, Lutsey PL, Hoofnagle AN, Misialek JR, Inker LA, et al. Biomarkers of Vitamin D status and risk of ESRD. *Am J Kidney Dis*. (2016) 67:235–42. doi: 10.1053/j.ajkd.2015.08.026
32. Lai L, Qian J, Yang Y, Xie Q, You H, Zhou Y, et al. Is the serum vitamin D level at the time of hospital-acquired acute kidney injury diagnosis associated with prognosis? *PLoS ONE*. (2013) 8:e64964. doi: 10.1371/journal.pone.0064964
33. Leaf DE, Croy HE, Abrahams SJ, Raed A, Waikar SS. Cathelicidin antimicrobial protein, vitamin D, and risk of death in critically ill patients. *Crit Care*. (2015) 19:80. doi: 10.1186/s13054-015-0812-1
34. Ersan S, Celik A, Tanrisev M, Kose I, Cavdar Z, Unlu M, et al. Pretreatment with paricalcitol attenuates level and expression of matrix metalloproteinases in a rat model of renal ischemia-reperfusion injury. *Clin Nephrol*. (2017) 88:231–8. doi: 10.5414/CN109121
35. Hamzawy M, Gouda SAA, Rashed L, Morcos MA, Shoukry H, Sharawy N. 22-oxacalcitriol prevents acute kidney injury via inhibition of apoptosis and enhancement of autophagy. *Clin Exp Nephrol*. (2019) 1:43–55. doi: 10.1007/s10157-018-1614-y
36. Kapil A, Singh JP, Kaur T, Singh B, Singh AP. Involvement of peroxisome proliferator-activated receptor gamma in vitamin D-mediated protection against acute kidney injury in rats. *J Surg Res*. (2013) 185:774–83. doi: 10.1016/j.jss.2013.07.017
37. Arfian N, Budiharjo S, Wibisono DP, Setyaningsih WAW, Romi MM, Saputri RLAANW, et al. Vitamin D ameliorates kidney ischemia reperfusion injury *via* reduction of inflammation and myofibroblast expansion. *Kobe J Med Sci*. (2019) 65:E138–43.
38. Silva Barbosa AC, Zhou D, Xie Y, Choi YJ, Tung HC, Chen X, et al. Inhibition of estrogen sulfotransferase (SULT1E1/EST) ameliorates ischemic acute kidney injury in mice. *J Am Soc Nephrol*. (2020) 31:1496–508. doi: 10.1681/ASN.2019080767
39. Lee J-W, Kim SC, Ko YS, Lee HY, Cho E, Kim M-G, et al. Renoprotective effect of paricalcitol *via* a modulation of the TLR4-NF-κB pathway in ischemia/reperfusion-induced acute kidney injury. *Biochem Biophys Res Commun*. (2014) 444:121–7. doi: 10.1016/j.bbrc.2014.01.005
40. Xu S, Chen Y-H, Tan Z-X, Xie D-D, Zhang C, Xia M-Z, et al. Vitamin D3 pretreatment alleviates renal oxidative stress in lipopolysaccharide-induced acute kidney injury. *J Steroid Biochem Mol Biol*. (2015) 152:133–41. doi: 10.1016/j.jsbmb.2015.05.009
41. Du J, Jiang S, Hu Z, Tang S, Sun Y, He J, et al. Vitamin D receptor activation protects against lipopolysaccharide-induced acute kidney injury through suppression of tubular cell apoptosis. *Am J Physiol Physiol*. (2019) 316:F1068–77. doi: 10.1152/ajprenal.00332.2018
42. Park JW, Cho JW, Joo SY, Kim CS, Choi JS, Bae EH, et al. Paricalcitol prevents cisplatin-induced renal injury by suppressing apoptosis and proliferation. *Eur J Pharmacol*. (2012) 683:301–9. doi: 10.1016/j.ejphar.2012.03.019

43. Hu Z, Zhang H, Yi B, Yang S, Liu J, Hu J, et al. VDR activation attenuate cisplatin induced AKI by inhibiting ferroptosis. *Cell Death Dis*. (2020) 11:1–11. doi: 10.1038/s41419-020-2256-z
44. Abdel Moneim LM, Helmy MW, El-Abhar HS. Co-targeting of endothelin-A and vitamin D receptors: a novel strategy to ameliorate cisplatin-induced nephrotoxicity. *Pharmacol Rep*. (2019) 71:917–25. doi: 10.1016/j.pharep.2019.04.018
45. Hur E, Garip A, Camyar A, Ilgun S, Ozisik M, Tuna S, et al. The effects of vitamin d on gentamicin-induced acute kidney injury in experimental rat model. *Int J Endocrinol*. (2013) 2013:313528. doi: 10.1155/2013/313528
46. El-Boshy M, BaSalamah MA, Ahmad J, Idris S, Mahbub A, Abdelghany AH, et al. Vitamin D protects against oxidative stress, inflammation and hepatorenal damage induced by acute paracetamol toxicity in rat. *Free Radic Biol Med*. (2019) 141:310–21. doi: 10.1016/j.freeradbiomed.2019.06.030
47. Abo El-Magd NF, Eraky SM. The molecular mechanism underlining the preventive effect of vitamin D against hepatic and renal acute toxicity through the NrF2/ BACH1/ HO-1 pathway. *Life Sci*. (2020) 244:117331. doi: 10.1016/j.lfs.2020.117331
48. Reis NG, Francescato HDC, de Almeida LF, Silva CGA da, Costa RS, Coimbra TM. Protective effect of calcitriol on rhabdomyolysis-induced acute kidney injury in rats. *Sci Rep*. (2019) 9:1–10. doi: 10.1038/s41598-019-43564-1
49. Greenberg A, Cheung AK, Coffman TM, Falk RJ, Jennette JC. Disorders of Calcium and Phosphorus Homeostasis. In: Greenberg A, editor. *Primer on Kidney Diseases*. Philadelphia, PA: Elsevier (2009). p. 169–79.
50. Deshpandey RP, Kumar HSA, Mathew S. Dyselectrolytemias and acid-base disorder in acute kidney injury. *Clin Queries Nephrol*. (2012) 1:70–5. doi: 10.1016/S2211-9477(11)70009-7
51. Rocha PN, Santos CS, Avila MO, Neves CL, Bahiense-Oliveira M. Hypercalcemia and acute kidney injury caused by abuse of a parenteral veterinary compound containing vitamins A, D, and E. *J Bras Nefrol*. (2011) 33:467–71. doi: 10.1590/S0101-28002011000400013
52. Markowitz GS, Perazella MA. Acute phosphate nephropathy. *Kidney Int*. (2009) 76:1027–34. doi: 10.1038/ki.2009.308
53. Di Mario F, Peyronel F, Greco P, Giunta R, Regolisti G, Fiaccadori E. A case of extreme hyperphosphatemia due to sodium phosphate enemas successfully treated with sustained low efficiency dialysis. *Clin Nephrol*. (2021) 95:62–4. doi: 10.5414/CN110345
54. Tebben PJ, Singh RJ, Kumar R. Vitamin D-mediated hypercalcemia: mechanisms, diagnosis, and treatment. *Endocr Rev*. (2016) 37:521–47. doi: 10.1210/er.2016-1070
55. Hilger J, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, et al. A systematic review of vitamin D status in populations worldwide. *Br J Nutr*. (2014) 111:23–45. doi: 10.1017/S0007114513001840
56. Chowdry AM, Azad H, Saleem Najar M, Mir I. *Acute Kidney Injury due to Overcorrection of Hypovitaminosis D: A Tertiary Center Experience in the Kashmir Valley of India*. (2017). Available at: http://www.sjkdt.org [accessed August 23, 2018] doi: 10.4103/1319-2442.220873
57. De Francesco Daher E, Mesquita Martiniano LV, Lopes Lima LL, Viana Leite Filho NC, de Oliveira Souza LE, Duarte Fernandes PHP, et al. Acute kidney injury due to excessive and prolonged intramuscular injection of veterinary supplements containing vitamins A, D and E: a series of 16 cases. *Nefrología*. (2017) 37:61–7. doi: 10.1016/j.nefroe.2016.12.010
58. Daher EF, Silva Júnior GB, Queiroz AL, Ramos LMA, Santos SQ, Barreto DMS, et al. Acute kidney injury due to anabolic steroid and vitamin supplement abuse: report of two cases and a literature review. *Int Urol Nephrol*. (2009) 41:717–23. doi: 10.1007/s11255-009-9571-8
59. Nasri H, Mubarak M. Renal injury due to vitamin D intoxication; a case of dispensing error. *J Ren Inj Prev*. (2013) 2:85–7. doi: 10.12861/jrip.2013.27
60. Kaur P, Mishra SK, Mithal A. Vitamin D toxicity resulting from overzealous correction of vitamin D deficiency. *Clin Endocrinol (Oxf)*. (2015) 83:327–31. doi: 10.1111/cen.12836
61. Kumar Bansal R, Tyagi P, Sharma P, Singla V, Arora V, Bansal N, et al. Iatrogenic hypervitaminosis D as an unusual cause of persistent vomiting: a case report. *J Med Case Rep*. (2014) 8:74. doi: 10.1186/1752-1947-8-74
62. Jacobus CH, Holick MF, Shao Q, Chen TC, Holm IA, Kolodny JM, et al. Hypervitaminosis D associated with drinking milk. *N Engl J Med*. (1992) 326:1173–7. doi: 10.1056/NEJM199204303261801
63. Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. *N Engl J Med*. (2001) 345:66–7. doi: 10.1056/NEJM200107053450115
64. Corden E, Higgins E, Smith C. Hypercalcaemia-induced kidney injury caused by the vitamin D analogue calcitriol for psoriasis: a note of caution when prescribing topical treatment. *Clin Exp Dermatol*. (2016) 41:899–901. doi: 10.1111/ced.12927
65. Aihara S, Yamada S, Oka H, Kamimura T, Nakano T, Tsuruya K, et al. Hypercalcemia and acute kidney injury induced by eldecalcitol in patients with osteoporosis: a case series of 32 patients at a single facility. *Ren Fail*. (2019) 41:88–97. doi: 10.1080/0886022X.2019.1578667
66. Tollitt J, Solomon L. Hypercalcaemia and acute kidney injury following administration of vitamin D in granulomatous disease. *BMJ Case Rep*. (2014) 2014:bcr2014203824. doi: 10.1136/bcr-2014-203824
67. Mason RS, Frankel T, Yuk Luen Chan, Lissner D, Posen S. Vitamin D conversion by sarcoid lymph node homogenate. *Ann Intern Med*. (1984) 100:59–61. doi: 10.7326/0003-4819-100-1-59
68. Adams JS, Gacad MA. Characterization of 1 alpha-hydroxylation of vitamin D3 sterols by cultured alveolar macrophages from patients with sarcoidosis. *J Exp Med*. (1985) 161:755–65. doi: 10.1084/jem.161.4.755
69. Lavender TW, Martineau AR, Quinton R, Schwab U. Severe hypercalcaemia following vitamin D replacement for tuberculosis-associated hypovitaminosis D. *Int J Tuberc Lung Dis*. (2012) 16:140. doi: 10.5588/ijtld.11.0368
70. Karmali R, Barker S, Hewison M, Fraher L, Katz DR, O'Riordan JLH. Intermittent hypercalcaemia and vitamin D sensitivity in Hodgkin's disease. *Postgrad Med J*. (1990) 66:757–60. doi: 10.1136/pgmj.66.779.757
71. Altun E, Kaya B, Paydaş S, Balal M. Milk alkali syndrome induced by calcitriol and calcium bicarbonate in a patient with hypoparathyroidism. *Indian J Endocrinol Metab*. (2013) 17:S191–3. doi: 10.4103/2230-8210.119568
72. Jeong JH, Bae EH. Hypercalcemia associated with acute kidney injury and metabolic alkalosis. *Electrolytes Blood Press*. (2010) 8:92–4. doi: 10.5049/EBP.2010.8.2.92
73. Asghar A, Islam N. A case report: giant cystic parathyroid adenoma presenting with parathyroid crisis after Vitamin D replacement. *BMC Endocr Disord*. (2012) 12:14. doi: 10.1186/1472-6823-12-14
74. Tsao Y-T, Wu C-C, Chu P. Immune reconstitution syndrome-induced hypercalcemic crisis. *Am J Emerg Med*. (2011) 29:244.e3–6. doi: 10.1016/j.ajem.2010.03.013

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.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 12 March 2021
doi: 10.3389/fnut.2021.627753

Evaluating the Impact of Goal Setting on Improving Diet Quality in Chronic Kidney Disease

Chi H. Chan[1]*, *Marguerite Conley*[2], *Marina M. Reeves*[3], *Katrina L. Campbell*[4,5,6] and *Jaimon T. Kelly*[5,6]*

[1] Faculty of Health Science and Medicine, Bond University, Gold Coast, QLD, Australia, [2] Department of Nutrition and Dietetics, Princess Alexandra Hospital, Brisbane, QLD, Australia, [3] Faculty of Medicine, School of Public Health, The University of Queensland, Brisbane, QLD, Australia, [4] Allied Health Services, Metro North Hospital and Health Service, Brisbane, QLD, Australia, [5] Centre of Applied Health Economics, Griffith University, Brisbane, QLD, Australia, [6] Menzies Health Institute Queensland, Griffith University, Gold Coast, QLD, Australia

Background: Improving diet quality in chronic kidney disease (CKD) is challenging due to a myriad of competing recommendations. Patient-centered goal setting can facilitate dietary behavior change; however, its role in improving diet quality in CKD has not been investigated.

Aim: The aim of the study is to evaluate the effects of goal setting on improving diet quality in stages 3–4 CKD.

Methods: Forty-one participants completed a 6-month dietitian-led telehealth (combined coaching calls and text messages) intervention as part of a larger RCT. Participants set one to two diet-related SMART goals and received weekly goal tracking text messages. Dietary intake was assessed using the Australian Eating Survey at baseline, 3, and 6 months, with diet quality determined using the Alternate Healthy Eating Index (AHEI).

Results: Significant improvements in AHEI (+6.9 points; 95% CI 1.2–12.7), vegetable (+1.1 serves; 95% CI 0.0–2.3) and fiber intake (+4.2 g; 95% CI 0.2–8.2) were observed at 3 months in participants setting a fruit and/or vegetable goal, compared with those who did not. However, no significant or meaningful changes were observed at 6 months. No other goal setting strategy appeared in effect on diet intake behavior or clinical outcomes in this group of CKD participants.

Conclusions: Patient-centered goal setting, particularly in relation to fruit and vegetable intake, as part of a telehealth coaching program, significantly improved diet quality (AHEI), vegetable and fiber intake over 3 months. More support may be required to achieve longer-term behavior change in stages 3–4 CKD patients.

Keywords: chronic kidney disease, diet quality, goal setting, self-managament, telehealth

OPEN ACCESS

Edited by:
Alice Sabatino,
University of Parma, Italy

Reviewed by:
Claudia D'alessandro,
Università degli Studi di Pisa, Italy
Angeles Espinosa,
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), Mexico

***Correspondence:**
Chi H. Chan
ianchan1230@gmail.com
Jaimon T. Kelly
jaimon.kelly@griffith.edu.au

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *10 November 2020*
Accepted: *05 February 2021*
Published: *12 March 2021*

Citation:
Chan CH, Conley M, Reeves MM, Campbell KL and Kelly JT (2021) Evaluating the Impact of Goal Setting on Improving Diet Quality in Chronic Kidney Disease. Front. Nutr. 8:627753. doi: 10.3389/fnut.2021.627753

INTRODUCTION

Chronic kidney disease (CKD) is a public health issue affecting over 10% of the global population (1). Dietary intake and lifestyle behaviors are important elements in the self-management of CKD and its associated comorbidities (2, 3). Diet recommendations have historically focused on restricting nutrients such as protein, sodium, potassium, and phosphate to slow the progression

of CKD and manage its associated conditions such as hyperkalemia and hyperphosphatemia. However, the evidence base for these nutrient restrictions is conflicting, and people with CKD struggle to adhere to these recommendations for a long term (4). Recent evidence has hypothesized that food-based dietary pattern approaches may improve CKD outcomes (4). Observational data have shown that a healthy dietary pattern is associated with decreased risks of all-cause mortality in people with CKD (5) and reduces risks of CKD comorbidities such as cardiovascular disease and diabetes mellitus (6, 7). A small number of randomized controlled trials (RCTs) have also shown that people with CKD can improve their diet quality in the short term (8). However, the long-term adherence to diet pattern interventions is unknown and remains a critical factor to address in helping patients succeed in changing their dietary behavior in practice for a long term (9–11).

Goal setting as a strategy for behavior change has been shown to be effective in CKD comorbidities management and may facilitate long-term behavior change through improved self-efficacy (12, 13). For example, in diabetes and heart failure patients, goal setting has been found to be beneficial for behavioral changes in dietary intake and physical activity (14), and improves self-efficacy and self-management skills (15, 16). People who set a specific, measurable, achievable, realistic, and timed (SMART) goal are likely to attain a successful outcome (17), and it is hypothesized that this might help people with CKD to achieve better dietary intake. However, the effect of SMART goal setting on improving diet quality in CKD-specific populations has not been evaluated to date.

A recent pilot RCT of a telehealth coaching program in people with stages 3–4 CKD showed significant and meaningful improvements in diet quality following 3 months of intensive coaching (8, 18). However, these effects were attenuated after 3 months of less-intensive coaching. As coaching was tailored to participant goals in this study, this has prompted the need to investigate whether specific goal setting influenced the change in diet quality in this sample of individuals with CKD. Therefore, this current study aimed to investigate whether specific dietary goal setting was associated with improvements in diet quality and other dietary and health indicators in people with stages 3–4 CKD.

METHODS

This study is a single-arm secondary analysis of intervention participants recruited from the previous ENTICE-CKD trial. The previous ENTICE-CKD study was a pilot RCT originally conducted in 80 participants ($n = 41$ intervention; $n = 39$ control) across three sites with stages 3–4 CKD (eGFR <60 ml/min/1.73 m^2), who owned a mobile phone (18). All participants were metabolically stable and were cleared to participate by their treating nephrologists. Each participants' nephrologist maintained responsibility for the patients' medical management throughout the study period. A single-arm analysis within the intervention group was the most appropriate to answer our specific research aim as the control group participants in the previous ENTICE-CKD study did not receive any intervention to set SMART goals nor had data collected on goal achievement throughout the study. This study conformed to the Declaration of Helsinki; all participants provided written informed consent, and the research protocol was approved by the Metro South Hospital and Health Service and Bond University Human Research Ethics Committees.

The previous ENTICE-CKD intervention is described in detail elsewhere (16, 18). Briefly, the previous ENTICE-CKD study was a telehealth intervention completed in two phases, phase 1 (baseline to 3 months) and phase 2 (3–6 months). **Figure 1** shows the study schema; the intervention participants received intensive telehealth coaching (telephone and text messages) fortnightly from the same Accredited Practicing Dietitian (APD), with weekly tailored text messages to support the coaching content in phase 1. Each coaching call addressed improving diet quality in line with the Australian Dietary Guidelines (19), which was further tailored to suit individual participant-associated comorbidities and their set goals. A program workbook was provided to all participants, which included sections relevant to SMART goal setting strategies and self-monitoring practice. In the initial coaching call, the dietitian coach guided participants through the workbook and worked with participants to set one to two diet-related SMART goals. The setting of each SMART goal was done collaboratively between the dietitian and the participant, based on a comprehensive medical and nutrition assessment and the participant stage of change. The purpose of the intervention was to improve diet quality, and therefore, each SMART goal set by participants was designed to address an area of dietary intake in order to achieve this, rather than the improvement in a clinical outcome. The dietitian provided evidence-based nutrition counseling using motivational interviewing techniques (18), addressing barriers to goal achievement, and action planning for the following 2 weeks. Participants also determined their individual preference for the timing and frequency of receiving text messages, which supported the coaching content and reminded participants of their set goals (detailed in **Table 1**). In the five subsequent coaching calls, the dietitian checked participants' progress in regard to their set goals and provided counseling support as per the study protocol (18). In phase 2, the intervention participants received no further coaching calls, however, and were continued to be sent the same tailored text messages at a frequency determined by the participants (protocol detailed in **Table 1**).

The tailored text messages in both phases were sent to individual participants using a web-based, semi-automated text message management platform (Propelo, www.propelo.com.au), developed and administered by The University of Queensland's School of Public Health (20). Tailored text messages were used to remind and track participants' goals each week (see **Table 1**). Participants were asked to text back either "yes" or "no" regarding their weekly goal achievement.

Data were collected at three time-points throughout the study including baseline, end-of phase 1 (3 months), and end-of phase 2 (6 months). The primary outcome was the change in the Alternate Healthy Eating Index (AHEI)-2010. The AHEI-10

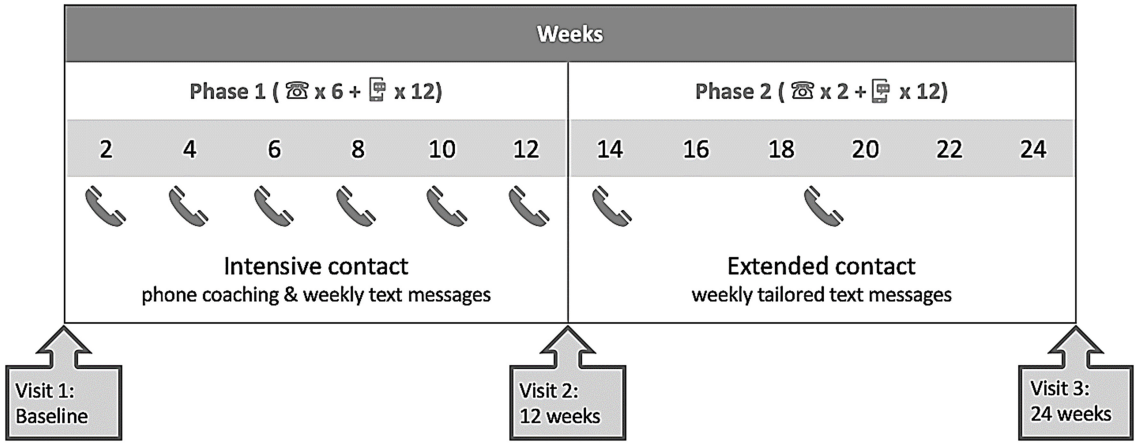

FIGURE 1 | Study scheme showing the intervention approach used in the ENTICE-CKD study.

TABLE 1 | Text message type and examples.

Message type	Example text	Frequency
Educational	Dietary fiber intake reduces your cholesterol levels and controls your blood sugar. Include whole grain bread and cereals, fruits and vegetables regularly	1–4 every 2 weeks
Self-monitoring	Hi, (name). Are you keeping track of your fruit/vegetable intake every day? Remember your goal to meet at least 5 serves this week	1–4 every 2 weeks
Goal check	Hi, (name). Did you reach your goal to eat 5 fruits/vegetables 4 times this week? Text me back yes or no to let me know	2–4 every 2 weeks
Educational permutations	Choose high-fiber, low-potassium breakfast cereals. Good choices are Multigrain Weetbix, Rolled Oats, Guardian, Oatbritz, and Special K	0–2 every 2 weeks

score is derived from the consumption of 11 food groups or nutrients: (1) vegetables, (2) fruits, (3) whole grains, (4) sugar-sweetened beverages and fruit juice, (5) nuts and legumes, (6) red and processed meat, (7) fish, (8) sodium, (9) alcohol, (10) trans-fat, and (11) long-chain fats. Each of the 11 components is scored from 1 (poor adherence) to 10 (perfect adherence), with the total AHEI-2010 diet quality score therefore ranging from 0 (non-adherence) to 110 (perfect adherence), the higher AHEI score. Further information about the AHEI-2010 and how it was collected and applied in this study can be found elsewhere (8). We based the diet quality rating categories on previous studies showing approximations (<38 points indicating a "low quality," 3–67 points as "intermediate," and >68 points as a "high" diet quality) (21). Diet consumption data for the AHEI-2010 components 1–9 were collected on the Australian Eating Survey and calculated using the Australian food composition databases, AusNut 2011-2013 and AusFoods Revision 5 (Australian Government Publishing Service, Canberra) over a 3-month period. Data on the AHEI-2010 compoents 10 and 11 were calculated using NUTTAB 2010 (database developed by the Food Standards Australia and New Zealand) and FoodWorks (version 18, The Nutrition Company, Long Valley, NJ, USA). Secondary outcomes, which related to participants' set goals, included fruit and vegetable intake, fiber intake, sodium intake, blood pressure, and body weight. Fruit and vegetable intake, fiber intake, and sodium intake were measured using the Australian Eating Survey. Body weight and blood pressure were collected as part of usual care where possible or by a trained site investigator who was blind to the treatment allocation, following a standardized protocol (8).

Total goal attainment was determined based on the number of "yes" responses to the weekly goal check text messages. The number of goal achievements was measured between 0 (i.e., no goal achieved) to 12 (i.e., all goals achieved) in each 12-week phase. If participants did not respond to the goal check message, these data were recorded as goal not achieved.

For statistical analysis, participant goals were categorized into either a "no goal" (received all other text messages but elected not to set a goal outside the dietary intervention targets), a "fruit and/or vegetable" goal (as the majority of participants set both fruit and vegetable intake goals, rather than one of these food groups separately), or a "healthy eating" goal. These three dietary goals were the most frequently set goals by participants with enough data available to conduct an exploratory analysis. The baseline-observation-carried-forward (BOCF) approach was applied to impute missing data in the current study. Data were checked for normality. One-way analyses of covariance (ANCOVA; adjusted for baseline) were conducted to determine potential differences in the primary and secondary outcomes differed across the two groups defined as whether participants

TABLE 2 | Baseline characteristics.

Characteristic	Participant ($n = 41$)
Age, years	63 ± 12
Gender, % of male	63
Ethnicity, *n* (%)	
Caucasian	35 (85)
Asian	2 (5)
European	2 (5)
Indigenous	1 (2.5
Other	1 (2.5)
Hypertension, *n* (%)	34 (83)
Diabetes, *n* (%)	16 (39)
Cardiovascular disease, *n* (%)	14 (34)
eGFR, ml/min/1.73 m^2	36 ± 12
Systolic blood pressure, mmHg	136 ± 18
Diastolic blood pressure, mmHg	80 ± 12
Weight, kg	96 ± 22
Body mass index, kg/m^2	33 ± 7
Alternate Healthy Eating Index	71.4 ± 11.8
Fruit, serves/day	1.5 ± 0.9
Vegetables, serves/day	4.2 ± 2.0
Sodium, mg	2,379 ± 1,392
Fiber, g	24.1 ± 9.1

Data were reported as mean ± SD.
eGFR, estimated glomerular filtration rate; g, grams; mg, milligrams; kg, kilograms.

had set one of the three listed goals or not, in each phase. Results from the analyses are presented as mean and 95% confidence interval (CI). A $p < 0.05$ (two sided) was considered statistically significant. However, given the exploratory nature of this pilot study, all results were also considered against minimal clinically important difference (MCID), which was informed by a thorough review of the literature and expert clinical guidance. For the purpose of this study, we defined MCID as 20% change in diet quality (AHEI score) (22), 5 grams (g) change in fiber intake (23), 0.5 serves in fruit intake (24), one serve in vegetable intake (24), 780 milligrams (mg) in sodium intake (25), 5 mmHg systolic blood pressure (SBP) (26), and 5% change in body weight (27). All statistical tests were performed using SPSS (version 26. *Chicago: SPSS Inc.*).

RESULTS

All 41 intervention participants from the previous ENTICE-CKD study were included in the analysis (63% male; mean age 63 ± 12 years; **Table 2**). Comorbidities were common across the population, 83% of participants having hypertension, 39% having diabetes, and 34% having cardiovascular disease.

At baseline (**Table 2**), the mean AHEI of participants was 71.4 points (rating in the "high" diet quality category). The average fruit and vegetable intake was 1.5 ± 0.9 serves and 4.2 ± 2.0 serves, respectively. The average fiber and sodium consumptions were 24.1 ± 9.1 g and 2,379 ± 1,392 mg, respectively. Participants had a mean body mass index (BMI) and SBP of 33 ± 7 kg/m^2 and 136 ± 18 mmHg, respectively.

The most common goals set by participants included "general healthy eating" goal ($n = 15$ in phase 1; $n = 21$ in phase 2), "fruit and/or vegetable" goal ($n = 16$ in phase 1; $n = 13$ in phase 2), and "no goal" ($n = 5$ in phase 1; $n = 7$ in phase 2). A total of 944 goal check messages were sent to participants throughout the trial, 365 messages in phase 1 and 579 messages in phase 2. Participants' response rates to goal check messages were 46.3% in phase 1 and 38.7% in phase 2, respectively, of which, 41.9% of participants stated they met their set goal in phase 1 and 34% in phase 2.

Table 3 shows the effect of goal setting on diet intake. Compared with participants who did not set a "fruit and/or vegetable" goal in phase 1 ($n = 25$), those that did ($n = 16$) had a statistically significant improvement in AHEI (+6.9 points, 95% CI 1.2–12.7; 10% increase), vegetable intake (1.1 serves per day, 95% CI 0.0–2.3), and fiber intake (+4.2 g, 95% CI 0.2–8.2). Fruit intake was the only variable shown to clinically meaningfully improve (+0.5 serves, 95% CI −0.1–1.1); however, it was not statistically significant. At 6 months, these associations were all attenuated; however, a significant (but unlikely clinically meaningful) increase in sodium intake (+413.7 mg, 95% CI 28–799.4) was observed in participants setting a "fruit and/or vegetable" goal ($n = 13$) compared with those who did not.

In those who set a "general healthy eating" goal (vs. those who did not), no statistically or clinically meaningful differences in any of the outcomes were observed at either 3 or 6 months. No associations were observed at 3 or 6 months in those who set "no goal" vs. those who set a goal.

There was no clinically or statistically significant effects observed for body weight or SBP (**Supplementary Table 1**).

DISCUSSION

This secondary analysis from the previous ENTICE-CKD study aimed to investigate the relationship between patient-centered goal setting and diet quality improvement and determine the specific dietary goals that might help people with CKD to improve their diet quality and clinical outcomes. Significant and potentially meaningful associations were primarily observed at 3 months. These results are exploratory and hypothesis generating and suggest that focusing on fruit and vegetable intake goals can help to promote a clinically significant short-term improvement in diet quality, vegetable and fruit intake, and dietary fiber intake with dietitian-led telehealth coaching.

Both diet quality and fiber intake are important in CKD self-management. Compared with other goal categories set by participants, "fruit and/or vegetable" goals appeared to be the strongest enabler of achieving an improved diet quality, vegetables and fiber intake in CKD patients, with the support of intensive telehealth coaching from a dietitian over 3 months. In one of the largest longitudinal analyses of continuous changes in the diet quality, a 20% improvement in AHEI was associated with an 8–17% reduced risk of all-cause mortality in people

TABLE 3 | Between group changes in AHEI and dietary intake across the two groups of participants who either set a specific goal compared with participants who did not, in each phase of the study.

Outcomes[#] Goal	Phase	AHEI (points)	Fruit (serves/day)	Vegetables (serves/day)	Fiber (g/day)	Sodium (mg/day)
Healthy eating goal[a]	Phase 1	−0.2 (−6.3, 5.9)	−0.3 (−1.0, 0.4)	0.6 (−0.6, 1.8)	0.6 (−3.7, 4.9)	109.8 (−407.9, 627.5)
	Phase 2	−1.0 (−7.3, 5.3)	−0.2 (−0.9, 0.4)	0.3 (−0.6, 1.3)	−0.3 (−3.6, 3.0)	−210.0 (−590.1, 170.2)
Fruit and/or vegetable goal[b]	Phase 1	6.9 (1.2, 12.7)*	0.5 (−0.1, 1.1)	1.1 (0.0, 2.3)*	4.2 (0.2, 8.2)*	−155.6 (−659.9, 348.6)
	Phase 2	−2.0 (−9.0, 5.0)	0.0 (−0.6, 0.7)	−0.5 (−1.5, 0.6)	0.4 (−3.1, 4.0)	413.7 (28.0, 799.4)*
No goal[c]	Phase 1	−4.5 (−13.4, 4.3)	−0.5 (−1.4, 0.5)	−0.7 (−2.4, 1.1)	−4.0 (−10.2, 2.1)	115.2 (−643.6, 874.0)
	Phase 2	1.1 (−7.4, 9.6)	0.0 (−0.8, 0.8)	0.2 (−1.1, 1.5)	−0.0 (−4.4, 4.3)	309.1 (−191.7, 810.0)

Data are reported as mean (95% CI).

[a]*Phase 1: "yes" n = 15; "no" n = 26. Phase 2: "yes" n = 21; "no" n = 20.*

[b]*Phase 1: "yes" n = 16; "no" n = 25. Phase 2: "yes" n = 13; "no" n = 28.*

[c]*Phase 1: "yes" n = 5; "no" n = 36. Phase 2: "yes" n = 7; "no" n = 34.*

[#]*Standard ANCOVA analysis reporting the mean (95% CI) change in the group of participants who set each specific goal, minus the change in participants who did not set each specific goal.*

*$p < 0.05$.

who ranked in the intermediate diet quality category (22). While the overall results of this exploratory study are far from conclusive, the AHEI improvement observed in phase 1 (+7 points; 10% improvement) is promising, particularly given the fact that our participants' baseline diet already ranked in the "high" diet quality category (22, 23). Similarly, with the noted clinical meaningful changes in fruit (0.5 serves) and vegetable intake (one serve), this placed participants mean intakes at two and five serves, respectively, in line with the Australian Dietary Guidelines (19). The fact that sodium intake increased by ∼400 mg at 6 months is interesting and unexpected. It is important to note that at 3 months, sodium intake decreased by a non-significant 150 mg, in line with the significant improvement in diet quality. While we are not able to determine the exact reason why this occurred, the 6-month period of the study was typically (for the vast majority of participants) occurring over the winter and spring seasons in Australia. These seasons present well-known challenges for people with CKD in controlling their sodium intake, typically due to choosing more tinned vegetables and prepared soups (28). This also highlights the challenge that some participants had in maintaining their dietary changes after the initial 3-month coaching period, where they could not speak to a dietitian to discuss these potential issues. Future telehealth coaching studies should ensure specific education content (both telephone coaching, but likely more importantly, extended text message support), which considers assisting patients choose low-sodium pre-prepared foods and provide seasonal recipes.

Fruits and vegetables have many properties, which might make them an appealing intervention strategy for people with CKD trying to improve their diet quality. Fruits and vegetables release potassium salts, which generate bicarbonate naturally, and can decrease the kidney acid load. Current best-practice guidelines recommend that people with stages 1–4 CKD consume a diet higher in fruits and vegetables to effectively manage metabolic acidosis (4). Fruits and vegetables also have a low bioavailability of dietary phosphorus and calcium, which limits its bioavailability due to the presence of phytate in vegetable forms of phosphorous, which can also promote better adherence to nutrient-restricted interventions (29).

Adequate daily intakes of fruits, vegetables, and fiber reflect a higher overall diet quality (30). Evidence shows that sufficient fiber intake reduces the risk of inflammatory reactions, which are directly linked with the progression of kidney diseases (31). Moreover, fiber is found to be related to inflammation metabolic acidosis and gut microbiota culture, which are also associated with CKD (32). Increasing dietary fiber intake may also attenuate imbalance in the gut microbiome, which is known to have a role in modification of protein-bound uremic toxins (33). A meta-analysis of 14 CKD controlled-feeding trials showed dietary fiber to significantly reduce serum urea and creatinine levels (34). As the most common dietary sources of fiber, increasing fruit and vegetable consumptions are likely to be the most practical way in which CKD patients can improve their fiber intake and overall diet quality.

No significant AHEI improvement was found at 6 months compared with the first 3 months of the study. However, this result is not conclusive due to the low participants' response rate to goal check text messages (<50% in phase 1 and approximately one third in phase 2). While it is critical to acknowledge the message response rate, it may also be important to consider the results in the context of the differences in intervention approaches used in each phase. Specifically, in phase 1, participants received coaching contact from the dietitian with six fortnightly telephone coaching and weekly tailored text messages for the first 3 months of the program, while in the second phase of the study, participants continued receiving the same tailored text messages but received no further telephone coaching with their dietitian. It was previously reported that previous ENTICE-CKD participants needed at least two coaching calls to start putting their set action plans in place (18). According to the achievement motivation theory, people tend to continue making positive changes once they have attained their set goals (35, 36). It remains unclear whether intervention decay observed in our study is commensurate with a reduction in coaching intensity. It is likely that more intensive support over a longer duration from a dietitian is needed to promote greater change (37).

An overview of the systematic reviews evaluating intervention components associated with increased effectiveness in dietary generally supports this theory, of a positive relationship between the number of intervention contacts over longer durations and self-reported dietary change (38). Whether or not this is the case specifically in CKD populations requires further investigation.

Furthermore, there were differences in the number of participants who set fruit and vegetable intake goals in each phase of the study. Specifically, in phase 2, less participants chose to continue their goal to improve their fruit and vegetable intake ($n = 16$ in phase 1 compared with $n = 13$ in phase 2). Instead, there appeared to be an increase in the number of participants who set a healthy eating goal in phase 2 compared with that in phase 1 ($n = 15$ and $n = 21$, respectively). This might indicate that participants felt that they had successfully achieved their goal to improve fruit and vegetable intake at 3 months and decided to set a more general healthy eating goal in phase 2. As mentioned above, it is likely that people with CKD still need more coaching over a longer period as mentioned. However, it could also be hypothesized that people with CKD may need more specific goals, such as a fruit or vegetable intake goals, compared with a general healthy eating goal, in order to achieve true change in diet quality. This hypothesis needs testing in future adequately powered randomized controlled trials.

This study has important limitations to consider. This is a *post-hoc* secondary analysis, which only evaluated a single arm of the previous ENTICE-CKD trial with no control group comparison. The findings in this study are therefore exploratory only, hypothesis-generating, and not conclusive. The small sample size is a factor influencing the accuracy of results. Participants showed diverse preferences for dietary goals throughout the previous ENTICE-CKD program, in line with the practical and patient-centered approach the intervention was underpinned by. While most participants determined that "healthy eating" and "fruit and/or vegetable" goals were important to them ($n = 13$ and $n = 21$, respectively), very few participants set goals such as a "weight reduction" goal ($n = 2$), and these goals could not be analyzed in a reliable or meaningful way. This limited our ability to explore the effect of specific goal setting on improving clinical outcomes. Participants showed a "high" diet quality score at baseline indicating healthy volunteer bias; this limitation may underestimate the potential benefits of dietary intervention evaluated in this study. To manage the issue of missing data, the principle of BOCF was applied to impute missing data, which may underestimate the treatment effect, or may ignore the possibility that people could regress or even worsen from baseline. Finally, while this is a patient-centered approach, our study relies almost entirely on self-reported data, which may reduce the confidence in the conclusions inferred.

In conclusion, patient-centered goal setting, which focuses on fruit and vegetable intake appeared to significantly improve diet quality, fruit and vegetable intake, and fiber intake in people with stages 3–4 CKD. No significant results were found at 6 months, which may be due to the reduction of coaching intensity and suggests that a longer-term telehealth coaching may be required in helping CKD patients to achieve long-term self-management. Further research evaluating longer-term interventions, with an emphasis on goal setting particularly around fruit and vegetable intake, will determine what effect on clinical outcomes are possible for people with CKD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request and clear and robust scientific protocol provided, without undue reservation.

ETHICS STATEMENT

The research protocol was approved by Metro South Hospital and Health Service and Bond University Human Research Ethics Committees. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC completed the data analysis and wrote the first draft of the manuscript. JK is the supervisor of this study who contributed to the study conception, original research data collection, reviewed the analysis results, and critically reviewed versions of the manuscript. MC participated in the original data collection and intervention design. MR and KC contributed to the study conception and critically reviewed the manuscript. All authors critically reviewed the manuscript and approved the final version of the manuscript.

FUNDING

This study was supported by a research support grant awarded by Kidney Health Australia via Australasian Kidney Trial Network (AKTN) and a Vice-Chancellors Research Award through Bond University.

ACKNOWLEDGMENTS

The authors would like to thank Ms. Evelyne Rathbone for her advice on statistical analysis. JK was supported through a Griffith University Postdoctoral Research Fellowship.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.627753/full#supplementary-material

REFERENCES

1. Bello AK, Levin A, Tonelli M, Okpechi IG, Feehally J, Harris D, et al. Assessment of global kidney health care status. *J Am Med Assoc.* (2017) 317:1864–81. doi: 10.1001/jama.2017.4046
2. Van Huffel L, Tomson CRV, Ruige J, Nistor I, Van Biesen W, Bolignano D. Dietary restriction and exercise for diabetic patients with chronic kidney disease: a systematic review. *PLos ONE.* (2014) 9:e113667. doi: 10.1371/journal.pone.0113667
3. Johnson DW, Atai E, Chan M, Phoon RK, Scott C, Toussaint ND, et al. KHA-CARI guideline: early chronic kidney disease: Detection, prevention and management. *Nephrology.* (2013) 18:340–50. doi: 10.1111/nep.12052
4. Kelly JT, Rossi M, Johnson DW, Campbell KL. Beyond sodium, phosphate and potassium: potential dietary interventions in kidney disease. *Semin Dialysis.* (2017) 30:197–202. doi: 10.1111/sdi.12580
5. Wai SN, Kelly JT, Johnson DW, Campbell KL. Dietary patterns and clinical outcomes in chronic kidney disease: the CKD.QLD nutrition study. *J Renal Nutrit.* (2017) 27:175–82. doi: 10.1053/j.jrn.2016.10.005
6. Reedy J, Krebs-Smith SM, Miller PE, Liese AD, Kahle LL, Park Y, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutrit.* (2014) 144:881–9. doi: 10.3945/jn.113.189407
7. Yu D, Zhang X, Xiang YB, Yang G, Li H, Gao Y, et al. Adherence to dietary guidelines and mortality: a report from prospective cohort studies of 134,000 Chinese adults in urban Shanghai. *Am J Clin Nutrit.* (2014) 100:693–700. doi: 10.3945/ajcn.113.079194
8. Kelly JT, Conley M, Hoffmann T, Craig JC, Tong A, Reidlinger DP, et al. A coaching program to improve dietary intake of patients with CKD: ENTICE-CKD. *Clin J Am Soc Nephrol.* (2020) 15:330–40. doi: 10.2215/CJN.12341019
9. Mekki K, Bouzidi-bekada N, Kaddous A, Bouchenak M. Mediterranean diet improves dyslipidemia and biomarkers in chronic renal failure patients. *Food Function.* (2010) 1:110–5. doi: 10.1039/c0fo00032a
10. Hannah J, Wells LM, Jones CH. The feasibility of using the Dietary Approaches to Stop Hypertension (DASH) Diet in people with chronic kidney disease and hypertension. *J Clin Nephrol Kidney Dis.* (2018) 3:1015. doi: 10.35841/clinical-nephrology3.1.10-11
11. Tyson CC, Lin PH, Corsino L, Batch BC, Allen J, Sapp S, et al. Short-term effects of the DASH diet in adults with moderate chronic kidney disease: a pilot feeding study. *Clin Kidney J.* (2016) 9:592–8. doi: 10.1093/ckj/sfw046
12. Clarke AL, Young HM, Hull KL, Hudson N, Burton JO, Smith AC. Motivations and barriers to exercise in chronic kidney disease: a qualitative study. *Nephrol Dialysis Transp.* (2015) 30:1885–92. doi: 10.1093/ndt/gfv208
13. Wright-Nunes JA, Luther JM, Ikizler TA, Cavanaugh KL. Patient knowledge of blood pressure target is associated with improved blood pressure control in chronic kidney disease. *Patient Educ Counsel.* (2012) 88:184–8. doi: 10.1016/j.pec.2012.02.015
14. Nothwehr F, Yang J. Goal setting frequency and the use of behavioral strategies related to diet and physical activity. *Health Educ Res.* (2007) 22:532–8. doi: 10.1093/her/cyl117
15. DeWalt DA, Davis TC, Wallace AS, Seligman HK, Bryant-Shilliday B, Arnold CL, et al. Goal setting in diabetes self-management: taking the Baby steps to success. *Patient Educ Counsel.* (2009) 77:218–23. doi: 10.1016/j.pec.2009.03.012
16. Kline KS, Scott LD, Britton AS. The use of supportive-educative and mutual goal-setting strategies to improve self-management for patients with heart failure. *Home Healthcare Now.* (2007) 25:502–10. doi: 10.1097/01.NHH.0000289104.60043.7d
17. Bovend'Eerdt TJ, Botell RE, Wade DT. Writing SMART rehabilitation goals and achieving goal attainment scaling: a practical guide. *Clin Rehab.* (2009) 23:352–61. doi: 10.1177/0269215508101741
18. Kelly JT, Warner MM, Conley M, Reidlinger DP, Hoffmann T, Craig J, et al. Feasibility and acceptability of telehealth coaching to promote healthy eating in chronic kidney disease: a mixed-methods process evaluation. *BMJ Open.* (2019) 9:e024551. doi: 10.1136/bmjopen-2018-024551
19. National Health and Medical Research Council. Australian dietary guidelines. In: *Ageing* DoHa, et. Canberra, ACT: Commonwealth of Australia. (2013) 36–44.
20. Fjeldsoe BS, Goode AD, Phongsavan P, Bauman A, Maher G, Winkler E, et al. Evaluating the maintenance of lifestyle changes in a randomized controlled trial of the 'get healthy, stay healthy' program. *JMIR mHealth uHealth.* (2016) 4:e42. doi: 10.2196/mhealth.5280
21. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutrit.* (2012) 142:1009–18. doi: 10.3945/jn.111.157222
22. Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A, et al. Association of changes in diet quality with total and cause-specific mortality. *N Engl J Med.* (2017) 377:143–53. doi: 10.1056/NEJMoa1613502
23. Mirmiran P, Yuzbashian E, Asghari G, Sarverzadeh S, Azizi F. Dietary fibre intake in relation to the risk of incident chronic kidney disease. *Br J Nutrit.* (2018) 119:479–85. doi: 10.1017/S0007114517003671
24. Wang X, Ouyang Y, Liu J, Minmin Z, Zhao G, Bao W, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ.* (2014) 349:g4490. doi: 10.1136/bmj.g4490
25. Maruta Y, Hasegawa T, Yamakoshi E, Nishiwaki H, Koiwa F, Imai E, et al. Association between serum Na-Cl level and renal function decline in chronic kidney disease: results from the chronic kidney disease Japan cohort (CKD-JAC) study. *Clin Exp Nephrol.* (2019) 23:215–22. doi: 10.1007/s10157-018-1631-x
26. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* (2009) 338:b1665. doi: 10.1136/bmj.b1665
27. Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord.* (1992) 16:397–415.
28. Beto JA, Schury KA, Bansal VK. Strategies to promote adherence to nutritional advice in patients with chronic kidney disease: a narrative review and commentary. *Int J Nephrol Renovasc Dis.* (2016) 9:21–33. doi: 10.2147/IJNRD.S76831
29. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis.* (2020) 76:S1–S107. doi: 10.1053/j.ajkd.2020.05.006
30. Wirt A, Collins CE. Diet quality-what is it and does it matter? *Public Health Nutrit.* (2009) 12:2473–92. doi: 10.1017/S136898000900531X
31. Krishnamurthy VM, Wei G, Baird BC, Murtaugh M, Chonchol MB, Raphael KL, et al. High dietary fiber intake is associated with decreased inflammation and all-cause mortality in patients with chronic kidney disease. *Kidney Int.* (2012) 81:300–6. doi: 10.1038/ki.2011.355
32. Chiavaroli L, Mirrahimi A, Sievenpiper JL, Jenkins DJA, Darling PB. Dietary fiber effects in chronic kidney disease: a systematic review and meta-analysis of controlled feeding trials. *Europ J Clin Nutrit.* (2015) 69:761. doi: 10.1038/ejcn.2014.237
33. Rossi M, Johnson DW, Xu H, Carrero JJ, Pascoe E, French C, et al. Dietary protein-fiber ratio associates with circulating levels of indoxyl sulfate and p-cresyl sulfate in chronic kidney disease patients. *Nutr Metab Cardiovasc Dis.* (2015) 25:860–5. doi: 10.1016/j.numecd.2015.03.015
34. Rossi M, Klein K, Johnson DW, Campbell KL. Pre-, pro-, and synbiotics: Do they have a role in reducing uremic toxins? A systematic review and meta-analysis. *Int J Nephrol.* (2012) 2012:673631. doi: 10.1155/2012/673631
35. Cassidy T. Social background, achievement motivation, optimism and health: a longitudinal study. *Counsel Psychol Quart.* (2000) 13:399–412. doi: 10.1080/713658501
36. Gollwitzer PM, Sheeran P. Implementation intentions and goal achievement: a meta-analysis of effects and processes. *Adv Exp Soc Psychol.* (2006) 38:69–119. doi: 10.1016/S0065-2601(06)38002-1
37. Goode AD, Reeves MM, Eakin EG. Telephone-delivered interventions for physical activity and dietary behavior change. *Am J Prevent Med.* (2012) 42:81–8. doi: 10.1016/j.amepre.2011.08.025
38. Greaves CJ, Sheppard KE, Abraham C, Hardeman W, Roden M, Evans PH, et al. Systematic review of reviews of intervention components associated with

increased effectiveness in dietary and physical activity interventions. *BMC Public Health.* (2011) 11:119. doi: 10.1186/1471-2458-11-119

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.

frontiers in Nutrition

BRIEF RESEARCH REPORT
published: 15 April 2021
doi: 10.3389/fnut.2021.622823

Ultrasound for Non-invasive Assessment and Monitoring of Quadriceps Muscle Thickness in Critically Ill Patients With Acute Kidney Injury

Alice Sabatino [1,2], Umberto Maggiore [1,2], Giuseppe Regolisti [1,2], Giovanni Maria Rossi [1,2], Francesca Di Mario [1,2], Micaela Gentile [1,2], Maria Teresa Farina [1,2] and Enrico Fiaccadori [1,2]*

[1] UO Nefrologia, Azienda Ospedaliera- Universitaria Parma, Parma, Italy, [2] Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy

Background and aims: Critically ill patients with acute kidney injury (AKI) undergo major muscle wasting in the first few days of ICU stay. An important concern in this clinical setting is the lack of adequate tools for routine bedside evaluation of the skeletal muscle mass, both for the determination of nutritional status at admission, and for monitoring. In this regard, the present study aims to ascertain if ultrasound (US) is able to detect changes in quadriceps muscle thickness of critically ill patients with acute kidney injury (AKI) over short periods of time.

Methods: This is a prospective observational study with a follow-up at 5 days. All adult patients with AKI hospitalized at the Renal ICU of the Parma University Hospital over 12 months, with a hospital stay before ICU admission no longer than 72 h, and with a planned ICU stay of at least 5 days, were eligible for the study. An experienced investigator assessed quadriceps rectus femoris and vastus intermedius thickness (QRFT and QVIT) at baseline and after 5 days of ICU stay.

Results: We enrolled 30 patients with 74 ± 11 years of age and APACHE II score of 22 ± 5. Muscle thickness decreased by 15 ± 13% within the first 5 days of ICU stay ($P < 0.001$ for all sites as compared to ICU admission). Patients with more severe muscle loss had lower probability of being discharged home (OR: 0.04, 95%CI: 0.00–0.74; $P = 0.031$).

Conclusions: In critically ill patients with AKI, bedside muscle US identifies patients with accelerated muscle wasting.

Keywords: acute kidney injury, body composition, critical care, muscle wasting, muscle ultrasound, intensive care unit

OPEN ACCESS

Edited by:
Alessio Molfino, Sapienza University of Rome, Italy

Reviewed by:
Paula Chiarello, University of São Paulo Ribeirão Preto, Brazil
Cassiana Regina de Góes, Universidade Federal de Lavras, Brazil

****Correspondence:***
Alice Sabatino
alice.sabatino86@gmail.com

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *29 October 2020*
Accepted: *17 March 2021*
Published: *15 April 2021*

Citation:
Sabatino A, Maggiore U, Regolisti G, Rossi GM, Di Mario F, Gentile M, Farina MT and Fiaccadori E (2021) Ultrasound for Non-invasive Assessment and Monitoring of Quadriceps Muscle Thickness in Critically Ill Patients With Acute Kidney Injury. Front. Nutr. 8:622823. doi: 10.3389/fnut.2021.622823

INTRODUCTION

Critically ill patients undergo major muscle wasting in the first few days of their ICU stay (1). Clinical consequences are represented by delayed functional recovery, difficult weaning from mechanical ventilation and increased mortality risk (1).

In this clinical setting an important cause of concern is the lack of adequate tools for routine bedside evaluation of the skeletal muscle mass (2). The reference methods considered as the gold

standard for the assessment of skeletal muscle, such as computed tomography (CT), magnetic resonance imaging (MRI), and dual energy X-ray absorptiometry (DEXA) are not feasible for routine evaluation and monitoring of muscle mass and body composition (2). On the other hand, currently used bedside tools, such as bioimpedance analysis (BIA) and anthropometry, are not accurate enough in critically ill patients (2), mainly due to the possible interference of fluid overload, frequently observed especially when Acute Kidney Injury (AKI) coexists. Recently, the use of ultrasound (US) for the assessment of muscle dimensions has aroused considerable interest, and its reliability and validity have been documented also in critically ill patients with AKI (3, 4). US technique seems to be poorly influenced not only by fluid overload, but also by the rapid and relevant fluid shifts typical of patients with AKI undergoing Kidney Replacement Therapy (KRT) (3).

On this premise, in the present study we aimed to assess whether US is able to detect changes in muscle thickness of patients with AKI over a short period of time.

MATERIALS AND METHODS

Patients

This is a prospective, longitudinal (5 days) observational study, conducted in the Renal ICU of the Parma University Hospital. Procedures were held in accordance to the Helsinki declaration and informed consent was obtained from patients or their next of kin. The study was approved by the local ethics committee (Comitato Etico di Area Vasta Emilia Nord, AVEN, Prot n. 43943 −03/12/2015).

All adult patients with AKI hospitalized in the Renal ICU from 15/03/2017 to 15/03/2018, with a hospital stay before ICU admission no longer than 72 hours, and with a predictable ICU stay of at least 5 days were eligible for the study. AKI was diagnosed according to KDIGO guideline criteria (5).

Already available data on quadriceps femoris US evaluation in healthy subjects (body mass index (BMI) $>$ 18.5 Kg/m^2, Subjective Global Assessment (SGA) class A, absence of chronic or acute illness) (6) were used for comparison with AKI patients, both at ICU admission and after 5 days of ICU stay.

Methods

US Technique

The same experienced investigator (renal dietitian) performed all of the measurements. Quadriceps rectus femoris thickness (QRFT) and quadriceps vastus intermedius thickness (QVIT) were measured by B-mode ultrasonography, wall tracking ultrasound system (Philips hd7xe) with a 7.5 MHz linear array transducer (L12-3 transducer), as previously described in detail (3). All US measurements were performed in duplicate and the average of the scores used in final analyses. The transducer was placed perpendicular to the long axis of the thigh with a large amount of gel and no pressure to avoid compression of the muscle. QRFT and QVIT were measured at the midpoint (RF Prox; VI Prox) and at the border between the lower third and upper two-thirds (RF Dist; Prox Dist) between the anterior superior iliac spine (ASIS) and the upper pole of the patella (3, 7). The right and left quadriceps values were assessed in both legs with the patient lying in a supine position with both knees extended but relaxed and toes pointing to the ceiling. The assessor was positioned on the side of the patient while performing the measurements, and was allowed to tilt the probe to obtain the best possible image, in which RF and VI would be aligned and centered. Measurements were performed directly on the US machine while obtaining the images. The vertical diameter of the muscles was measured on the inner edge of the muscle fascia. US was performed twice during ICU stay, at baseline (at ICU admission) and after 5 days since the first measurement. Muscle US took <20 min to complete the image acquisition and perform the measurements.

Demographics, clinical data, renal function and outcome: data were collected as per institutional routine at the time of ICU admission and during ICU stay, with special regard to demographic, body weight and height, clinical and laboratory data, renal function, acute and chronic comorbidities, severity of illness (APACHE II score), data on renal replacement therapy (RRT), length of stay and mortality.

Outcomes: muscle loss after 5 days.

Statistical Analysis

Results are expressed as mean and standard deviation for continuous variables with normal distribution, or median and range for non-parametric data, and as frequencies for categorical variables. Group differences were analyzed using Student *t*-test and Mann-Whitney's *U*-test for parametric and non-parametric data, respectively to assess difference between means of the control group and the patient group. ANCOVA was used to adjust the analysis by age and sex.

We examined the difference between muscle thickness at baseline and at 5 days after admission by mixed-effects models with patients fitted as random effects, and the four-way interaction term between time and each of the three sites of measurements (RF vs. VI, Left vs. Right, Proximal vs. Distal) fitted as fixed effects. We examined the relation between baseline comorbidities and change in muscle thickness by mixed-effects ANCOVA models in which muscle thickness at 5 days after admission was included as dependent variate and baseline thickness was included as covariate, in order to adjust for the correlation between change in muscle thickness and random differences in baseline values. We examined the relation between change in muscle thickness and ICU outcome (discharge, transferal to other health care facility, death) in two steps. First, we estimated the individual change over time in muscle thickness by the best linear unbiased predictions (BLUPs) of the random slope from mixed-effects random coefficients models. Then, we fitted a multinomial logistic regression model where outcome (discharge, prolonged stay, death) was the dependent variable and the individual random slope the independent variable. Because of sparse data concerning mortality (five patients only) we did not report the findings on mortality. A two-sided *P* value of less than 0.05 was regarded as statistically significant. Stata Release 16 (StataCorp, College Station, TX, US) was used for all the analyses.

TABLE 1 | Demographic and clinical data.

Variables	Patients ($n = 30$)	Healthy subjects ($n = 35$)
Age	74 (10.6)	41 (10.0)*
Male sex (*n*, %)	21/30 (70)	15/35 (43)*
Body weight (Kg)	82 (13.2)	70.5 (16.6)*
Height (m)	1.67 (0.09)	1.70 (0.09)
BMI (Kg/m^2)	29 (4.6)	24.3 (4.6)*
APACHE II	22 (5)	NA
Main admission diagnosis (*n*, %)		
— Renal	18/30 (60)	NA
— Sepsis	4/30 (14)	NA
— Respiratory	3/30 (10)	NA
— Vascular	3/30 (10)	NA
— Malignancy	1/30 (3)	NA
— Cardiac	1/30 (3)	NA
Surgical status (*n*, %)		
— Urgent	2/30 (7)	NA
— Programmed	3/30 (10)	NA
— Non-surgical	25/30 (83)	NA
Chronic comorbidities (*n*, %)		
— Hypertension	23/30 (77)	NA
— Diabetes mellitus	11/30 (37)	NA
— COPD	7/30 (23)	NA
— Ischemic cardiopathy	7/30 (23)	NA
— Heart failure	8/30 (27)	NA
— Peripheral vascular disease	5/30 (17)	NA
— Immunocompromised	2/30 (7)	NA
— Chronic liver disease	2/30 (7)	NA
— Malignancy	6/30 (20)	NA
— Chronic kidney disease (not on dialysis)	11/30 (37)	NA
Acute complications at first muscle US (*n*, %)		NA
— Sepsis	12/30 (40)	NA
— Invasive mechanical ventilation	4/30 (13)	NA
— Non-invasive mechanical ventilation	7/30 (23)	NA
— Oliguria	20/30 (67)	NA
— Vasoactive drug need	7/30 (23)	NA
— Renal replacement therapy	21/30 (70)	NA
ICU outcome (*n*, %)		
— Death	5/30 (17)	NA
Hospital outcome (*n*, %)		
— Death	9/30 (30)	NA
— Discharged home	15/30 (50)	NA
— Transferred to long-stay/rehabilitation ward	2/30 (7)	NA
— Transferred to another hospital	4/30 (13)	NA
ICU LOS median, range)	15 (4-72)	NA
Hospital LOS (median, range)	34 (7-138)	NA
Biochemical data		
sCr (mg/dl)	6.3 (4)	NA
BUN (mg/dl)	81.7 (36)	NA
Albumin (g/dl)	2.8 (0.6)	NA
CRP (mg/dl)	109.2 (68.1)	NA

*Data expressed as mean (standard deviation), frequencies and median (range). * $P < 0.001$ in comparison to AKI patients. BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; NIMV, non-invasive mechanical ventilation; sCr, serum creatinine.*

Sample Size Calculations

No data are currently available in the literature on US evaluation and monitoring of quadriceps muscle mass in patients with AKI. In a recent study on ICU patients (8) 22 patients were enrolled in order to detect a 16% reduction in the quadriceps rectus femoris thickness after 5 days of ICU stay, with a power of 80% and a probability of type I error equal to 0.05. We enrolled 30 patients to account for possible drop-outs.

RESULTS

Table 1 shows the baseline characteristics of the 30 patients studied. Seventy percent (21/30) were male with a mean ± SD age of 74 ± 11 years;, and they represented a severely critically ill cohort (APACHE II was 22 ± 5). A total of 472 images were analyzed across the 30 patients. Eighty-three percent of patients (25/30) were non-surgical patients and the main admission diagnosis in the ICU was renal, followed by sepsis. On average, patients were polymorbid (2.8 ± 1.7 comorbidities per patient), hypertension being the most frequent comorbidity. As to the usual renal function, 37% (11/30) had basal eGFR values <60 ml/min/1.73 m^2 (CKD stages 2 to 5 non dialysis). At the time of first US evaluation, all of the patients had stage 3 AKI; in 21/30 patients (70%) RRT was started as 10–12 h lasting sustained low-efficiency dialysis. Oliguria was common (67%), as was sepsis (40%). ICU mortality was 17% (5/30); hospital mortality was 30% (9/30). The median (range) length of ICU stay was 15 (4-72) days, while the length of hospital stay was 34 (7-138). C-reactive protein was 109.2 mg/dL (± 68.1).

Patients With AKI in Comparison to Healthy Subjects

Demographic characteristics of control group (35 healthy subjects) are shown in **Table 1**, while US quadriceps muscle data are illustrated in **Figure 1**. In general, the control group was younger and leaner than patients. At univariate analysis (**Figure 1**), muscle thickness of patients differed from that of the control group for all sites, both at T1 and T2. We also performed an adjusted analysis using ANCOVA corrected for age and sex. In the adjusted analysis, no difference was found between T1 values of muscle thickness and control group values; however, the difference between T2 values and the control group values remained statistically significant.

Changes in Muscle Thickness by US

Baseline (T1) and after 5 days (T2) mean ± SD values for RF and VI thickness are illustrated in **Figure 1**; the difference between means was statistically significant for all sites ($P < 0.001$). On average, there was a mean clinically relevant reduction of 15% (± 12%) in every site of measurement within the first 5 days of ICU stay (**Table 2**). Changes in VI Prox and Dist thickness (16–19%) were greater than in RF Prox and Dist thickness (11–13%).

We did not find any association between baseline muscle thickness, inflammatory status (assessed by CRP and serum albumin), as well as chronic and acute comorbidities, with muscle loss (**Supplementary Table 1**). Patients with the more severe muscle loss had a higher probability of having a prolonged

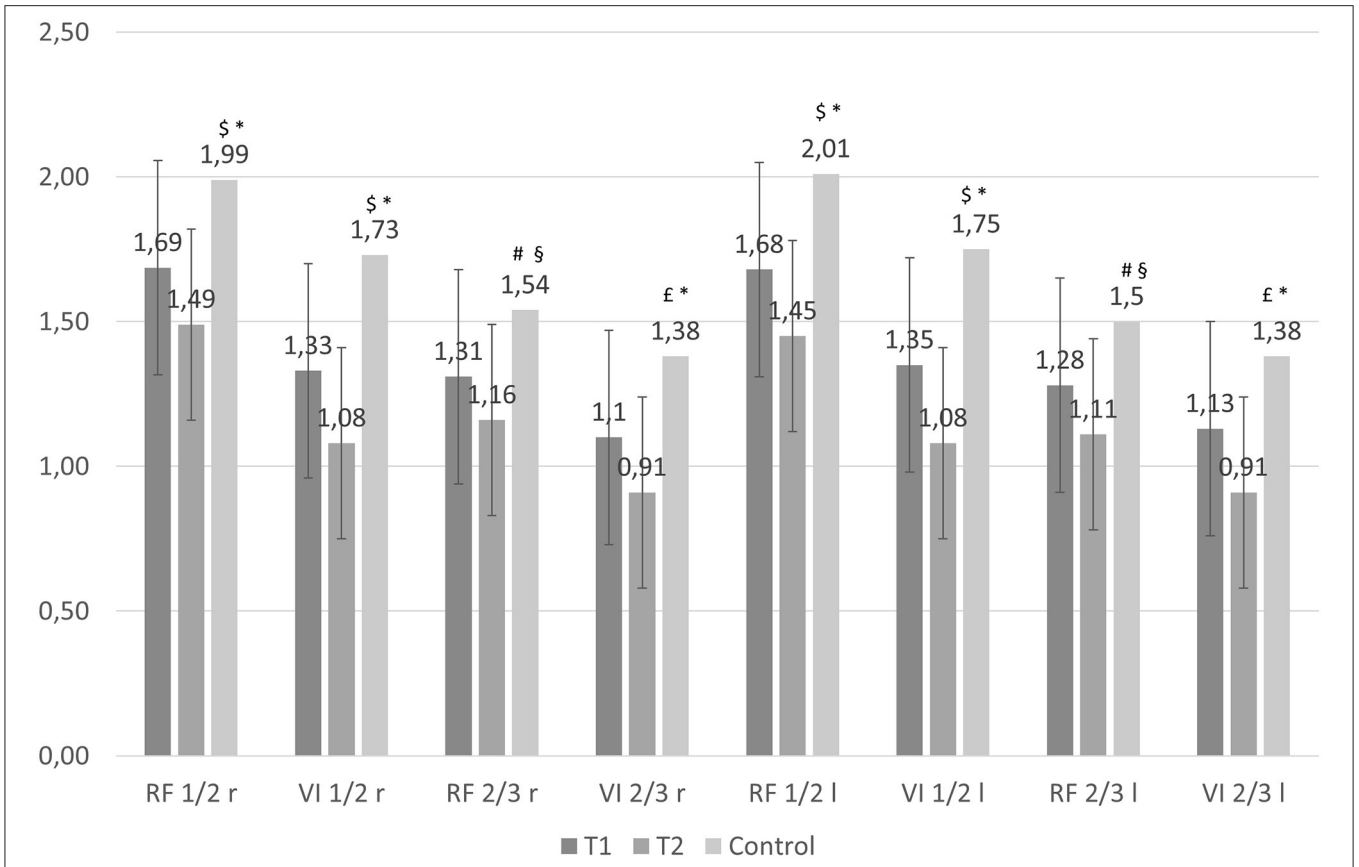

FIGURE 1 | Muscle thickness of patients with AKI (baseline, T1, and after 5 days, T2), and control group. The first 2 columns represent the mean and 95 percent confidence interval (vertical bar) of muscle thickness at each measurement site as estimated by the mixed effect model, at baseline (T1) and after 5 days (T2). The third column represents the control group. The average difference between baseline and 5 days was statistically significant at all measurement sites ($P < 0.001$). When comparing the difference between patients and healthy subjects, muscle thickness was different between controls and baseline (T1) values of patients: $^{\$}P = 0.001$, $^{\#}P < 0.05$, $P < 0.01$; $P < 0.001$ in comparison to muscle thickness of patients after 5 days (T2). After adjusting the analysis for age and sex using ANCOVA, no statistically significant difference was found between T1 values and controls; when comparing to T2 values, muscle thickness difference remained statistically significant for all sites: $^{*}P < 0.01$, $^{\S}P < 0.05$.

TABLE 2 | Average percent reduction of muscle thickness after 5 days of ICU stay.

Muscle site	Average reduction (SD)
QRFT Prox r ($n = 29$)	11% (8%)
QVIT Prox r ($n = 28$)	18% (14%)
QRFT Dist r ($n = 30$)	11% (10%)
QVIT Dist r ($n = 30$)	17% (12%)
QRFT Prox l ($n = 30$)	13% (10%)
QVIT Prox l ($n = 29$)	19% (16%)
QRFT Dist l ($n = 30$)	12% (10%)
QVIT Dist l ($n = 30$)	16% (15%)
All measurements ($n = 236$)	15% (12%)

Dist, distal; Prox, proximal; QRFT, quadriceps rectus femoris thickness; QVIT, quadriceps vastus intermedius thickness; Values expressed as mean (standard deviation).

hospital stay, which was determined by being transferred to another hospital instead of discharged home (OR: 0.04, 95%CI: 0.00- 0.74; $P = 0.031$) (**Figure 2**).

DISCUSSION

Our study confirms that muscle loss may occur early and rapidly in the first 5 days of ICU stay, and extends previous observations in general ICU patients also to patients with AKI.

At baseline, values of muscle thickness were not different from those of younger healthy subjects when the analysis were adjusted for age and sex. They were also similar to values previously reported in another study assessing elderly healthy subjects (9). However, at day 5, muscle mass was significantly reduced, both in comparison to baseline values and in comparison to the control group.

In our study, the amount of muscle loss was similar to that observed in critically ill patients (8); in particular, at day 5, the VI muscle had the most important reduction in comparison to the RF muscle. Rectus femoris is often described as a power muscle designed to assist in fast movements, while VI is considered a stabilizing muscle that is important for maintaining posture. The identification of which muscles are more affected by immobilization and critical illness in ICU patients could

provide important indications in order to more precisely target rehabilitation according to the type of muscle predominantly affected (VI-postural or RF-power).

We demonstrated that an inverse relationship exists between the severity of muscle loss and the probability of discharge home. Although we can't ascertain the causal relationship between muscle loss and outcome due to the small sample size, baseline sarcopenia assessed by US predicts adverse discharge disposition (death/transferal to nursing facilities) (10). In addition, muscle loss during ICU stay is a major contributor to functional disability (11). However, despite the rapidly loss faced during the first week of ICU stay, it remains unclear whether it is the change in muscle size from baseline or the total amount of muscle mass at admission that is the most important predictor of functional outcome and mortality (12). In our study, baseline muscle thickness did not correlate to the amount of muscle loss, which is in accordance to previous studies investigating muscle wasting in critically ill patients (11).

Despite its increasingly recognized importance, the assessment of muscle mass is challenging in the ICU setting, especially when inflammation and fluid imbalance are present. Currently available bedside methods (such as anthropometry and bioimpedance spectroscopy [BIS]) have important intrinsic limitations, due for example to fluid shifts typical of critically ill patients with AKI (13). Current recommended reference methods are hardly feasible in this clinical setting. Dual energy X-Ray absorptiometry (DEXA), which has been used and recommended by recent Consensus on sarcopenia to assess appendicular skeletal muscle mass (14), is also influenced by hydration status, because it assumes that lean body mass has a constant hydration of 73%, which is not the case in critically ill patients with AKI (15). In addition, DEXA is not feasible at the bedside and involves patient radiation exposure. Computed tomography (CT) has been recently used to assess muscle mass and its correlation with mortality in critically ill patients (16). Despite its excellent accuracy, CT is expensive,

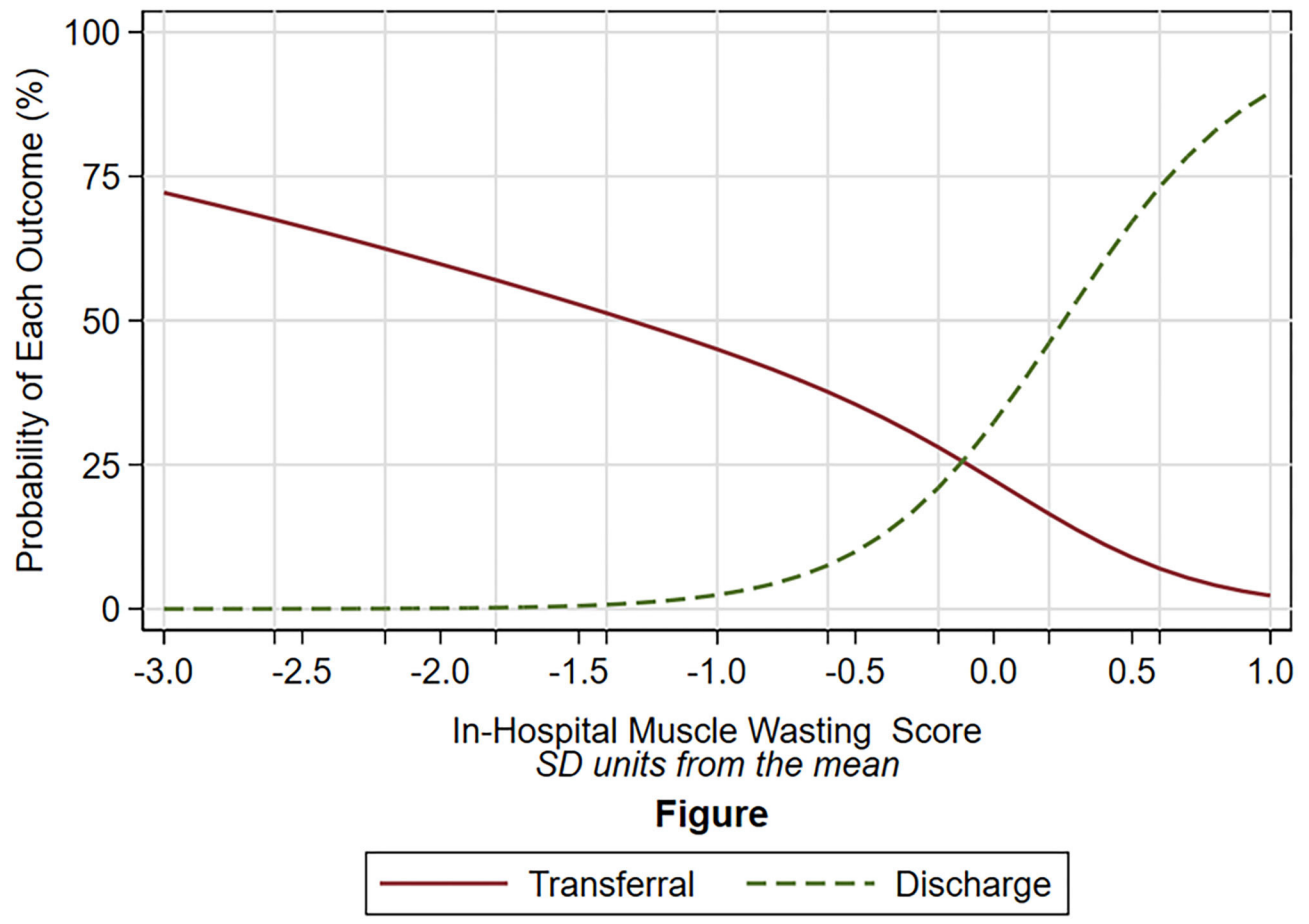

FIGURE 2 | Probability of discharge (dot green line) and of transferal to rehabilitation unit (solid red line) according to the degree of muscle wasting (x-axis). The degree of muscle wasting is expressed as standard deviation unit from the mean, in which a negative number indicates higher muscle wasting, a positive number lower muscle wasting. The different shape of the relation between the dot green line and the solid red line was statistically significant ($P = 0.031$). The probability of discharge was based on multinomial logistic model (mortality is not plotted because only five patients died). The independent variable of the multinomial logistic model was the degree of muscle wasting which was estimated by the mixed models (see text).

requires specialized personnel, and is available for muscle mass assessment only when CT is necessary for other diagnostic procedures on the lung or the abdomen. In recent years, muscle US has been increasingly studied in the kidney patient setting. Specifically, the reliability of the muscle US technique applied in the present study has been already reported in critically ill patients with AKI, along with excellent intraclass correlation coefficient (ICC) for inter and intra-operator comparisons (3). This methodology has already been validated in patients with AKI against muscle CT (4). Despite the lack of reference values to be applied at baseline and identify patients with pre-ICU low muscle mass and, therefore, increased nutritional risk, in the present study we showed that quadriceps muscle US is useful to monitor nutritional status of critically ill patients with AKI, and that increased muscle loss reduces the chance of being discharged home.

The main limitation of the present study relies in the small sample size, that does not allow further analysis regarding the effect of muscle loss and baseline muscle assets on mortality or functional outcomes. Further studies will be needed on larger cohorts of patients with AKI to allow for such analyses.

In conclusion, muscle wasting occurs early and rapidly within the first 5 days of ICU stay in critically ill patients with AKI. Muscle US is a sensible and feasible tool for the detection of muscle wasting even in this clinical setting; moreover, it is easy to use, cheap and time-efficient. In the future, studies defining cut-off values for muscularity are needed to allow the early identification of patients with low muscle mass at ICU admission.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico di Area Vasta Emilia Nord, AVEN, Prot n. 43943 −03/12/2015. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS: investigation, methodology, validation, and writing–original draft. UM: formal analysis, writing–review and editing. GR, GMR, MG, and MF: writing–review and editing. FD: resources, writing–review and editing. EF: supervision, writing–review and editing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.622823/full#supplementary-material

REFERENCES

1. Na A, O'Brien JM, Jr., Hoffmann SP, Phillips G, Garland A, Finley JC, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med.* (2008) 178:261–8. doi: 10.1164/rccm.200712-1829OC
2. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. *J Cachexia Sarcopenia Muscle.* (2018) 9:269–78. doi: 10.1002/jcsm.12268
3. Sabatino A, Regolisti G, Bozzoli L, Fani F, Antoniotti R, Maggiore U, et al. Reliability of bedside ultrasound for measurement of quadriceps muscle thickness in critically ill patients with acute kidney injury. *Clin Nutr.* (2017) 36:1710–5. doi: 10.1016/j.clnu.2016.09.029
4. Sabatino A, Regolisti G, di Mario F, Ciuni A, Palumbo A, Peyronel F, et al. Validation by CT scan of quadriceps muscle thickness measurement by ultrasound in acute kidney injury. *J Nephrol.* (2020) 33:109–17. doi: 10.1007/s40620-019-00659-2
5. Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int.* (2012) 2:1–138. doi: 10.1038/kisup.2012.7
6. Sabatino A, Regolisti G, Delsante M, Di Motta T, Cantarelli C, Pioli S, et al. Noninvasive evaluation of muscle mass by ultrasonography of quadriceps femoris muscle in End-Stage Renal Disease patients on hemodialysis. *Clin Nutr.* (2019) 38:1232–9. doi: 10.1016/j.clnu.2018.05.004
7. Tillquist M, Kutsogiannis DJ, Wischmeyer PE, Kummerlen C, Leung R, Stollery D, et al. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. *JPEN J Parenter Enteral Nutr.* (2014) 38:886–90. doi: 10.1177/0148607113501327
8. Parry SM, El-Ansary D, Cartwright MS, Sarwal A, Berney S, Koopman R, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. *J Crit Care.* (2015) 30:1151 e9–14. doi: 10.1016/j.jcrc.2015.05.024
9. Baldwin CE, Bersten AD. Alterations in respiratory and limb muscle strength and size in patients with sepsis who are mechanically ventilated. *Phys Ther.* (2014) 94:68–82. doi: 10.2522/ptj.20130048
10. Mueller N, Murthy S, Tainter CR, Lee J, Riddell K, Fintelmann FJ, et al. Can sarcopenia quantified by ultrasound of the rectus femoris muscle predict adverse outcome of surgical intensive care unit patients as well as frailty? A prospective, observational cohort study. *Ann Surg.* (2016) 264:1116–24. doi: 10.1097/SLA.0000000000001546
11. Puthucheary Z, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. *JAMA.* (2013) 310:15. doi: 10.1001/jama.2013.278481
12. Puthucheary ZA, Hart N. Skeletal muscle mass and mortality - but what about functional outcome? *Crit Care.* (2014) 18:110. doi: 10.1186/cc13729
13. Carrero JJ, Johansen KL, Lindholm B, Stenvinkel P, Cuppari L, Avesani CM. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. *Kidney Int.* (2016) 90:53–66. doi: 10.1016/j.kint.2016.02.025
14. Bauer J, Morley JE, Schols A, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: A Time for Action. An SCWD position paper.

J Cachexia Sarcopenia Muscle. (2019) 10:956–61. doi: 10.1002/jcsm.12483

15. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. *Am J Physiol.* (1996) 271(6 Pt 1):E941–51. doi: 10.1152/ajpendo.1996.271.6.E941
16. Akkoc I, Toptas M, Yalcin M, Demir E, Toptas Y. Psoas muscle area measured with computed tomography at admission to intensive care unit: prediction of in-hospital mortality in patients with pulmonary embolism. *Biomed Res Int.* (2020) 2020:1586707. doi: 10.1155/2020/1586707

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.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 21 May 2021
doi: 10.3389/fnut.2021.683393

Performance of Bioelectrical Impedance and Anthropometric Predictive Equations for Estimation of Muscle Mass in Chronic Kidney Disease Patients

Natália Tomborelli Bellafronte[1], Lorena Vega-Piris[2], Guillermina Barril Cuadrado[3] and Paula Garcia Chiarello[4]*

[1] Post-graduate Program in Health Sciences, Ribeirão Preto Faculty of Medicine, University of São Paulo, Ribeirão Preto, Brazil, [2] Methodology Unit, Instituto de Investigación Sanitaria del Hospital Universitario de la Princesa, Madrid, Spain, [3] Nephrology Department, Hospital Universitario de la Princesa, Madrid, Spain, [4] Department of Health Sciences, Ribeirão Preto Faculty of Medicine, University of São Paulo, Ribeirão Preto, Brazil

OPEN ACCESS

Edited by:
Alice Sabatino, University of Parma, Italy

Reviewed by:
Elane Hortegal, Federal University of Maranhão, Brazil
Barbara Perez Vogt, Federal University of Uberlandia, Brazil
Nayrana Reis, São Paulo State University, Brazil

***Correspondence:**
Natália Tomborelli Bellafronte
natalia.bellafronte@usp.br

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *20 March 2021*
Accepted: *26 April 2021*
Published: *21 May 2021*

Citation:
Bellafronte NT, Vega-Piris L, Cuadrado GB and Chiarello PG (2021) Performance of Bioelectrical Impedance and Anthropometric Predictive Equations for Estimation of Muscle Mass in Chronic Kidney Disease Patients. Front. Nutr. 8:683393. doi: 10.3389/fnut.2021.683393

Background: Patients with chronic kidney disease (CKD) are vulnerable to loss of muscle mass due to several metabolic alterations derived from the uremic syndrome. Reference methods for body composition evaluation are usually unfeasible in clinical settings.

Aims: To evaluate the accuracy of predictive equations based on bioelectrical impedance analyses (BIA) and anthropometry parameters for estimating fat free mass (FFM) and appendicular FFM (AFFM), compared to dual energy X-ray absorptiometry (DXA), in CKD patients.

Methods: We performed a longitudinal study with patients in non-dialysis-dependent, hemodialysis, peritoneal dialysis and kidney transplant treatment. FFM and AFFM were evaluated by DXA, BIA (Sergi, Kyle, Janssen and MacDonald equations) and anthropometry (Hume, Lee, Tian, and Noori equations). Low muscle mass was diagnosed by DXA analysis. Intra-class correlation coefficient (ICC), Bland-Altman graphic and multiple regression analysis were used to evaluate equation accuracy, linear regression analysis to evaluate bias, and ROC curve analysis and kappa for reproducibility.

Results: In total sample and in each CKD group, the predictive equation with the best accuracy was $AFFM_{Sergi}$ (men, $n = 137$: ICC = 0.91, 95% CI = 0.79–0.96, bias = 1.11 kg; women, $n = 129$: ICC = 0.94, 95% CI = 0.92–0.96, bias = −0.28 kg). $AFFM_{Sergi}$ also presented the best performance for low muscle mass diagnosis (men, kappa = 0.68, AUC = 0.83; women, kappa = 0.65, AUC = 0.85). Bias between $AFFM_{Sergi}$ and $AFFM_{DXA}$ was mainly affected by total body water and fat mass. None of the predictive equations was able to accurately predict changes in AFFM and FFM, with all ICC lower than 0.5.

Conclusion: The predictive equation with the best performance to asses muscle mass in CKD patients was $AFFM_{Sergi}$, including evaluation of low muscle mass

diagnosis. However, assessment of changes in body composition was biased, mainly due to variations in fluid status together with adiposity, limiting its applicability for longitudinal evaluations.

Keywords: anthropometry, bioelectrical impedance, body composition, chronic kidney disease, dual energy X-ray absorptiometry, fat free mass, lean mass, sarcopenia

INTRODUCTION

Lean body mass reserve, whose major component is skeletal muscle, is an essential reserve that provides amino acids to support processes such as injury repair and the immune response (1, 2). Therefore, lean body mass plays an important role in clinical outcomes and disease progress, with low lean body mass related to worse prognosis and shorter survival (3). Appendicular lean mass, which encompasses the lean soft tissue in the limbs and is mainly composed of skeletal muscle mass, is the variable of choice for low muscle mass diagnosis (4) and is considered as a key parameter for nutritional status evaluation.

Body composition technologies such as computed tomography, magnetic resonance imaging and dual energy X-ray absorptiometry (DXA) provide objective information about skeletal muscle mass (5). DXA, the most available one of them, has become recognized for its ability to accurately and precisely measure total body composition (5), in a three compartment level (fat mass, lean soft tissue and bone mineral content) (6). However, DXA is not a bedside technique, requires patient transportation to the instrument and has high cost, thus hampering its use in routine practice.

Given the unfeasibility to apply reference methods in clinical settings, there is a growing interest in more suitable techniques for body composition evaluation, such as anthropometry and bioelectrical impedance analysis (BIA). Equations using BIA parameters have been validated to predict fat free mass (FFM, lean mass + bone mineral content) in healthy individuals (7). Methods for prediction of appendicular fat free mass (AFFM, FFM of the limbs) from BIA were also developed in healthy elderly subjects (8), in healthy adults with validation in heart, lung and liver transplant patients (9); and also in non-dialysis-dependent (NDD) chronic kidney disease (CKD) patients (10). Furthermore, methods to predict FFM have been developed from anthropometric measures in healthy (11) and non-obese adults (12), as well as in NDD (13) and hemodialysis (HD) (14) CKD patients.

Patients with CKD are vulnerable to loss of muscle mass due to several metabolic alterations derived from the uremic syndrome (15–18). The metabolic disorders already present in NDD patients (16) become more evident in more advanced stages of CKD when peritoneal dialysis (PD) and HD treatments are established (3). Even after kidney transplant (KTx) nutritional status is difficult to recover (18). Accordingly, body composition of CKD patients worsens with disease progression (19), with lean tissue loss, sometimes masked by edema and usually preceding weight loss. As body composition is a biomarker for prognosis and helps to monitor clinical interventions, its assessment needs to be part of CKD routine care, although it is often imprecise in clinical settings.

The routine use of simplified methods such as BIA and anthropometry in hospital settings may improve the evaluation of nutritional status allowing clinicians to identify individuals who would benefit most from targeted interventions, as well as to reliably monitor longitudinal changes. Therefore, the primary aim of this study was to assess the accuracy of equations using BIA and anthropometry measures, compared to DXA, to estimate FFM and AFFM for cross-sectional and longitudinal assessment, in NDD, HD, PD, and KTx CKD patients. Secondary, we evaluated the capacity of surrogate methods to diagnose low muscle mass.

MATERIALS AND METHODS

This was a longitudinal study that evaluated clinically stable NDD, HD, PD, and KTx CKD patients from a nephrology outpatient clinic at Ribeirão Preto Medical School University Hospital (University of São Paulo, São Paulo, Brazil) and at a specialized dialysis clinic, the Nephrology Service of Ribeirão Preto. Patients with CKD were enrolled between 2017 and 2019. Inclusion criteria were: age $\geq$18 and $\leq$60 years and under regular treatment for at least 6 months; for NDD patients, estimated glomerular filtration rate (eGFR) $\leq$44 ml/min; for PD patients, absence of peritonitis in the previous 30 days and dialysis for at least 3 months; for HD patients, 4-h dialysis session, three times per week, through an arteriovenous fistula and dialysis for at least 3 months; for KTx patients, transplant for at least 6 months and eGFR $\geq$ 45 ml/min.

Exclusion criteria were presence of malignant diseases, acute infections and inflammation, human immunodeficiency virus, chronic lung disease, liver and heart failure, pregnancy or lactation, having amputations or an electronic implant, wheelchair user or inpatient, body weight >140 kg or BMI >40kg/m^2.

This study was conducted according to the principles of the Declaration of Helsinki, the protocol was approved by the human research ethics committee of Ribeirão Preto Medical School University Hospital. All selected patients were invited by the researcher and those interested in participating the

Abbreviations: AFFM, appendicular fat free mass; ANOVA, analyses of variance; BIA, multifrequency bioelectrical impedance spectroscopy; BMI, body mass index; CKD, chronic kidney disease; DXA, dual energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; FFM, fat free mass; HD, hemodialysis; ICC, intraclass correlation coefficient; KTx, kidney transplant; NDD, non-dialysis-dependent; OH, over-hydration; PD, peritoneal dialysis; R^2, coefficient of determination; Δ, body composition changes (prospective measurement—cross-sectional measurement); 95% CI, 95% confidence intervals.

study read and signed the informed consent form before the procedures began.

Protocol and Data Collection

Demographic and clinical data were collected from electronic medical records. Blood samples were taken within 1 d to 1 week before study assessment to determine laboratory parameters. Analyses were performed at the University Hospital's central laboratory. Serum creatinine was determined by kinetic method (creatinine calibrated to IDMS: COBAS 6000 [Roche/Hitachi]). The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI Creatinine 2009 equation). Dialysis patients had the weekly clearance of urea adjusted for total body water, with Kt/V determination in the week before the assessment.

Anthropometry and BIA were assessed by a single experienced dietician and DXA by a trained technician. All measures were performed consecutively at the same visit, after an 8-h fast (for HD group, 4-h fast), in patients with empty urinary bladder, drainage of the peritoneal dialysate, 30 min after the midweek HD session, advised to avoid strenuous physical activity in the previous day, wearing light clothes, without shoes and on the right side of the body (except if a fistula was present).

The second evaluation was performed 10 ± 2 months later. All measurements were performed exactly with the same protocol as the first evaluation and with the same equipment, dietician and technician for DXA, BIA and anthropometry assessments.

Anthropometric Measurements

Anthropometric measurements included body weight at the nearest 0.1 kg using a balance beam scale (Filizola®, São Paulo, Brazil); height, waist, calf and mid arm muscle circumferences at the nearest 0.1 cm. BMI was also calculated.

A flexible plastic tape with graduated scale was applied to measure circumferences. Waist circumference was measured at the umbilical scar level (20). Calf circumference was measured with subjects seating down, knees at 90° and at the calf greatest circumference (21). Mid arm circumference and triceps skinfold thickness were measured for mid arm muscle circumference calculation (22). Triceps skin fold thickness was assessed with an adipometer (Lange®, Cambridge Scientific Industries, Inc), three measures were taken and their mean was applied.

Hand grip strength was evaluated by a handheld pneumatic dynamometer (Charder®, MG 4800) with subjects seated and asked to grip as hard as possible for three times with 1 min intervals. The highest value was recorded (23).

BIA

Multi-frequency spectroscopy BIA (BCM, Fresenius Medical Care, Bad Homburg, Germany) was performed with a tetra-polar whole-body wrist-to-ankle protocol (24) after 10-min adaptation in a supine position. The variables resistance, reactance, resistance index (resistance [ohm] divided by squared height [cm^2]) and phase angle were provided at 50 kHz frequency; total body water, extracellular water and body cell mass (25), were provided by the software manufacturer.

Hydration status was assessed by over-hydration (OH) index provided by the BIA equipment (26, 27). Hydration disturbance was considered if OH $> +1.1$ L or OH < -1.1 L (28).

DXA

DXA (Hologic Discovery A, USA, Bedford, MA) was performed to evaluate lean mass, appendicular lean mass, AFFM, FFM, fat mass and fat mass of the trunk (6). Daily calibration of the device was performed before each assessment by scanning a spine phantom. A whole body scan was done after 10 min adaptation in supine position.

Predictive Equations of the Study

Supplementary Table 1 presents all the predictive equations herein evaluated, with information about BIA equipment applied, reference method against which the equation was validated and the population used for development of each equation. All BIA equations (7–10) evaluated in this study were developed with a tetra-polar whole-body wrist to ankle protocol.

Low Muscle Mass Definition

As no cutoff points to define low muscle mass are available for CKD patients, we applied definition based on the literature: appendicular lean mass <15 kg for women and <20 kg for men, assessed by DXA, according to the new European consensus on sarcopenia (4).

Statistical Analysis

Sample size was calculated based on the measurement of low muscle mass prevalence in CKD population. We assumed a minimum expected prevalence of 30% for all groups, with estimation of at least 80 patients for each CKD treatment group with a 5% precision and no correction for small population size (29).

Qualitative variables were presented as relative (percentage, %) and absolute (number, n) frequencies. Quantitative variables were expressed as measures of central tendency (mean) and dispersion (standard deviation).

Normality was tested with Shapiro-Wilk test with homoscedasticity evaluated. The differences between groups were performed by independent *T*-test or analysis of variance (ANOVA) adjusted by Bonferroni post-test, as appropriate. Categorical variables were compared by χ^2-test.

For regression analysis, collinearity of data was observed.

Binary logistic regression analysis was performed to estimate the odds ratio for the potential diagnostic for low muscle mass. A multivariate analysis was carried out to evaluate de confounding effect of sex, age and weight.

DXA was considered the reference method for FFM and AFFM against which the predictive equations were validated for accuracy, for cross-sectional and body composition change data (prospective—cross-sectional data [Δ]).

Intraclass correlation coefficient (ICC) (30) was calculated to analyze agreement in a group level by comparing AFFM and FFM assessments by DXA analysis with predicted values.

The 5% error tolerance between measured and predict value (95% limits of agreement) was calculated as the percentage of

the sample whose predicted value was within 0.95–1.05 fold the measured value.

Multiple regression analysis was also performed between measured and estimated values. The coefficient of determination (R^2) is useful as it reflects the percentage of variation in the measurements by one method that is related to the variation in the other method (31). The standard error of the estimate provides information about the degree of the error (31).

Agreement at individual level between DXA data and predictive equations was evaluated by the Bland-Altman graphic (32) calculating the 95% limits of individual agreement (mean bias between the two methods ± 1.96 SD).

The best performing equation to be considered as surrogate for DXA analysis, in the total sample and in each CKD subgroup, was defined based on the combination of two criteria: (a) the highest ICC value with the narrowest 95% Confidence interval (95% CI); (b) the highest R^2 and lowest standard error of the estimate. In addition, Bland-Altman bias with limit of agreement and also 5% error tolerance were taken into account.

For the best predictive equations, linear regression analyses were performed to determine the proportional bias between surrogate and reference methods.

Also, the inter-agreement between the DXA predictor of low muscle mass (appendicular lean mass) and the best predictive equation was quantified by Cohen's kappa coefficient. The sensitivity and specificity values were also estimated, and receiving operator characteristics curve analysis was carried out, assigning good reproducibility to area under the curve >80% (33).

TABLE 1 | Clinical data, anthropometry, BIA and body composition analyze of CKD subgroups stratified by sex.

	NDD		HD		PD		KTx	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Cross-sectional data								
Sample size	46	37	35	44	8	15	48	33
Age (years)	49 ± 10^{a}	48 ± 10^{a}	44 ± 12^{a}	49 ± 8^{a}	37 ± 12^{b}	42 ± 12^{b}	50 ± 8^{a}	48 ± 9^{a}
eGFR (mL/min/1.73 m^2)	19.3 ± 9.27^{a}	17.8 ± 7.53^{a}	NA	NA	NA	NA	71.20 ± 16.78^{b}	69.00 ± 20.79^{b}
KT/V	NA	NA	1.48 ± 0.19	1.84 ± 0.72	2.72 ± 0.52	2.53 ± 0.51	NA	NA
Dialysis/KTx time (mo)	NA	NA	66 ± 55	81 ± 67	11 ± 9	18 ± 20	96 ± 64	86 ± 57
Weight (kg)	84 ± 15.6^{a}	$69 \pm 16.3^{a*}$	69 ± 13.9^{b}	64 ± 13^{b}	79 ± 15^{b}	$59 \pm 9^{b*}$	76 ± 12^{b}	$64 \pm 11^{b*}$
Hand grip strength (kg)	38.8 ± 9.57^{ab}	$21.9 \pm 5.77^{ab*}$	36.6 ± 7.21^{a}	$20.4 \pm 4.98^{a*}$	45.5 ± 6.66^{ab}	$22.5 \pm 6.85^{ab*}$	40.6 ± 7.55^{b}	$21.7 \pm 4.90^{b*}$
Phase angle (°)	6.19 ± 1.06^{a}	$5.6 \pm 0.77^{a*}$	6.34 ± 0.94^{a}	$5.4 \pm 1.19^{a*}$	6.2 ± 0.65^{a}	5.6 ± 1.01^{a}	6.3 ± 0.78^{a}	$5.5 \pm 0.68^{a*}$
Resistance index (cm^2/ohm)	67.8 ± 10.73^{a}	47.5 ± 9.43^{a}	54.1 ± 11.8^{b}	39.8 ± 8.05^{b}	65.5 ± 10.14^{ab}	44.0 ± 7.87^{ab}	59.9 ± 8.66^{a}	41.2 ± 6.09^{a}
Total body water (L)	42.9 ± 5.46^{a}	$31.6 \pm 4.93^{a*}$	36.2 ± 5.55^{b}	$27.7 \pm 5.13^{b*}$	42.0 ± 6.08^{abc}	$29.5 \pm 3.99^{abc*}$	39.0 ± 4.96^{c}	$28.1 \pm 3.47^{c*}$
OH (L)	1.05 ± 2.01^{a}	$0.09 \pm 1.38^{a*}$	-0.18 ± 1.99^{b}	-0.66 ± 1.49^{b}	1.30 ± 0.70^{a}	$0.25 \pm 1.51^{a*}$	0.39 ± 1.02^{ab}	$-0.14 \pm 0.87^{ab*}$
Body cell mass (kg)	28.7 ± 5.21^{a}	$18.6 \pm 3.17^{a*}$	25.2 ± 4.50^{b}	$15.6 \pm 4.69^{b*}$	28.6 ± 5.37^{ab}	$18.8 \pm 3.22^{ab*}$	26.5 ± 5.28^{ab}	$15.8 \pm 2.78^{ab*}$
Appendicular lean mass (kg)	23.5 ± 3.92^{a}	$15.9 \pm 3.32^{a*}$	20.2 ± 3.54^{b}	$13.9 \pm 2.78^{b*}$	23.9 ± 5.21^{ab}	$14.1 \pm 2.30^{ab*}$	21.4 ± 3.27^{ab}	$13.8 \pm 2.15^{ab*}$
Lean mass (kg)	50.9 ± 8.03^{a}	$36.5 \pm 7.27^{a*}$	43.9 ± 7.75^{b}	$33.0 \pm 5.89^{b*}$	48.1 ± 9.18^{b}	$31.7 \pm 4.34^{b*}$	45.7 ± 6.49^{b}	$32.0 \pm 5.05^{b*}$
Fat mass (kg)	24.5 ± 8.62^{a}	26.1 ± 9.34^{a}	17.3 ± 8.72^{b}	$24.2 \pm 8.50^{a*}$	22.1 ± 7.92^{a}	20.8 ± 5.63^{a}	22.0 ± 6.67^{a}	$25.2 \pm 7.30^{a*}$
Δ data (prospective analysis—cross-sectional analysis)								
Sample size	16	9	6	12	8	15	20	9
Weight (kg)	-1.35 ± 3.08	-0.21 ± 1.97	0.15 ± 4.64	-0.76 ± 1.76	-1.84 ± 2.78	-1.75 ± 3.35	0.18 ± 3.17	-2.72 ± 4.70
Hand grip strength (kg)	-3.71 ± 5.44	-0.70 ± 2.28	-2.00 ± 6.43	-1.07 ± 4.45	-0.70 ± 2.89	-1.08 ± 4.10	-2.24 ± 5.18	-0.65 ± 4.36
Phase angle (°)	-0.07 ± 0.64	-0.22 ± 0.46	-0.17 ± 0.89	-0.20 ± 0.51	0.45 ± 0.25	0.12 ± 0.62	0.00 ± 0.40	0.03 ± 0.36
Resistance index (cm^2/ohm)	-3.42 ± 9.61	-0.27 ± 5.12	4.93 ± 14.18	1.01 ± 3.40	-4.42 ± 5.22	-2.78 ± 7.64	-0.72 ± 3.67	-1.90 ± 4.46
Total body water (L)	-1.68 ± 3.33	-0.34 ± 2.25	2.00 ± 4.98	0.05 ± 1.66	-1.42 ± 2.60	-1.34 ± 2.52	-0.19 ± 1.91	-1.00 ± 2.45
OH (L)	-0.32 ± 2.01	0.20 ± 0.82	0.80 ± 2.88	0.30 ± 0.82	-1.08 ± 0.47	-0.38 ± 1.53	-0.27 ± 0.86	-0.22 ± 0.46
Body cell mass (kg)	-1.70 ± 3.66	-0.66 ± 2.84	1.88 ± 5.22	-0.04 ± 2.51	-0.40 ± 4.22	-0.96 ± 1.68	-0.07 ± 2.44	-0.36 ± 2.78
Appendicular lean mass (kg)	-0.78 ± 1.78	-0.18 ± 1.18	-0.98 ± 1.95	-0.54 ± 1.32	-1.16 ± 3.02	-1.23 ± 1.51	-0.53 ± 0.98	-1.05 ± 2.27
Lean mass (kg)	-1.74 ± 3.61	-1.06 ± 2.83	-2.23 ± 3.81	-1.09 ± 2.83	-1.84 ± 4.45	-2.27 ± 2.59	-0.81 ± 2.27	-2.39 ± 5.63
Fat mass (kg)	0.18 ± 3.91	0.78 ± 2.51	2.26 ± 6.25	0.19 ± 2.68	0.25 ± 6.33	0.57 ± 2.74	1.05 ± 2.59	0.20 ± 4.70

*Data presented as mean ± standard deviation. BIA, bioelectrical impedance analyze; CKD, chronic kidney disease; HD, hemodialysis; KTx, kidney transplant; OH, over-hydration; NA, not applied; NDD, non-dialysis-dependent; PD, peritoneal dialysis. Body cell mass, resistance index, phase angle data by bioelectrical impedance analyze. Appendicular lean mass, lean mass, fat mass by dual energy X-ray absorptiometry analyze. *Independent T-test between sex ($p \leq 0.05$). ^{abc}ANOVA with Bonferroni post-test ($p \leq 0.008$).*

Pearson correlation was applied to assess association between variables.

Significance was set at $p \leq 0.05$ except if adjustment for multiple comparisons was necessary. All statistics were performed with SPSS version 23 (IBM, Armonk, NY, USA).

RESULTS

Low Muscle Mass Diagnosis

CKD was secondary to systemic arterial hypertension (29%), glomerulonephritis (25%) and diabetes mellitus (10%). Clinical data, BIA, anthropometric and DXA measurements of CKD subgroups stratified by sex are shown in **Table 1**. PD patients were younger ($p \leq 0.008$). Hand grip strength, appendicular lean mass and lean mass were lower for women than men. HD group had the lowest value of appendicular lean mass and fat mass, and NDD the highest measurement of appendicular lean mass. Total body water and OH were lower for women than men and for HD, and higher for NDD and PD patients. In the prospective analysis, all groups and both sexes lost muscle mass and strength, and gained fat mass.

Low muscle mass affected more women (63%, $n = 81$) than men (37%, $n = 51$) ($p \leq 0.05$), was more prevalent among HD (70%, $n = 55$) and less in NDD (30%, $n = 24$) than the other CKD patients (PD, 52%, $n = 12$; KTx, 52%, $n = 42$) ($p \leq 0.008$).

The evaluation of factors related to the odds ratio for low muscle mass diagnosis is presented in **Table 2**. As NDD patients had the lowest prevalence of low muscle mass and the highest appendicular lean mass they were chosen as reference group. HD patients had more than 5 times and KTx about 3 times the risk for low muscle mass compared to NDD. Adiposity was a risk factor in the multivariate analysis adjusted for sex, age, and weight.

Accuracy of Predictive Equations to Estimate FFM and AFFM

The agreement of predicted AFFM and FFM in comparison with AFFM and FFM from DXA for the total sample is presented in **Table 3**, and for each CKD group as supplementary material (NDD, **Supplementary Table 2**; HD, **Supplementary Table 3**; KTx, **Supplementary Table 4**; it was not possible to evaluated the PD group because of its small sample size). Agreement analysis was also performed according to the results of R^2 and standard error of the estimate in the total sample and is presented in **Table 4** for cross-sectional and prospective evaluations. Bland-Altman and scatter plot graphics for $AFFM_{Sergi}$ and $AFFM_{Kyle}$ equations compared with AFFM by DXA are presented in **Figure 1** and **Supplementary Figure 1**, respectively, for cross-sectional and body composition change data.

For cross-sectional data, considering the total sample and each CKD subgroup, FFM prediction equations did not performed well, $AFFM_{Sergi}$ and $AFFM_{Kyle}$ presented the best performance according to the highest ICC with narrowest 95%CI and the highest R^2 with lowest standard error of the estimate, in addition to the lowest bias and limits of agreement as well as the highest percentage within the 5% tolerance. Regarding body composition changes, none of the predictive equations was able to accurately predict changes in AFFM and FFM, with all ICC lower than 0.5.

Analysis of Interfering Factors for the Best Predictive Equations

We then investigated which variables were associated with bias between the best predictive equations ($AFFM_{Sergi}$ and $AFFM_{Kyle}$)

TABLE 2 | Odds Ratio of low muscle mass diagnosis in total sample ($n = 266$).

	Unadjusted			Adjusted by sex, age and weight		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***
Sex (reference: men)	0.351	0.214–0.578	0.000			
CKD treatment (reference: NDD)						
HD	5.978	3.032–11.788	0.000	5.155	1.779–14.940	0.003
PD	2.846	1.102–7.350	0.031	1.236	0.261–5.851	0.790
KTx	2.809	1.468–5.375	0.002	3.154	1.143–8.704	0.027
Weight (kg)	0.837	0.803–0.873	0.000			
BMI (kg/m^2)	0.738	0.683–0.797	0.000	1.079	0.734–1.340	0.679
Hand grip strength (kg)	0.927	0.904–0.951	0.000	0.906	0.849–0.967	0.003
Phase angle (°)	0.649	0.501–0.840	0.0001	0.760	0.482–1.200	0.628
Resistance index (cm^2/ohm)	0.863	0.832–0.894	0.000	0.831	0.772–0.895	0.000
Body cell mass (kg)	0.837	0.786–0.880	0.000	0.746	0.660–0.842	0.000
Fat mass (kg)	0.903	0.872–0.935	0.000	2.035	1.606–2.578	0.000
Fat mass of trunk (kg)	0.831	0.783–0.883	0.000	1.765	1.466–2.125	0.000

BMI, body mass index; CKD, chronic kidney disease; HD, hemodialysis; KTx, kidney transplant; NDD, non-dialysis-dependent; OR, odds ratio; PD, peritoneal dialysis. Body cell mass, resistance index, phase angle data by bioelectrical impedance analyze. Fat mass and fat mass of the trunk by dual energy X-ray absorptiometry analyze. Low muscle mass according to the Revised European consensus (4) applying appendicular lean mass measurement by dual energy X-ray assessment. OR by binary logistic regression. For regression model analysis, the following variables were evaluated: age (years); estimated glomerular filtration ratio (mL/min/1.73 m^2); KT/V; creatinine (mg/dL); urea (mg/dL); weight (kg), height (m); overhydration index (L); extracellular water (L); intracellular water (L); total body water (L); waist circumference (cm); calf circumference (cm); mid arm circumference (cm); mid arm muscle circumference (cm); resistance (ohm); reactance (ohm); the variables present in this table.

TABLE 3 | Agreement between DXA and prediction equations for AFFM and FFM in total sample stratified by sex.

Body composition variable	Men												Women											
	DXA or prediction equation		Bland-Altman analysis				ICC analysis			Pearson correlation		5% tolerance	DXA or prediction equation		Bland-Altman analysis				ICC analysis			Pearson correlation		5% tolerance
			Bias (DXA-prediction)		LOA		ICC	(95% CI)							Bias (DXA-prediction)		LOA		ICC	(95%CI)				
	$\bar{x}$	SD	$\bar{x}$	SD	Lower	Upper	*r*	Lower	Upper	*r*	*p*	% (n)	$\bar{x}$	SD	$\bar{x}$	SD	Lower	Upper	*r*	Lower	Upper	*r*	*p*	% (n)
Cross-sectional data *n* = 137													**Cross-sectional data *n* = 129**											
$AFFM_{DXA}$ (kg)	23.16	4.11											15.32	3.02										
$AFFM_{Sergi}$ (kg)	22.05	3.31	1.11	1.83	−2.47	4.70	0.915	0.795	0.956	0.90	0.000	50 (69)	15.61	2.60	−0.28	1.26	−2.76	2.19	0.945	0.921	0.962	0.91	0.000	42 (54)
$AFFM_{Kyle}$ (kg)	23.90	3.76	−0.73	1.82	−4.30	2.83	0.935	0.892	0.959	0.90	0.000	44 (61)	16.16	2.93	−0.83	1.24	−3.28	1.61	0.935	0.815	0.969	0.91	0.000	39 (50)
$AFFM_{Macdonald}$ (kg)	22.10	3.21	1.05	2.11	−3.08	5.18	0.804	0.686	0.880	0.86	0.00	42 (57)	13.86	2.53	1.45	1.82	−2.11	5.01	0.692	0.284	0.846	0.80	0.000	24 (31)
FFM_{DXA} (kg)	48.99	8.23											34.87	6.42										
$FFM_{TianHGS}$ (kg)	50.32	6.65	−1.29	3.90	−8.93	6.35	0.852	0.782	0.898	0.88	0.000	42 (58)	36.25	5.90	−1.34	2.96	−7.14	4.46	0.865	0.768	0.917	0.89	0.000	41 (53)
$FFM_{TianMAMC}$ (kg)	53.09	6.82	−4.10	3.77	−11.48	3.28	0.764	0.140	0.909	0.89	0.000	32 (43)	37.56	6.05	−2.69	3.00	−8.57	3.19	0.809	0.366	0.919	0.88	0.000	30 (39)
$FFM_{NooriHGS}$ (kg)	40.22	7.85	8.80	8.69	−8.23	25.83	0.262	−0.048	0.505	0.42	0.000	22 (30)	23.72	5.12	11.18	6.54	−1.63	23.99	0.129	−0.076	0.360	0.38	0.000	5 (6)
$FFM_{NooriMAMC}$ (kg)	48.32	6.12	0.66	4.04	−7.96	8.57	0.842	0.785	0.885	0.88	0.000	42 (57)	45.34	5.40	−10.46	3.00	−16.34	−4.58	0.342	−0.036	0.712	0.88	0.000	2 (3)
FFM_{Hume} (kg)	53.05	6.40	−4.06	4.13	−12.15	4.03	0.732	0.181	0.886	0.87	0.000	30 (41)	41.49	5.64	−6.61	3.16	−12.80	6.19	0.540	−0.078	0.833	0.87	0.000	7 (9)
$FFM_{Janssen}$ (kg)	30.21	4.53	18.78	5.11	8.76	28.79	0.141	−0.033	0.437	0.83	0.000	0 (0)	18.91	3.44	15.96	4.11	7.90	24.01	0.118	−0.029	0.388	0.81	0.000	0 (0)
FFM_{Lee} (kg)	33.91	3.84	15.08	5.36	4.57	25.58	0.174	−0.052	0.486	0.85	0.000	0 (0)	23.37	3.39	11.50	3.91	3.83	19.16	0.203	−0.049	0.538	0.86	0.000	0 (0)
Δ data *n* = 47													**Δ data *n* = 40**											
$AFFM_{DXA}$ (kg)	−0.78	1.66											−0.78	1.58										
$AFFM_{Sergi}$ (kg)	−2.86	1.50	2.09	1.73	−1.30	5.48	0.361	−0.194	0.671	0.41	0.000	0 (0)	−4.25	0.93	3.47	1.37	0.77	6.17	0.177	−0.115	0.504	0.50	0.000	0 (0)
$AFFM_{Kyle}$ (kg)	−3.20	1.88	2.43	1.97	−1.43	6.29	0.339	−0.196	0.653	0.39	0.000	0 (0)	−5.08	1.16	2.43	1.97	−1.43	6.29	0.158	−0.085	0.480	0.52	0.000	0 (0)
$AFFM_{Macdonald}$ (kg)	−0.31	1.84	−0.45	1.94	−4.25	3.35	0.385	0.117	0.603	0.39	0.000	0 (0)	−0.21	1.02	−0.56	1.43	−3.36	2.80	0.391	0.106	0.620	0.46	0.000	0 (0)
FFM_{DXA} (kg)	−1.48	3.19											−1.71	3.50										
$FFM_{TianHGS}$ (kg)	−0.27	1.33	−1.18	2.95	−6.96	4.60	0.117	−0.144	0.378	0.17	0.263	0 (0)	−0.54	1.31	−1.17	3.00	−7.05	4.71	0.329	0.043	0.572	0.54	0.000	0 (0)
$FFM_{TianMAMC}$ (kg)	−0.03	1.53	−1.47	3.16	−7.66	4.72	0.173	−0.081	0.419	0.25	0.09	0 (0)	−0.61	1.43	−1.09	3.03	−7.02	4.84	0.338	0.050	0.579	0.51	0.000	0 (0)
$FFM_{NooriHGS}$ (kg)	−2.27	4.68	0.90	5.58	−10.03	11.83	−0.021	−0.311	0.274	−0.023	0.881	0 (0)	−0.80	3.49	−0.90	3.18	−7.13	5.33	0.472	0.324	0.747	0.58	0.000	0 (0)
$FFM_{NooriMAMC}$ (kg)	0.04	1.33	−1.54	3.13	−7.67	4.59	0.155	−0.093	0.400	0.25	0.08	0 (0)	−0.51	1.23	−1.19	3.10	−7.26	4.88	0.279	−0.007	0.532	0.48	0.000	0 (0)
FFM_{Hume} (kg)	−0.18	1.08	−1.32	3.12	−7.43	4.79	0.123	−0.123	0.375	0.22	0.12	0 (0)	−0.39	0.96	−1.32	3.10	−7.39	4.75	0.243	−0.039	0.500	0.52	0.000	0 (0)
$FFM_{Janssen}$ (kg)	−0.52	3.21	−0.93	3.63	−8.04	6.18	0.352	0.081	0.577	0.36	0.01	0 (0)	−0.35	2.14	−1.36	3.07	−7.37	4.65	0.403	0.115	0.631	0.49	0.000	0 (0)
FFM_{Lee} (kg)	−0.13	0.80	−1.36	3.10	−7.43	4.71	0.094	−0.152	0.347	0.22	0.12	0 (0)	−0.32	0.79	−1.38	3.16	−7.57	4.81	0.202	−0.075	0.464	0.53	0.000	0 (0)

AFFM, appendicular fat free mass; DXA, dual energy X-ray absorptiometry; FFM, fat free mass; ICC, intraclass correlation coefficient; LOA, limits of individual agreement; Δ, body composition changes data (second assessment—first assessment). Bias calculated as DXA data—Prediction equation value; 5% tolerance between DXA and prediction equations (Prediction equation/DXA from 0.95 to ≤ 1.05).

TABLE 4 | Performance of prediction equations in total sample ($n = 266$).

Prediction equation	R^2 (coefficient of determination)	Standard error of the estimate (kg)
Cross-sectional data $n = 266$		
$AFFM_{Sergi}$	0.91	1.58
$AFFM_{Kyle}$	0.91	1.57
$AFFM_{Macdonald}$	0.86	1.98
$FFM_{TianHGS}$	0.88	3.47
$FFM_{TianMAMC}$	0.88	3.46
$FFM_{NooriHGS}$	0.52	7.12
$FFM_{NooriMAMC}$	0.63	6.27
FFM_{Hume}	0.86	3.73
$FFM_{Janssen}$	0.82	4.25
FFM_{Lee}	0.84	4.05
Δ data $n = 87$		
$AFFM_{Sergi}$	0.14	1.50
$AFFM_{Kyle}$	0.13	1.51
$AFFM_{Macdonald}$	0.16	1.48
$FFM_{TianHGS}$	0.13	2.97
$FFM_{TianMAMC}$	0.14	3.09
$FFM_{NooriHGS}$	0.05	3.11
$FFM_{NooriMAMC}$	0.13	3.12
FFM_{Hume}	0.13	3.11
$FFM_{Janssen}$	0.16	3.06
FFM_{Lee}	0.14	3.09

AFFM, appendicular fat free mass; FFM, fat free mass.

and AFFM by DXA (**Table 5**). The differences between the two methods were affected by sex, resistance index, total body water, AFFM and fat mass for $AFFM_{Sergi}$ (adjusted $r^2 = 0.95$) and $AFFM_{Kyle}$ (adjusted $r^2 = 0.94$), for cross-sectional data and for body composition change data ($AFFM_{Sergi}$ adjusted $r^2 = 0.96$ and $AFFM_{Kyle}$ adjusted $r^2 = 0.97$).

Analysis of Reproducibility for the Best Predictive Equations

The reproducibility of $AFFM_{Sergi}$ and $AFFM_{Kyle}$ for low muscle mass diagnosis, using appendicular lean mass by DXA and according to the cutoffs proposed by the European revised consensus on sarcopenia (4), is presented in **Table 6**. The inter-agreement was quantified by kappa values, according to sex and CKD subgroups. In total sample and in each CKD subgroup, $AFFM_{Sergi}$ had a better performance than $AFFM_{Kyle}$, with Kappa from moderate to substantial agreement, and with good performance among NDD and KTx patients and poor performance among HD patients.

Correlations

Given the poor performance of prediction equations in predict changes of body composition, we performed correlation analysis to investigate if there is some surrogate variable with good correlation with cross-sectional data and muscle mass changes, being as an alternative measurement for longitudinal evaluations (**Table 7**).

DISCUSSION

Our study showed that $AFFM_{Sergi}$ was the best equation to predict AFFM in CKD, with good performance for low muscle mass diagnosis among NDD and KTx patients, and poor performance among HD patients. FFM equations did not perform well. Fat mass and total body water were important factors that interfered with accuracy of prediction equations, mainly for longitudinal evaluations. None of the predictive equations was accurate for assessment of changes in AFFM and FFM. Resistance index presented the best correlation with appendicular lean mass and lean mass in cross-sectional and longitudinal assessment, highlighting as an alternative measurement for longitudinal evaluations. Multivariate analysis after adjustment for sex, age and weight, revealed HD, KTx and adiposity as risk factors for low muscle mass.

$AFFM_{Sergi}$ (8) equation was recommended by the revised European consensus on sarcopenia (4) as a way to standardize BIA estimation since its assessments vary widely depending on the device applied (34). $AFFM_{Kyle}$ (9) was chosen because it was the first widely evaluated predictive equation for AFFM developed with spectroscopy BIA. Both equations were validated against DXA and presented the best performances. For the others equations, some factors may have interfered with the accuracy of the estimations, such as the protocol applied for body composition assessment. While Noori et al. (14) carried out measurements in a non-HD day, in our study evaluations were conducted after the midweek HD session. Probably, the different time-to-perform lower the accuracy, since fluid status is one of the main factors interfering with accuracy of BIA for body composition evaluations (35).

Macdonald et al. (10), developed the equation with NDD CKD patients with eGFR of 45.9 ± 28.8 ml/min, much higher than eGFR in our NDD group and lower than eGFR in our KTx sample. As $AFFM_{Macdonald}$ is strongly associated with eGFR (10), it is important to take into consideration this parameter for $AFFM_{Macdonald}$ estimations, and probably was the reason for the worse performance in our sample. Tian et al. (13) developed their equations from NDD CKD patients with an eGFR of 27 mL/min/1.73 m^2. Although this value is higher than the eGFR in our sample, it is closer than eGFR from Macdonald sample. Tian equations presented better performance for FFM than $AFFM_{Macdonald}$, although lower than $AFFM_{Sergi}$ and $AFFM_{Kyle}$.

Another important factor is the BIA equipment applied for the development and validation of the predictive equation. All BIA devices involve application of a weak and alternating current through the body. However, they are not interchangeable. The number of frequencies (simple, multiple frequency or spectroscopy), the electronic circuitry, and the mathematical models (linear regression–derived population-specific equations or mathematical biophysical modeling by Cole model and Hanai's mixture theory) (36) applied for each device result in different predictions of water and body composition and also

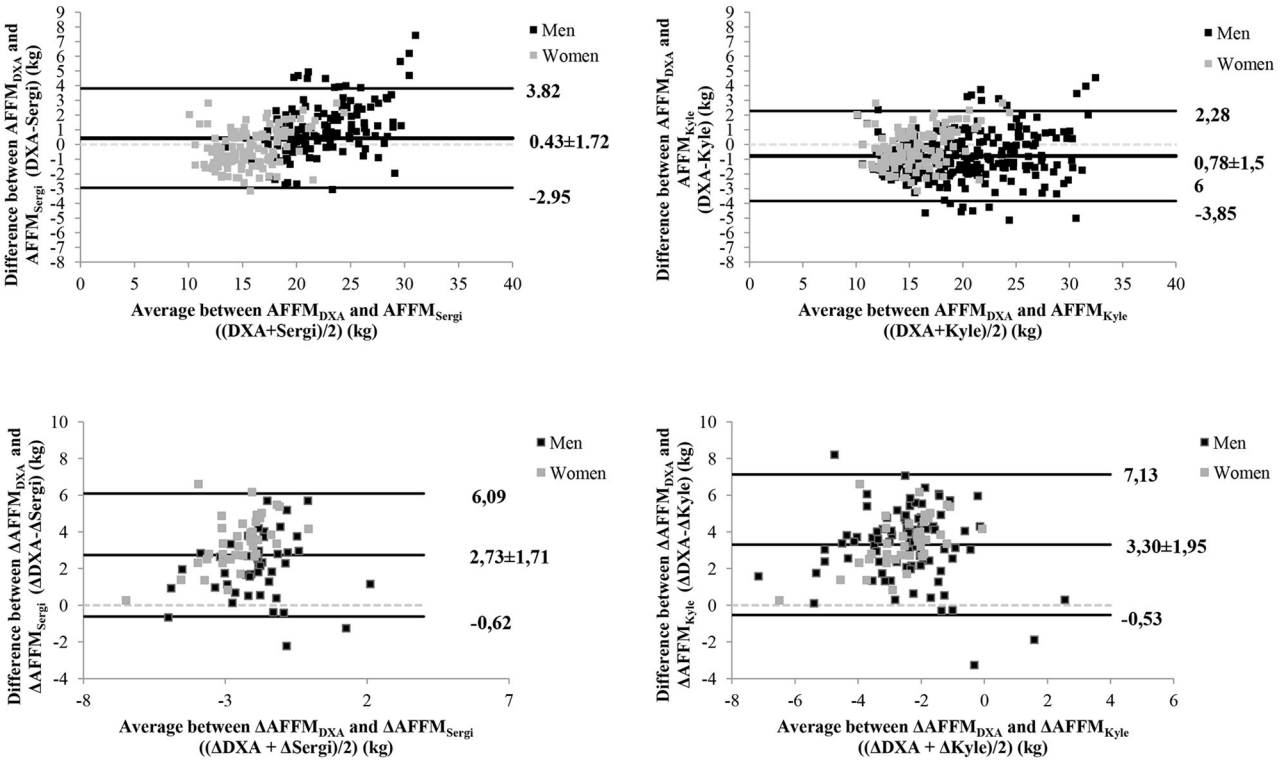

FIGURE 1 | Bland-Altman plots for $AFFM_{Sergi}$ and $AFFM_{Kyle}$ predictive equations compared with DXA results, in total sample, for cross-sectional and body composition changes data (Δ).

in raw values that are not interchangeable (35). As could be seen in **Supplementary Table 1**, different BIA was applied for development of the equations herein evaluated.

All methods for evaluation of body composition are indirect, requiring assumptions that may not hold true in illness (5). Failure to account for the precision error in the reference method applied to validate the estimated measurement may contribute to misinterpretation and scaling error (37). This could contribute to decrease the accuracy of $AFFM_{Janssen}$ (7), FFM_{Lee} (12), and FFM_{Hume} (11) as they apply other reference methods than DXA.

It is essential to establish the ability of bedside methods to detect changes over time. In our study, none of the evaluated predictive equations had at least a good ICC for muscle mass changes, including $AFFM_{Sergi}$ and $AFFM_{Kyle}$. We took into account that the expected level of change in the body composition compartment was sufficiently high to be detected by the reference method, and confirmed that it was also detectable by the bedside method (24). Our total sample had a mean percentage of change [(second assessment –first assessment)/first assessment *100)] in AFFM of $-3.71 \pm 8.32\%$, measured by DXA, $-1.37 \pm 6.33\%$ by $AFFM_{Sergi}$ and $-1.46 \pm 7.32\%$ by $AFFM_{Kyle}$. Similarly to DXA, $AFFM_{Sergi}$, and $AFFM_{Kyle}$ were able to detect changes in AFFM, although the direction of the change (gain or loss) and the quantity were poorly predicted, as confirmed by the low ICC and correlation and scatter plot graphics with fixed bias. Probably the fluid shift present in CKD and also the variation of adiposity lowered the accuracy of longitudinal assessment, as total body water and fat mass were important bias for prediction values. Therefore, $AFFM_{Sergi}$ or $AFFM_{Kyle}$ might not be appropriate for follow-up analysis.

The advantages of BIA compared with reference methods are mainly the portability of the device, ease of use, and its affordability. Its use to assess body composition has increased in daily practice, mainly due to validation studies. Close adherence to recommended measurement protocols (38) as well as a standardized time to perform, are important to minimize potential errors, mainly for longitudinal evaluation (38). However, estimation of body composition in CKD is prone to error because underlying assumptions such as hydration of FFM at 73%, stable distribution of extracellular to intracellular water, and predictability of body geometry are not met in this disease, especially in patients with altered hydration or excess adiposity (38). Prediction of AFFM seems to be less affected by the underlying considerations, but, as shown by our results, has limited accuracy in prospective assessment. The use of segmental BIA could improve prediction, despite studies showing controversial results (39, 40).

As pointed out by Mulasi et al. (41) it is unlikely that any algorithm can be relied upon for accurate whole-body estimates in patients with excess adiposity or altered fluid status, both conditions present in CKD. Excess adiposity (BMI $\geq$ 25 kg/m^2) was present in 60% of our total sample and over-hydration

TABLE 5 | Simple and multiple linear regression models for factors associated with bias in agreement between DXA and prediction equations in total sample.

	$AFFM_{DXA} - AFFM_{Sergi}$ (kg)								$AFFM_{DXA} - AFFM_{Kyle}$ (kg)							
	Simple linear regression model				Multiple linear regression model				Simple linear regression model				Multiple linear regression model			
	Coefficient	95% CI		*p*	Coefficient	95% CI		*p*	Coefficient	95% CI		*p*	Coefficient	95% CI		*p*
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Cross-sectional data (*n* = 266)																
Intercept					−0.443	−0.738	−0.148	0.003					0.775	0.491	1.060	0.000
Sex	1.400	1.018	1.783	0.000	−1.404	−1.559	−1.249	0.000	0.099	−0.280	0.478	0.607	−1.885	−2.035	−1.735	0.000
RI (cm^2/ohm)	0.048	0.033	0.062	0.000	−0.038	−0.052	−0.024	0.000	−0.008	−0.022	0.006	0.263	−0.086	−0.099	−0.072	0.000
TBW (L)	0.096	1.018	1.783	0.000	−0.328	−0.363	−0.294	0.000	−0.002	−0.027	0.023	0.856	−0.322	−0.355	−0.288	0.000
AFFM (kg)	0.214	0.185	0.243	0.000	0.865	0.836	0.893	0.000	0.079	0.045	0.114	0.000	0.865	0.837	0.893	0.000
FM (kg)	−0.042	−0.067	−0.018	0.001	−0.077	−0.084	−0.070	0.000	−0.047	−0.069	−0.025	0.000	−0.074	−0.080	−0.068	0.000
Body composition change (Δ) Data (*n* = 87)																
Intercept					3.958	3.838	4.077	0.000					4.745	4.619	4.870	0.000
Sex	−1.384	−2.062	−0.705	0.000	−1.368	−1.522	−1.215	0.000	−1.874	−2.616	−1.131	0.000	−1.881	−2.042	−1.720	0.000
IR (cm^2/ohm)	−0.073	−0.125	−0.022	0.006	−0.076	−0.107	−0.440	0.000	−0.121	−0.176	−0.065	0.000	−0.125	−0.158	−0.091	0.000
TBW (L)	−0.175	−0.305	−0.045	0.090	−0.224	−0.306	−0.142	0.000	−0.290	−0.431	−0.149	0.000	−0.222	−0.308	−0.136	0.000
AFFM (kg)	0.661	0.481	0.841	0.000	0.846	0.777	0.914	0.000	0.580	0.349	0.811	0.000	0.842	0.770	0.913	0.000
FM (kg)	−0.298	−0.378	−0.219	0.000	−0.083	−0.110	−0.550	0.000	−0.298	−0.396	−0.200	0.000	−0.086	−0.115	−0.057	0.000

AFFM, appendicular fat free mass; DXA, dual energy X-ray absorptiometry; FM, fat mass; RI, resistance index; TBW, total body water. IR and TBW by bioelectrical impedance analysis. AFFM and FM by dual energy X-ray analysis. For regression model analysis, the following variables were evaluated: sex (1 man, 0 woman); age (years); estimated glomerular filtration ratio (mL/min/1.73 m^2); KT/V; creatinine (mg/dL); urea (mg/dL); weight (kg), height (m); overhydration index (L); extracellular water (L); intracellular water (L); total body water (L); extracellular to total body water ratio; body cell mass (kg); lean mass, fat-free mass and fat mass by DXA analysis as well as their indexes; the variables present in this table.

TABLE 6 | Reproducibility of AFFM prediction equations to evaluate low muscle mass compared to DXA as reference.

	Inter-agreement		Low muscle mass diagnostic performance					
	Kappa	*p*	Sensibility (%)	Specificity (%)	AUC	95% CI		Significance level
						Lower	Upper	
DXA *vs.* AFFM$_{Sergi}$								
Total sample ($n = 266$)	0.676	0.000	73.48	94.02	0.838	0.786	0.889	0.000
Men ($n = 137$)	0.680	0.000	74.50	91.86	0.832	0.753	0.911	0.000
Women ($n = 129$)	0.650	0.000	72.83	97.91	0.854	0.788	0.920	0.000
NDD-CKD patients ($n = 83$)	0.809	0.000	78.26	98.33	0.883	0.780	0.986	0.000
Men ($n = 46$)	0.862	0.000	88.88	97.29	0.931	0.806	1.000	0.000
Women ($n = 37$)	0.757	0.000	71.42	100.00	0.857	0.708	1.000	0.000
HD-CKD patients ($n = 79$)	0.464	0.000	72.72	79.16	0.759	0.643	0.876	0.000
Men ($n = 35$)	0.364	0.031	30.00	66.66	0.683	0.501	0.866	0.050
Women ($n = 44$)	0.542	0.000	74.28	100.00	0.871	0.769	0.973	0.001
KTx-CKD patients ($n = 81$)	0.633	0.000	69.04	94.87	0.820	0.723	0.916	0.000
Men ($n = 48$)	0.689	0.000	70.00	96.42	0.832	0.701	0.964	0.000
Women ($n = 33$)	0.520	0.001	68.18	90.90	0.795	0.636	0.955	0.006
DXA *vs.* AFFM$_{Kely}$								
Total sample ($n = 266$)	0.510	0.000	53.03	97.76	0.754	0.694	0.814	0.000
Men ($n = 137$)	0.585	0.000	33.33	96.51	0.649	0.549	0.750	0.004
Women ($n = 129$)	0.341	0.000	65.43	100.00	0.827	0.757	0.897	0.000
NDD-CKD patients ($n = 83$)	0.570	0.000	47.82	100.00	0.739	0.600	0.878	0.001
Men ($n = 46$)	0.315	0.003	22.00	100.00	0.611	0.383	0.840	0.306
Women ($n = 37$)	0.691	0.000	64.28	100.00	0.821	0.659	0.984	0.001
HD-CKD patients ($n = 79$)	0.388	0.000	60.00	87.5	0.738	0.623	0.852	0.001
Men ($n = 35$)	0.283	0.069	50.00	80.00	0.650	0.466	0.834	0.134
Women ($n = 44$)	0.439	0.000	65.71	100.00	0.829	0.710	0.947	0.003
KTx-CKD patients ($n = 81$)	0.443	0.000	45.23	100.00	0.726	0.615	0.838	0.000
Men ($n = 48$)	0.280	0.005	25.00	100.00	0.625	0.458	0.792	0.143
Women ($n = 33$)	0.538	0.000	63.63	100.00	0.818	0.677	0.960	0.003

AFFM, appendicular fat free mass; AUC, area under the curve; DXA, dual energy X-ray absorptiometry; HD, hemodialysis; KTx, kidney transplant therapy; NDD, non-dialysis-dependent. Patients were classified with low muscle mass according to cutoffs values for ALM proposed by revised European consensus (4): appendicular lean mass <15 kg for women and <20 kg for men, assessed by DXA.

(OH > + 1.1) in 40%. As BIA provides indirect estimates of body composition from the measurement of resistance of body tissues to an electric current, raw data might be an option to predicted values (42). In our sample, the only parameter with good correlation with longitudinal variation in lean mass and appendicular lean mass was the resistance index. In agreement with other authors (42) we suggest that raw measurements of BIA could provide better objective biomarkers of nutritional status than predicted values. This is an important issue for BIA applicability in clinical settings, mainly in CKD where it is already applied for fluid management. Another point that should not be underestimated is that, more often lately, clinicians have limited time to search the literature to identify the most suitable equation for the patient being evaluated; therefore, the only alternative is to directly apply the prediction provided by the device without knowing its appropriateness or interpreting the raw data.

Low muscle mass was present in more than 30% of patients in all CKD groups, highlighting that the nutritional status was compromised even among non-elderly patients. The NDD group was less affected by low muscle mass, although these patients also presented an important prevalence. A higher prevalence of low muscle mass was observed in HD patients, in agreement with other studies (43) suggesting that muscle wasting could progress as kidney function declines (19). Likewise, increased inflammation and metabolic acidosis promoted by the dialysis process accelerate protein degradation (44). Similarly to our results, other studies showed an important prevalence of low muscle mass among KTx patients (45), which could be related to previous dialysis therapy (90% of our patients underwent HD before KTx with a median duration of 40 months, 6–65) and with body composition deterioration after transplant (18), demonstrating the challenges of recovering nutritional status in CKD.

CKD patients lost muscle mass and gained fat mass, worsening their nutritional status, which is associated with worse quality of life and higher mortality (46). Thus, screening, prevention, and treatment of muscle loss should have high priority in CKD patients.

TABLE 7 | Correlations between surrogate methods and DXA in total sample ($n = 266$).

Variable	Correlation coefficient	*p*
Cross-sectional data $n = 266$		
Correlations with appendicular lean mass (DXA)		
Mid arm muscle circumference (cm)	0.73	0.000
Calf circumference (cm)	0.65	0.000
Resistance index (cm^2/ohm)	0.91	0.000
Phase angle (°)	0.35	0.000
Body cell mass (kg)	0.82	0.000
$AFFM_{Sergi}$ (kg)	0.95	0.000
$AFFM_{Kyle}$ (kg)	0.95	0.000
Correlation with len mass (DXA)		
Mid arm muscle circumference (cm)	0.74	0.000
Calf circumference (cm)	0.65	0.000
Resistance index (cm^2/ohm)	0.92	0.000
Phase angle (°)	0.29	0.000
Body cell mass (kg)	0.78	0.000
$AFFM_{Sergi}$ (kg)	0.96	0.000
$AFFM_{Kyle}$ (kg)	0.96	0.000
Δ data $n = 87$		
Correlation with Δ appendicular lean mass (DXA)		
Mid arm muscle circumference (cm)		>0.05
Calf circumference (cm)	0.34	0.000
Resistance index (cm^2/ohm)	0.68	0.000
Phase angle (°)		>0.05
Body cell mass (kg)	0.37	0.000
$AFFM_{Sergi}$ (kg)	0.38	0.000
$AFFM_{Kyle}$ (kg)	0.37	0.000
Correlation with Δ lean mass (DXA)		
Mid arm muscle circumference (cm)		>0.05
Calf circumference (cm)	0.34	0.000
Resistance index (cm^2/ohm)	0.70	0.000
Phase angle (°)		>0.05
Body cell mass (kg)	0.40	0.000
$AFFM_{Sergi}$ (kg)	0.41	0.000
$AFFM_{Kyle}$ (kg)	0.40	0.000

AFFM, appendicular fat free mass; Δ, body composiiton change (prospective assessment - cross-sectional assessment).

Total fat mass and trunk fat mass are risk factors for low muscle mass. Systemic and muscle oxidative stress, persistent inflammation, insulin resistance and hormonal alterations due to the presence of excess adipose tissue (47) lead to changes in muscle metabolism. These result in reduction of lean mass to fat mass ratio (48). Accordingly, the risk of skeletal muscle loss should also be considered in CKD patients with obesity, the most challenging patients for nutritional status evaluation as not only fluid status may impair their body composition assessment but also excess adiposity could mask loss of muscle mass. As provided by our results, fat mass was an important factor in bias for prediction of AFFM. So, obese patients could benefit most from use of raw BIA data for longitudinal evaluation of muscle mass.

The study's main limitations are the exclusion of patients over 60 years of age, the low sample size of the PD group and the short time of longitudinal assessment, which precludes analysis of exposure/outcome association and limits the evaluation of prediction equations for assessment of changes in body composition. Additionally, body thickness, hydration status, and diseases with water retention can affect DXA results (6). Therefore, in our DXA analysis of body composition, data from CKD patients with excess fat and fluid retention could be prone to errors that may promote a scaling error leading to misinterpretation of predicted values. On the other hand, the present study presents several strengths. First, the evaluation of CKD patients was carried out under treatment conditions such as HD and PD, as well as for NDD patients and patients after KTx therapy, which are more rarely evaluated. Moreover, the study includes DXA as reference method applied to all patients, together with a cross-sectional and longitudinal assessment. Additionally, we evaluated a wide variety of BIA and anthropometry predictive equations through a comprehensive statistical analysis including not only assessment of accuracy and agreement but also sensitivity and specificity analysis with discriminative power to detect low muscle mass.

In conclusion, accuracy and reproducibility analysis in the present study indicates that the predictive equation $AFFM_{Sergi}$ can be an alternative technique to assess muscle mass in CKD patients, and could be useful for low muscle mass diagnosis in NDD and KTx patients, with limited applicability for patients under HD. However, prediction of changes in AFFM may be biased, mainly due to variations in fluid status together with the presence of high adiposity, limiting the applicability of $AFFM_{Sergi}$ equation for longitudinal evaluations. As resistance index from BIA presented the best correlation with cross-sectional and longitudinal data of lean mass evaluated by reference method, we suggest that raw data from BIA could provide better information about progression of muscle mass in CKD, mainly in patients with dehydration or hiperhydration and excess adiposity. More studies are needed to better understand the relationship between nutritional status and also clinical prognosis with raw data from BIA as a way to easily obtain quick and objective measurements suitable to be tracked over time. Body composition evaluations are a priority for CKD patients, given the worsening of their nutrition status over time. Patients in HD, after KTx and with obesity are at higher risk for low muscle mass diagnosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Research Ethics Committee of Ribeirao Preto Medical School University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NB, PC, and GC contributed to the conception of the research. NB contributed to the design of the research, acquisition of the data, and drafted the manuscript. NB and LV-P contributed to the analysis and interpretation of data. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

FUNDING

This research was funded by Coordenação de aperfeiçoamento de pessoal de nível superior (CAPES) (NB, Grant No. 001). The funding agency of the project did not participate in the study design, data analysis and interpretation, writing of the article, or in the decision to send it to the present journal.

ACKNOWLEDGMENTS

We sincerely appreciate all participants for their kind cooperation in our study. We also wish to acknowledge all of the investigators in our study and the hospital staff members, and also the CAPES for funding the research.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.683393/full#supplementary-material

REFERENCES

1. Argilés JM, Campos N, Lopez-Pedrosa JM, Rueda R, Rodriguez-Mañas L. Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. *J Am Med Dir Assoc.* (2016) 17:789–96. doi: 10.1016/j.jamda.2016.04.019
2. Landi F, Camprubi-Robles M, Bear DE, Cederholm T, Malafarina V, Welch AA, et al. Muscle loss: the new malnutrition challenge in clinical practice. *Clin Nutr.* (2019) 38:2113–20. doi: 10.1016/j.clnu.2018.11.021
3. Yajima T, Arao M, Yajima K, Takahashi H, Yasuda K. The associations of fat tissue and muscle mass indices with all-cause mortality in patients undergoing hemodialysis. *PLoS ONE.* (2019) 14:e0211988. doi: 10.1371/journal.pone.0211988
4. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Writing group for the european working group on sarcopenia in older people 2 (EWGSOP2), and the extended group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* (2019) 48:16–31. doi: 10.1093/ageing/afy169
5. Sabatino A, D'Alessandro C, Regolisti G, di Mario F, Guglielmi G, Bazzocchi A, et al. Muscle mass assessment in renal disease: the role of imaging techniques. *Quant Imaging Med Surg.* (2020) 10:1672–86. doi: 10.21037/qims.2020.03.05
6. Messina C, Albano D, Gitto S, Tofanelli L, Bazzocchi A, Ulivieri FM, et al. Body composition with dual energy X-ray absorptiometry: from basics to new tools. *Quant Imaging Med Surg.* (2020) 10:1687–98. doi: 10.21037/qims.2020.03.02
7. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. *J Appl Physio.* (2000) 89:465–71. doi: 10.1152/jappl.2000.89.2.465
8. Sergi G, De Rui M, Veronese N, Bolzetta F, Berton L, Carraro S, et al. Assessing appendicular skeletal muscle mass with bioelectrical impedance analysis in free-living Caucasian older adults. *Clin Nutr.* (2015) 34:667–73. doi: 10.1016/j.clnu.2014.07.010
9. Kyle UG, Genton L, Hans D, Pichard C. Validation of a bioelectrical impedance analysis equation to predict appendicular skeletal muscle mass (ASMM). *Clin Nutr.* (2003) 22:537–43. doi: 10.1016/s0261-5614(03)00048-7
10. Macdonald JH, Marcora SM, Jibani M, Roberts G, Kumwenda MJ, Glover R, et al. Bioelectrical impedance can be used to predict muscle mass and hence improve estimation of glomerular filtration rate in non-diabetic patients with chronic kidney disease. *Nephrol Dial Transplant.* (2006) 21:3481–7. doi: 10.1093/ndt/gfl432
11. Hume R. Prediction of lean body mass from height and weight. *J Clin Pathol.* (1966) 19:389–91. doi: 10.1136/jcp.19.4.389
12. Lee RC, Wang Z, Heo M, Ross R, Janssen I, Heymsfield SB. Total-body skeletal muscle mass: development and cross-validation of anthropometric prediction models. *Am J Clin Nutr.* (2000) 72:796–803. doi: 10.1093/ajcn/72.3.796
13. Tian X, Chen Y, Yang ZK, Qu Z, Dong J. Novel equations for estimating lean body mass in patients with chronic kidney disease. *J Ren Nutr.* (2018) 28:156–64. doi: 10.1053/j.jrn.2017.09.004
14. Noori N, Kovesdy CP, Bross R, Lee M, Oreopoulos A, Benner D, et al. Novel equations to estimate lean body mass in maintenance hemodialysis patients. *Am J Kidney Dis.* (2011) 57:130–9. doi: 10.1053/j.ajkd.2010.10.003
15. Fahal IH. Uraemic sarcopenia: aetiology and implications. *Nephrol Dial Transplant.* (2014) 29:1655. doi: 10.1093/ndt/gft070
16. Gamboa JL, Roshanravan B, Towse T, Keller CA, Falck AM, Yu C, et al. Skeletal muscle mitochondrial dysfunction is present in patients with CKD before initiation of maintenance hemodialysis. *Clin J Am Soc Nephrol.* (2020) 15:926–36. doi: 10.2215/CJN.10320819
17. Bataille S, Chauveau P, Fouque D, Aparicio M, Koppe L. Myostatin and muscle atrophy during chronic kidney disease. *Nephrol Dialysis Transplant.* (2020) 2015:gfaa129. doi: 10.1093/ndt/gfaa129
18. Nanmoku K, Kawabata N, Kinoshita Y, Shinzato T, Kubo T, Shimizu T, et al. Deterioration of presarcopenia and its risk factors following kidney transplantation. *Clin Exp Nephrol.* (2020) 24:379–83. doi: 10.1007/s10157-019-01835-1
19. Zhou Y, Hellberg M, Svensson P, Höglund P, Clyne N. Sarcopenia and relationships between muscle mass, measured glomerular filtration rate and physical function in patients with chronic kidney disease stages 3-5. *Nephrol Dial Transplant.* (2018) 33:342–8. doi: 10.1093/ndt/gfw466
20. Gordon CC, Chumlea WC, Roche AF. Stature recumbent length and weight. In: Lohman TG, Roche AF, Martorell R, editors. *Anthropometric Standardization Reference Manual.* Champaign, IL: Human Kinetics Books (1988).
21. World health organization. *WHO 1995 Physical Status. Use and Anthropometry.pdf.* Geneva: World Health Organ Tech Rep Ser (1995).
22. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr.* (1981) 34:2540–5. doi: 10.1093/ajcn/34.11.2540
23. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing.* (2011) 40:423–9. doi: 10.1093/ageing/afr051
24. Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: a tutorial on research considerations and clinical applications. *JPEN J Parenter Enteral Nutr.* (2015) 39:787–822. doi: 10.1177/0148607115595227
25. Wang Z, St-Onge MP, Lecumberri B, Pi-Sunyer FX, Heshka S, Wang J, et al. Body cell mass: model development and validation at the cellular level of body composition. *Am J Physiol Endocrinol Metab.* (2004) 286:E123–8. doi: 10.1152/ajpendo.00227.2003
26. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, et al. Body fluid volume determination via body

composition spectroscopy in health and disease. *Physiol Meas.* (2006) 27:921–33. doi: 10.1088/0967-3334/27/9/012
27. Chamney PW, Wabel P, Moissl UM, Müller MJ, Bosy-Westphal A, Korth O, et al. A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr.* (2007) 85:80–9. doi: 10.1093/ajcn/85.1.80
28. Oh KH, Baek SH, Joo KW, Kim DK, Kim YS, Kim S, et al. Control of fluid balance guided by body composition monitoring in patients on peritoneal dialysis (COMPASS) study. Does routine bioimpedance-guided fluid management provide additional benefit to non-anuric peritoneal dialysis patients? Results from COMPASS clinical trial. *Perit Dial Int.* (2018) 38:131–8. doi: 10.3747/pdi.2016.00241
29. Arya R, Antonisamy B, Kumar S. Sample size estimation in prevalence studies Indian. *J Pediatr.* (2012) 79:1482–8. doi: 10.1007/s12098-012-0763-3
30. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med.* (2016) 15:155–63. doi: 10.1016/j.jcm.2016.02.012
31. Saracino G, Jennings LW, Hasse JM. Basic statistical concepts in nutrition research. *Nutr Clin Pract.* (2013) 28:182–93. doi: 10.1177/0884533613478636
32. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* (1986) 1:307.e10.
33. McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, Guyatt G. Tips for teachers of evidencebased medicine: 3. Understanding and calculating kappa. *CMAJ.* (2004) 171:18. doi: 10.1503/cmaj.050708
34. Bellafronte NT, Diani LM, Vega-Piris L, Cuadrado GB, Chiarello PG. Comparison between dual-energy x-ray absorptiometry and bioelectrical impedance for body composition measurements in adults with chronic kidney disease: a cross-sectional, longitudinal, multi-treatment analysis. *Nutrition.* (2021) 82:111059. doi: 10.1016/j.nut.2020.111059
35. Bellafronte, NT, Batistuti MR, dos Santos NZ, Holland H, Romão EA, et al. Estimation of body composition and water data depends on the bioelectrical impedance device. *J Electri Bioimped.* (2018) 9:96–105. doi: 10.2478/joeb-2018-0014
36. Matthie JR. Bioimpedance measurements of human body composition: critical analysis and outlook. *Expert Rev Med Devices.* (2008) 5:239–61. doi: 10.1586/17434440.5.2.239
37. Raimann JG, Zhu F, Wang J, Thijssen S, Kuhlmann MK, Kotanko P, et al. Comparison of fluid volume estimates in chronic hemodialysis patients by bioimpedance, direct isotopic, and dilution methods. *Kidney Int.* (2014) 85:898–908. doi: 10.1038/ki.2013.358
38. Lukaski HC. Evolution of bioimpedance: a circuitous journey from estimation of physiological function to assessment of body composition and a return to clinical research. *Eur J Clin Nutr.* (2013) 67:S2–9. doi: 10.1038/ejcn.2012.149
39. Nickerson BS, McLester CN, McLester JR, Kliszczewicz BM. Agreement between 2 segmental bioimpedance devices, BOD POD, and DXA in obese adults. *J Clin Densitom.* (2020) 23:138–48. doi: 10.1016/j.jocd.2019.04.005
40. Hurt RT, Ebbert JO, Croghan I, Nanda S, Schroeder DR, Teigen LM, et al. The comparison of segmental multifrequency bioelectrical impedance analysis and dual-energy x-ray absorptiometry for estimating fat free mass and percentage body fat in an ambulatory population. *JPEN J Parenter Enteral Nutr.* (2020). doi: 10.1002/jpen.1994. [Epub ahead of print].
41. Mulasi U, Kuchnia AJ, Cole AJ, Earthman CP. Bioimpedance at the bedside: current applications, limitations, and opportunities. *Nutr Clin Pract.* (2015) 30:180–93. doi: 10.1177/0884533614568155
42. Han BG, Lee JY, Kim JS, Yang JW. Clinical significance of phase angle in non-dialysis CKD stage 5 and peritoneal dialysis patients. *Nutrients.* (2018) 10:1331. doi: 10.3390/nu10091331
43. Ziolkowski SL, Long J, Baker JF, Simard JF, Chertow GM, Leonard MB. Sarcopenia, relative sarcopenia and excess adiposity in chronic kidney disease. *JCSM Clin Rep.* (2018) 3:1–11. doi: 10.17987/jcsm-cr.v3i1.55
44. Lim VS, Ikizler TA, Raj DS, Flanigan MJ. Does hemodialysis increase protein breakdown? Dissociation between whole-body amino acid turnover and regional muscle kinetics. *J Am Soc Nephrol.* (2005) 16:862–8. doi: 10.1681/ASN.2004080624
45. Chan W, Chin SH, Whittaker AC, Jones D, Kaur O, Bosch JA, et al. The associations of muscle strength, muscle mass, and adiposity with clinical outcomes and quality of life in prevalent kidney transplant recipients. *J Ren Nutr.* (2019) 29:536–47. doi: 10.1053/j.jrn.2019.06.009
46. Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Long-term changes in nutritional status are associated with functional and mortality outcomes among community-living older adults. *Nutrition.* (2019) 66:180–6. doi: 10.1016/j.nut.2019.05.006
47. Yang X, Bi P, Kuang S. Fighting obesity: when muscle meets fat. *Adipocyte.* (2014) 3:280–9. doi: 10.4161/21623945.2014.964075
48. Wilkinson TJ, Gould DW, Nixon DGD, Watson EL, Smith AC. Quality over quantity? Association of skeletal muscle myosteatosis and myofibrosis on physical function in chronic kidney disease. *Nephrol Dial Transplant.* (2019) 34:1344–53. doi: 10.1093/ndt/gfy139

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.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 31 May 2021
doi: 10.3389/fnut.2021.686245

Association of Phase Angle, but Not Inflammation and Overhydration, With Physical Function in Peritoneal Dialysis Patients

Vanessa Mota Silva[1], Maryanne Zilli Canedo Silva[2], Barbara Perez Vogt[3], Nayrana Soares Carmo Reis[2], Fabiana Lourenço Costa[2], Mariana Souza Dorna[2], Marcos Ferreira Minicucci[2] and Jacqueline Costa Teixeira Caramori[2]*

[1] Clinical Hospital of Botucatu Medical School, Multiprofessional Specialization in Adult and Elderly Health, São Paulo State University, UNESP, Botucatu, Brazil, [2] Internal Medicine Department, Botucatu Medical School, São Paulo State University, UNESP, Botucatu, Brazil, [3] Graduate Program in Health Sciences, Medicine Faculty, Federal University of Uberlândia (UFU), Uberlândia, Brazil

Introduction: Muscle mass depletion, overhydration, and inflammatory state have been related to impaired physical function in chronic kidney disease patients. The relationship between bioelectrical impedance analysis (BIA) parameters, such as hydration status and phase angle (PhA), with physical function in peritoneal dialysis (PD), is still not well-established. Therefore, the objective was to evaluate the association of BIA parameters (overhydration index and PhA) and inflammatory markers with physical function in patients on PD.

Methods: The present cross-sectional study enrolled PD patients. Multifrequency BIA was performed to obtain overhydration index and PhA. The Short Physical Performance Battery (SPPB) test battery was applied to assess physical function. The time to complete the 4-m gait test and sit-to-stand test was also considered for physical function assessment. The inflammatory markers tumor necrosis factor-alpha and C-reactive protein levels were determined. Multiple linear regression models were performed, with the physical function variables as dependent variables, adjusted for age, diabetes, and sex.

Results: Forty-nine PD patients were enrolled, 53.1% ($n = 26$) women; mean age, 55.5 ± 16.3 years. There were significant correlations between PhA and SPPB ($r = 0.550$, $p < 0.001$), time of 4-m gait test ($r = -0.613$, $p < 0.001$) and sit-to-stand test and ($r = -0.547$, $p < 0.001$). Overhydration index was significantly correlated with SPPB, 4-m gait test ($r = 0.339$, $p = 0.017$), and sit-to-stand test ($r = 0.335$, $p = 0.019$). Inflammatory markers were not significantly correlated with physical function parameters. In the multiple linear regression analysis, PhA was associated with physical function parameters, even after adjustments. Overhydration index was associated with all physical function tests only in the models with no adjustments.

Conclusion: PhA was independently associated with physical function in PD patients. Inflammatory markers and overhydration index were not associated with physical function.

Keywords: bioelectrical impedance, functional capacity, inflammation, phase angle, overhydration, short physical performance battery

OPEN ACCESS

Edited by:
Carla Maria Avesani, Karolinska Institutet, Sweden

Reviewed by:
Fabiana Nerbass, FUNDACÃO PRÓ-RIM, Brazil
Nilian Souza, National Cancer Institute (INCA), Brazil

****Correspondence:***
Barbara Perez Vogt
barbaravogt@ufu.br

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *26 March 2021*
Accepted: *06 May 2021*
Published: *31 May 2021*

Citation:
Silva VM, Silva MZC, Vogt BP, Reis NSC, Costa FL, Dorna MS, Minicucci MF and Caramori JCT (2021) Association of Phase Angle, but Not Inflammation and Overhydration, With Physical Function in Peritoneal Dialysis Patients. Front. Nutr. 8:686245. doi: 10.3389/fnut.2021.686245

INTRODUCTION

Bioelectrical impedance analysis (BIA) has been used in clinical practice to assess patients with chronic kidney disease (CKD) on dialysis. BIA provides raw data regarding electrical current conductivity through the body tissues, such as resistance and reactance. The relation among these parameters may be converted into physiological parameters related to body composition and hydration status (1).

BIA was recommended by the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative in the Nutrition Guideline in CKD, as a method capable of assessing body composition in patients on hemodialysis. However, there is insufficient evidence to suggest using BIA to assess body composition in peritoneal dialysis (PD) patients (2).

Regarding hydration status evaluation, one of the parameters obtained by BIA is the overhydration index (OH), which assesses fluid overload by the difference between measured and expected extracellular water in normal situations (3). OH is considered an important predictor of the evolution of patients on dialysis, as it helps with blood pressure control (4). Moreover, OH has been associated with lower survival in both hemodialysis and PD patients (5, 6).

Phase angle (PhA), a measure of the relationship between resistance and reactance, reflects cell membranes integrity, cellularity, and cell function (7). PhA has been related to hydration status (8), nutritional status (9), and mortality risk (10) in PD patients.

CKD is characterized by metabolic and hormonal disturbances, which culminates in skeletal muscle wasting and disfunction. Decreased physical function has been associated with poor outcomes, such as disability, falls, fracture, hospitalization, and mortality (11). In dialysis and non-dialysis CKD patients, muscle mass depletion, overhydration, and inflammatory state have been related to impaired physical function (12, 13).

However, the relationship between BIA parameters, such as hydration status and PhA, with physical function in PD is still not well-established. Therefore, the objective of the study is to evaluate the association of BIA parameters (OH and PhA) and inflammatory markers with physical function in patients with CKD on PD.

METHODS

This was a secondary analysis of data from a study previously published (14), which enrolled patients aged 18 years or above, with CKD on PD (for at least 3 months) at the Dialysis Unit from the Clinics Hospital of Botucatu Medical School (Botucatu, Brazil). The protocol was approved by the Ethics and Research Committee (CAAE 61634816.4.0000.5411), and the participants gave written informed consent.

Clinical, demographic data, and routine laboratory tests were collected from medical records (sex, age, comorbidities, underlying disease, PD modality, Kt/V, serum hemoglobin, creatinine, urea, albumin, C-reactive protein).

Inflammatory Markers

Blood collection was performed in the morning, after PD. C-reactive protein levels were determined by immunoassay (Vitros, Johnson and Johnson Clinical Diagnostics, Rochester, NY) at the specialized chemistry laboratory of the Hospital of Botucatu Medical School. Blood samples were centrifuged, aliquoted, and kept frozen at −80°C for tumor necrosis factor-alpha (TNF-α) levels determination, using an enzyme-linked immunosorbent assay according to the manufacturer's instructions (R&D System, Inc., Minneapolis, USA).

Bioelectrical Impedance Analysis

All the patients underwent anthropometric and bioimpedance assessment with no dialysate in the peritoneal cavity in the morning, after PD. Measurements of body weight, height, and calculation of body mass index were carried out.

Multifrequency BIA (Body Composition Monitor, BCM—Fresenius Medical Care®, Germany) was performed with the patients in the recumbent position and all metal accessories removed. The BCM measures body resistance and reactance to electrical currents of 50 discrete frequencies, ranging from 5 to 1,000 kHz. Values of OH and PhA in the frequency of 50 kHz were considered. The OH was obtained by the BCM device, considering the difference between the measured extracellular water (ECW) and the predicted values based on fixed hydration on lean and adipose tissue mass.

Physical Function Assessment

To assess physical function, the Short Physical Performance Battery (SPPB) was used. This assessment was performed at the same day of BIA, after PD. SPPB is composed of a set of three tests: balance, a 4-m gait and sit-to-stand tests. These tests are useful to predict the performance of the lower limbs. The scores were assigned to each test, ranging from zero to four (15, 16).

Besides the SPPB total score, the time to complete the 4-m gait test and sit-to-stand test was considered for physical function assessment.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to assess the normality of the data. Data were expressed as mean and standard deviation, median, and interquartile variation, according to the distribution. Frequencies were expressed as percentages.

Comparisons between male and female, and between diabetic and non-diabetic patients were performed using Student's *t* or Mann–Whitney tests.

The patients were grouped according to OH and PhA tertiles. Tertiles were compared, using one-way ANOVA with Tukey *post-hoc* or Kruskal–Wallis with Dunn *post-hoc* test.

Correlations between physical function parameters and other variables were assessed. For this, Pearson and Spearman coefficient correlations were used.

Multiple linear regression models were performed, with the physical function variables as dependent variables, adjusted for age, diabetes, and sex.

TABLE 1 | Clinical and nutritional characteristics of PD patients.

Variables	Total ($n = 49$)
Dialysis vintage (months)	10.0 (5.0–18.0)
Kt/V total*	2.2 ± 0.5
Kt/V peritoneal**	1.4 (1.1–1.7)
Kt/V renal**	0.6 (0.3–1.1)
Weight (kg)	68.8 ± 15.5
Body Mass Index (Kg/m²)	25.8 ± 4.3
Phase angle (°)	5.4 ± 1.1
Overhydration (L)	0.8 ± 1.1
Hemoglobin (mg/dL)	11.3 ± 1.5
Urea (mg/dL)	99.3 ± 24.9
Creatinine (mg/dL)	9.1 ± 2.8
Albumin (g/dL)	3.6 ± 0.4
C-reactive protein (mg/L)	0.5 (0.5–1.0)
Tumor necrosisfactor-alpha (ng/L)	16.9 (13.8–21.4)

Data are expressed as numbers only, mean ± standard deviation, number (%), or median (interquartile range).
*Kt/V: Fractional clearance of urea; *n = 47; **n = 46.*

The analyses were performed, using IBM SPSS Statistics V22.0 (IBM Corp., Armonk, NY, USA). The level of significance was set at $p < 0.05$.

RESULTS

Forty-nine PD patients were enrolled, with mean age 55.5 ± 16.3 years, 53.1% ($n = 26$) female. The patients in different modalities of PD were included, 61.2% ($n = 30$) in continuous cyclic PD, 34.7% ($n = 17$) in night intermittent PD, and 4.1% ($n = 2$) in continuous ambulatory PD. The most prevalent comorbidities were arterial hypertension (79.6%, $n = 39$) and diabetes (26.5%, $n = 13$). The main underlying diseases were glomerulonephritis, 18.4% ($n = 9$); diabetic nephropathy, 16.3% ($n = 8$); hypertensive nephropathy, 16.3% ($n = 8$); undetermined, 24.5% ($n = 12$); and other causes, 24.5% ($n = 12$). Clinical and nutritional characteristics of PD patients are shown in **Table 1**.

Results of physical function assessments of both genders were compared. There were no differences between male and female (SPPB: $p = 0.324$, gait test: $p = 0.109$ and sit-to-stand test: $p = 0.248$). In the comparison between the patients with diabetes or not, there were differences regarding age ($p = 0.003$), SPPB ($p = 0.025$) and sit-to-stand test ($p = 0.009$). OH ($p = 0.184$), PhA ($p = 0.193$), CRP ($p = 0.572$), TNF-α ($p = 0.937$), and gait test ($p = 0.150$) did not differ between diabetic and non-diabetic patients.

Forty-seven patients (96.0%) reached the maximum score in the balance test. The results of physical function assessments and inflammatory markers are shown in **Table 2**, as well as the comparison among OH tertiles. OH ranged from −1.0 to 3.2 L. PhA ranged from 3.2° to 7.8°. The comparison among PhA tertiles is shown on **Table 3**.

In the correlation analysis, there was a positive correlation between PhA and SPPB and negative correlations of PhA with time of a 4-m gait and sit-to-stand tests. OH was negatively correlated with the total SPPB score, and positively correlated with a 4-m gait and sit-to-stand tests. Inflammatory markers were not significantly correlated with physical function parameters (**Table 4**). Dialysis vintage, renal Kt/V, BMI, urea, and hemoglobin were not significantly correlated with physical function tests. Albumin was correlated only with the gait test ($r = -0.400$, $p = 0.004$). Creatinine was correlated with all the physical function test (SPPB $r = 0.389$, $p = 0.006$; gait test $r = -0.430$, $p = 0.002$; sit-to-stand $r = -0.379$, $p = 0.007$).

Multiple linear regression models were performed with the SPPB, gait test, and sit-to-stand test as dependent variables (**Table 5**). Age and diabetes were chosen as adjustments due to the association with physical function in univariate analysis. Sex was also included as an adjustment. Although serum creatinine was correlated with physical function tests, in multiple linear regression models, creatinine did not improve or change the results. Therefore, as the sample size is small, we did not add creatinine to the final models.

In the multiple linear regression final models, OH was associated with all physical function tests only in the models with no adjustments. PhA was independently associated with all physical function tests after adjustments, except with the gait test when diabetes was included as an adjustment.

DISCUSSION

Although BIA has been used in the last decades for body composition assessment, it is not a direct method for this evaluation (7). BIA is based on electrical properties of tissues, and the body compartments are estimated from equations that include raw impedance parameters and anthropometric measurements (17).

More recently, the use of raw and associated impedance parameters has gained attention. Kidney failure patients are characterized by fluid imbalance, which turn BIA even more valuable. Huang et al. showed that age, diabetes, and fluid overload were independently associated with lower PhA in PD patients. Moreover, in the same study, lower PhA was associated with higher cardiovascular and all-cause mortality (10). Increased OH values were associated with mortality risk, as evidenced in a systematic review, enrolling studies with kidney failure patients (18).

The present study aimed to evaluate the association of BIA parameters (PhA and OH), and inflammation with physical function in PD patients. PhA was positively correlated with the SPPB total score and negatively correlated with the time to complete a 4-m gait and sit-to-stand tests. As expected, these results show the association of increased PhA with better physical function.

In addition to the association of PhA with better physical function, OH was negatively correlated with the SPPB total score and positively correlated with the time to complete the 4-m gait and sit-to-stand tests. The patients in the third tertile had worse physical function compared with the first tertile. However, OH was not independently associated with physical function after adjustments in multiple analyses.

TABLE 2 | Comparison of different parameters among overhydration tertiles in patients on peritoneal dialysis ($n = 49$).

Variables	1st Tertile OH < 0.27 ($n = 17$)	2nd Tertile OH ≥0.27 to <1.26 ($n = 16$)	3rd Tertile OH ≥ 1.26 ($n = 16$)	*p*
Age (years)	52.4 ± 14.4	52.4 ± 16.8	61.8 ± 16.8	0.172
Female sex [*n* (%)]	10 (58.8)	8 (50.0)	8 (50.0)	0.841
PD modality [*n* (%)]				0.862
CAPD	1 (5.9)	0	1 (6.2)	
CCPD	10 (58.8)	11 (68.8)	9 (56.3)	
NIPD	6 (35.3)	5 (31.2)	6 (37.5)	
Short physical performance battery (points)	10.0 (9.0–11.0)	9.5 (8.0–10.8)	8.5 (7.0–9.8)[a]	0.035
Gait test (seconds)	4.21 (3.5–5.3)	4.4 (4.1–5.2)	5.0 (4.5–7.1)[a]	0.029
Sit-to-stand test (seconds)	15.2 ± 3.6	15.8 ± 3.9	19.5 ± 4.7[ab]	0.009
C-reactive protein (mg/L)	0.5 (0.5–1.3)	0.5 (0.5–0.6)	0.6 (0.5–1.4)	0.387
Tumor necrosisfactor-alpha (ng/L)	16.94 (14.54–23.23)	17.4 (11.6–21.3)	15.5 (13.7–20.0)	0.527

Data are expressed as numbers only, mean ± standard deviation, number (%), or median (interquartile range). Comparison using one-way ANOVA with the Tukey post-hoc test or Kruskal–Wallis with Dunn post-hoc. [a]$p < 0.05$ when compared with first tertile; [b]$p < 0.05$ when compared with second tertile.

TABLE 3 | Comparison of different parameters among phase angle tertiles in patients on peritoneal dialysis ($n = 49$).

Variables	1st Tertile PhA <4.92 ($n = 16$)	2nd Tertile PhA ≥4.92 to ≤5.87 ($n = 17$)	3rd Tertile PhA >5.87 ($n = 16$)	*p*
Age (years)	67.8 ± 12.0	54.9 ± 13.2[a]	43.7 ± 14.4[ab]	0.000
Female sex [*n* (%)]	10 (62.5)	11 (64.7)	5 (31.2)	0.103
PD modality [*n* (%)]				0.622
CAPD	1 (6.2)	1 (5.9)	0	
CCPD	8 (50.0)	10 (58.8)	12 (75.0)	
NIPD	7 (43.8)	6 (35.3)	4 (25.0)	
Short physical performance battery (points)	8 (7.0–9.0)	10 (9.0–11.0)[a]	10 (9.2–11.0)[a]	0.002
Gait test (seconds)	6.2 (4.8–7.0)	4.5 (4.0–5.1)[a]	4.2 (3.6–4.5)[a]	0.000
Sit-to-stand test (seconds)	20.0 ± 4.4	16.0 ± 4.4[a]	14.5 ± 2.2[a]	0.001
C-reactive protein (mg/L)	0.5 (0.5–1.6)	0.5 (0.5–1.3)	0.5 (0.5–0.7)	0.412
Tumor necrosisfactor-alpha (ng/L)	16.7 (14.2–20.9)	14.5 (11.1–17.4)	19.8 (15.6–23.2)	0.058

Data are expressed as numbers only, mean ± standard deviation, number (%), or median (interquartile range). Comparison using one-way ANOVA with the Tukey post-hoc test or Kruskal–Wallis post-hoc. [a]$p < 0.05$ when compared with first tertile; [b]$p < 0.05$ when compared with second tertile.

Inflammation is considered one of the aspects that lead to decrease of physical function (19, 20). Since overhydration status may increase inflammation in PD patients (21), we expected an association of both inflammatory markers and OH with physical function. However, the inflammatory markers considered in our study were not associated with worse physical function, as well as OH.

In the hemodialysis patients, the presence of fluid overload can slow the gait speed. The fluid overload significantly impacts on the physical performance of the patients over time, as observed in a longitudinal study by Carlos et al. (12). On the other hand, excessive fluid withdrawal in hemodialysis sessions can lead to intradialytic hypotension, which is associated with a reduced gait after a dialysis session (22, 23).

In PD, data about the impact of increased fluid on the physical function assessed by walking are scarce. A walking variable may be reduced in these patients due to conditions such as physical inactivity, peripheral neuropathy, and muscle strength (24). However, such variables were not evaluated in the present study, which may be an explanation for the lack of association of physical function with OH in the regression model.

In the multiple linear regression analyses, the association of PhA with the sit-to-stand test and SPPB was maintained even after adjusting for age, diabetes, and sex. All the physical function tests used in the present study reflect common daily living activities, i.e., getting up from a chair or walking small distances. Moreover, these tests are easy, fast, portable, and inexpensive procedures to measure physical performance.

PhA has been associated with physical function in many conditions. Recently, Vincenzo et al. (25) have showed in a metanalysis that PhA is decreased in sarcopenic subjects. Kosoku et al. (26) found a negative correlation between PhA and sarcopenia in kidney transplant recipients. Sarcopenia is defined as the presence of both muscle mass and physical function decrease (27).

TABLE 4 | Correlations between bioimpedance parameters and physical function tests in patients on peritoneal dialysis ($n = 49$).

Variables	Phase angle (°)		OH (L)		CRP (mg/L)		TNF-α (ng/L)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Short physical performance battery (points)	0.550	0.000	−0.316	0.027	−0.013	0.931	0.110	0.450
4-meter gait test (seconds)	−0.613	0.000	0.339	0.017	0.136	0.350	−0.169	0.245
Sit-to-stand test (seconds)	−0.547*	0.000	0.335*	0.019	0.020	0.894	−0.131	0.368

OH, overhydration; CRP, C-reactive protein; TNF-α, Tumor necrosis factor-alpha.
**Pearson coefficient correlation. Coefficients with no sign refer to Spearman coefficient correlation.*

TABLE 5 | Multiple linear regression models with short physical performance battery, the gait test, and the sit-to-stand test as dependent variables in patients on peritoneal dialysis ($n = 49$).

Dependent variable	Independent variable	Model	β	CI 95%	*p*	Adjusted R^2
Short physical performance battery (points)	Phase angle (°)	1	0.544	0.474–1.261	<0.001	0.281
		2	0.324	0.058–0.977	0.028	0.359
		3	0.340	0.085–1.000	0.021	0.370
		4	0.325	0.008–1.028	0.047	0.356
	Overhydration (L)	1	−0.306	−0.913 to −0.042	0.032	0.075
		2	−0.208	−0.701–0.053	0.090	0.331
		3	−0.194	−0.684–0.079	0.117	0.328
		4	−0.206	−0.701–0.059	0.095	0.339
Gait test (seconds)	Phase angle (°)	1	−0.585	−1.439 to −0.607	<0.001	0.329
		2	−0.356	−1.102 to −0.142	0.012	0.417
		3	−0.369	−1.125 to −0.166	0.009	0.424
		4	−0.293	−1.038–0.014	0.056	0.430
	Overhydration (L)	1	0.289	0.015–0.974	0.044	0.064
		2	0.184	−0.089–0.716	0.124	0.365
		3	0.172	−0.114–0.701	0.154	0.359
		4	0.192	−0.063–0.717	0.098	0.418
Sit-to-stand test (seconds)	Phase angle (°)	1	−0.547	−3.226 to −1.228	<0.001	0.285
		2	−0.372	−2.712 to −0.315	0.014	0.329
		3	−0.391	−2.774 to −0.410	0.009	0.353
		4	−0.373	−2.836 to −0.199	0.025	0.339
	Overhydration (L)	1	0.335	0.231–2.429	0.019	0.093
		2	0.246	−0.007–1.965	0.052	0.296
		3	0.229	−0.084–1.901	0.072	0.300
		4	0.242	−0.019–1.945	0.054	0.319

Model 1: no adjustments; Model 2: adjusted by age; Model 3: adjusted by age and diabetes; Model 4: adjusted by age, diabetes, and sex.

Although the relationship between PhA and physical function in PD is still not well-established, there are studies associating PhA with muscle function in other CKD populations. Muscle function, assessed by handgrip strength, was associated with PhA in maintenance hemodialysis (28, 29) and kidney transplant recipients (30). Moreover, in the hemodialysis patients, PhA was associated with exercise tolerance, which was assessed by a 6-min step test, and peak torque of knee extensors (28).

A possible explanation for the relationship between PhA and physical function is based on cellular structures and its interaction with the electrical current. The structure and the function of cells are dependent on cell membranes, which are composed of electrically non-conducting lipid bilayers with associated proteins (31). The protein–lipid–protein sandwiched structure provides a reactance to the applied alternating current (32). The reactance arises from cell membranes, while resistance from extra- and intracellular fluid (17). The impedance is the result of two vectors representing resistance and reactance. PhA is the angle between impedance and resistance. Therefore, the higher the reactance, the larger the PhA will be for a given resistance (33). In other words, the higher PhA, the better cell membrane structure, cell mass, cellular integrity, and cell function.

The main limitation of this study is the single-center small sample size, which does not allow the inclusion of many variables in the multiple analyses. However, due to the scarcity of studies assessing the association of PhA and OH with physical function

in PD, the results may be significant for PD patients. Thus, studies with a larger number of patients are still necessary.

In conclusion, bioimpedance parameters (PhA and OH) were correlated with physical function tests, but only PhA was independently associated with physical function tests in the PD patients. Inflammatory markers were not associated with physical function in this sample. In this sense, easy-to-apply tools with good accuracy are important to identify the risk of reduced physical function, allowing interventions to avoid worse outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of the Faculty of Medicine of Botucatu-Universidade Estadual Paulista (UNESP). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VMS, MZCS, BPV, and JCTC were responsible for the research idea and the study design. VMS, MZCS, NSCR, MSD, and FLC performed the data acquisition. VMS, MZCS, and BPV performed the data analysis and the interpretation, were involved in the statistical analysis, and drafted the manuscript. BPV, JCTC, and MFM were responsible for supervision and mentorship. All the authors provided intellectual content to the work and gave final approval of the version to be published.

ACKNOWLEDGMENTS

We acknowledge the patients and health care staff from the Dialysis Unit of the Clinics Hospital of Botucatu Medical School.

REFERENCES

1. Lukaski HC. Evolution of bioimpedance: a circuitous journey from estimation of physiological function to assessment of body composition and a return to clinical research. *Eur J Clin Nutr*. (2013) 67:S2–9. doi: 10.1038/ejcn.2012.149
2. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero J-J, Chan W, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis*. (2020) 76:S1–107. doi: 10.1053/j.ajkd.2020.05.006
3. Wabel P, Chamney P, Moissl U, Jirka T. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purif*. (2009) 27:75–80. doi: 10.1159/000167013
4. Davies SJ, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. *Kidney Int*. (2014) 86:489–96. doi: 10.1038/ki.2014.207
5. Koh K-H, Wong H-S, Go K-W, Morad Z. Normalized bioimpedance indices are better predictors of outcome in peritoneal dialysis patients. *Perit Dial Int*. (2011) 31:574–82. doi: 10.3747/pdi.2009.00140
6. Paniagua R, Ventura M-J, Ávila-Díaz M, Hinojosa-Heredia H, Méndez-Durán A, Cueto-Manzano A, et al. NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrol Dial Transplant*. (2010) 25:551–7. doi: 10.1093/ndt/gfp395
7. Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis – clinical relevance and applicability of impedance parameters. *Clin Nutr*. (2012) 31:854–61. doi: 10.1016/j.clnu.2012.05.008
8. Ellis KJ. Human body composition: *in vivo* methods. *Physiol Rev*. (2000) 80:649–80. doi: 10.1152/physrev.2000.80.2.649
9. Han B-G, Lee JY, Kim J-S, Yang J-W. Clinical Significance of phase angle in non-dialysis CKD stage 5 and peritoneal dialysis patients. *Nutrients*. (2018) 10:1331. doi: 10.3390/nu10091331
10. Huang R, Wu M, Wu H, Ye H, Peng Y, Yi C, et al. Lower phase angle measured by bioelectrical impedance analysis is a marker for increased mortality in incident continuous ambulatory peritoneal dialysis patients. *J Ren Nutr*. (2020) 30:119–25. doi: 10.1053/j.jrn.2019.06.006
11. Roshanravan B, Robinson-Cohen C, Patel Kv, Ayers E, Littman Aj, de Boer Ih, et al. Association between physical performance and all-cause mortality in CKD. *J Am Soc Nephrol*. (2013) 24:822–30. doi: 10.1681/ASN.2012070702
12. Carlos C, Grimes B, Segal M, Johansen K. Predialysis fluid overload and gait speed: a repeated measures analysis among patients on chronic dialysis. *Nephrol Dial Transplant*. (2020) 35:1027–31. doi: 10.1093/ndt/gfz272
13. Navaneethan SD, Kirwan JP, Remer EM, Schneider E, Addeman B, Arrigain S, et al. Adiposity, physical function, and their associations with insulin resistance, inflammation, and adipokines in CKD. *Am J Kidney Dis*. (2021) 77:44–55. doi: 10.1053/j.ajkd.2020.05.028
14. Silva MZC da, Vogt BP, Reis NS do C, Caramori JCT. Update of the European consensus on sarcopenia: what has changed in diagnosis and prevalence in peritoneal dialysis? *Eur J Clin Nutr*. (2019) 73:1209–11. doi: 10.1038/s41430-019-0468-z
15. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. (1994) 49:M85–94. doi: 10.1093/geronj/49.2.M85
16. Guralnik JM, Branch LG, Cummings SR, Curb JD. Physical performance measures in aging research. *J Gerontol*. (1989) 44:M141–6. doi: 10.1093/geronj/44.5.M141
17. Kyle UG, Bosaeus I, Lorenzo ADD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis—part I: review of principles and methods. *Clin Nutr*. (2004) 23:1226–43. doi: 10.1016/j.clnu.2004.06.004
18. Tabinor M, Elphick E, Dudson M, Kwok CS, Lambie M, Davies SJ. Bioimpedance-defined overhydration predicts survival in end stage kidney failure (ESKF): systematic review and subgroup meta-analysis. *Sci Rep*. (2018) 8:1–14. doi: 10.1038/s41598-018-21226-y
19. Brinkley TE, Leng X, Miller ME, Kitzman DW, Pahor M, Berry MJ, et al. Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. *J Gerontol A Biol Sci Med Sci*. (2009) 64A:455–61. doi: 10.1093/gerona/gln038
20. Cesari M, Penninx BWJH, Pahor M, Lauretani F, Corsi AM, Williams GR, et al. Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J Gerontol Ser A*. (2004) 59:M242–8. doi: 10.1093/gerona/59.3.M242
21. Avila-Díaz M, Ventura M-J, Valle D, Vicenté-Martínez M, García-González Z, Cisneros A, et al. Inflammation and extracellular volume expansion are related to sodium and water removal in patients on peritoneal dialysis. *Perit Dial Int*. (2006) 26:574–80. doi: 10.1177/089686080602600510
22. Abreo AP, Glidden D, Painter P, Lea J, Herzog CA, Kutner NG, et al. Association of physical function with predialysis blood pressure in patients on hemodialysis. *BMC Nephrol*. (2014) 15:177. doi: 10.1186/1471-2369-15-177
23. Wolfgram DF, Lathara Z, Szabo A, Whittle J. Dialytic hemodynamics are associated with changes in gait speed. *Hemodial Int*. (2017) 21:566–74. doi: 10.1111/hdi.12515

24. Zemp DD, Giannini O, Quadri P, de Bruin ED. Gait characteristics of CKD patients: a systematic review. *BMC Nephrol*. (2019) 20:1–12. doi: 10.1186/s12882-019-1270-9
25. Vincenzo OD, Marra M, Gregorio AD, Pasanisi F, Scalfi L. Bioelectrical impedance analysis (BIA) -derived phase angle in sarcopenia: a systematic review. *Clin Nutr*. (2020). doi: 10.1016/j.clnu.2020.10.048
26. Kosoku A, Uchida J, Nishide S, Kabei K, Shimada H, Iwai T, et al. Association of sarcopenia with phase angle and body mass index in kidney transplant recipients. *Sci Rep*. (2020) 10:1–8. doi: 10.1038/s41598-019-57195-z
27. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. (2019) 48:16–31. doi: 10.1093/ageing/afy169
28. Brito CP, Moraes IG, Luders C, Brito CMM de, Yamaguti WP. Relationship of phase angle and peak torque of knee extensors with the performance in six-minute step test in haemodialysis patients. *BMC Nephrol*. (2021) 22:1–9. doi: 10.1186/s12882-021-02256-7
29. Beberashvili I, Azar A, Sinuani I, Shapiro G, Feldman L, Stav K, et al. Bioimpedance phase angle predicts muscle function, quality of life and clinical outcome in maintenance hemodialysis patients. *Eur J Clin Nutr*. (2014) 68:683–9. doi: 10.1038/ejcn.2014.67
30. Reis AS dos, Santos HO, Limirio LS, Oliveira EP de. Phase angle is associated with handgrip strength but not with sarcopenia in kidney transplantation patients. *J Ren Nutr*. (2019) 29:196–204. doi: 10.1053/j.jrn.2018.10.005
31. Cooper GM. Cell membranes. In: Cooper GM, editor. *The Cell: A Molecular Approach*, 2nd ed. Sunderland, MA: Sinauer Associates (2000).
32. Bera TK. Bioelectrical impedance methods for noninvasive health monitoring: a review. *J Med Eng*. (2014) 2014:e381251. doi: 10.1155/2014/381251
33. Barbosa-Silva MCG, Barros AJD. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. *Curr Opin Clin Nutr Metab Care*. (2005) 8:311–7. doi: 10.1097/01.mco.0000165011.69943.39

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.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 31 May 2021
doi: 10.3389/fnut.2021.686513

Agreement of Single-Frequency Electrical Bioimpedance in the Evaluation of Fat Free Mass and Fat Mass in Peritoneal Dialysis Patients

*Nayrana Soares do Carmo Reis, Francieli Cristina Delatim Vaninni, Maryanne Zilli Canedo Silva, Rogério Carvalho de Oliveira, Fabrício Moreira Reis, Fabiana Lourenço Costa, Luis Cuadrado Martin and Pasqual Barretti**

Internal Medicine Department, Botucatu Medical School, São Paulo State University, Botucatu, Brazil

OPEN ACCESS

Edited by:
Alice Sabatino, University of Parma, Italy

Reviewed by:
Jeroen Peter Kooman, Maastricht University Medical Centre, Netherlands
Sharmela Sahathevan, National University of Malaysia, Malaysia

****Correspondence:***
Pasqual Barretti
pbarretti@uol.com.br

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *27 March 2021*
Accepted: *06 May 2021*
Published: *31 May 2021*

Citation:
Reis NSdC, Vaninni FCD, Silva MZC, de Oliveira RC, Reis FM, Costa FL, Martin LC and Barretti P (2021) Agreement of Single-Frequency Electrical Bioimpedance in the Evaluation of Fat Free Mass and Fat Mass in Peritoneal Dialysis Patients. Front. Nutr. 8:686513. doi: 10.3389/fnut.2021.686513

Background: Protein-energy wasting is related to impairment of quality of life and lower survival of end-stage kidney disease (ESKD) patients. The evaluation of body composition, especially fat free mass (FFM) and fat mass (FM), is important for the prediction of outcomes in these individuals. The aim of this study was to compare the FFM and FM measurements obtained by single-frequency bioimpedance (SF-BIA) and by a multiple frequency bioimpedance (MF-BIA) device, using dual energy X-ray absorptiometry (DXA) peritoneal dialysis (PD) patients.

Methods: This was a cross-sectional study involving adult patients undergoing regular PD, in which we performed SF-BIA, MF-BIA, and DXA at the same visit. To compare the bioimpedance values with DXA, we used: Person correlation (r), intraclass correlation coefficient (ICC), and Bland-Altman concordance analysis.

Results: The sample consisted of 50 patients in the PD, with mean age of 55.1 ± 16.3 years. Both bioimpedance methods showed a strong correlation ($r > 0.7$) and excellent reproducibility (ICC > 0.75) compared to DXA. According to the Bland-Altman diagram, SF-BIA showed agreement in body compartment measurements, with no proportionality bias ($p > 0.05$), without systematic bias for FFM (−0.5 ± 4.9, 95% CI −1.8 to 0.9, $p = 0.506$), and for FM (0.3 ± 4.6, $p = 0.543$). MF-BIA did not present a proportionality bias for the FFM, but it underestimated this body compartment by 2.5 ± 5.4 kg ($p = 0.002$). In addition, MF-BIA presented proportionality bias for FM.

Conclusion: SF-BIA was a more accurate assessing method than MBIA for FFM and FM measurements in PD patients. Because it is a low-cost, non-evaluator-dependent measurement and has less systematic bias, it can also be recommended for fat mass and free-fat mass evaluation in PD patients.

Keywords: nutrition, dialysis, peritoneal dialysis, electrical bioimpedance, dual energy x-ray absorbsiometry

INTRODUCTION

Protein-energy wasting (PEW) is a common condition in end-stage kidney disease (ESKD) patients. PEW is reported in 8–54% of dialysis patients and is strongly associated with adverse clinical outcomes, as an increased hospitalization rate and lower survival and has prevention and deceleration of difficult management in these individuals (1, 2). On the other hand, higher body mass index (BMI) values have been associated with better outcomes, in contrast to the association in the general population. This phenomenon has been referred to as the "obesity paradox" (3). However, the causes of this possible protective effect are still unclear since BMI does not provide accurate information about body composition or which compartment has the greatest protective effect, and this measure is likely to perform worse in dialysis patients than in the general population (4–6).

This context highlights the importance of assessing body composition to monitor and predict outcomes in ESKD patients. There are several tools for assessing body composition, with emphasis on dual energy X-ray absorptiometry (DXA), which is considered a reference method capable of more reliably estimating bone, fat, and muscle mass (7, 8). However, few clinics have access to this method, since it requires radiological medicine facilities, generating a high cost for its routine use (9).

Among the most accessible methods are electrical bioimpedance (BIA) analyses. It consists of a non-invasive and relatively low-cost method, which is easy-to-use and portable, and does not require a skilled operator, allowing reproducible results. However, this measurement can be influenced by factors related to ESKD, such as hydration status (8, 10).

BIA methods can be classified into two main categories: single-frequency BIA (SF-BIA) and multiple frequency BIA (MF-BIA). SF-BIA normally operates at a frequency of 50 kHz. This frequency and the impedance are directly proportional the total amount of body water and allows, subsequently, to establish estimates of fat-free mass. In this model, the body is divided into two parts: fat mass (FM) and fat free mass (FFM), with FM defined indirectly as the difference between body weight and FFM. This model assumes that FFM has a constant hydration of 73%. MF-BIA is based on the principle that analyzes of body compartments, using specific frequencies, yield more accurate results. It was found that at low frequencies the current moves around the cells, while at high frequencies the current penetrates the cells. Therefore, proposed that ECW should be estimated at low frequencies (5 kHz), while ICW should be estimated at high frequencies (1 MHz) (11). However, there is no consensus on which of these methods is more reliable for the assessment of body compartments such as fat-free mass (FFM) and fat mass (FM) in dialysis patients, especially peritoneal dialysis (PD), and contradictory results have been reported (12–16).

A recent update to the Clinical Practice Guideline for Nutrition in Chronic Kidney Disease (KDOQI) (8) reports that there is insufficient evidence to suggest the use of bioelectrical impedance to assess body composition of PD patients and recommends conducting future research in this group to determine the validity and reliability of these measurements in PD patients. Therefore, the aim of this study was to compare the FFM and FM measurements obtained by SF-BIA and a MF-BIA device, using DXA as the reference standard, in PD patients.

MATERIALS AND METHODS

This cross-sectional study was approved by our Institutional Ethics and Research Committee (CAAE 39704314.3.0000.5411) and involved adult end-stage kidney disease (ESKD) patients undergoing PD for at least 90 days at a single Brazilian university center. The sample size calculation was performed based on a pilot study, estimating a minimum correlation coefficient of 0.6 between the tested methods and DXA, with statistical power of 0.9 and an alpha error of 0.05.

Patients' enrollment occurred between January 2017 and May 2018. All eligible patients were invited to participate of the research and those included signed their informed consent term. We did not include patients under 18 years, with cardiac pacemakers, implanted defibrillators, and those with limb amputation, because these factors would make the nutritional assessments unreliable. We performed all body composition in patients without abdominal dialysate. A skilled examiner performed SF-BIA, MF-BIA, and DXA at the same time, with a maximum interval of 2 h between the assessments.

Dual Energy X-Ray Absorptiometry (DXA)

FFM and FM were quantified by DXA using the Hologic® Discovery a device. The integrated software calculated lean mass (kg), FM (kg), bone mineral content (kg), lean mass index (kg/m2), and fat mass index (kg/m2). FFM was considered the sum of lean mass and bone mineral content.

Electrical Bioimpedance

For the SF-BIA assessments, we used a Biodynamics® model 450, 800 μA, 50 kHz device and evaluated FFM (kg), FM (kg), and phase angle. The equations used to assess these measurements were based on the Kushner & Scholler proposals (16). We performed MF-BIA using the Fresenius Medical Care® Body Composition Monitor, and the body compartment measurements were estimated using a specific software provided by the manufacturer, whose formulas are based on those proposed by Moissl et al. (17). BCM assumes a division of body mass into 3 compartments: lean tissue mass (LTM), adipose tissue mass (ATM), and hyperhydration index (OH). In addition, it provides fat (kg) values consisting of hydration-free fat tissue. For comparison purposes with DXA (which divides the body into 2 body compartments), we initially used: FFM = LTM (kg) + OH (L) and FFM = total body weight (kg) - fat (kg); FM = ATM (kg) and FM = fat (kg). The analyzes using FFM = LTM (kg) + OH (L) and FM = ATM (kg) presented broader agreement limits, with greater need for adjustment. Therefore, our analyzes for BCM were based on the division of body compartments using the fat (kg) measurement provided by the device.

Statistical Analysis

The results were expressed as the mean ± standard deviation, median (interquartile range) or percentage. Continuous variables with a normal distribution were analyzed using Student's *t*-test,

and those with a non-normal distribution by the non-parametric Mann-Whitney test. To compare categorical variables, we used the Chi square test.

The correlation strength between the measurements was calculated using Pearson's correlation coefficient, while the agreement between the methods was evaluated using the intraclass correlation coefficient (ICC) and the Bland-Altman analysis. The following criteria were considered for ICC: ICC $<$ 0.4, poor reproducibility; 0.4 $\leq$ ICC $<$ 0.75, satisfactory reproducibility; and ICC $\geq$ 0.75, excellent reproducibility.

We used Bland-Altman analysis to determine the systematic and proportionality bias between the values obtained by the tested methods and DXA. Systematic bias was assessed using Student's *t*-test for one sample, checking if the average of the differences between the methods would be equal to "0." The proportionality bias was assessed using linear regression to determine if the difference between the methods was biased by the magnitude of the measure, considering the difference between DXA and the tested method values as a dependent variable and the mean of them as an independent variable. The presence of proportionality bias classified the method as not in agreement with DXA.

The total population and subgroups were assessed, in which patients were divided according to sex, median age, and median BMI. The graphical representation of the Bland-Altman diagram is shown by means of dispersion diagrams. Continuous lines correspond to the average of the differences between the tested methods, and the DXA and dashed black lines represent the limits of agreement with 95% reliability (mean difference $\pm$ 2 $\times$ standard deviation).

We used a linear regression analysis to select predictors for the development of new equations aiming to quantify body compartments, in which the dependent variables were the FFM and FM values obtained by DXA. The equations were established using data from the tested methods in combination with demographic variables (age, sex, weight, and height). All analyzes were made using the IBM SPSS STATISTICS version 23 software, and the criterion of statistical significance corresponded to a $p < 0.05$.

RESULTS

Demographic, Clinical, and Nutritional Characteristics

The flowchart of the patients enrolled in the study is described in **Figure 1**. We included 50 PD patients whose demographic and clinical characteristics are shown in **Table 1**. **Table 2** shows the hydration status and nutritional and laboratory parameters of the study group. A strong correlation ($r > 0.7$) and excellent reproducibility (ICC $\geq$ 0.75) of the body composition measurements were observed between the methods tested and DXA in PD patients (**Supplementary Material**).

Agreement Between SF-BIA and DXA

Figure 2 shows the Bland-Altman agreement diagram for FFM and FM measured by SF-BIA and DXA. SF-BIA presented an accurate assessment of the body compartments, with no systematic or proportionality bias for FFM (-0.5 ± 4.9, $p = 0.50$) and FM (0.3 ± 4.6, $p = 0.543$) (**Figure 2** and **Table 3**). This result was maintained in the subgroup assessment, except in the assessment of patients aged <56 years, in which the values obtained were influenced by the magnitude of the measure (proportionality bias). In addition, considering that the excess ECW is not included in the assessment of ATM, unlike DEXA, which can influence the results, we performed two Pearson's simple linear regression analysis between the difference between BCM (FFM and FM) and DEXA measurements with OH. The linear regression coefficient (r) regarding FFM and OH and FM and OH was, respectively, -0.2 ($p = 0.115$) and 0.2 ($p = 0.093$) (**Supplementary Material**).

Agreement Between MF-BIA and DXA

Despite not showing proportionality bias, the MF-BIA values underestimated FFM by 2.5 ± 5.4 kg in PD patients (**Table 4**). For this compartment, we found agreement between MF-BIA and DXA only for men and patients with BMI $\geq$ 25 kg/m2. For FM, we observed proportionality bias (**Figure 3** and **Table 4**). In men, MF-BIA values agreed to the reference standard. In those aged $\geq$56 years, FM was overestimated by 2.9 ± 5.4 kg.

Predictors of FFM and FM

To minimize the systematic errors observed in most evaluations, we developed equations for the prediction of FFM and FM in PD patients (**Chart 1**), based on regression analyses (**Supplementary Material**). Since there was agreement in the PD patients regarding the values of FFM and FM obtained through SF-BIA and DXA, it was not necessary to construct adjustment equations for this subgroup.

DISCUSSION

To our knowledge, this study was the first to test the agreement of FFM and FM measurements performed by SF-BIA and MF-BIA methods against a reference standard, such as DXA, in PD patients. Our results showed that the correlations between these methods and DXA were strong, as described in previous reports (10, 18). However, the correlation coefficient alone is not sufficient to suggest agreement between methods; an adequate concordance analysis is required. Our results showed that SF-BIA can be considered reliable in FFM and FM assessment in PD patients. This finding has great importance, since nutritional status is associated with dialysis outcomes (19). Previous studies by our group have shown that BIA measurements are associated with cardiovascular outcomes (20).

Huang et al. (21) followed up patients for ∼8 years, reporting that greater FFM was able to predict better patient and technique survival in PD patients. Kang et al. (22) showed an association of low appendicular mass (assessed by DXA) with all-cause mortality in incident PD patients. A recent systematic review and meta-analysis, including four studies and more than 50,000 PD patients, showed a higher mortality risk in patients with lower BMI values (23). However, the BMI *per se* does not discriminate body components such as FFM and FM, which can be estimated by more specific methods.

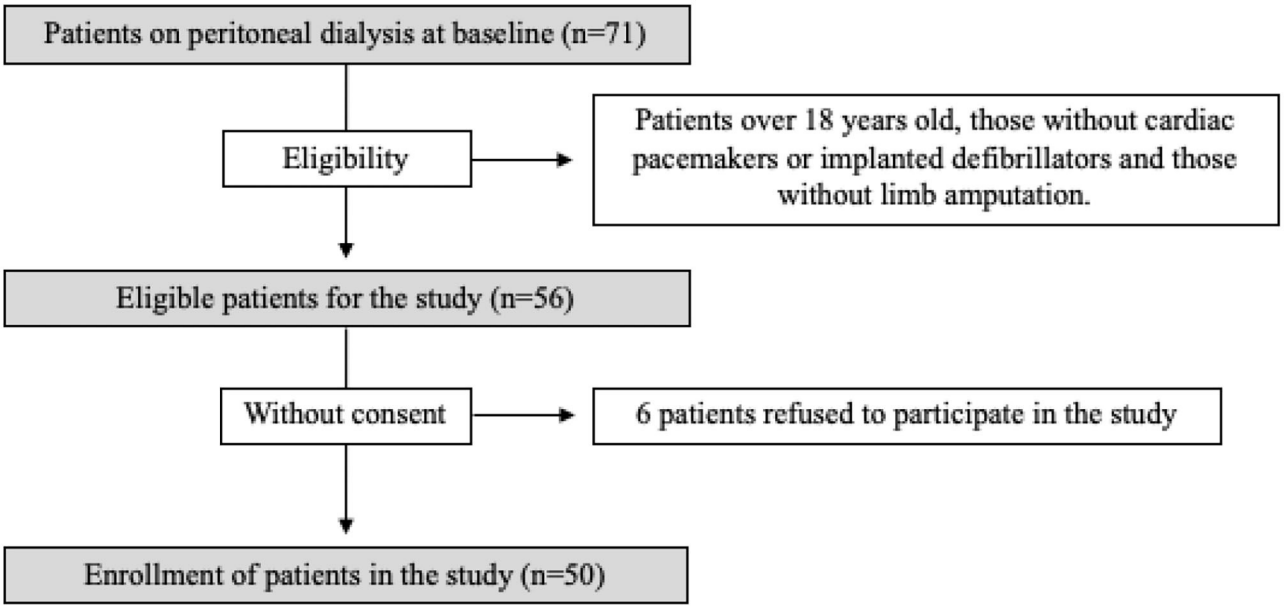

FIGURE 1 | The enrollment flowchart of the study patients.

TABLE 1 | Demographic and clinical characteristics of study patients.

	Peritoneal dialysis			
	Total (*n* = 50)	**Man (*n* = 23)**	**Women (*n* = 27)**	***p***
Age (y)	55.1 ± 16.3	54.4 ± 15.4	55.7 ± 17.3	0.787
Race/ethnicity (%)				
Caucasian	90.0	100.0	85.2	0.316
Black	2.0	0.0	3.7	
Brown	2.0	0.0	7.4	
Yellow	6.0	0.0	3.7	
Scholarity (<9 years of study)	64.0	65.2	65.4	0.990
Dialysis vintage (months)	9 (5-17)	7 (5-14)	11 (6-18)	0.163
CKD etiology (%)				
DM	22.0	30.4	14.8	0.658
SAH	16.0	21.7	37.5	
GCN	16.0	8.7	22.2	
Others	46.0	39.2	25.5	
SBP	140 (120–160)	140 (120–170)	140 (120–150)	0.285
DBP	80 (70–100)	80 (70–100)	80 (70–100)	0.889

Values are presented as mean ± standard deviation, median, and interquartile range or percentage. $p < 0.05$. CKD, Chronic kidney disease; DM, Diabetes Mellitus; SAH, Systemic Arterial Hypertension; GCN, Glomerulus Chronic Nephritis; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure.

PD patients have less variation in hydration status due to the continuous nature of their therapy (24), which can contribute significantly to agreement of body compartments using the instruments available in clinical practice, especially when compared to HD patients, who normally retain 1–4 liters over the interdialytic interval (10).

In the evaluation of the FFM, the MF-BIA did not present proportionality bias; however, it underestimated this measure. As the error occurred systematically, the measurement of FFM by these methods can also be considered possible, provided that adjustments are made to the values obtained. Konings et al. (25) found wide limits of agreement between MF-BIA and DXA, when assessed the body composition of 40 PD patients, with a strong influence on the hydration status. Differently, there was a proportional bias between DEXA and FM, which could be a consequence of the excess ECW not being included in

TABLE 2 | Hydration status and nutritional and laboratory parameters of study patients.

	Peritoneal dialysis			
	Total (*n* = 50)	**Man (*n* = 23)**	**Woman (*n* = 27)**	***p***
BMI (kg/m^2)	25.8 ± 4.3	26.9 ± 4.1	24.8 ± 4.3	0.079
FFM_ SF-BIA (kg)	47.8 ± 11.6	57.0 ± 11.1	41.6 ± 6.1	<0.001
FM_ SF-BIA (kg)	20.3 ± 7.6	21.1 ± 8.3	19.6 ± 7.0	0.493
LTM_MF-BIA (kg)	37.5 ± 10.8	43.5 ± 10.0	28.8 ± 5.8	<0.001
ATM_MF-BIA (kg)	31.5 ± 11.2	31.7 ± 11.1	31.3 ± 11.4	0.897
Fat_MF-BIA (kg)	23.1 ± 8.2	23.3 ± 8.2	23.0 ± 8.4	0.901
FFM (TBM-Fat)_MF-BIA (kg)	45.8 ± 11.8	54.7 ± 10.7	38.2 ± 5.9	<0.001
FFM (LTM+OH)_MF-BIA (kg)	36.3 ± 10.8	44.3 ± 9.8	29.5 ± 5.6	<0.001
OH	0.8 ± 1.1	0.9 ± 1.1	0.7 ± 1.1	0.517
OH/ECW (%)	5.0 ± 7.2	5.0 ± 6.0	5.0 ± 8.2	0.975
FFM_DXA (kg)	48.2 ± 11.1	56.6 ± 9.2	41.1 ± 6.0	<0.001
FM_DXA (kg)	20.6 ± 6.4	21.1 ± 6.7	20.3 ± 6.3	0.647
FFM_DXA (%)	69.7 ± 6.1	72.9 ± 6.0	67.3 ± 5.0	0.001
FM_DXA (%)	30.1 ± 6.1	27.1 ± 6.0	32.7 ± 5.0	0.001
LTI_DXA (kg/m^2)	18.0 ± 2.7	19.6 ± 2.6	16.7 ± 2.0	<0.001
FTI_DXA (kg/m^2)	7.8 ± 2.5	7.3 ± 2.3	8.3 ± 2.5	0.184
Albumin (g/dl)	3.6 ± 0.4	3.8 ± 0.4	3.5 ± 0.4	0.012
Creatinine (mg/dl)	9.1 ± 2.9	9.9 ± 3.1	8.4 ± 2.6	0.078
Hemoglobin (g/dl)	11.1 ± 1.8	11.8 ± 2.0	10.5 ± 1.3	0.008
TC (mg/dl)	151 ± 31	142 ± 33	160 ± 27.8	0.042
CRP (mg/dl)	0.6 (0.5–0.9)	0.5 (0.5–1.1)	0.6 (0.5–0.9)	0.925

Values are presented as mean ± standard deviation, median and interquartile range. p < 0.05. ATM, Adipose tissue mass; ECW, Extracellular water; TC, total cholesterol; DXA, dual energy x-ray densitometry; BMI, body mass index; FTI, Fat tissue index; LTI, Lean tissue index; FM, Fat mass; FFM, Fat-free mass; LTM, Lean tissue mass; OH, hyperhydration index; RCP, C-reactive protein; TG, triglyceride; TBW, total body mass; %, percentage.

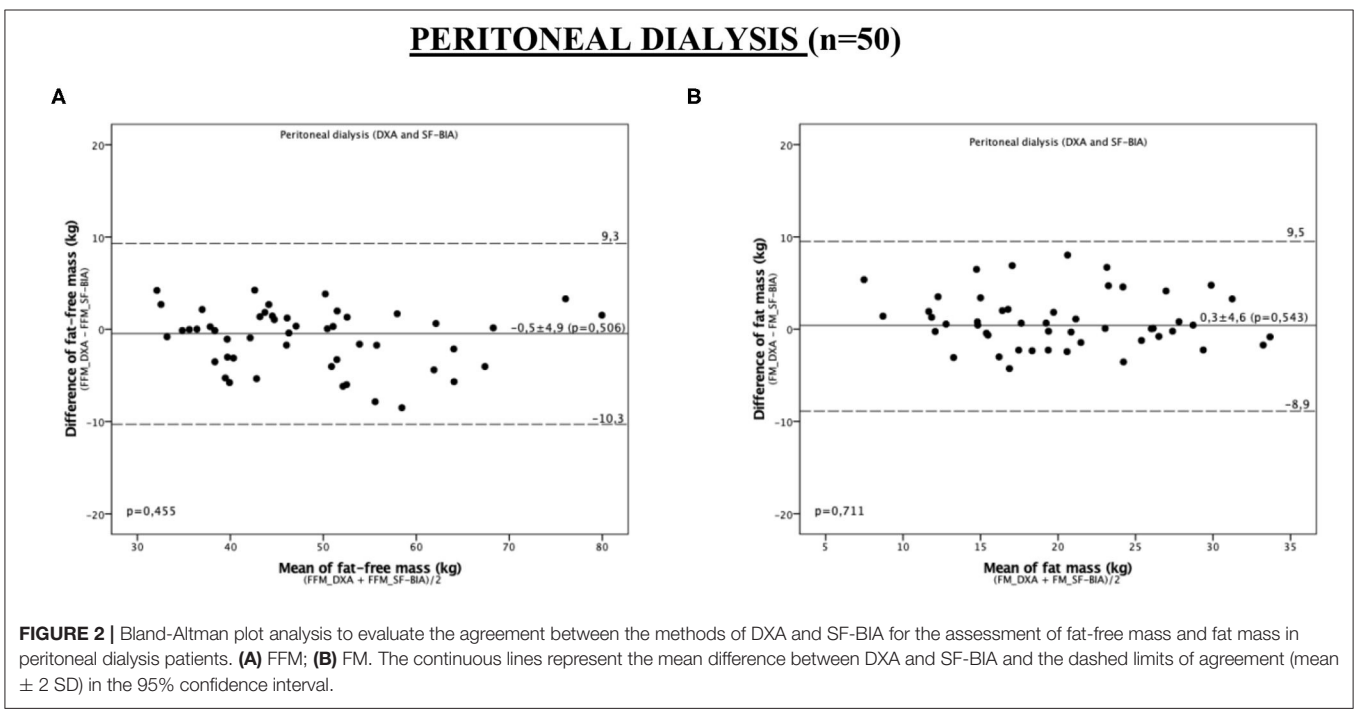

FIGURE 2 | Bland-Altman plot analysis to evaluate the agreement between the methods of DXA and SF-BIA for the assessment of fat-free mass and fat mass in peritoneal dialysis patients. **(A)** FFM; **(B)** FM. The continuous lines represent the mean difference between DXA and SF-BIA and the dashed limits of agreement (mean ± 2 SD) in the 95% confidence interval.

TABLE 3 | Agreement between the measurements obtained by DXA and single-frequency bioimpedance in the assessment of body composition in study patients.

	Peritoneal dialysis			
		Systematic bias		Proportionalaty bias
DXA vs. SF-BIA	**Bias**	**IC 95%**	***P***	
Total (*N* = 50)				
Fat-free mass (kg)	−0.5±4.9	−1.8 a 0.9	0.506	0.455
Fat mass (kg)	0.3 ± 4.6	−0.9 a 1.7	0.543	0.053
Man (*n* = 23)				
Fat-free mass (kg)	−0.4 ± 6.7	−3.2 a 2.5	0.789	0.351
Fat mass (kg)	0 ± 6.2	−2.6 a 2.7	0.973	0.187
Women (*n* = 27)				
Fat-free mass (kg)	−0.5 ± 2.6	−1.6 a 0.5	0.298	0.822
Fat mass (kg)	0.7 ± 2.6	−0.3 a 1.7	0.178	0.127
Age < 56 years (*n* = 24)				
Fat-free mass (kg)	−0.5 ± 6.3	−3.2 a 2.1	0.681	0.746
Fat mass (kg)	0.7 ± 6.0	−1.8 a 3.2	0.564	0.014
Age ≥ 56 years (*n* = 26)				
Fat-free mass (kg)	−0.4 ± 3.2	−1.7 a 0.9	0.535	0.332
Fat mass (kg)	0.1 ± 2.8	−1.0 a 1.2	0.854	0.588
BMI < 25 kg/m^2 (*n* = 24)				
Fat-free mass (kg)	−0.7 ± 3.0	−2.0 a 0.6	0.263	0.168
Fat mass (kg)	0.8 ± 3.0	−0.5 a 2.1	0.204	0.055
BMI ≥ 25 kg/m^2 (*n* = 26)				
Fat-free mass (kg)	−0.2 ± 6.2	−2.7 a 2.3	0.844	0.472
Fat mass (kg)	0 ± 5.7	−2.3 a 2.3	0.980	0.128

p < 0.05. PD, Peritoneal dialysis; DXA, dual energy x-ray densitometry; CI, Confidence interval; BMI, body mass index; SF-BIA, Single-frequency bioimpedance.

TABLE 4 | Agreement between the measurements obtained by DXA and multiple-frequency bioimpedance in the assessment of body composition in study patients.

	Peritoneal dialysis			
		Systematic bias		Proportionality bias
DXA vs. MF-BIA	**bias**	**IC 95%**	***p***	
Total (*N* = 50)				
Fat-free mass (kg)	2.5 ± 5.4	0.9 a 4.0	0.002	0.403
Fat mass (kg)	−2.5 ± 4.9	−3.9 a −1.1	0.001	0.005
Man (*n* = 23)				
Fat-free mass (kg)	2.0 ± 6.6	−0.9 a 4.8	0.166	0.527
Fat mass (kg)	−2.2 ± 5.8	−4.7 a 0.3	0.087	0.205
Women (*n* = 27)				
Fat-free mass (kg)	2.9 ± 4.1	1.2 a 4.5	0.001	0.848
Fat mass (kg)	−2.8 ± 4.1	−4.3 a −1.1	0.002	0.003
AGE < 56 years (*n* = 24)				
Fat-free mass (kg)	2.2 ± 5.0	0.1 a 4.3	0.041	0.748
Fat mass (kg)	–2.0 ± 4.4	−3.9 a −0.1	0.036	0.003
AGE ≥ 56 years (*n* = 26)				
Fat-free mass (kg)	2.7 ± 5.8	0.4 a 5.1	0.025	0.164
Fat mass (kg)	−2.9 ± 5.4	−5.1 a −0.7	0.011	0.222
BMI < 25 kg/m^2 (*n* = 24)				
Fat-free mass (kg)	2.2 ± 3.1	0.9 a 3.6	0.002	0.584
Fat mass (kg)	−2.0 ± 3.1	−3.3 a −0.7	0.004	0.003
BMI ≥ 25 kg/m^2 (*n* = 26)				
Fat-free mass (kg)	2.7 ± 6.9	−0.1 a 5.5	0.058	0.307
Fat mass (kg)	−2.9 ± 6.2	−5.4 a −0.4	0.024	0.023

p < 0.05. PD, Peritoneal dialysis; DXA, dual energy x-ray densitometry; CI, Confidence interval; BMI, body mass index; MF-BIA, Multiple frequency bioimpedance.

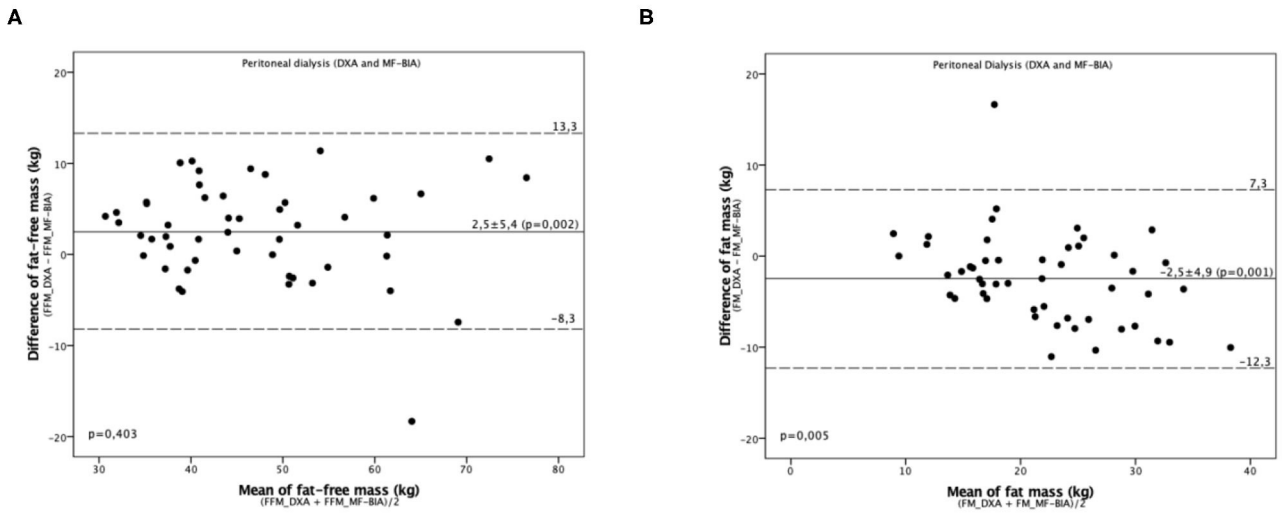

FIGURE 3 | Bland-Altman plot analysis to evaluate the agreement between the methods of DXA and MF-BIA for the assessment of fat-free mass and fat mass in peritoneal dialysis patients. **(A)** FFM **(B)** FM. The continuous lines represent the mean difference between DXA and MF-BIA and the dashed limits of agreement (mean ± 2 SD) in the 95% confidence interval.

CHART 1 | Prediction equations for FFM and FM in PD patients.

FAT-FREE MASS

$FFM_{MF-BIA} = -22{,}972 + 0{,}039 \times$ age (years) $- 3{,}077 \times$ sex (0 if M; 1 if F) $+ 0{,}498 \times$ weight (kg) $+ 15{,}886 \times$ height (m) $+ 2{,}244 \times$ PA (frequency 50) $+ 2{,}011 \times$ OH.

FAT MASS

FM_{MF-BIA} = weight (kg) $- [-22{,}972 + 0{,}039 \times$ age (years) $- 3{,}077 \times$ sex (0 if M; 1 if F) $+ 0{,}498 \times$ weight (kg) $+ 15{,}886 \times$ height (m) $+ 2{,}244 \times$ PA (f frequency 50) $+ 2{,}011 \times$ OH].

PA, Phase angle; MF-BIA, Multifrequency Bioimpedance; SF-BIA, Unifrequency Bioimpedance; M, Male; F, Female; FM, Fat mass; FFM, Fat-free mass; OH, hyperhydration index.

the assessment of FM, unlike DEXA. However, the absence of significant correlation between the differences of BCM and DEXA FM measurements and OH contradicts this possibility.

Since our results showed low agreement with MF-BIA in the body composition assessment with DXA, we constructed predictive equations to quantify FFM and FM in PD patients. The main differences in body composition measurements between BIA devices are prediction equations and alternating current frequencies. While SF-BIA analysis depends on the use of regression models, MF-BIA devices often use fit equations for a polynomial curve. In addition, each device is calibrated using its own equation and software. Therefore, despite the theoretical expectation of MF-BIA devices being more promising and reliable from a clinical perspective for the assessment of body composition, we suggest that single frequency devices are not inferior to multifrequency devices, and this has already been shown in previous studies (26). However, some adjustments in mathematical models can be applied in order to improve the agreement of the MF-BIA measures, such as the formulas we propose in our study, despite the need for validation. Predictive equations can have great relevance due to the impossibility of routine evaluation of body compartments using a reference method such as DXA due to its high complexity and high costs. However, it is important to highlight that the validation of the new equations still needs to be performed in a larger and independent population sample.

A potential limitation of our study is the absence of a gold standard in the assessment of body FFM in dialysis patients, since DXA assumes a constant hydration value. Despite this, DXA is still considered as the reference method by the KDOQI guideline (8) for assessment of body composition in ESKD patients. Its strengths are related to the moment when the evaluations were performed, with all the measurements taken on the same day by a single trained evaluator. In addition, the verification of the agreement was not limited to the evaluation of the systematic bias (as in other existing studies) but also included the objective analysis of the proportionality bias, constituting a more precise analysis.

In conclusion, the current results showed that SF-BIA agreed with DX in the evaluation of FFM and FM in PD patients, in opposite to MF-BIA measurements. Because its low-cost and being a non-examinator dependent method, SF-BIA can be recommended for the evaluation of free-fat mass and fat mass in PD patients.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Ethics and Research Committee of the Botucatu Medical School, São Paulo Paulo State University (Brazil). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NR, FV, and PB were responsible for conceptualization and methodology. NR, MS, FR, and FC performed data acquisition. NR, RO, and LM performed data analysis and interpretation. NR and FV were involved in formal analysis and wrote the original draft. NR, FV, MS, FR, LM, and PB revised and edited the manuscript. FV, LM, and PB were responsible for supervision and mentorship. All authors provided intellectual content of critical importance to the work and gave final approval of the version to be published.

FUNDING

This study was supported by National Council for Scientific and Technological Development (CNPq).

ACKNOWLEDGMENTS

Our acknowledgments to all patients and the team from the Dialysis Unit of the Clinics Hospital of Botucatu Medical School.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.686513/full#supplementary-material

REFERENCES

1. Carrero JJ, Thomas F, Nagy K, Arogundade F, Avesani CM, Chan M, et al. Global prevalence of protein-energy wasting in kidney disease: a meta-analysis of contemporary observational studies from the international society of renal nutrition and metabolism. *J Ren Nutr*. (2018) 28:380–92. doi: 10.1053/j.jrn.2018.08.006
2. Hanna RM, Ghobry L, Wassef O, Rhee CM, Kalantar-Zadeh K. A practical approach to nutrition, protein-energy wasting, sarcopenia, and cachexia in patients with chronic kidney disease. *Blood Purif*. (2020) 49:202–11. doi: 10.1159/000504240
3. Kalantar-Zadeh K, Streja E, Kovesdy CP, Oreopoulos A, Noori N, Jing J, et al. The obesity paradox and mortality associates with surrogates of body size. *Mayo Clin Proc*. (2010) 85:991–1001. doi: 10.4065/mcp.2010.0336
4. Kittiskulnam P, Johansen KL. The obesity paradox: a further consideration in dialysis patients. *Semin Dial*. (2019) 32:485–9. doi: 10.1111/sdi.12834
5. Noori N, Kovesdy CP, Dukkipati R, Kim Y, Duong U, Bross R, et al. Survival predictability of lean and fat mass in men and women undergoing maintenance hemodialysis. *Am J Clin Nutr*. (2010) 92:1060–70. doi: 10.3945/ajcn.2010.29188
6. Kalantar-Zadeh K, Streja E, Molnar MZ, Lukowsky LR, Krishnan M, Kovesdy CP, et al. Mortality prediction by surrogates of body composition: an examination of the obesity paradox in hemodialysis patients using composite ranking score analysis. *Am J Epidemiol*. (2012) 175:793–803. doi: 10.1093/aje/kwr384
7. Locatelli F, Fouque D, Heimburger O, Drüeke TB, Cannata-Andía JB, Hörl WH, et al. Nutritional status in dialysis patients: a European consensus. *Nephrol Dial Transplant*. (2002) 17:563–72. doi: 10.1093/ndt/17.4.563
8. National Kidney Foundation. KDOQI clinical practice guideline for nutrition in CKD: 2020 UPDATE. *Am J Kidney Dis*. (2020) 76:S1. doi: 10.1053/j.ajkd.2020.05.006
9. Fürstenberg A, Davenport A. Assessment of body composition in peritoneal dialysis patients using bioelectrical impedance and dual-energy x-ray absorptiometry. *Am J Nephrol*. (2011) 33:150–6. doi: 10.1159/000324111
10. Bross R, Chandramohan G, Kovesdy CP, Oreopoulos A, Noori N, Golden S, et al. Comparing body composition assessment tests in long-term hemodialysis patients. *Am J Kidney Dis*. (2010) 55:885–96. doi: 10.1053/j.ajkd.2009.12.031
11. Lukaski HC. Biological indexes considered in the derivation of the bioelectrical impedance analysis. *Am J Clin Nutr*. (1996) 64(Suppl 3):397S−404S. doi: 10.1093/ajcn/64.3.397S
12. Kamimura MA, Avesani CM, Cendoroglo M, Canziani MEF, Draibe SA, Cuppari L. Comparison of skinfold thicknesses and bioelectrical impedance analysis with dual-energy X-ray absorptiometry for the assessment of body fat in patients on long term haemodialysis therapy. *Nephrol Dial Transplant*. (2003); 18:101–5. doi: 10.1093/ndt/18.1.101
13. Rodrigues NC, Sala PC, Horie LM, Dias MC, Torrinhas RS, Romão JE Jr, et al. Bioelectrical impedance analysis and skinfold thickness sum in assessing body fat mass of renal dialysis patients. *J Ren Nutr*. (2012) 22:409–15. doi: 10.1053/j.jrn.2012.01.024
14. Lim PS, Chen CH, Zhu F, Kotanko P, Jeng Y, Hu CY, et al. Validating body fat assessment by bioelectric impedance spectroscopy in Taiwanese hemodialysis patients. *J Ren Nutr*. (2017) 27:37–44. doi: 10.1053/j.jrn.2016.08.003
15. Donadio C, Halim AB, Caprio F, Grassi G, Khedr B, Mazzantini M. Single- and multi-frequency bioelectrical impedance analyses to analyse body composition in maintenance haemodialysis patients: comparison with dual-energy x-ray absorptiometry. *Physiol Meas*. (2008) 29:S517–24. doi: 10.1088/0967-3334/29/6/S43
16. Kushner RF, Schoeller DA. Estimation of total body water by bioelectrical impedance analysis. *Am J Clin Nutr*. (1986) 44:417–24. doi: 10.1093/ajcn/44.3.417
17. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, et al. Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas*. (2006) 27:921–33. doi: 10.1088/0967-3334/27/9/012
18. Noori N, Kovesdy CP, Bross R, Lee M, Oreopoulos A, Benner D, et al. Novel equations to estimate lean body mass in maintenance hemodialysis patients. *Am J Kidney Dis*. (2011) 57:130–9. doi: 10.1053/j.ajkd.2010.10.003
19. Toledo FR, Antunes AA, Vannini FC, Silveira LV, Martin LC, Barretti P, et al. Validity of malnutrition scores for predicting mortality in chronic hemodialysis patients. *Int Urol Nephrol*. (2013) 45:1747–52. doi: 10.1007/s11255-013-0482-3
20. De Araujo Antunes A, Vannini FD, de Arruda Silveira LV, Barretti P, Martin LC, Caramori JC. Associations between bioelectrical impedance parameters and cardiovascular events in chronic dialysis patients. *Int Urol Nephrol*. (2013) 45:1397–403. doi: 10.1007/s11255-012-0337-3

21. Huang JW, Lien YC, Wu HY, Yen CJ, Pan CC, Hung TW, et al. Lean body mass predicts long-term survival in Chinese patients on peritoneal dialysis. *PLoS ONE*. (2013) 8:e54976. doi: 10.1371/journal.pone.0054976
22. Kang SH, Cho KH, Park JW, Do JY. Low appendicular muscle mass is associated with mortality in peritoneal dialysis patients: a single-center cohort study. *Eur J Clin Nutr*. (2017) 71:1405–10. doi: 10.1038/ejcn.2017.104
23. Ahmadi SF, Zahmatkesh G, Streja E, Mehrotra R, Rhee CM, Kovesdy CP, et al. Association of body mass index with mortality in peritoneal dialysis patients: a systematic review and meta-analysis. *Perit Dial Int*. (2016) 36:315–25. doi: 10.3747/pdi.2015.00052
24. Woodrow G, Devine Y, Cullen M, Lindley E. Application of bioelectrical impedance to clinical assessment of body composition in peritoneal dialysis. *Perit Dial Int*. (2007) 27:496–502. doi: 10.1177/089686080702700504
25. Konings CJ, Kooman JP, Schonck M, van Kreel B, Heidendal GAK, et al. Influence of fluid status on techniques used to assess body composition in peritoneal dialysis patients. *Perit Dial Int*. (2003) 23:184–90. doi: 10.1177/089686080302300215
26. Yalin SF, Gulcicek S, Avci S, Erkalma Senates B, Altiparmak MR, et al. Single-frequency and multi-frequency bioimpedance analysis: what is the difference? *Nephrology*. (2018) 23:438–45. doi: 10.1111/nep.13042

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.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 25 June 2021
doi: 10.3389/fnut.2021.688369

The Association Between Dietary Inflammatory Index and Parathyroid Hormone in Adults With/Without Chronic Kidney Disease

*Zheng Qin, Qinbo Yang, Ruoxi Liao and Baihai Su**

Department of Nephrology, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China

Aims: We aimed to assess the association between dietary inflammation index (DII) with parathyroid hormone (PTH) and hyperparathyroidism (HP) in adults with/without chronic kidney disease (CKD).

Methods: Data were obtained from the 2003–2006 National Health and Nutrition Examination Survey (NHANES). The participants who were <18 years old, pregnant, or missing the data of DII, PTH, and CKD were excluded. DII was calculated based on a 24-h dietary recall interview for each participant. Weighted multivariable regression analysis and subgroup analysis were conducted to estimate the independent relationship between DII with PTH and the HP in the population with CKD/non-CKD.

Results: A total of 7,679 participants were included with the median DII of −0.24 (−2.20 to 1.80) and a mean PTH level of 43.42 ± 23.21 pg/ml. The average PTH was 45.53 ± 26.63 pg/ml for the participants in the highest tertile group compared with 41.42 ± 19.74 pg/ml in the lowest tertile group ($P < 0.0001$). The rate of HP was 11.15% overall, while the rate in the highest DII tertile was 13.28 and 8.60% in the lowest DII tertile ($P < 0.0001$). The participants with CKD tended to have higher PTH levels compared with their counterparts (61.23 ± 45.62 vs. 41.80 ± 19.16 pg/ml, $P < 0.0001$). A positive association between DII scores and PTH was observed ($\beta = 0.46$, 95% CI: 0.25, 0.66, $P \leq 0.0001$), and higher DII was associated with an increased risk of HP (OR = 1.05, 95% CI: 1.02, 1.08, $P = 0.0023$). The results from subgroup analysis indicated that this association was similar in the participants with different renal function, gender, age, BMI, hypertension, and diabetes statuses and could also be appropriate for the population with CKD.

Conclusions: Higher consumption of a pro-inflammatory diet appeared to cause a higher PTH level and an increased risk of HP. Anti-inflammatory dietary management may be beneficial to reduce the risk of HP both in the population with and without CKD.

Keywords: dietary inflammatory index, parathyroid hormone, chronic kidney disease, hyperparathyroidism, National Health and Nutrition Examination Survery

OPEN ACCESS

Edited by:
Carla Maria Avesani, Karolinska Institutet, Sweden

Reviewed by:
Alisson Diego Machado, University of São Paulo, Brazil
Rosa Maria Affonso Moyses, University of São Paulo, Brazil

****Correspondence:***
Baihai Su
imsbh@163.com

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *30 March 2021*
Accepted: *01 June 2021*
Published: *25 June 2021*

Citation:
Qin Z, Yang Q, Liao R and Su B (2021) The Association Between Dietary Inflammatory Index and Parathyroid Hormone in Adults With/Without Chronic Kidney Disease. Front. Nutr. 8:688369. doi: 10.3389/fnut.2021.688369

INTRODUCTION

Parathyroid hormone (PTH) is a single-stranded peptide hormone, containing 84 amino acids, which are synthesized and secreted by the chief cells of the parathyroid gland, with the main function of increasing the serum Ca^{2+} and decreasing the serum phosphorus levels (1). The secretion of PTH is also mainly regulated by th zvbe concentration of serum Ca^{2+} and phosphorus (2, 3). Serum Ca^{2+} regulates PTH secretion through the interaction with calcium-sensitive receptors (CASR) on the surface of parathyroid cells (4, 5). Serum phosphorus enhances the stability of PTH mRNA and stimulates the proliferation of parathyroid cells to increase the secretion of PTH both directly and indirectly (3, 6). Bone and kidney are the main target organs of PTH (7–9). For a variety of pathological reasons, the parathyroid glands can secrete excessive PTH and cause hyperparathyroidism (HP), which can be classified as primary, secondary, and tertiary (10). HP appeared to be associated with an increased risk of poor clinical outcomes and death, which is often observed in patients with chronic kidney disease (CKD) (11).

Chronic kidney disease refers to a chronic clinical condition of renal, structural, and functional disorders and is characterized by a higher inflammation status (12). Recent studies have revealed the global prevalence of CKD to be about 10%, as well as the increasing disease burdens (13–15). In patients with CKD, abnormal regulation in calcium, phosphorus, vitamin D, and PTH is accompanied by a decline in renal function, which could lead to secondary HP, which is associated with the increased risk of fracture, cardiovascular disease, and death (16–18). Thus, the management of the PTH level in patients with CKD is of great significance.

The association between inflammation and PTH remains unclear. Several animal and human studies indicated that the PTH level may be associated with inflammation (19–21). Previous studies observed a decreased inflammation status after parathyroidectomy in patients with HP (22, 23). However, the inflammation level after parathyroidectomy varies widely among studies; both increased (24) and even no-change results (25) have been reported before. Chen et al. (19) found that inflammatory markers, including C-reactive protein (CRP), red cell distribution width (RDW), and platelet-to-lymphocyte ratio (PLR) levels increased with increasing serum PTH concentration in the US adults, indicating a positive relationship between inflammation and PTH. In *in vitro* studies, several inflammatory cytokines, such as interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), etc., have been proved to enhance PTH synthesis and secretion through nuclear factor-κB (NF-κB) and affect CASR transcription (26–28). It could be inferred that the consumption of an inflammatory diet may also have an impact on the PTH. Dietary inflammatory index (DII) was a literature-derived and population-based scoring system designed to evaluate the inflammatory potential of diets (29). A positive value for DII corresponded to an pro-inflammatory diet, and a negative value for DII corresponded to an anti-inflammatory diet. The higher scores suggested a more pro-inflammatory effect, and the more negative scores suggested a more anti-inflammatory effect. In fact, previous studies indicated a significant association between DII and the risk of various cancers (30, 31), obesity (32), cardiovascular disease (33), sarcopenia (34), and so on. However, the association between the dietary inflammatory potential and PTH has not been reported before.

In this study, we aimed to assess the impact of DII on PTH and HP, using data from the National Health and Nutrition Examination Survey (NHANES). We hypothesized that the increased consumption of pro-inflammatory diet would be associated with higher PTH levels and increased risk of HP. In addition, with regard to the fact that patients with CKD may have more elevated PTH levels than the population with non-CKD, we further examined this association in subgroups stratified by renal function.

MATERIALS AND METHODS

Study Population

In this study, we obtained data from the NHANES. NHANES is a program of studies administered by the National Center for Health Statistics (NCHS), part of the U.S. Centers for Disease Control and Prevention (CDC), aimed to assess the health and nutrition status of the U.S. population through interviews, physical examinations, and laboratory tests. The NHANES is conducted on a 2-year cycle, and the data are still being updated. Because this study adopted a stratified multistage probability sampling method, the included samples had good representativeness (35). All NHANES data are publicly available at www.cdc.gov/nchs/nhanes/.

This study was based on the data from two 2-year NHANES surveys from 2003 to 2006. A total of 20,470 participants were enrolled at first; after the exclusion of individuals aged <18 years old ($n = 9,287$), who were pregnant ($n = 520$), missing the dietary data relating to DII ($n = 1,161$), missing the data of diagnosing CKD ($n = 1,821$), and missing the data of PTH ($n = 2$), 7,679 participants were included in our final analysis (**Figure 1**).

The NCHS Ethics Review Board granted the human subject approval for the conduction of NHANES, and written informed consent was obtained from all the participants.

Exposure and Outcome Definitions

Dietary inflammation index was designed as an exposure variable. The dietary data in NHANES were obtained by a 24-h dietary recall interview at the mobile examination center (MEC) (36), which have been validated by the Nutrition Methodology Working Group before (37). The data of 24-h dietary recall interviews were used to calculate the DII scores for each individual, and it could quantify the inflammatory potential of diets. A higher positive DII score indicated a pro-inflammatory diet, and a lower negative DII score indicated an anti-inflammatory diet (29). A total of 27 food parameters were available in NHANES and were used for the calculation of DII, including anti-inflammatory food parameters (alcohol, β-carotene, fibers, folic acid, magnesium, zinc, selenium, vitamin A, vitamin B-6, vitamin C, vitamin E, monounsaturated fatty acid, niacin, riboflavin, n-3 fatty acid, n-6 fatty acid, polyunsaturated fatty acid, caffeine, and thiamin), and pro-inflammatory

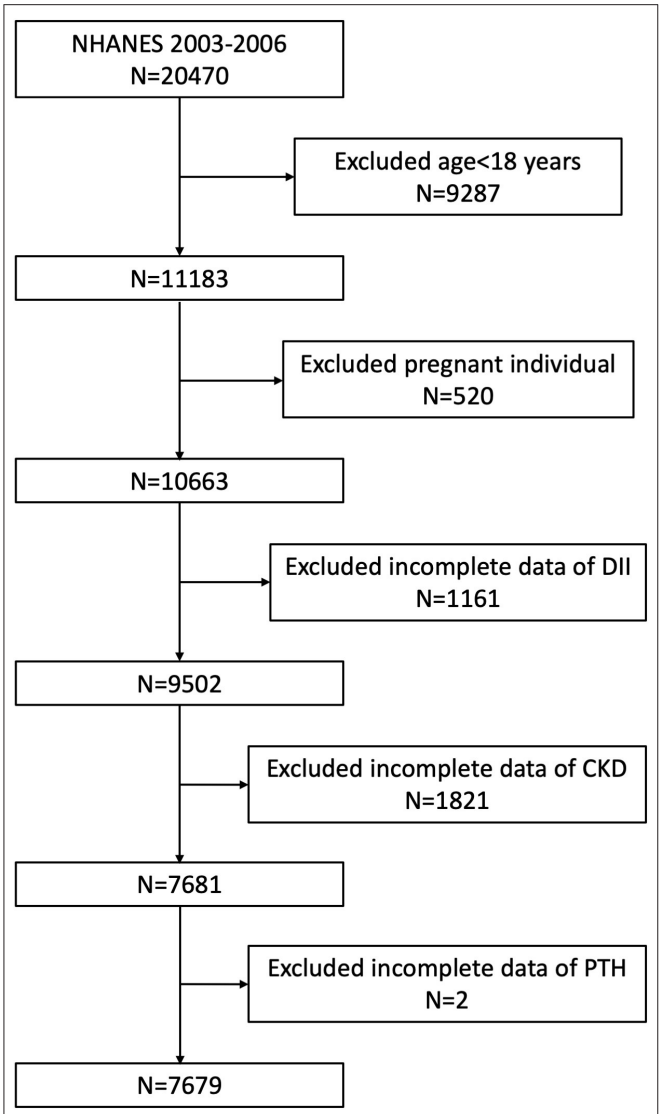

FIGURE 1 | A flowchart of the sample selection from NHANES 2003–2006.

food parameters (cholesterol, carbohydrates, energy, fats, iron, vitamin B-12, protein, and saturated fat). Studies have shown that the predictive ability was not affected when <30 dietary parameters were used to calculate DII scores (38–40). DII was analyzed as a continuous variable, and the participants were divided into tertiles from the total sample for further analysis.

The PTH level and HP were designed as outcome variables. The Elecsys 1010 analyzer (Roche Diagnostics) was used to determine the serum intact PTH level. The Elecsys 1010 analyzer was a fully automatic run-oriented analyzer system for the determination of immunological tests, using the ECL/Origen electrochemiluminescent process. All components and reagents for routine analysis were integrated into the analyzer. PTH was measured on the Elecsys 1010, using a sandwich principle. There was no difference in the equipment, lab method, or lab site between the combined two survey cycles in our analysis. HP was defined as PTH > 65 pg/ml according to previous studies (1, 41). The detailed process of measuring PTH was available at www.cdc.gov/nchs/nhanes/.

Other Study Variables

Baseline variables in this study included age (years), gender, race, educational level, systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body mass index (kg/m^2), serum glucose (mg/dl), serum phosphorus (mg/dl), serum iron (ug/dl), serum CRP (mg/dl), serum 25 (OH) D (nmol/L), serum calcium (mg/dl), urinary creatinine (mg/dl), urinary albumin (mg/L), urinary creatinine (mg/dl), eGFR (ml/min/1.73 m^2), parathyroid hormone (pg/ml), hypertension, diabetes, albuminuria, low eGFR, and CKD. All detailed measurement processes of study variables were publicly available at www.cdc.gov/nchs/nhanes/.

We calculated urinary albumin: creatinine ratio (ACR) and defined albuminuria as ACR > 30 mg/g. The data about gender, age, and serum creatinine were used to calculate the estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) according to the CKD Epidemiology Collaboration equation for each participant (42), and eGFR lower than 60 ml/min/1.73 m^2 was used to define low eGFR. We defined CKD as the presence of either albuminuria or low eGFR according to Kidney Disease: Improving Global Outcomes 2012 recommendations (12).

Statistical Analysis

All statistical analyses were conducted according to CDC guidelines (43). All estimates were calculated, accounting for NHANES sample weight. Continuous variables were presented as mean with SD or a median with an interquartile range, and categorical variables were presented as frequency or percentage. Either weighted Student's *t*-test (for continuous variables) or weighted chi-square test (for categorical variables) were conducted to calculate the differences in different DII groups (tertiles). To examine the association between DII and PTH levels, weighted multivariable linear regression explored PTH as a continuous variable, and weighted multivariable logistic regression for HP was used as a categorical variable in three different models. In model 1, no covariates were adjusted. Model 2 was adjusted for gender, age, and race. Model 3 was adjusted for gender, age, race, education level, serum glucose, serum phosphorus, serum iron, serum calcium, serum CRP serum, serum 25 (OH) D, systolic blood pressure, diastolic blood pressure, body mass index, hypertension, diabetes, chronic kidney disease, protein intake, calcium intake, and phosphorus intake. To further explore the association between DII with PTH and HP in different population settings, the subgroup analysis was performed by stratified weighted multivariate regression analysis. In addition, it has been well-recognized that patients with CKD often have elevated parathyroid hormone levels; the CKD status was treated as a prespecified potential effect modifier. An interaction term was added to test the heterogeneity of associations between the subgroups. $P < 0.05$ was considered statistically significant. All analysis was performed using Empower software (www. empowerstats.com; X&Y solutions, Inc., Boston MA) and R version 3.4.3 (http://www.R-project.org, The R Foundation).

RESULTS

Baseline Characteristics of Participants

The weighted demographic characteristics and other covariates of included individuals were shown in **Table 1**. A total of 7,679 participants were included in this study, of whom 48.34% were males and 51.66% were females, with an average age of 46.73 ± 18.80 years old. Median DII was −0.24 (−2.20 to 1.80), and the ranges of DII for tertiles 1–3 were −6.60 to −1.50, −1.50 to 1.08, and 1.08 to 6.50, respectively. Among different tertiles of DII, gender, race, education level, systolic blood pressure, diastolic blood pressure, serum iron, serum CRP, serum 25 (OH) D, urinary creatinine, serum creatinine, parathyroid hormone, and HP, whether having hypertension, diabetes, low eGFR and CKD, were significantly different, while no significant difference was observed in BMI, serum glucose, serum phosphorus, serum calcium, urinary albumin, eGFR, and whether having albuminuria between different tertiles. Mean PTH was 43.42 ± 23.21 pg/ml, and the average PTH was 45.53 ± 26.63 pg/ml for the participants in the highest tertile group compared with 41.42 ± 19.74 pg/ml in the lowest tertile group ($P < 0.0001$). The rate of HP was 11.15% overall, while the rate in the highest DII tertile was 13.28 and 8.60% in the lowest DII tertile ($P < 0.0001$).

As for the PTH levels of the participants based on different renal conditions, the participants with albuminuria, low eGFR, and CKD tended to have higher PTH levels compared with their counterparts. In the CKD group, mean PTH was 68.40 ± 55.29 pg/ml for the highest tertile group while 51.12 ± 32.84 pg/ml for the lowest tertile group ($P = 0.0002$). Mean PTH was 68.45 ± 55.36 pg/ml for the highest tertile and 51.42 ± 32.91 pg/ml for the lowest tertile in the low eGFR group ($P = 0.0003$). In the albuminuria group, mean PTH was 131.86 ± 94.31 pg/ml for the highest tertile group while 95.06 ± 110.67 pg/ml for the lowest tertile group; however, there was no significant difference ($P = 0.7248$). Mean eGFR of the patients with CKD was 48.96 ± 10.64 ml/min/1.73 m^2, and 1.78% of them were <15 ml/min/1.73 m^2. We also calculated the mean PTH level according to different stages of CKD. The PTH level in the participants with CKD, stages 1 to 5, was 40.50 ± 18.45, 43.58 ± 19.97, 56.01 ± 32.16, 122.30 ± 81.21, and 239.12 ± 136.89 pg/ml. The participants tended to show a higher PTH level with the CKD progression (**Table 2**).

For the prevalence of HP, participants with reduced renal function tended to have higher rates of HP. In the population with CKD, 28.07% of the participants had HP, while it was 9.61% for those without CKD. Similar results could be observed in the albuminuria and low-eGFR population as well (Albuminuria: 54.86 vs. 11.08%, low eGFR: 28.13 vs. 9.62%) (**Table 2**).

Higher DII Was Associated With Higher PTH Level and Higher Risk of HP

Weighted multivariable regression analysis was conducted to estimate the association of DII with the PTH level and HP in three different models (**Table 3**). The results revealed a positive association between DII scores and PTH with statistical significance (Model 1, $\beta = 0.71$, 95% CI: 0.51, 0.90, $P < 0.0001$; Model 2, $\beta = 0.58$, 95% CI: 0.38, 0.77, $P < 0.0001$; Model 3, $\beta = 0.46$, 95% CI: 0.25, 0.66, $P \leq 0.0001$). According to the results of the fully adjusted model (Model 3), each unit of the increased DII score was associated with a PTH increase by.46 pg/ml, suggesting that the higher DII scores were associated with a higher PTH level. This association remained statistically significant after DII was grouped as tertiles. The fully adjusted effect size (reference to Tertile 1) was 1.56 (95% CI: 0.28, 2.84, $P = 0.0167$) for Tertile 2 and 2.66 (95% CI: 1.31, 4.01, $P = 0.0001$) for Tertile 3.

In terms of HP, we also observed that increased DII was associated with a higher risk of HP (Model 1, OR = 1.07, 95% CI: 1.05, 1.10, $P < 0.0001$; Model 2, OR = 1.07, 95% CI: 1.04, 1.09, $P < 0.0001$; Model 3, OR = 1.05, 95% CI: 1.02, 1.08, $P = 0.0023$). In Model 3, which adjusted for all covariates, the results indicated that each unit of increased DII score was associated with a 5% increase of risk of HP. In sensitivity analysis, the adjusted OR (reference to Tertile 1) was 1.27 (95% CI: 1.05, 1.55, $P = 0.0157$) for Tertile 2 and 1.32 (95% CI: 1.09, 1.61, $P = 0.0054$) for Tertile 3, suggesting a stable positive relationship between increased DII and higher risk of HP with statistical significance.

Subgroup Analysis

We conducted the subgroup analysis stratified by low eGFR, CKD, gender, age, BMI, hypertension, and diabetes to further explore the association of DII with the PTH level and HP in different population settings by stratified weighted multivariate regression analysis and tested the interactions (**Table 4**). Regarding the correlation between DII scores and the PTH level, the test for interaction was significant for low eGFR (P for interaction = 0.0004) and CKD *P* (for interaction = 0.0003), indicating significant dependence on renal function. However, the positive association was statistically significant both in subgroups stratified by low eGFR and in subgroups stratified by CKD (all P for trend < 0.05). In subgroups stratified by gender, age, BMI, hypertension, and diabetes, the positive association between DII and PTH was still significant (*P* for trend < 0.05) and P for interaction >0.05, suggesting that the correlation between DII scores and the PTH level was similar in the population with different gender, age, BMI, hypertension status, and diabetes status.

As for the association between DII scores and HP, results of subgroup analysis stratified by CKD or no CKD demonstrated that DII was positively associated with a higher risk of HP (OR = 1.07, *P* for trend = 0.0023) in the CKD subgroup, and a similar result (OR = 1.04, *P* for trend = 0.0121) was observed in the non-CKD group. In addition, an interaction test was performed to evaluate if there was any significant dependence of the effect modifier (CKD) on the association. *P* for interaction >0.05 means no significant dependence, indicating that the magnitude of the association was the same for the population with/without CKD (*P* for interaction = 0.4942). Similarly, we did not find any significant dependence on low eGFR, gender, age, BMI, hypertension status, and diabetes status (all *P* for interaction > 0.05). These results indicated that the positive association between DII scores and HP was similar in the population with different renal function conditions (including CKD and low eGFR), gender, age, BMI, hypertension status, and diabetes status

TABLE 1 | Weighted baseline characteristics of the participants according to different dietary inflammatory indexes (DIIs).

DII	Overall −0.24 (-2.20∼1.80)	Tertile 1 (−6.60∼-1.50)	Tertile 2 (−1.50∼1.08)	Tertile 3 (1.08∼6.50)	*P*-value
Age (years)	46.73 ± 18.80	45.59 ± 17.88	47.51 ± 19.13	47.26 ± 19.46	0.0003
Gender (%)					
Male	48.34	60.84	46.40	35.06	<0.0001
Female	51.66	39.16	53.60	64.94	
Race (%)					
Mexican American	12.36	12.42	13.10	11.45	0.0003
Other hispanic	3.18	2.92	3.18	3.50	
Non-hispanic white	64.84	66.83	65.22	61.95	
Non-hispanic black	14.77	13.25	13.98	17.53	
Others	4.86	4.58	4.52	5.58	
Education level (%)					
Less than high school	22.34	19.88	22.40	25.31	<0.0001
High school or general educational development	25.39	23.98	25.02	27.56	
Above high school	52.08	55.97	52.43	46.90	
Others	0.18	0.17	0.15	0.23	
Systolic blood pressure (mmHg)	122.59 ± 18.55	121.71 ± 16.48	123.43 ± 19.30	122.76 ± 20.03	0.0043
Diastolic blood pressure (mmHg)	70.18 ± 13.32	71.02 ± 12.86	69.60 ± 13.72	69.78 ± 13.39	0.0002
Body mass index (kg/m^2)	28.20 ± 6.64	28.13 ± 6.47	28.35 ± 6.70	28.11 ± 6.77	0.3685
Glucose, serum (mg/dl)	96.83 ± 30.23	96.63 ± 28.77	96.91 ± 30.54	96.98 ± 31.61	0.9074
Phosphorus, serum (mg/dl)	3.84 ± 0.57	3.85 ± 0.57	3.84 ± 0.57	3.85 ± 0.58	0.7647
Iron, serum (μg/dl)	87.38 ± 36.47	91.77 ± 36.78	85.76 ± 35.00	83.77 ± 37.13	<0.0001
C-reactive protein, serum (mg/dl)	0.41 ± 0.83	0.33 ± 0.63	0.42 ± 0.80	0.48 ± 1.04	<0.0001
25(OH)D, serum (nmol/L)	59.96 ± 22.12	61.73 ± 21.49	60.02 ± 22.31	57.68 ± 22.46	<0.0001
Calcium, serum (mg/dl)	9.52 ± 0.35	9.53 ± 0.35	9.52 ± 0.35	9.51 ± 0.35	0.2978
Hypertension (%)					
Yes	29.58	25.26	32.51	31.71	<0.0001
No	70.42	74.74	67.49	68.29	
Diabetes (%)					
Yes	7.43	5.97	8.69	7.82	<0.0001
No	92.57	94.03	91.31	92.16	
Creatinine, urine (mg/dl)	127.53 ± 79.52	127.38 ± 75.49	123.34 ± 77.40	132.39 ± 86.15	0.0004
Albumin, urine (mg/L)	32.22 ± 225.38	28.30 ± 214.83	33.67 ± 230.78	35.44 ± 231.85	0.4891
Serum creatinine (mg/dl)	0.91 ± 0.29	0.94 ± 0.20	0.91 ± 0.36	0.89 ± 0.30	<0.0001
eGFR (ml/min/1.73 m^2)	91.94 ± 23.47	91.93 ± 21.63	91.79 ± 23.75	92.14 ± 25.27	0.8722
Albuminuria (%)					
Yes	0.16	0.13	0.13	0.22	0.6457
No	99.84	99.87	99.87	99.78	
Low eGFR (eGFR < 60 ml/min/1.73 m^2, %)					
Yes	8.28	6.34	8.64	10.27	<0.0001
No	91.72	93.66	91.36	89.73	
CKD (%)					
Yes	8.33	6.42	8.66	10.30	<0.0001
No	91.67	93.58	91.34	89.70	
Hyperparathyroidism (%)					
Yes	11.15	8.60	12.07	13.28	<0.0001
No	88.85	91.40	87.93	86.72	
Parathyroid hormone (pg/ml)	43.42 ± 23.21	41.42 ± 19.74	43.75 ± 23.29	45.53 ± 26.63	<0.0001

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

TABLE 2 | Parathyroid hormone (PTH) and the prevalence of hyperparathyroidism (HP) based on different renal population settings, weighted.

		DII Tertile 1 (−6.60∼-1.50)	DII Tertile 2 (−1.50∼1.08)	DII Tertile 3 (1.08∼6.50)	*P* for trend
Parathyroid hormone (pg/ml)					
Albuminuria					
Yes	111.73 ± 89.59	95.06 ± 110.67	99.18 ± 32.35	131.86 ± 94.31	0.7248
No	43.31 ± 22.80	41.35 ± 19.25	43.67 ± 23.19	45.34 ± 25.98	<0.0001
Low-eGFR[a]					
Yes	61.35 ± 45.69	51.42 ± 32.91	61.86 ± 41.57	68.45 ± 55.36	0.0003
No	41.80 ± 19.17	40.74 ± 18.31	42.03 ± 19.91	42.91 ± 19.31	0.0005
CKD[b]					
Yes	61.23 ± 45.62	51.12 ± 32.84	61.91 ± 41.53	68.40 ± 55.29	0.0002
Stage 1	40.50 ± 18.45	39.22 ± 17.38	40.39 ± 18.79	42.19 ± 19.18	<0.0001
Stage 2	43.58 ± 19.97	42.70 ± 19.27	44.29 ± 21.15	43.97 ± 19.44	0.1859
Stage 3	56.01 ± 32.16	48.81 ± 25.91	58.73 ± 36.05	59.15 ± 31.84	0.0011
Stage 4	122.30 ± 81.21	126.26 ± 84.37	93.96 ± 59.24	155.64 ± 89.70	0.0603
Stage 5	239.12 ± 136.89	75.00 ± 0.00	169.02 ± 124.24	265.17 ± 131.93	0.5695
No	41.80 ± 19.16	40.76 ± 18.31	42.02 ± 19.91	42.91 ± 19.31	0.0006
Hyperparathyroidism (%)					
Albuminuria					
Yes	54.86	26.34	67.48	66.91	0.0431
No	11.08	8.57	11.99	13.16	<0.0001
Low-eGFR[a]					
Yes	28.13	19.66	28.24	34.49	0.0018
No	9.62	7.85	10.54	10.85	0.0005
CKD[b]					
Yes	28.07	19.40	28.45	34.39	0.0014
Stage 1	8.88	7.14	8.78	11.08	0.0011
Stage 2	10.63	8.75	12.93	10.52	0.0127
Stage 3	24.87	17.78	25.53	29.86	0.0145
Stage 4	79.47	72.64	66.94	98.94	0.0400
Stage 5	78.57	0.00	42.71	90.54	0.1868
No	9.61	7.86	10.51	10.86	0.0005

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

[a]Low eGFR was defined as eGFR < 60 ml/min/1.73 m^2.

[b]CKD stage 1: eGFR ≥ 90 ml/min/1.73 m^2; stage 2: 60 ml/min/1.73 m^2 ≤ eGFR < 90 ml/min/1.73 m^2; stage 3: 30 ml/min/1.73 m^2 ≤ eGFR < 60 ml/min/1.73 m^2; stage 4: 15 ml/min/1.73 m^2 ≤ eGFR < 30 ml/min/1.73 m^2; stage 5: eGFR < 15 ml/min/1.73 m^2.

and could also be appropriate for the participants with reduced renal function.

DISCUSSION

In this cross-sectional study with 7,679 adults, a significant positive association of DII with the PTH level and HP was observed, indicating that higher consumption of pro-inflammatory diet may contribute to the higher PTH level and an increased risk of HP. The association between the exposure variable and outcome variables was still stable after adjustment for covariates. Subgroup analysis stratified by the renal condition (low eGFR and CKD) and other variables showed that this positive association was not affected, suggesting that this association could be appropriate for the population with different renal function conditions, gender, age, BMI, hypertension status, and diabetes status.

To our knowledge, this is the first study that assesses the association between the dietary inflammatory potential with the PTH level and the risk of HP. Patel et al. (44) investigated whether dietary calcium intake will influence the serum PTH concentrations in apparently healthy Indian adolescents and found that subjects with higher calcium intake had lower PTH. Cheung et al. (45) suggested that low dietary magnesium intake could alter the vitamin D-PTH relationship in adults who were overweight or obese. In another study assessing the effect of the dietary approaches to stop hypertension (DASH) diet, which is rich in fiber and low-fat dairy and is useful for lowering blood pressure on the PTH level, no significant effect was observed (46). Additionally, the cause-and-effect relationship between PTH and inflammation still remains controversial. Cheng et al. (19)

TABLE 3 | Association between DII, PTH, and HP, weighted.

	β/OR[a] (95% CI[b]), P value		
	Model 1[c]	**Model 2[d]**	**Model 3[e]**
Parathyroid hormone			
DII (continuous)	0.71 (0.51, 0.90) <0.0001	0.58 (0.38, 0.77) <0.0001	0.46 (0.25, 0.66) <0.0001
DII categories			
Tertile 1	Reference	Reference	Reference
Tertile 2	2.33 (1.09, 3.56) 0.0002	1.77 (0.54, 2.99) 0.0049	1.56 (0.28, 2.84) 0.0167
Tertile 3	4.11 (2.84, 5.39) <0.0001	3.31 (2.03, 4.60) <0.0001	2.66 (1.31, 4.01) 0.0001
Hyperparathyroidism			
DII (continuous)	1.07 (1.05, 1.10) <0.0001	1.07 (1.04, 1.09) <0.0001	1.05 (1.02, 1.08) 0.0023
DII categories			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.48 (1.26, 1.75) <0.0001	1.43 (1.21, 1.68) <0.0001	1.27 (1.05, 1.55) 0.0157
Tertile 3	1.57 (1.33, 1.85) <0.0001	1.49 (1.26, 1.76) <0.0001	1.32 (1.09, 1.61) 0.0054

Insensitivity analysis—dietary inflammatory index was converted from a continuous variable to a categorical variable (tertiles).

[a] β: effect sizes; OR: odds ratio.

[b] 95% CI: 95% confidence interval.

[c] Model 1: no covariates were adjusted.

[d] Model 2: adjusted for gender, age, and race.

[e] Model 3: adjusted for gender, age, race, education level, serum glucose, serum calcium, serum phosphorus, serum iron, serum C-reactive protein serum, serum 25(OH)D, systolic blood pressure, diastolic blood pressure, body mass index, hypertension, diabetes, chronic kidney disease, protein intake, calcium intake, and phosphorus intake.

assessed the association between the PTH level and inflammatory markers among the U.S. adults and reported that higher inflammatory markers were associated with a higher PTH level. Similar results have been reported before in other studies (22, 47–49). Another study observed upregulation of inflammatory genes in the adipose tissue from primary patients with HP when compared with the healthy controls (19). However, conflicting results were found for the effects of inflammatory markers on patients with HP after parathyroidectomy: both increased (24, 50, 51) and decreased (22) and even unchanged levels of inflammatory markers have been reported (52). The inconsistent results indicated an unclear cause-and-effect association between PTH and inflammation. The results of this study indicated that higher pro-inflammatory dietary intake was positively associated with PTH and an increased risk of HP; in another way, a higher inflammatory level may be associated with a higher PTH level and a higher risk of HP. The association was similar in the population with different renal function conditions, gender, age, BMI, hypertension status, and diabetes status according to the subgroup analysis.

Regarding the positive association between DII scores and the PTH level, we observed significant dependence on low eGFR (P for interaction = 0.0004) and CKD (P for interaction = 0.0003), indicating that renal function may be affected by this association. Serious disorders of calcium and phosphorus metabolism were commonly observed in patients with CKD; we speculated that the effect of the pro-inflammatory diet on PTH may be interfered by the metabolism disorder (53). The interplay between Renin-Angiotensin-Aldosterone System (RAAS) and PTH may also influence this association (54). What is more, patients with end-stage CKD were treated with hemodialysis usually, and the management of hemodialysis can affect the calcium and phosphorus metabolic status (55, 56). However, the data of hemodialysis in NHANES were missing, so we could not exclude the influence of different dialysis modes or conduct further analysis. Additionally, it was worth noting that this positive association was still statistically significant both in subgroups stratified by low eGFR and CKD (all P-value < 0.05), suggesting that, although, renal function may affect this association, it was similar in the population with/without low eGFR and CKD.

The exact mechanism of this positive association of DII with PTH and HP remains unclear. A possible explanation to support the results might be the effect of diet on pro-inflammatory markers, such as IL-8, TNF-α, etc., Previous studies have demonstrated that inflammation was closely associated with the activation of the NF-κB pathway (57–59). NF-κB could serve as a direct regulator of genes related to cell proliferation, such as cyclin D1, p21, p27, and p53, thus, involved in cell cycles (60, 61). It also plays a key role in angiogenesis and tumor growth by promoting antiapoptotic mechanisms and the expression of inflammatory cytokines; in turn, these cytokines also contribute to its activation (62, 63). NF-κB could play a role in PTH regulation as well. Mao et al. (26) found that local NF-κB activation could promote the synthesis and secretion of PTH and mediated the transcriptional activation of PTH directly. We hypothesized that the elevated inflammatory level may lead to the activation of NF-κB; thus, similar regulation by NF-κB may underlie the development of parathyroid hyperplasia and enhanced PTH synthesis and secretion. Angeletti et al. (27) evaluated the effects of IL-8 on the PTH level by incubation of parathyroid cells with recombinant IL-8 *in vitro* and found that IL-8 increased both PTH secretion and PTH mRNA expression. A previous study also reported that TNF-α could affect CASR transcription *via* NF-κB in human renal tubular cells (64). A significant down-expression of CASR mRNA, thus, upsetting the Ca^{2+} set point and enhancing the sensitivity of parathyroid glands to Ca^{2+} concentration may be another potential explanation of our results.

One of the strengths of our study was that it was based on nationwide, population-based sampling survey data, and sample weights were adopted, which make the study much more representative. It is noteworthy that we performed subgroup analysis stratified by different renal functions and found that this association was similar in different population settings and could also be appropriate for the participants with CKD. However, the limitations of this study cannot be ignored. First, due to the cross-sectional study design, we cannot make a causal inference. Second, the food intake data were based on a 24-h dietary recall; a recall bias was inevitable, and the daily variability of food intake cannot be reflected. With regard to DII scores, a total of 45 food parameters were included according to the design,

TABLE 4 | Subgroup analysis stratified by different variables, weighted.

DII	Parathyroid hormone		Hyperparathyroidism	
	β[a] (95% CI[b]), *P* for trend	P for interaction	OR[c] (95% CI), *P* for trend	*P* for interaction
Low-eGFR[d]				
Yes	1.65 (0.30, 3.01) 0.0171	0.0004	1.10 (1.04, 1.17) 0.0018	0.7108
No	0.33 (0.15, 0.51) 0.0003		1.04 (1.01, 1.08) 0.0121	
CKD				
Yes	1.73 (0.39, 3.08) 0.0116	0.0003	1.07 (1.01, 1.16) 0.0023	0.4942
No	0.33 (0.15, 0.50) 0.0003		1.04 (1.01, 1.08) 0.0121	
Gender				
Male	0.47 (0.20, 0.74) 0.0006	0.8715	1.04 (1.00, 1.09) 0.0469	0.5675
Female	0.43 (0.12, 0.73) 0.0061		1.05 (1.01, 1.10) 0.0206	
Age				
<60 years old	0.32 (0.10, 0.53) 0.0038	0.0588	1.04 (1.00, 1.08) 0.0444	0.5734
≥60 years old	0.89 (0.41, 1.37) 0.0003		1.07 (1.01, 1.12) 0.0137	
BMI				
BMI < 25 kg/m^2	0.48 (0.15, 0.81) 0.0042	0.7475	1.11 (1.05, 1.17) 0.0004	0.1499
BMI ≥ 25 kg/m^2	0.47 (0.21, 0.73) 0.0003		1.02 (1.01, 1.06) 0.0039	
Hypertension				
Yes	0.69 (0.21, 1.17) 0.0053	0.1696	1.04 (0.99, 1.09) 0.0862	0.7086
No	0.34 (0.14, 0.55) 0.0009		1.05 (1.01, 1.09) 0.0071	
Diabetes				
Yes	1.09 (0.12, 2.06) 0.0287	0.1881	1.09 (0.98, 1.21) 0.1276	0.3318
No	0.40 (0.20, 0.61) 0.0001		1.04 (1.01, 1.08) 0.0035	

The results show that the subgroup analysis was adjusted for all presented covariates except the effect modifier. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.
[a] β: effect sizes.
[b] 95% CI: 95% confidence interval.
[c] OR: odd ratio.
[d] Low eGFR was defined as eGFR < 60 ml/min/1.73 m^2.

but only 27 food parameters were available in the NHANES data. Although, previous studies reported that the predictive ability was not affected when <30 dietary parameters were used with DII calculating (38–40), the impact on accuracy cannot be ignored. Third, HP was defined as intact PTH > 65 pg/ml in our analysis. However, optimal PTH levels in CKD stages 3–5 remain unknown (65). Although most of the participants with CKD in this study were in stage 1 and stage 2, we also used this HP definition in patients with CKD stages 3–5; thus, it may affect the accuracy. In addition, some potential confounders, such as the hemodialysis condition (the patients with non-dialysis dependent or hemodialysis CKD, a hemodialysis type, etc.,), drugs use, and fibroblast growth factor 23 (FGF23), may influence this association, but these confounders were not available in NHANES data (56, 66–68). Another limitation was that PTH was only assayed at a single time point; thus, no repeat measurements of PTH were conducted.

CONCLUSION

In this cross-sectional study with 7,679 adults, a significant positive association between DII with PTH and HP was observed, indicating that higher consumption of pro-inflammatory potential correlates positively with the higher PTH level and an increased risk of HP. This association exists both in the populations with CKD and with no CKD. Our finding suggests that anti-inflammatory dietary management may reduce the risk of HP. Further research and clinical settings are still needed to validate their potential application.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: www.cdc.gov/nchs/nhanes/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the NCHS Ethic Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZQ: data analysis, software, and writing of the original draft. QY: formal analysis and software. RL: methodology and writing

of the original draft. BS: conceptualization, funding acquisition, writing, reviewing, and editing. All the authors approved the final version.

FUNDING

This work was supported by the State Key Research Programme of China (Grant nos. 2016YFC1103004 and 2016YFC1103003), the National Natural Science Foundation of China (Grant no. 82000702), the Science and Technology Achievement Transformation Fund of West China Hospital of Sichuan University (Grant no. CGZH19006), National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Grant no. Z2018B10), and Med+ Biomaterial Institute of West China Hospital/West China School of Medicine of Sichuan University (Grant no. ZYME20001).

ACKNOWLEDGMENTS

We thank the assistance of Yingfei Xu in data processing.

REFERENCES

1. Raposo L, Martins S, Ferreira D, Guimarães JT, Santos AC. Vitamin D, parathyroid hormone and metabolic syndrome – the PORMETS study. *BMC Endocr Disord.* (2017) 17:71. doi: 10.1186/s12902-017-0221-3
2. Bilezikian JP, Cusano NE, Khan AA, Liu J-M, Marcocci C, Bandeira F. Primary hyperparathyroidism. *Nat Rev Dis Primers.* (2016) 2:16033. doi: 10.1038/nrdp.2016.33
3. Naveh-Many T, Rahamimov R, Livni N, Silver J. Parathyroid cell proliferation in normal and chronic renal failure rats. The effects of calcium, phosphate, vitamin D. *J Clin Invest*. (1995) 96:1786–93. doi: 10.1172/JCI118224
4. Brown EM. The pathophysiology of primary hyperparathyroidism. *J Bone Miner Res*. (2002) 17(Suppl. 2):N24–9. doi: 10.1359/jbmr.2002.17.11.2087
5. Paolo RG, Selene P. Does angiotensin II regulate parathyroid hormone secretion or not? *Clini Endocrinol*. (2018) 89:568–9. doi: 10.1111/cen.13798
6. Moallem E, Kilav R, Silver J, Naveh-Many T. RNA-protein binding and post-transcriptional regulation of parathyroid hormone gene expression by calcium and phosphate. *J Biol Chem*. (1998) 273:5253–9. doi: 10.1074/jbc.273.9.5253
7. Sitges-Serra A, Bergenfelz A. Clinical update: sporadic primary hyperparathyroidism. *Lancet.* (2007) 370:468–70. doi: 10.1016/S0140-6736(07)61213-6
8. Silverberg SJ, Clarke BL, Munro P, Francisco B, Stephanie B, Cusano NE, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab.* (2014) 99:3580–94. doi: 10.1210/jc.2014-1415
9. Smit MA, Van K, Joke V, Charlotte VN, SnjeŽana K. Clinical guidelines and PTH measurement: does assay generation matter? *Endocr Rev.* (2019) 40:1468–80. doi: 10.1210/er.2018-00220
10. Shindo M, Lee JA, Lubitz CC, Mccoy KL, Orloff LA, Tufano RP, et al. The changing landscape of primary, secondary, and tertiary hyperparathyroidism: highlights from the American College of Surgeons Panel, "what's new for the surgeon caring for patients with hyperparathyroidism". *J Am Coll Surg.* (2016) 222:1240–50. doi: 10.1016/j.jamcollsurg.2016.02.024
11. Kritchevsky SB, Tooze JA, Neiberg RH, Schwartz GG, Hausman DB, Johnson MA, et al. 25-Hydroxyvitamin D, parathyroid hormone, and mortality in black and white older adults: The health ABC study. *J Clin Endocr Metab*. (2012) 97:4156–65. doi: 10.1210/jc.2012-1551
12. Chapter 1: definition classification of CKD. *Kidney Int Suppl.* (2013) 3:19–62. doi: 10.1038/kisup.2012.64
13. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan C, Lasserson DS, et al. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. *PLoS ONE.* (2016) 11:e0158765. doi: 10.1371/journal.pone.0158765
14. Ackland P. Prevalence, detection, evaluation, and management of chronic kidney disease. *BMJ*. (2014) 348:f7688. doi: 10.1136/bmj.f7688
15. Jager KJ, Fraser SDS. The ascending rank of chronic kidney disease in the global burden of disease study. *Nephrol Dial Transplant*. (2017) 32:ii121–28. doi: 10.1093/ndt/gfw330
16. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, therapeutic options. *Clin J Am Soc Nephrol.* (2011) 6:913–21. doi: 10.2215/CJN.06040710
17. Block GA, Martin KJ, de Francisco ALM, Turner SA, Avram MM, Suranyi MG, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med.* (2004) 350:1516–25. doi: 10.1056/NEJMoa031633
18. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev*. (2001) 22:477–501. doi: 10.1210/edrv.22.4.0437
19. Cheng S-P, Liu C-L, Liu T-P, Hsu Y-C, Lee J-J. Association between parathyroid hormone levels and inflammatory markers among US adults. *Mediators Inflamm.* (2014) 2014:709024. doi: 10.1155/2014/709024
20. Christensen MHE, Dankel SN, Nordbo Y, Varhaug JE, Almas B, Lien EA, et al. Primary hyperparathyroidism influences the expression of inflammatory and metabolic genes in adipose tissue. *PLoS ONE.* (2011) 6:e20481 doi: 10.1371/journal.pone.0020481
21. Lutfioglu M, Sakallioglu U, Sakallioglu EE, Diraman E, Ciftci G, Tutkun F. Dietary-induced hyperparathyroidism affects serum and gingival proinflammatory cytokine levels in rats. *J Periodontol.* (2010) 81:150–7. doi: 10.1902/jop.2009.090353
22. Grey A, Mitnick MA, Shapses S, Ellison A, Gundberg C, Insogna K. Circulating levels of interleukin-6 and tumor necrosis factor-alpha are elevated in primary hyperparathyroidism and correlate with markers of bone resorption–a clinical research center study. *J Clin Endocrinol Metab.* (1996) 81:3450–4. doi: 10.1210/jcem.81.10.8855783
23. Alakus H, Goksu M. Does parathyroidectomy affect the neutrophil/lymphocyte ratio, a systemic inflammatory marker? *Cureus.* (2021) 13:7. doi: 10.7759/cureus.13708
24. Farahnak P, Lrfars G, Sten-Linder M, Nilsson IL. Mild primary hyperparathyroidism: vitamin d deficiency and cardiovascular risk markers. *J Clin Endocrinol Metabol.* (2011) 96:2112–8. doi: 10.1210/jc.2011-0238
25. Bollerslev J, Rosen T, Mollerup CL, Nordenström J, Baranowski M, Franco C, et al. Effect of surgery on cardiovascular risk factors in mild primary hyperparathyroidism. *J Clin Endocrinol Metab*. (2009) 94:2255–61.
26. Mao J, Wang M, Ni L, Gong W, Jiang X, Zhang Q, et al. Local NF-kappaB activation promotes parathyroid hormone synthesis and secretion in uremic patients. *Endocrinology.* (2021). doi: 10.1210/endocr/bqab084
27. Angeletti RH, D'Amico T, Ashok S, Russell J. The chemokine interleukin-8 regulates parathyroid secretion. *J Bone Min Res.* (1998) 13:1232–7. doi: 10.1359/jbmr.1998.13.8.1232
28. Hendy GN, Canaff L. Calcium-sensing receptor gene: regulation of expression. *Front Physiol.* (2016) 7:12. doi: 10.3389/fphys.2016.00394
29. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert J. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr.* (2014) 17:1689–96. doi: 10.1017/S1368980013002115
30. Shivappa N, Godos J, Hebert JR, Wirth MD, Piuri G, Speciani AF, et al. Dietary inflammatory index and colorectal cancer risk-a meta-analysis. *Nutrients.* (2017) 9:17. doi: 10.3390/nu9091043
31. Zahedi H, Djalalinia S, Asayesh H, Mansourian M, Abdar ZE, Gorabi AM, et al. A higher dietary inflammatory index score is associated with a higher risk of incidence and mortality of cancer: a comprehensive systematic review and meta-analysis. *Int J Preventive Med.* (2020) 11:24. doi: 10.4103/ijpvm.IJPVM_332_18
32. Ruiz-Canela M, Zazpe I, Shivappa N, Hebert JR, Sanchez-Tainta A, Corella D, et al. Dietary inflammatory index and anthropometric measures of obesity in a population sample at high cardiovascular risk from the PREDIMED (PREvencion con DIeta MEDiterranea) trial. *Br J Nutr.* (2015) 113:984–95. doi: 10.1017/S0007114514004401

33. Ji M, Hong X, Chen M, Chen T, Zhang N. Dietary inflammatory index and cardiovascular risk and mortality: a meta-analysis of cohort studies. *Medicine.* (2020) 99:e20303. doi: 10.1097/MD.0000000000020303
34. Geng J, Deng L, Shi Q, Bian H, Su B. Dietary inflammatory potential and risk of sarcopenia: data from national health and nutrition examination surveys. *Aging.* (2020) 13:1913–28. doi: 10.18632/aging.202141
35. Zipf G, Chiappa M, Porter KS, Ostchega Y, Dostal J. National health and nutrition examination survey: plan and operations, 1999-2010. *Vital Health Stat.* (2013) 1:1–37.
36. Mazidi M, Kengne AP, Vatanparast H. Association of dietary patterns of American adults with bone mineral density and fracture. *Public Health Nutr.* (2018) 21:2417–23. doi: 10.1017/S1368980018000939
37. Plan and operation of the third National Health and Nutrition Examination Survey, 1988-94. *Vital Health Stat.* (1994):1–407.
38. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr.* (2014) 17:1825–33. doi: 10.1017/S1368980013002565
39. Park Y, Choi MK, Lee SS, Shivappa N, Han K, Steck SE, et al. Dietary inflammatory potential and risk of mortality in metabolically healthy and unhealthy phenotypes among overweight and obese adults. *Clin Nutr.* (2018) 38:682–8. doi: 10.1016/j.clnu.2018.04.002
40. Mohsen M, Nitin S, Wirth M, Hebert JR, Kengne AP. Greater dietary inflammatory index score is associated with higher likelihood of chronic kidney disease. *Br J Nutr.* (2018) 120:204–9. doi: 10.1017/S0007114518001071
41. Chen L, Pei JH, Kuang J. Moderators of the association between serum parathyroid hormone and metabolic syndrome in participants with elevated parathyroid hormone: NHANES 2003-2006. *Horm Metab Res.* (2020) 52:509–16. doi: 10.1055/a-1148-2546
42. Levey AS, Stevens LA, Schmid CH, Zhang YP, Castro AF, Feldman HI, et al. Chronic kidney dis epidemiology, a new equation to estimate glomerular filtration rate. *Ann Intern Med.* (2009) 150:604–12. doi: 10.7326/0003-4819-150-9-200905050-00006
43. Johnson CL, Paulose-Ram R, Ogden CL, Carroll M, Curtin LR. National health and nutrition examination survey: analytic guidelines, 1999-2010. *Vital Health Stat 2.* (2013) 161:1–24.
44. Patel P, Mughal MZ, Patel P, Yagnik B, Kajale N, Mandlik R, et al. Dietary calcium intake influences the relationship between serum 25-hydroxyvitamin D-3 (25OHD) concentration and parathyroid hormone (PTH) concentration. *Arch Dis Childhood.* (2016) 101:316–9. doi: 10.1136/archdischild-2015-308985
45. Cheung MM, DeLuccia R, Ramadoss RK, Aljahdali A, Volpe SL, Shewokis PA, et al. Low dietary magnesium intake alters vitamin D-parathyroid hormone relationship in adults who are overweight or obese. *Nutr Res.* (2019) 69:82–93. doi: 10.1016/j.nutres.2019.08.003
46. Hassoon, Michos ED, Miller ER III, Crisp Z, Appel LJ. Effects of different dietary interventions on calcitriol, parathyroid hormone, calcium, and phosphorus: results from the DASH trial. *Nutrients.* (2018) 10:367. doi: 10.3390/nu10030367
47. Guo C, Holland P, Jackson B, Hannon R, Rogers A, Harrison B, et al. Immediate changes in biochemical markers of bone turnover and circulating interleukin-6 after parathyroidectomy for primary hyperparathyroidism. *Eur J Endocrinol.* (2000) 142:451. doi: 10.1530/eje.0.1420451
48. Ogard CG, Engelmann MD, Kistorp C, Nielsen SL, Vestergaard H. Increased plasma N-terminal pro-B-type natriuretic peptide and markers of inflammation related to atherosclerosis in patients with primary hyperparathyroidism. *Clin Endocrinol.* (2005) 63:493–8. doi: 10.1111/j.1365-2265.2005.02363.x
49. Emam AA, Mousa SG, Ahmed KY, Al-Azab AA. Inflammatory biomarkers in patients with asymptomatic primary hyperparathyroidism. *Med Princ Pract.* (2011) 21:249–53. doi: 10.1159/000334588
50. Halabe A, Shohat B. Effect of parathyroid adenoma excision on interleukin-6 (IL-6) and IL-2 receptor levels. *Metabolism.* (2000) 49:192–4. doi: 10.1016/s0026-0495(00)91247-2
51. Almqvist EG, Bondeson AG, Bondeson L, Svensson J. Increased markers of inflammation and endothelial dysfunction in patients with mild primary hyperparathyroidism. *Scand J Clin Lab Invest.* (2011) 71:139–44. doi: 10.3109/00365513.2010.543694
52. Bollerslev J, Rosen T, Mollerup CL, Nordenstroem J, Baranowski M, Franco C, et al. Effect of surgery on cardiovascular risk factors in mild primary hyperparathyroidism. *J Clin Endocrinol Metabol.* (2009) 94:2255–61. doi: 10.1210/jc.2008-2742
53. Cannata-Andia JB, Martin-Carro B, Martin-Virgala J, Rodriguez-Carrio J, Bande-Fernandez JJ, Alonso-Montes C, et al. Chronic kidney disease-mineral and bone disorders: pathogenesis and management. *Calcif Tissue Int.* (2021) 108:410–22. doi: 10.1007/s00223-020-00777-1
54. Zheng MH, Li F, Xu F, Lin X, Yuan LQ. The interplay between the renin-angiotensin-aldosterone system and parathyroid hormone. *Front Endocrinol.* (2020) 11:539. doi: 10.3389/fendo.2020.00539
55. Cozzolino M, Ciceri P. Serum PTH levels in dialysis: better safe than sorry. *Ther Adv Endocrinol Metabol.* (2020) 11. doi: 10.1177/2042018820974172
56. Lotfollahi L, Ossareh S, Neyestani TR. Evaluation of 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D levels in maintenance hemodialysis patients. *Iran J Kidney Dis.* (2021) 15:31–7.
57. Roshanravan N, Shabestari AN, Alamdari NM, Ostadrahimi A, Separham A, Parvizi R, et al. A novel inflammatory signaling pathway in patients with slow coronary flow: NF-kappaB/IL-1beta/nitric oxide. *Cytokine.* (2021) 143:155511. doi: 10.1016/j.cyto.2021.155511
58. Delhase M. IkappaB kinase and NF-kappaB signaling in response to pro-inflammatory cytokines. *Methods Mol Biol.* (2003) 225:7–17. doi: 10.1385/1-59259-374-7:7
59. Rahman A, Fazal F. Blocking NF-kappaB: an inflammatory issue. *Proc Am Thorac Soc.* (2011) 8:497–503. doi: 10.1513/pats.201101-009MW
60. Viatour P, Merville MP, Bours V, Chariot A. Phosphorylation of NF-kappa B and I kappa B proteins: implications in cancer and inflammation. *Trends Biochem.Sci.* (2005) 30:43–52. doi: 10.1016/j.tibs.2004.11.009
61. Kumar A, Takada Y, Boriek AM, Aggarwal BB. Nuclear factor-kappa B: its role in health and disease. *J Mol Med.* (2004) 82:434–48. doi: 10.1007/s00109-004-0555-y
62. Sakamoto K, Maeda S, Hikiba Y, Nakagawa H, Hayakawa Y, Shibata W, et al. Constitutive NF-kappa B Activation in colorectal carcinoma plays a key role in angiogenesis, promoting tumor growth. *Clin Cancer Res.* (2009) 15:2248–58. doi: 10.1158/1078-0432.CCR-08-1383
63. He J, Qin M, Chen Y, Hu Z, Ye L, Hui T. EZH2 promotes extracellular matrix degradation *via* nuclear factor-kappa B (NF-kappa B) and p38 signaling pathways in pulpitis. *Inflammation.* (2021). doi: 10.1007/s10753-021-01470-7
64. Canaff L, Hendy GN. NF-kappa B mediates transcriptional up-regulation of the human calcium-sensing receptor gene by pro-inflammatory cytokines. *Faseb J.* (2003) 17:A185.
65. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl.* (2017) 7:e1. doi: 10.1016/j.kisu.2017.10.001
66. Zeng SF, Querfeld U, Feger M, Haffner D, Hasan AA, Chu C, et al. Relationship between GFR, intact PTH, oxidized PTH, non-oxidized PTH as well as FGF23 in patients with CKD. *Faseb J.* (2020) 34:15269–81. doi: 10.1096/fj.202000596R
67. Imafuku T, Tanaka M, Tokunaga K, Miyamura S, Kato H, Tanaka S, et al. Effect of cinacalcet on the redox status of albumin in secondary hyperparathyroidism patients receiving hemodialysis. *Biol Pharm Bull.* (2020) 43:1583–90. doi: 10.1248/bpb.b20-00472
68. Hall R, Platt A, Wilson J, Ephraim PL, Hwang AS, Chen AN, et al. Comparative effectiveness, trends in mineral metabolism treatment strategies in patients receiving hemodialysis in the United States. *Clin J Am Soc Nephrol.* (2020) 15:1603–13. doi: 10.2215/CJN.04350420

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.

frontiers in Nutrition

REVIEW
published: 12 August 2021
doi: 10.3389/fnut.2021.701386

How to Overcome Anabolic Resistance in Dialysis-Treated Patients?

Giacomo Garibotto[1], Michela Saio[1], Francesca Aimasso[2], Elisa Russo[1,3], Daniela Picciotto[1,3], Francesca Viazzi[1,3], Daniela Verzola[1], Alessandro Laudon[4], Pasquale Esposito[1,3] and Giuliano Brunori[4]*

[1] Department of Internal Medicine, University of Genoa, Genova, Italy, [2] Clinical Nutrition Unit, Istituto di Ricerca a Carattere Scientifico Ospedale Policlinico San Martino, Genova, Italy, [3] Clinica Nefrologica, Dialisi e Trapianto, IRCCS Ospedale Policlinico San Martino, Genova, Italy, [4] Division of Nephrology and Dialysis, Ospedale Santa Chiara, Trento, Italy

A current hypothesis is that dialysis-treated patients are "anabolic resistant" i. e., their muscle protein synthesis (MPS) response to anabolic stimuli is blunted, an effect which leads to muscle wasting and poor physical performance in aging and in several chronic diseases. The importance of maintaining muscle mass and MPS is often neglected in dialysis-treated patients; better than to describe mechanisms leading to energy-protein wasting, the aim of this narrative review is to suggest possible strategies to overcome anabolic resistance in this patient's category. Food intake, in particular dietary protein, and physical activity, are the two major anabolic stimuli. Unfortunately, dialysis patients are often aged and have a sedentary behavior, all conditions which *per se* may induce a state of "anabolic resistance." In addition, patients on dialysis are exposed to amino acid or protein deprivation during the dialysis sessions. Unfortunately, the optimal amount and formula of protein/amino acid composition in supplements to maximixe MPS is still unknown in dialysis patients. In young healthy subjects, 20 g whey protein maximally stimulate MPS. However, recent observations suggest that dialysis patients need greater amounts of proteins than healthy subjects to maximally stimulate MPS. Since unneccesary amounts of amino acids could stimulate ureagenesis, toxins and acid production, it is urgent to obtain information on the optimal dose of proteins or amino acids/ketoacids to maximize MPS in this patients' population. In the meantime, the issue of maintaining muscle mass and function in dialysis-treated CKD patients needs not to be overlooked by the kidney community.

Keywords: nutrition, muscle, protein synthesis, hemodialysis, peritoneal dialysis, CKD

OPEN ACCESS

Edited by:
Alice Sabatino, University of Parma, Italy

Reviewed by:
Colleen McKenna, University of Illinois at Urbana-Champaign, United States
Wesley Visser, Erasmus Medical Center, Netherlands

****Correspondence:***
Giacomo Garibotto
gari@unige.it

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *27 April 2021*
Accepted: *12 July 2021*
Published: *12 August 2021*

Citation:
Garibotto G, Saio M, Aimasso F, Russo E, Picciotto D, Viazzi F, Verzola D, Laudon A, Esposito P and Brunori G (2021) How to Overcome Anabolic Resistance in Dialysis-Treated Patients? Front. Nutr. 8:701386. doi: 10.3389/fnut.2021.701386

INTRODUCTION

Dialysis-treated patients with end-stage renal disease (ESRD) have a high prevalence of protein-energy wasting (PEW), a condition of muscle and visceral protein stores loss which is not completely accounted for by a low nutrient intake (1). There is a strong association between surrogates of muscle mass and survival in this patients' population (2, 3); therefore, the need for increased medical attention for nutrition in advanced kidney disease is a high clinical priority.

Muscle protein synthesis (MPS), serving either the maintenance of muscle protein during fasting and body anabolism during feeding, is central to the processes of sustaining and shaping body cell mass. Dietary proteins or amino acids (AA), and physical activity are the two major anabolic stimuli that increase MPS (4). If combined, these two factors offer the major available anabolic stimulus in humans (**Figure 1**). Several other factors, including the dietary protein amount and composition, and the timing of protein ingestion can also influence the anabolic responses.

Recent understanding of the mechanisms which regulate protein metabolism in chronic kidney disease (CKD) has allowed us to understand the role of acidosis, insulin resistance and inflammation on intracellular signals which promote PEW by activating muscle protein degradation (MPD) (5). Even more importantly, Zhang et al. (6) were able to demonstrate that CKD stimulates chromatin-modifying, nucleolar protein 66 (NO66), that downregulates MPS via a demethylase mechanism, giving us a new perspective on the pathophysiology of uremia-related wasting syndrome. Better than to describe mechanisms leading to muscle wasting in dialysis patients, the scope of this narrative review is to analyze current understanding of the dietary and non-dietary modulators of MPS as major determinants of muscle mass in humans, in order to suggest to suggest possible strategies to stimulate MPS and, at least in part, overcome anabolic resistance in dialysis-treated patients with CKD.

THE RESPONSE OF MPS TO PROTEIN FEEDING

The MPS response to protein is influenced by both the amount and the type of protein, and the time of feeding.

Protein Amount

The hyperaminoacidemia reached after protein ingestion is "primary anabolic" since it increases MPS rates, and to a minor degree, decreases muscle protein degradation (MPD) (7, 8). Several investigators have studied the optimal amount of protein for the maximal stimulation of MPS in humans (7–14). As demonstrated in early studies (14), the muscle anabolic response to AA/protein ingestion is time-limited in the rested state; after 2–3 h from AA ingestion, MPS undergoes a state of "tachiphylaxis" in spite of ongoing EAA availability and upregulation of mechanistic target of rapamycin complex 1 (mTORC1) signaling (14). This 'muscle full' condition is refractory to the intake of additional nutrient signals/substrates regulating MPS, is not induced by muscle blood flow and does not appear to be dependent on the amount of protein ingested (4, 14). Instead, the 'muscle full' set-point can be delayed by physical exercise to allow additional use of EAA for MPS (4).

The dose-response of myofibrillar MPS to increasing amounts of whey protein at rest and after exercise has been studied in young subjects by Witard et al. (8). They observed that a 20-g dose of whey protein (containing ∼10 g essential AAs) is sufficient for the maximal stimulation of MPS both at rest and during physical exercise, while a greater dose stimulates amino acid oxidation. However, in elderly subjects, more protein with respect to younger subjects is needed to maximally stimulate MPS in exercised and rested muscle (15).

Protein Type

Also AA composition of the dietary protein influences the MPS response. Lower essential AA (EAA) content, particularly of leucine, lysine, and/or methionine has been shown to be responsible for the lower anabolic capacity of low biological vs. high biological value proteins (16, 17). Apart from their AA content, the nutritional value of proteins ingested with the diet depends also on a series of factors, including their chemical score, net utilization, and digestibility corrected AA score (PDCAAS) (18). Many of these factors are better for animal-based than for plant-based protein sources (19). Both the PDCAAS and the Digestible Indispensable AA Score (DIAAS) are used to assess the ability of dietary protein to satisfy the body's AA requirements (18, 19).

Protein ingestion and physical exercise possess a synergistic interaction on the stimulation of MPS (20, 21). Protein ingestion provides, among the EAA and non-essential AA needed for MPS, also leucine, which stimulates protein translation. In addition, protein and carbohydrate ingestion increase serum levels of insulin, which has a mild stimulatory effect on MPS (20–22) and decreases MPD. Another factor which makes protein differently anabolic is the splanchnic AA removal from circulation (23, 24). As an example, proteins from soy undergo an important splanchnic first-pass, whereas milk proteins are directed to peripheral sites. In comparison to soy or carbohydrate, milk consumption has a greater anabolic effect in young subjects in the post-exercise period (25).

The content of essential AA in plant vs. animal-based proteins is likely the major determinant of their different muscle anabolic effects. Plant proteins have lower essential AA content, in particular of methionine and lysine, than animal-based and muscle protein (17). Of note, the intake of AAs is highest in diets containing prevalently meat protein, followed by fish, and is lowest in diets containing only plant protein (26); accordingly, plasma levels of methionine, tryptophan and tyrosine are lowest in vegans, suggesting dietary deficiency for these AA. In addition, owing to their different structure and/or content in phytic acid and protease inhibitors, plant proteins are less digestible than animal proteins (17). Therefore, it has been suggested to consume different plant proteins with complementary essential AA composition to optimize a full pattern of dietary AA, especially for elderly subjects (17). In long-term studies, at low (≈0.8 g/kg/day) protein intake, plant proteins have lower ability to stimulate MPS and to cause muscle anabolism vs. animal proteins. However, the anabolic effect of plant- and animal-based proteins is similar if the protein intake is raised to 1.1–1.2 g/kg (17).

Timing of Protein Ingestion

Protein consumption in western countries exceeds the Recommended Dietary Allowances (RDA), i.e., the protein amount that is be consumed daily to meet population needs and to prevent protein deficiencies. However, in many countries the

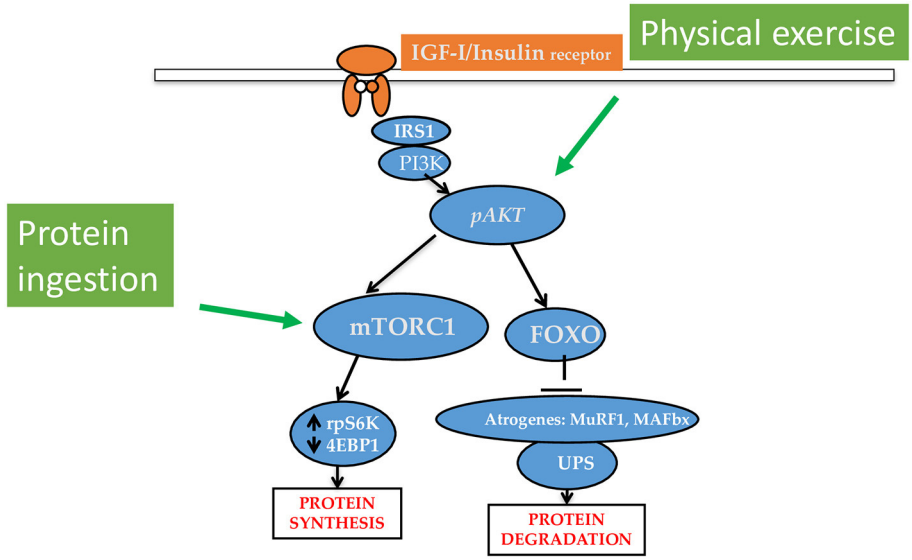

FIGURE 1 | Major intracellular pathways underlying the anabolic effects of protein/amino acid/keto acid intake and physical exercise. The ingestion of protein, amino acids or keto acid of essential amino acids increases muscle protein synthesis (MPS) rates. Physical exercise upregulates phosphorylated Akt to increase MPS and decrease protein degradation. Protein ingestion and physical exercise have synergistic interaction on the stimulation of MPS.

intake is shifted toward the evening meal. In healthy subjects, the rate of MPS is 25% increased when food is distributed during the day, compared to a pattern with protein consumed at the evening meal (27). This finding may have important implications for increasing MPS in subjects who experience a resistance to the stimuli of MPS. Further, immediate post-exercise nutrient ingestion has been shown to increase the accretion of whole body and leg protein more than in a late (3-h) period (28).

Protein ingestion before sleep, if combined with physical activity, is also potentially anabolic (29) and has been suggested to represent a nutritional strategy to increase muscle mass in the elderly. However, there is no study in dialysis-treated patients.

PHYSICAL ACTIVITY

In healthy subjects, resistance exercise augments the MPS rates, resulting in muscle hypertrophy (30) and also increases the expression of contractile, metabolic, and stress response proteins (31). In addition, muscle hypertrophy is associated with improved gait velocity and stair-climbing power even in very old individuals (32, 33). Aerobic fitness increases both markers of mitochondrial biogenesis and MPS (p-P70S6k) (34). In addition aerobic exercise training increases vagal tone and decreases sympathetic tone (35).

Early studies have shown that a single session of exercise increases MPS rates (36, 37). Despite this increase in MPS, if there is no food ingestion, the net muscle protein balance persists to be negative, even if to a lesser extent than in the pre-exercise period (37). During post-exercise recovery period, an increase in AA levels and supply to skeletal muscle from orally administered AA stimulates MPS and, even if to a less extent, inhibits MPD rates, resulting in muscle protein anabolism (21). Also the ingestion of carbohydrate improves muscle net protein balance (i.e., the difference between MPS and MPD) after resistance exercise; however, this effect is smaller as compared to protein/AA feeding (38). Therefore, post-exercise protein/AA ingestion is more commonly used to maximize anabolism. In addition to protein intake, body composition, age, and/or sex, and usual physical activity may influence the MPS response to feeding (28).

AGING AND COMMON KIDNEY DISEASE COMORBIDITIES WHICH IMPAIR MPS

Several conditions are recognized to impair the MPS response to protein, thus causing "anabolic resistance" and limiting the muscle hypertrophic response.

Aging

The progressive aging-associated muscle atrophy, which frequently presents with muscle weakness and slow motion, is the most common type of muscle atrophy observed in humans (39). With aging, the risk of both CKD and declining capacities such as reduced strength and cognition increases (40); this risk is maximized in subjects developing "accelerated biological aging" (41). Sensory–motor functioning is very common in frail individuals who are at highly vulnerable for loss of independence in activities of day living, fall and mortality (42). Since the population in the western countries aged > 65 is expected to rapidly increase in the next years (43), CKD and age-related losses in skeletal muscle function and mass are considered as an extremely important public health issue (44).

Both quantitative and qualitative modifications of muscle biology and function are observed in elderly subjects. Early

computed tomography studies (45) have shown that aging is associated with a loss of lean mass, with fat and connective tissues replacing muscle. These changes in muscle composition are considered to be consequence of a decreased MPS rates with aging (46).

The age-related muscle atrophy has been described as a slow but unrelenting process, with functional loss varying largely among individuals, which is observed in all elderly subjects, including those healthy and physically active (41, 47). Although the study of sarcopenia is complicated by muscle-specific differences among species and in the response to aging (41), there is consensus that anabolic stimuli do not efficiently activate the IGFI/PI3K/Akt/PKB/mTORC1 pathway (displayed in **Figure 1**) in elderly people, and this anabolic resistance is believed to play a major role in causing sarcopenia and reduced muscle recovery after an injury (41). In accordance with this view, acute activation of the pAkt/FoxO axis has been shown to be of benefit in the elderly (48). In addition, similarly to cancer cachexia, the age-associated low-grade systemic inflammation plays an important role in the pathogenesis of sarcopenia (49). How renal disease abnormalities overlap or potentiate those occurring with aging is still unexplored.

Inactivity

Immobilization or sedentarism induces a status of "anabolic resistance" with reduced fasted and fed-state MPS. The effects of reduced use on skeletal muscle are in part similar to those observed during aging (50), and the increased sedentary behavior occurring in old age (51) has been suggested the be major cause of the aging-related sarcopenia.

Long-term immobilization in bed causes a more marked decrease in muscle strength than in muscle mass (52). However, changes at cellular and subcellular levels have shown that long-term immobilization causes a significant loss of contractile proteins, that is even greater than the decrease in muscle fiber force generation capacity (53).

Low Energy Intake

A crucial aspect of the nutritional balance is the amount of energy ingested. From studies based on nitrogen (N) balance in the last century, it is known that the protein metabolism is influenced by the amount of energy intake (54–57). Of note, if dietary energy is supplied in amounts sufficient to meet body needs, protein intake strongly influences N balance. In healthy subjects, the administration of excess energy spares the loss of labile proteins, and reduces the time to adapt to a low protein diet. The supply of excess energy results in increased availability of ingested protein, with decrease in protein requirement (58). In keeping with this finding, N balance appears to be more influenced by changes in dietary energy supply at low protein intakes, and the N-sparing effect of energy is blunted when protein intake increases (59). These observations have practical implications, since protein requirements are determined when the requirements for energy are met.

To explain the mechanisms underlying the responses of protein metabolism to changes in protein intake, several years ago Young et al. (60, 61) studied whole body protein metabolism in 12 young men fed a low protein diet (0.6 g egg protein/kg/day) associated with a maintenance energy level or a 25% energy excess. In the fed-state the rate of leucine oxidation tended to be lower, while N balance and net protein balance were higher, when dietary energy was increased. These studies indicate that the oxidation of essential AA is sensitive and varies according to the levels of energy intake, with higher oxidation at low intakes.

HD patients have reduced dietary energy intake (62) and progressively lose muscle mass with time, even if body fat seems to be better preserved than lean mass (63). Studies on the dietary energy requirements of adult HD patients have been assessed by measuring energy expenditure by indirect calorimetry and/or by the use of N balance (63, 64). The results of these studies are not uniform. Some studies reported that dietary energy needs are not different from those of normal adults (65), whereas other studies showed increased energy expenditures (66). Inflammation has been reported to be associated with an increase in energy requirements (67). A few studies in HD patients have evaluated energy expenditure during both at rest and activities daily living. Shah et al. (68) measured dietary energy requirements for 92 days in 13 HD patients residing in a metabolic research ward while receiving a constant energy intake. Their average energy intake was 31 kcal/kg/day calculated from energy intake and change in fat and fat-free calories, which was 28 kcal/day. However, a wide variability in dietary intake among individual patients was observed (range: 26–36 kcal/Kg/day) (68). Dietary intake correlated strongly with their body weight, but was less closely related to their measured resting energy expenditure (REE). Overall, the data from this study show that, on the average, dietary energy requirements of sedentary, clinically stable HD patients are similar to those of age-matched sedentary normal subjects. However, due to the high individual variability in energy requirements, careful individual monitoring of the nutritional status of HD-treated patients is necessary (68).

Despite the importance of energy intake on protein requirements in N balance-based studies, the MPS response to food has been largely focused on the effects of orally administered protein or AA. However, food is usually eaten as a "mixed" meal. One of the main reasons for focusing on isolated protein ingestion is that protein provides essential AA for protein synthesis, while carbohydrates and fats ingested alone are only mildly muscle-anabolic. Protein absorption is delayed when carbohydrate are co-ingested with proteins, without however reducing the MPS response (69). However, protein and carbohydrate ingestion increase systemic insulin, which has a modest stimulatory effect on MPS and decreases MPD (38).

A few studies have focused on the effects of fat co-ingestion on the MPS response. Following physical exercise, the leg removes a greater amount of AA after the ingestion of high-fat milk compared with skim milk (70). In addition, the ingestion of whole eggs (18 g protein, 17 g fat) has been shown to cause a greater increase in post-exercise MPS rates than an isonitrogenous amount of egg whites or egg whites (18 g protein, 0 g fat) (71). This differential response may be due to the greater content of fat and/or micronutrients in whole eggs. Accordingly, fat co-ingestion (237 g of whole milk as compared to far-free milk) may increase the MPS response to protein in the

post-exercise period (71). However, MPS is blunted by a high fat content (72, 73).

MPS is a process that "*per se*" requires energy (74). HD patients display muscle mitochondrial morphological and dysfunctional changes, which might limit the availability of energy for MPS or impair the efficiency of MPS in terms of energy costs. The energy requirements of whole-body PS have been estimated to account for ∼20% of resting energy expenditure (REE) in humans (75). Since muscle protein turnover accounts for ∼40% of whole-body protein turnover in humans, one could estimate the cost of MPS to be ∼8–10% of REE. The cost of MPS is likely similar to control subjects in wasted HD patients. When both MPS and REE have been concurrently studied in non-inflamed, wasted HD patients before and during Growth Hormone (GH) administration (76) the variations in REE and MPS were significantly correlated suggesting that changes in MPS account for a significant fraction of REE changes. On that ground the energy cost of MPS was estimated to be ∼5 kcal/g, which is similar to the normal condition (76).

Diabetes Mellitus

Insulin is an anabolic hormone. Major effects of insulin's action are to suppress protein degradation and up-regulate anabolic pathways (77). While in type 1 diabetic subjects muscle wasting results from overexpression of genes involved in the ubiquitin proteasome pathway, in type 2 diabetes a decrease in insulin sensitivity favors muscle atrophy. A decrease insulin's response in muscle may take place owing to alterations in the insulin signaling pathways secondary to inflammation, glucotoxicity, increased circulating free fatty acids and metabolic acidosis (78, 79). Furthermore, the activation of new anti-anabolic or catabolic pathways, such as the myostatin/activin A system, may occur (79).

Patients with type 2 diabetic kidney disease often show a series of metabolic and nutritional changes linked both to diabetes and kidney failure, including insulin resistance and cardiovascular comorbidities (80), protein-energy wasting and sarcopenia (81). These patients undergo an increase in MPD, an effect primarily mediated by the ubiquitin-proteasome pathway (82, 83). On a kinetic basis, an increase in MPD is often associated with an increase in MPS. However, this seems not to be the case for diabetic kidney disease. In a recent study Zanetti et al. (84) observed that patients with diabetic kidney disease have a catabolic pattern of whole body protein turnover, associated with a 10% decrease in MPS (84). Therefore, multiple changes in protein metabolism, including an increase in protein degradation not associated with an adequately-matched change in protein synthesis account for accelerated wasting in patients with type 2 diabetic nephropathy.

Sepsis

Chronic uremia has for long been recognized as a state of acquired immunodeficiency (85, 86). Sepsis is recognized as the second leading cause of death in ESRD (87, 88). Besides infections from indwelling catheters, numerous other factors, including aging, diabetes, hypoalbuminemia, immunosuppressive therapy, the dialysis procedure, uremia and increased leptin levels (89, 90) can favor infections in ESRD patients.

Sepsis causes a rapid and significant loss of body protein, in part due to development of an impairment of MPS alone or in association with increases in MPD (91). Septic cachexia has been defined as a life-threatening condition of metabolic inflammatory complex associated with multiple organ dysfunction (91). The metabolic changes induced by the systemic inflammatory response, including mitochondrial dysfunction and metabolic shift (91, 92), are closely connected by a wide array of signaling molecules. In several tissues, including skeletal muscle, the expression of pro-inflammatory cytokines is regulated by Toll-like receptors (TLRs) (92). During sepsis, muscle TLRs monitor for the presence of endotoxin (92, 93) and, when activated by microbial products, induce a local inflammatory response leading to the activation of pro-inflammatory genes. In addition, TLRs can be activated by heat shock proteins and/or endogenous signals of tissue injury (93). Recent observations suggest that TLR4 link the innate immunity activation with the uremic state in skeletal muscle (9). In predialysis CKD patients, an upregulation of TLR4 in muscle is predicted by the residual renal function, suggesting that endotoxins or danger-associated molecular patterns (DAMPS) produced or retained in the pre-uremic state mediate TLR4 activation (94). These findings suggest that in uremic patients muscle inflammation is due to an overexpression of TLR4 (94). The potential for septic cachexia to serve as a novel target disease state to improve clinical outcomes is reviewed elsewhere (92).

Metabolic Acidosis

A normal bicarbonate serum concentration (serum $HCO3^{-}$ between 24 and 26 mmol/l) is the recommended target in renal patients. While metabolic acidosis is one of the most important, yet treatable, among factors contributing to accelerated protein catabolism in dialysis patients (79), its effects on MPS are less established. In rats made acidotic (mean pH 7.22) by intragastric administration of NH_4Cl (95), protein synthesis substantially decreased in muscle (96). In another study, induction of metabolic acidosis with NH_4Cl in normal individuals (mean attained $HCO3^{=}$ 16 mmol/l) caused a significant reduction in MPS, while albumin synthesis remained unchanged (95); conversely, chronic NH_4Cl -induced metabolic acidosis (mean $HCO3^{=}$ 15 mmol/l) was reported to significantly decrease the albumin fractional synthesis, without effects on MPS (97). Lofberg et al. (98) studied the effects of the correction of metabolic acidosis on muscle protein metabolism in 16 HD patients who were randomized to increase or decrease bicarbonate supplementation (blood bicarbonate levels increased from 17.8 to 27.1 mmol/l in the first, and decreased from 26.6 to 18.6 mmol/l in the second group). Muscle protein net balance improved when acidosis was corrected, mainly as a consequence of changes in protein degradation while protein synthesis was unaffected.

In consideration of these discordant findings, it is unclear if mild acidosis may affects MPS. Clearly, metabolic acidosis is potentially anti-anabolic, since it can decrease the release of GH and IGF-1 and induce insulin resistance (79). However, the effects

of acidosis on the anabolic effects of protein feeding in dialysis patients have not been studied so far.

Hemodialysis Procedure

The mechanisms underlying muscle wasting in HD patients involve a large number of factors, including inflammation, anorexia, metabolic acidosis, anabolic hormone resistance, and the loss of AAs and protein (mainly albumin) in the dialysate (99–104). HD acutely decreases MPS and upregulates protein degradation (99–101). Different mechanisms underlie this catabolic response, including losses of AAs and proteins into the dialysis fluid and the upregulation of protein catabolism by the interaction of immunocompetent blood cells with the dialysis membrane. Loss of AAs is very variable (from 4 to 12 g) (102–105), and is directly proportional to the AA plasma levels, dyalisate area and blood flow. In addition, protein losses into dialysate (2–3 g) as well as protein adsorption to the dialysis membrane and tubing can occur. Newer dialyzers with medium cut-off membranes, which are designed to improve clearance of middle molecules, are associated with increased albumin losses (106), even if with large variability (107).

A current hypothesis is that the inflammatory state observed in a significant number of HD patients is boosted by the HD procedure, which might increase the risk of cardiovascular complications and cachexia. Boivin et al. (108) showed that HD increases interleukin-6 (IL-6) and the caspase-3-mediated cleavage of actomyosin, the contractile protein made by the actin-myosin complex In addition, protein degradation was higher in patients during the HD procedure as compared the pre-HD period.

The activation of the complement with its downward inflammatory responses may be an additional mechanism leading to wasting in HD patients (109, 110). By a proteomic approach, Mares et al. (110), by eluting proteins adsorbed to the polysulfone dialyzer membranes, studied the processes that take place on the dialysis membranes. These proteins included ficolin-2 (a component of innate immunity that contributes to the immune recognition of pathogens), and complement C3c fragment. Of note, their data suggest that the polysulfone dialyzer initiates the lectin pathway of complement activation (111). In addition, a current hypothesis is that the anaphylatoxins C3a and C5a, bradykinin, thrombin and factor Xa can induce the activation of endothelial cells in the vascular wall, a process which may lead to inflammation and accelerated atherogenesis (112). However, there is a lack of controlled studies exploring the muscle proteolytic response to different filter materials.

Peritoneal Dialysis

One of the untoward effects of PD is the loss of proteins and AAs into the dialysate effluent. Patients undergoing PD lose both AAs (1–3.5 g/day), and a consistent amount of proteins (5–10 g per day), mainly albumin (113–115). The continuous loss of proteins and AAs is estimated to account for almost one-third of the increase in dietary protein requirements, but poor appetite or anorexia limit intakes in many patients (116, 117). When muscle AA kinetics has been studied during the PD procedure, it was observed that PD causes an acute decrease in MPS, which has been associated to the combined effect of hyperinsulinemia and AA losses (118).

CKD has been considered for years a state of "anabolic resistance" (119). However, only a few recent studies give support to this hypothesis and show that the muscle anabolic response to protein ingestion is blunted in dialysis-treated patients.

CKD causes a series of gastrointestinal abnormalities. including motility disorders, gastric achlorhydria, pancreopathy and small bowel bacterial overgrowth, which may impair protein absorption as demonstrated by the use of a ^{13}C protein breath test (120). At muscle level, Chen et al. observed that leucine-stimulated mTOR signaling (121) and GH-stimulated insulin-like growth factor-1 (IGF-I) expression (122) are partly attenuated in chronically uremic rats. In addition, the same authors observed that acute metabolic acidosis blunts the leucine-induced increase in MPS in rat muscle (123).

In patients with CKD, after protein ingestion the plasma AA paten to peripheral tissues is abnormal, with a more marked rise in non-essential AAs, as compared to essential AAs (124–126). Studies performed by whole body leucine kinetics in CKD patients have shown that whole body protein synthesis is resistant to stimulation by hyperaminoacidemia while the response of protein turnover to high insulin levels is normal (127). In addition, in patients with CKD and mild metabolic acidosis insulin sensitivity of muscle protein metabolism is overall preserved at insulin levels in the high (∼8–9-fold increased vs basal) physiological range; however, muscle insulin's sensitivity in the low physiological range is impaired (128). This observation suggests that CKD patients may need higher insulin levels to decrease MPD after a low glycemic index meal, such as breakfast. In contrast, the muscle insulin's sensitivity at raised insulin levels, as may take place with larger meals containing refined carbohydrates, appears to be normally maintained.

Recently, van Vliet et al. (129) observed that in HD patients, the ingestion of a mixed-meal containing 20 g protein failed to increase MPS. Unfortunately, basal rates of MPS were ∼2-fold increased in HD patients as compared to control subjects, a finding that might have impaired the ability of researchers to demonstrate any meal-induced MPS effect. In a recent study, Draicchio et al. (130) observed that whole body protein turnover rate decreased in HD patients after the ingestion of a mixed-meal compared with controls, suggesting that AA were poorly absorbed from the meal or dyregulated AA metabolism.

HD patients may also display "anabolic resistantance" to physical exercise. In the "PEAK" study Cheema et al. (131) randomized 49 patients to a 12-week resistance training during routine HD treatment or usual care. Physical exercise improved muscle strength, mid-thigh and mid-arm circumference, as compared to controls, but was not followed by statistically significant difference in muscle cross sectional area (an index of muscle hypertrophy). Mulsted et al. (132) studied 29 HD patients before and after completing 16 weeks of strength training. Before the training period, the participants were randomly assigned to receive a protein or a non-protein drink after every training session. Strength training did not result in muscle hypertrophy,

while it was associated with increases in muscle strength and power (132).

Taken together, the available data in experimental models and in humans suggest that HD patients are resistant to the most important anabolic stimuli, i.e., protein and physical exercise. If so, HD patients, in addition to well-tailored exercise programs, need to eat more than the 20 g high-quality protein which is necessary to obtain an optimal MPS response in healthy subjects (8). As an example, elderly subjects, who are also considered to be "anabolic resistant", need 35 grams of protein-i.e. ∼18 g essential AAs) for the maximal stimulation of MPS in exercised and rested muscle (132, 133). However, this large amount of AAs, if not efficiently used for MPS, could boost ureagenesis, toxins and acid production. As an alternative, the use of keto acids (KA) of essential AA might offer an anabolic stimules with less N. It appears therefore urgent to obtain informations on the optimal dose of protein and/or oral AA/KA to maximize MPS in HD patients.

DISCUSSION: HOW TO OVERCOME ANABOLIC RESISTANCE IN DIALYSIS-TREATED PATIENTS?

In this narrative review, we have briefly summarized our current evidence on factors which regulate MPS in humans, as a background information for effective treatment of patients with advanced CKD, mainly those on maintenance HD.

Consider Amount, Quality, and Timing of Ingested Proteins

According to the current NKF KDOQI/AND guidelines, "nutritional counseling should aim to achieve a dietary intake of 1.2 g protein and 30–35 kcal/kg body weight/day in dialysis patients at risk of malnutrition" (134). This can be obtained through increased intake of nutrients, food fortification, and/or the provision of oral nutritional supplementation. However, despite strong attention to nutritional requirements, many dialysis-treated patients do not meet the current guidelines (1, 103, 104).

Quality of dietary proteins needs also to be checked. Plant proteins contribute to a large part of daily protein intake in the world population (135) and plant-based low protein diets are encountering increasing success for the prevention and treatment of several comorbidities associated with CKD (136). In addition, plant protein-based diets may correct many of the uremia-associated abnormalities (137–140). However, both in young and elderly subjects, plant proteins have a lower ability to increase MPS than animal proteins, when protein intake is low (≈0.8 g/kg/day) (17, 141). Of note, in elderly subjects, plant- and animal-based proteins are similarly anabolic when plant protein intake is adequate (1.1–1.2 g/kg) (17, 141), although no study is available in HD patients. Therefore, increasing the intake of plant protein to 1.2 g/kg may be the first option to offer when dietary plant-based protein content is low. Other approaches have been suggested to increase the anabolism induced by plant protein (141). These may include: 1) considering different plant protein sources; 2) combining animal and plant proteins; 3) supplementing plant-based diets with essential AA or KA of essential AA (141).

One of the current debates on nutritional treatment of dialysis patients is how to increase dietary protein intake without causing hyperphosphatemia, which is associated with all-cause and cardiovascular mortality (142). However, HD patients may have both poor nutritional status and hyperphosphatemia. Often nephrologists handle with hyperphosphatemia by prescribing both phosphate binders and restriction of protein-rich foods, an effect which may, however, boost wasting. Recently, Yamamoto et al. (143) observed that the practice of recommending an increase in dietary protein intake for HD patients with concurrent low serum albumin and high phosphate levels was associated with higher serum creatinine and potentially lower all-cause mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS) study-phase 4 (2009–2011, follow-up 1.6 years). According to this observation recommending the liberalization of protein intake together with hyperphosphatemia management may be a critical practice for better nutritional status and outcomes in HD patients. However, prospective RCTs are needed to determine the impact of protein intake liberalization on protein status and hard outcomes in malnourished, hyperphosphatemic HD patients.

Allow Eating During HD

In many dialysis centers HD patients are fasting throughout the entire dialysis session, for fear of hypotension or vomiting (144). In addition, patients are often suggested not eating before the session, so it is very common that those on an afternoon HD session miss their noon meal (or they miss their breakfast if they have a planned morning HD session). For these reasons, nutrient intakes are often lower than recommended on dialysis-treatment days as compared with non-dialysis days.

In acute studies, feeding protein during HD treatment has been shown to cause a positive whole body protein balance (145). Providing meals during the HD treatment can increase overall nutrient intake and as well as the percentage of patients who reach nutritional targets (146). To replete AA pools, protein-rich foods have been recommended during and after the HD session; additionally, it is worth recognizing that wanting of protein-rich foods increases immediately after dialysis (147). Allowing patients to eat regularly during HD has been associated with better essential AA kinetics (148), nutritional status, quality of life, and possibly clinical outcomes [see for review ref. (149)].

In patients with gastrointestinal symptoms or who do not tolerate eating during HD treatment, intradialytic parenteral nutrition (IDPN) is used to prevent HD-related catabolism (150, 151), but the nutritional effects of this treatment may require long-time. Although a prospective study did not show an advantage of adding IDPN to oral nutritional supplementation on in malnourished HD patients, the improvement in serum prealbumin was associated with a decrease in morbidity and mortality (152).

Deleaval et al. (153) recently showed that the addition of branched-chain AAs (BCAAs) in the dialysis fluid may help to

maintain their physiological plasma levels and MPS. Clearly, the clinical usefulness of this approach needs to be tested.

Intraperitoneal AA + Glucose in PD Patients

PD shifts muscle protein metabolism to a status of reduced anabolism, a condition potentially harmful if nutrient intake is diminished or during superimposed diseases (154). Results from clinical trials on the use of intraperitoneal AAs (IPAA), including both RCTs and non-RCTs, were inconclusive [see ref. (121) for review] because of insufficient sample size and/or the occurrence of confounding conditions (121). Currently, IPAA are recommended when protein and energy intake are unattainable (121).

In an acute study (118), MPS was stimulated when AAs were supplemented intraperitoneally in combination with dextrose. The combined use of dextrose and AAs resulted in a cumulative anabolic and anticatabolic effect, because of the decrease in MPD (induced by insulin) and the stimulation of MPS (induced by AA availability) as compared to dextrose. Canepa et al. (155) in a study using an automatic PD cycler (APD) to simultaneously infuse glucose and AA (proportion of 3:1) in pediatric patients observed that the combined treatment was associated with a better metabolic profile, with maintenance of adequate non-protein calorie/nitrogen ratio. Therefore, these findings support the use of combined glucose-AA solutions, to improve utilization of AA for MPS while controlling urea levels (155). More recently, Tjiong et al. (156, 157) in an open label, cross-over study, compared the effects of a mixture of AA and glucose vs. glucose only containing dialysate, in 2 periods of 7 days each in eight APD-treated patients. They concluded that APD with dialysate composed of a mixture of AA and glucose acutely improves protein metabolism, and that this gain made during the night persists to a considerable extent for 24 h. However, no long term RCT is available on the effects of combined use of IPAA + glucose on nutritional status and harder outcomes.

Oral Nutrition Supplements

The administration of oral nutritional supplements (ONS) is used to maintain nutritional status (156), when dietary counseling alone is not sufficient to fill the gap between actual intakes and target requirements. Patients are advised to take ONS preferably 1 h after meals rather than as a meal replacement (156). Essential AA supplements offer the possibility to increase MPS; many observational studies have shown that in the short term, ONS can improve albumin and blood EAA profile in HD patients (156). A recent meta-analysis in HD patients shows that if short-term (3 months) ONS use increases BMI and serum albumin levels, prolonged (> 3 months) supplementation does not causes such effects (158). Recently, Pokkrong et al. (159) observed that ONS administered to 80 HD patients was associated with an improvement in energy, protein, fat, fiber and magnesium intake and 29–24% decrease in malnutrition-inflammation score (MIS), while the improvement in serum albumin was slight (5.3–3.3%). A Cochrane meta-analysis (160) included 22 studies (1,278 participants, 79% on HD and 21% on PD); however, the authors pointed out that many studies were at unclear risk of selection, performance, and reporting bias. Overall, it is likely that protein-based ONS increase serum albumin and prealbumin (mainly in malnourished patients), as well as anthropometric measures. However, it is unclear if these results may translate into clinically relevant outcomes. In a recent meta-analysis Liu et al. (161) pointed out that large well-designed RCTs in this population are required. There is also little information on the effects of different AA formulas prescription.

Ketoacids and Hydroxyacid Analogs

Even less information on the anabolic effect for ONS containing AA and KA is available in the HD or PD setting. Currently, AA and KAs containing supplements are associated to low protein diets (LPDs) or very-low protein diets (VLPDs) in patients with CKD4-5 (162, 163); these supplements have phosphate-chelating properties, are likely anabolic, can substantially postpone time to renal replacement therapy and decrease uremic toxicity (162); very recently, they have also been shown to protect patients with diabetic CKD from CV mortality (164).

Ketoacids (KA) of essential AA in general and ketoisocaproate (Kic) in particular, have been shown to reduce muscle protein degradation. In particular, in experimental models of CKD, a LPD supplemented with KAs compared to an LPD alone was able to downregulate the activity of the ubiquitin-proteasome system and to protect skeletal muscle from atrophy and oxidative damage (165). KAs can also maintain the activity of the mitochondrial electron transport chain complex and increase mitochondrial respiration (166). In the perfused heart muscle, branched-chain α-ketoacids (BCKA) increase the phosphorylation of the translational repressor 4E-BP1 as well as multiple proteins in the MEK-ERK pathway, leading to an increase in PS (167).

The Branched-chain amino acid transaminase (BCAT) enzyme reaction is reversible and maintains the equilibrium between the BCAA and their respective KA. Skeletal muscle contributes by the largest fraction of leucine deamination, reamination, and oxidation in the body in humans (168, 169). During fasting leucine is preferentially deaminated to Kic in muscle (168, 169). However, because of the reversibility of the BCAT reaction, the administration of KA can increase intracellular their respective AA level, mostly important the concentration of leucine. In an earlier study, Escobar et al. (170) observed that the infusion of Kic in the neonatal pig, stimulated MPS similarly to infusion of leucine. Both treatments increased intracellular leucine concentrations within the range 2–4-fold, a level considered to be essential for mTORC1 activation. More, recently it has been shown that BCKA are preferentially reaminated and activate protein synthesis in the heart (167) an effect that on a long term, could favor heart hypertrophy in conditions associated with elevated BCAA levels, such as obesity.

Recently, Fuchs et al. (171) were able to show that feeding old male subjects with 6 g BCAA, 6 g BCKA and 30 g milk proteins equally increased MPS; however, following the ingestion of milk protein MPS rates persisted to be high, while the postprandial MPS increase was short-lived following the ingestion of both

BCAA and BCKA. On the one hand these findings suggest that a complete essential AAs pattern needs to be provided to allow a prolonged postprandial increase in MPS; on the other hand, it leads to the speculation that KA are truly anabolic and may be considered to treat PEW in HD patients. However, Li et al. (172) in a small prospective, randomized, controlled, single-center study observed that the KA supplementation did not improve neither plasma AA nor body composition. The ability to use a low-volume/small-quantity BCKA supplement to efficiently stimulate MPS, while avoiding excess N intake, warrants additional trials to define formulas, dosing and examine long-term clinically relevant outcomes.

Endurance and Resistance Training

Early studies in HD patients have suggested that physical exercise prevents cardiovascular diseases, by ameliorating cardiovascular risk factors as well as cardiac autonomic control and left ventricular systolic function (173–175). In the HD-associated catabolic outline, it is not surprising that great interest has been given to physical exercise as a means to improve muscle strength and function. Kopple et al. (176), to study potential mechanisms by which exercise training ameliroates exercise capacity, randomized 80 HD patients into endurance training, strength training, endurance plus strength training or no training. At the end of the intervention, there was no whole body neither regional lean and fat mass in any groups. However, the investigators were able to demonstrate several muscle transcriptional changes that would favor muscle anabolism, including increases in muscle IGF-I and decrease in myostatin (176).

Among the treatment options to prevent loss of muscle mass and function in ESRD patients, endurance or resistance exercise appears to be the most useful. Several cohort studies have investigated the effects of endurance exercise training on physical function, aerobic capacity and muscle strength in HD patients. Results from these trials have showed benefits in terms of physical function, cardiovascular disease (CVD) risk, and quality of life (QOL) [see for review refs. (177, 178)]. Also expert opinion reports (179, 180), position statements (181) and guidelines (182) have suggested that physical exercise needs to be considered as standard of care treatment in patients with CKD, including HD patients. These indications are similar to recommendations for the general population (183).

Either "intradialytic cycling," with patients cycling on ergometers during the HD session and out-of-center ("interdialytic") exercise appear to have similar results (184). However, some apparently discrepant results have also been reported (185). Two major RCTs have been recently published on the effect of physical exercise in HD patients. Koh et al. (174) randomized 70 HD patients to intradialytic or home-based exercise training or usual care for 6 months. In the intradialytic arm, patients underwent three training sessions per week on a cycle ergometer, while in the home-based exercise arm patients were provided with a walking program to achieve the same weekly physical activity; the primary outcome was assessed as a change in performance on the 6-min walk test. Unfortunately, the authors found no significant differences among groups in the 6-month study period (174). More recently, Manfredini et al. (186), in a large 6-month randomized multicenter trial in HD patients, showed that personalized walking exercise program at home was associated with significant benefits on physical function, including the 6-min walking test, five times sit-to-stand test, cognitive function score and quality of social interaction score (186). Importantly, patients with the highest adherence to the exercise protocol had the largest performance improvement, suggesting a dose-response effect from the exercise. More recently, Exel et al. (187) studied 107 HD patients randomly divided into two groups: stretching and resistance exercise. Intervention programs were performed for 8 weeks, three times a week. Resistance exercise caused an increase in muscle strength and distance walked, as compared to stretching (187).

It has been outlined (185) that the reasons for the apparently discrepant results from training studies are possibly related to the need of enrolling a large number of patients to detect significant results. Another problem is the low volume and intensity of the exercise prescription, which may have accounted for the relatively modest functional improvements (185). So a current hypothesis is that exercise interventions might fail to produce clinically significant improvements in HD patients, primarily because the volume and intensity of the exercise prescribed is insufficient (185).

In summary, several meta-analyses (174, 177, 178, 184, 188, 189) show a statistically significant improvement in physical function and quality of life after 3–6 months of endurance exercise training in HD patients. However, no conclusion can be reached for elderly HD patients, since a few studies are existing focusing on them (190). In addition, a major problem stems from the low percentage of HD patients who are able to perform physical exercise. ESRD patient are more commonly sedentary and tend to avoid exercise (191); additionally, the dialysis population is more often aged, frail, depressive and with many comorbid conditions which are major obstacles to exercising. Finally, often the HD personnel has lack of expertise or resource to start an exercise program (192).

Combining Nutrition and Physical Exercise

The combination of physical exercise and nutrition provides the strongest muscle anabolic stimulus in humans. In the elderly, who are "anabolic resistant" combining exercise with protein supplementation provides an enhanced anabolic response (193). Several studies have addressed the issue of the efficacy of this combined treatment in HD patients [see ref. (192) for review]. Likewise, early studies in HD patients has showed that a single bout of either endurance or resistance exercise enhances the anabolic response to nutritional supplements (194). However, the results from long-term interventions have been less favorable (132, 195–197).

Many factors are likely to contribute to the modest advantages of exercise in HD patients, including limited exercise prescriptions and intradialytic training (192). A greater exercise dose or enhanced nutritional support may be needed to demonstrate the potentiated additive benefits of these treatments (192). Clearly, defining the role of exercise in CKD remains a top research priority.

Other Treatments to Increase MPS and Muscle Mass

Beta-Hydroxy-Beta-Methyl Butyrate

HMB is a downstream metabolite of leucine. HMB is present at low concentrations in muscle, and its turnover is about 0.7% of that of leucine (198). Better than being used alone, HMB is often consumed with other AAs or as part of a multiple ONS. Initial studies on the use of HMB in healthy volunteers demonstrated a high anabolic effect (199). Despite some RCTs have not detected any positive effects on muscle mass, strength and function from HMB supplementation, HMB is still considered a nutritional compound that may possess the potential to attenuate the rate of muscle loss in conditions of anabolic resistance (198, 200), probably as a long-term treatment (201).

There is very little information on HMB metabolism in CKD. A large percentage of plasma HMB is excreted into urine; however, from the observation that leucine and Kic pools are reduced in CKD4-5 (94), one would imply that also HMB is reduced in muscle. We also have no information on the effects of HD on HMB plasma levels. Since HMB molecular weight is low (m.w.118) it is likely removed by HD. HMB is available in many ONS on the market, but whether if it can promote anabolism in dialysis-treated patients is not known. Fitschen et al. (202) observed no significant effect of HMB supplementation on body composition, bone density, strength, fall risk and quality of life in a double-blind, placebo-controlled, randomized trial in 35 HD patients. However, on analysis of plasma HMB concentrations, 5 of 16 patients (31%) in the HMB arm were found to be non-compliant at 3 or 6 months (202). Therefore, the role of HMB supplementation in patients who are on dialysis is still not completely explored.

Omega 3 (n-3) Fatty Acids

Omega 3 (n-3) Fatty Acids (n-3 FA) have been shown in both young and older adults to have favorable effects on muscle insulin sensitivity, inflammation and anabolism (203–205). McGlory et al. (206), by utilizing intravenous hyperinsulinemic and hyperaminoacidemic clamps have shown that a moderate dose (∼4 g) of n-3 FA supplementation augments MPS rates both in healthy young and older adults (206).

Deger et al. (207) studied the effect of the administration of n-3 FA (2.9 g/d) over 12 weeks on muscle protein turnover in HD patients with systemic inflammation. N-3 FA supplementation was associated with decrease of forearm MPD but did neither influence MPS nor muscle net protein balance. In a recent meta-analysis Rondanelli et al. (208) studied the effect of n-3 FA and docosahexaenoic acid (DHA) supplementation on fat free mass and physical performance in patients with various chronic diseases. Daily n-3 FA + DHA supplementation (from 0.7 to 3.36 g) decreased the time of Time Up and Go (TUG) test, and the fat free mass had an improvement trend which was however not statistically significant. Overall, these data suggest that n-3 FA + DHA might have a positive effect on physical performance, and that their use may improve some sarcopenia component.

Testosterone

Hypogonadism is commonly observed in men with CKD, which occurs as an effect of both depressed hypothalamic-pituitary-gonadal axis functionality and androgen synthesis (209, 210). Hypogonadism may contribute to several common adult complications in males with CKD (209, 210). Testosterone's downward signal acts to offset some of the catabolic pathways which are activated by uremia. Testosterone promotes satellite cell recruitment and increases MPS through stimulation of androgen receptors and activation of the insulin-like growth factor-1 (IGF-1) pathway (211). In humans, the anabolic action of testosterone is mediated via an enhancement of the efficiency of MPS, i.e., the MPS rate relative to the availability of AA (211). Long-term testosterone users develop hypertrophy of both Type I and Type II muscle fibers (211).

Low testosterone levels are associated with reduced fat free mass and muscle strength both in CKD and in HD patients (209, 210). Furthermore, Chiang et al. (212) recently were able to show that low plasma testosterone is strictly related to declining physical function, frailty, and muscle wasting in HD patients, which suggests that the CKD-associated decrease in testosterone levels may contribute to the procatabolic environment. However, current guidelines do not recommend routinely prescribing testosterone to all elderly men with low testosterone concentrations, but suggest that testosterone therapy is offered on an individualized basis, after explicit discussion of its potential risks and benefits, to elderly men who have symptoms suggestive of testosterone deficiency and consistently low morning testosterone concentrations (211).

Growth Hormone

Growth Hormone (GH) is anabolic both through the IGF-I downward pathway and a direct effect on skeletal muscle (213). GH deficiency is associated with muscle atrophy and GH administration causes muscle hypertrophy (214). GH treatment has been reported to have beneficial effects in elderly subjects (215). Although GH and IGF-I replacement in GH deficient adults has proven anabolic, this is not an unequivocal finding, possibly due to differences in dosage, and time on treatment (216).

Short stature is commonly observed in children with CKD, even after renal transplantation. The CKD-related GH insensitivity is characterized by deficiency of functional IGF-1, and can be overcome by the administration of supraphysiological doses of recombinant human GH (rhGH); long-term rhGH treatment stimulates IGF1 synthesis, increases longitudinal growth and likely improves adult height (216).

RhGH has been licensed for the treatment of CKD-related growth failure in Europe, North America and many other high-income countries (217). In children, CKD is associated to significant muscle wasting (217). Concurrent rhGH therapy causes higher leg lean body mass Z-scores, compared to untreated-children (218). Similarly, small randomized trials of rhGH in malnourished adult dialysis patients showed benefits including weight gain, improved MPS (219) and performance (220, 221). The OPPORTUNITY™ Trial (222) examined whether rhGH reduces mortality in hypoalbuminemic HD

patients. Secondary end points were effects on number of hospitalizations, cardiovascular events, lean body mass (LBM), serum proteins, exercise capacity, QoL and adverse events. Although the OPPORTUNITY™ Trial was terminated early owing to slow recruitment, treatment with rhGH, compared to placebo, improved certain factors associated with cardiovascular disease risk factors, without adverse outcomes.

Denosumab

In postmenopausal women, a major role in the development of osteoporosis is played by the increased activity of receptor activator of nuclear factor kappa-B ligand (RANKL) (223). The binding of RANKL to its cognate receptor RANK drives a series of events triggering differentiation, activity, and survival of osteoclasts. Denosumab is a monoclonal antibody which binds RANKL, thus interfering with osteoclast differentiation, activation and survival. Denosumab is currently approved for the treatment of osteoporosis in postmenopausal women at risk of fracture. In is interesting that in elderly subjects osteoporosis and sarcopenia have similar risk factors, underscoring muscle-bone interactions, which may result in wasting, falls, and fractures. The combined existence of osteoporosis and sarcopenia (osteosarcopenia) is an emerging definition, which is cause of a significant health burden (224). Kirk et al. (224) observed in a large cohort of community-dwelling older adults that risk factors associated with osteosarcopenia include older age, female gender, physical inactivity, low body mass index, higher fat mass and the coexistence of chronic diseases, including CKD. Osteosarcopenia is suggested to be caused by reduced mechanical loading, and altered crosstalk between muscle, bone, and fat cells. It is interesting that, in addition to nutritional treatment and physical exercise, Denosumab, may be offered to osteosarcopenic patients (225). By inhibiting RANKL, Denosumab decreases bone resorption, increases bone mineral density (BMD), and reduces new fractures in postmenopausal women with osteoporosis (225). In a non-randomized study of community-dwelling older adults denosumab treatment improved balance, fear of falling, and physical function (226), suggesting that denosumab may increase muscle strength and mass.

Studies have examined the denosumab-activated pathways in skeletal muscle. RANK is also expressed in skeletal muscle and can activate the NF-κB pathway, which mainly inhibits AKT/mTORC1 signal and myogenic differentiation, leading to muscle loss (227, 228). Mice overexpressing RANKL (HuRANKL-Tg+) undergo muscle atrophy, lower limb force and maximal speed (228). Interestingly, the administration of denosumab to HuRANKL-Tg+ mice increases limb force and muscle mass, increases muscle insulin sensitivity and downregulates myostatin gene expression (228). These findings suggest that RANKL decreases, while its inhibition improves, muscle strength and insulin sensitivity both in osteoporotic mice and humans. In dialysis patients on might expect a similar effect, although no study is available.

Vitamin D

Vitamin D deficiency is associated with muscle functional impairment and falls (229). Even if the vitamin D receptor

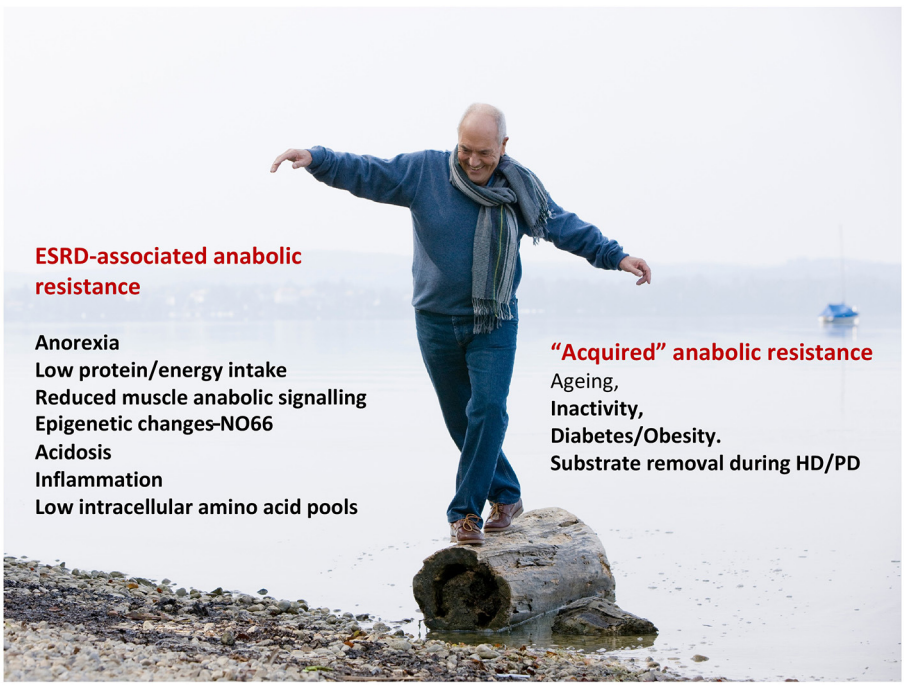

FIGURE 2 | The dialysis patient balancing between the anabolic resistance associated to End Stage Renal Disease (ESRD) and the "acquired" anabolic resistance led by advancing age, inactivity, diabetes and substrate depletion during dialysis treatments (Shutterstock source).

(VDR) is expressed at low levels in skeletal muscle, the deletion of VDR in the myocyte decreases muscle size and strength (230). Vitamin D has in muscle both genomic and non-genomic effects, which regulate cellular differentiation and proliferation. The non-genomic effects include the regulation of membrane calcium channels (which suggest a role for vitamin D in muscle contraction) mitochondrial function, insulin signaling and muscle substrate metabolism. In addition, studies conducted in cell culture systems and animals suggest that both vitamin D and conjugated linoleic acids (CLAs) stimulate MPS. Although some studies have shown that supplementation with vitamin D in the general population has a positive effect on muscle function, including athletic performance, falls and strength (231, 232), not all results are univocal. In a recent trial in 32 sedentary, older adults both Vitamin D and/or CLA supplementation, did not have effects on MPS (233). Similarly, there is not enough evidence to understand the role of vitamin D on musculoskeletal outcomes in the CKD population (231). However, given that this lack of evidence does not necessarily indicate no effect on musculoskeletal health (231), vitamin D might be considered to improve muscle strength and physical performance in renal patients, especially those who have low 25(OH)D plasma levels (<20 ng/mL-50 nmol/L).

Other Micronutrients

There is some evidence that the MPS response to feeding may be augmented by the use of micronutrients, mainly those contained in the yolk (vitamin D, vitamin E, vitamin A, zinc, selenium, and cholesterol) (234, 235). However, if and to what extent micronutrients potentiate the anabolic effects of protein feeding or physical exercise in dialysis-treated patients still needs to be established.

Other Treatments

Several other targets to increase MPS, such as targeting pro-inflammatory cytokines, manipulation of transforming growth factor (TGF) family members, satellite cells and stimulation of mitochondrial biogenesis, which are currently under study, are reviewed elsewhere (3, 236).

In conclusion, the importance of maintaining muscle mass and MPS is often underlooked in patients with kidney diseases. HD patients are often exposed to AA or protein deprivation, which causes low circulating and tissue levels of essential AAs. Anorexia or fasting prescribed during the dialytic treatments can potentially decrease MPS. These settings associate with several abnormalities occurring in CKD that stimulate protein degradation and/or decrease MPS. Recent observations suggest that skeletal muscle is "anabolic resistant" in HD patients and that greater amounts of proteins than in healthy subjects are needed to maximally stimulate MPS. Accordingly, the dialysis patient needs to cope with the CKD-associated intrinsic anabolic resistance, and the "acquired" anabolic resistance led by advancing aging, inactivity, diabetes and substrate depletion (**Figure 2**), The combination of physical exercise and protein/AA feeding provides the strongest muscle anabolic stimulus in humans; however the major gaps in our current knowledge of nutritional treatment of dialysis-treated patients with CKD include optimal formulas and amount of protein, ONS and exercise paradigms, and research on how to incorporate effective management approaches into clinical care.

AUTHOR CONTRIBUTIONS

GG and DV conceived the review. MS and FA performed literature research. GG, FV, GB, and DV wrote the manuscript. ER, DP, AL, and PE reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

FUNDING

This study was supported by grants from the University of Genoa (Finanziamento di Ateneo).

REFERENCES

1. Carrero JJ, Fridtjof T, Nagy K, Arogundade F, Avesani CM, Chan, et al. et al. Global prevalence of protein-energy wasting in kidney disease: a meta-analysis of contemporary observational studies from the international society of renal nutrition and metabolism. *J Ren Nutr.* (2018) 28:380–92. doi: 10.1053/j.jrn.2018.08.006
2. Noori N, Kopple JD, Kovesdy CP, Feroze U, Sim JJ, Murali B, et al. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. *Clin J Am Soc Nephrol.* (2010) 5:2258–68. doi: 10.2215/CJN.02080310
3. Stenvinkel P, Carrero JJ, von Walden F, Ikizler TA, Nader GA. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. *Nephrol Dialysis Transplant.* (2016) 31:1070–7. doi: 10.1093/ndt/gfv122
4. Deane CS, Ely IA, Wilkinson DJ, Smith K, Phillips BE, Atherton PJ. Dietary protein, exercise, ageing and physical inactivity: interactive influences on skeletal muscle proteostasis. *Proc Nutr Soc.* (2020) 7:1–12. doi: 10.1017/S0029665120007879
5. Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. *Nat Rev Nephrol.* (2014) 10:504–16. doi: 10.1038/nrneph.2014.112
6. Zhang L, Chen Q, Chen Z, Wang Y, Gamboa JL, Ikizler A, et al. Mechanisms regulating muscle protein synthesis in CKD. *J Am Soc Nephrol.* (2020) 31:2573–87. doi: 10.1681/ASN.2019121277
7. Trommelen J, Betz MW, van Loon LJC. The muscle protein synthetic response to meal ingestion following resistance-type exercise. *Sports Med.* (2019) 49:185–97. doi: 10.1007/s40279-019-01053-5
8. Witard OC, Jackman SR, Breen L, Smith K, Selby A, Tipton KD. Myofibrillar muscle protein synthesis rates subsequent to a meal in response to increasing doses of whey protein at rest and after resistance exercise. *Am J Clin Nutr.* (2014) 99:86–95. doi: 10.394/acjcn.112.055517
9. Volpi E, Ferrando AA, Yeckel CW, Tipton KD, Wolfe RR. Exogenous amino acids stimulate net muscle protein synthesis in the elderly. *J Clin Invest.* (1998) 101:2000–7. doi: 10.1172/JCI939
10. Moore DR, Robinson MJ, Fry JL, Tang JE, Glover EI, Wilkinson SB, et al. Ingested protein dose response of muscle and albumin synhesis after resistance exercise in young men. *Am J Clin Nutr.* (2009) 89:161–8. doi: 10.3945/ajcn.2008.26401

11. Koopman R, van Loon LJC. Aging, exercise, and muscle protein metabolism. *J Appl Physiol*. (2009) 106:2040–8. doi: 10.1152/japplphysiol.91551.2008
12. Paddon-Jones D, Short KR, Campbell WW, Volpi E, Wolfe RR. Role of dietary protein in the sarcopenia of aging. *Am J Clin Nutr*. (2008) 87:1562S−6. doi: 10.1093/ajcn/87.5.1562S
13. Phillips SM. The science of muscle hypertrophy: making dietary protein count. *Proc Nutr Soc*. (2011) 70:100–3. doi: 10.1017/S002966511000399X
14. Atherton PJ, Etheridge T, Watt PW, Wilkinson D, Selby A, Rankin D, et al. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. *Am J Clin Nutr*. (2010) 92:1080–8. doi: 10.3945/ajcn.2010.29819
15. Olaniyan ET, O'Halloran F, McCarthy AL. Dietary protein considerations for muscle protein synthesis and muscle mass preservation in older adults. *Nutr Res Rev*. (2020) 34:147–57. doi: 10.1017/S0954422420000219
16. Wilkinson SB, Tarnopolsky MA, Macdonald MJ, Macdonald JR, Armstrong D, Phillips SM. Consumption of fluid skim milk promotes greater muscle protein accretion following resistance exercise than an isonitrogenous and isoenergetic soy protein beverage. *Am J Clin Nutr*. (2007) 85:1031–40. doi: 10.1093/acjcn/85.4.1031
17. Berrazaga I, Micard V, Gueugneau M, Walrand S. The Role of the anabolic properties of plant- versus animal-based protein sources in supporting muscle mass maintenance: a critical review. *Nutrients*. (2019) 11:1825. doi: 10.3390/nu11081825
18. FAO/WHO. *Report of the Joint FAO/WHO Expert Consultation Paper 5*. Rome: Food and Agriculture Organization of the United Nations (1991).
19. Herreman L, Nommensen P, Pennings B, Laus MC. Comprehensive overview of the quality of plant- and animal-sourced proteins based on the digestible indispensable amino acid score. *Food Sci Nutr*. (2020) 8:5379–91. doi: 10.1002/fsn3.1809
20. Biolo G, Tipton KD, Klein S, Wolfe RR. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. *Am J Physiol*. (1997) 273:E122–9. doi: 10.1152/ajpendo.1997.273.1.E122
21. Tipton KD, Ferrando AA, Phillips SM, Doyle DJ, Wolfe RR. Postexercise net protein synthesis in human muscle from orally administered amino acids. *Am J Physiol*. (1999) 276:E628–34. doi: 10.1152/ajpendo.1999.276.4.E628
22. Kimball SR, Farrel PA, Jefferson LS. Role of insulin in translational control of protein synthesis in skeletal muscle by amino acids or exercise. *J Appl Physiol*. (2002) 93:1168–80. doi: 10.1152/japplphysiol.00221.2002
23. Bos C, Metges CC, Gaudichon C, Petzke KJ, Pueyo ME, Morens C, et al. Postprandial kinetics of dietary amino acids are the main determinant of their metabolism after soy or milk protein ingestion in humans. *J Nutr*. (2003) 133:1308–15. doi: 10.1093/jn/133.5.1308
24. Foullet H, Mariotti F, Gaudichon C, Bos C, Tomé D. Peripheral and splanchnic metabolism of dietary nitrogen are differently affected by the protein source in humans as assessed by compartmental modeling. *J Nutr*. (2002) 132:125–33. doi: 10.1093/jn/132.1.125
25. Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, et al. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. *Am J Clin Nutr*. (2007) 86:373–81. doi: 10.1093/ajcn/86.2.373
26. Schmidt JA, Rinaldi S, Scalbert A, Ferrari P, Achaintre D, Gunter J, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: A cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr*. (2016) 70:306–12. doi: 10.1038/ejcn.2015.144
27. Mamerow MM, Mettler JA, English KL, Casperson SL, Arentson-Lantz E, Sheffield-Moore M, et al. Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults. *J Nutr*. (2014) 144:876–80. doi: 10.3945/jn.113.185280
28. Levenhagen DK, Gresham JD, Carlson MG, Maron DJ, Borel MJ. Postexercise nutrient intake timing in humans is critical to recovery of leg glucose and protein homeostasis. *Am J Physiol Endocrinol Metab*. (2001) 280:E982–93. doi: 10.1152/ajpendo.2001.280.6.E982
29. Snijders T, Trommelen J, Kouw IWK, Holwerda AM, Verdijk LB, van Loon JC. The impact of presleep protein ingestion on the skeletal muscle adaptive response to exercise in humans: an update. *Front Nutr*. (2019) 6:17. doi: 10.3389/fnut.2019.00017
30. Goldspink G, Scutt A, Jaenicke T, Taray L, Gerlach GF. Stretch and force generation induce rapid hypertrophy and myosin isoform gene switching in adult skeletal muscle. *Biochem Soc Trans*. (1991) 19:368–73. doi: 10.1042/bst0190368
31. Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Cantó C, et al. The NAD(+)/Sirtuin pathway modulates longevity through activation of mitochondrial. UPR and FOXO signaling. *Cell*. (2013) 154:430–41. doi: 10.1016/j.cell.2013.06.016
32. Bassey EJ, Fiatarone MA, O'Neill EF, Kelly M, Evans WJ, Lipsitz LA. Leg extensor power and functional performance in very old men and women. *Clin Sci*. (1992) 82:321–7. doi: 10.1042/cs0820321
33. Evans. WJ. Exercise, nutrition, and aging. *Clin Geriatr Med*. (1995) 11:725–73.
34. Beetham KS, Howden EJ, Fassett RG, Petersen A, Trewin AJ, Isbel NM, et al. High-intensity interval training in chronic kidney disease: A randomized pilot study. *Scand J Med Sci Sport*. (2019) 29:1197–204. doi: 10.1111/sms.13436
35. Deligiannis A, Kouidi E, Tourkantonis A. Effects of physical training on heart rate variability in patients on hemodialysis. *Am J Cardiol*. (1999) 84:197–202.
36. Biolo G, Maggi SP, Williams BD, Tipton KD, Woolfe RR. Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. *Am J Physiol*. (1995) 268:E514–20. doi: 10.1152/ajpendo.1995.268.3.E514
37. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. *Am J Physiol*. (1997) 273:E99–107. doi: 10.1152/ajpendo.1997.273.1.E99
38. Børsheim E, Cree MG, Tipton KD, Elliot TA, Aarsland A, Wolfe RR. Effect of carbohydrate intake on net muscle protein synthesis during recovery from resistance exercise. *Am J Physiol*. (2004) 96:674–8. doi: 10.1152/japplphysiol.00333.2003
39. Larsson L, Degens H, Li M, Salviati L, Lee YI, Thompson W, et al. Sarcopenia: aging-related loss of muscle mass and function. *Physiol Rev*. (2019) 99:427–511. doi: 10.1152/physrev.00061.2017
40. Koren MJ, Blumen HM, Ayers EI, Verghese J, Abramowitz MK. Cognitive dysfunction and gait abnormalities in CKD. *Clin J Am Soc Nephrol*. (2021) 16:694–704. doi: 10.2215/CJN.16091020
41. Sartori R, Romanello V, Sandri M. Mechanisms of muscle atrophy and hypertrophy: implications in health and disease. *Nat Commun*. (2021) 12:330. doi: 10.1038/s41467-020-20123-1
42. Elliott ML, Caspi A, Houts RM, Ambler A, Broadbent JM. Disparities in the pace of biological aging among midlife adults of the same chronological age have implications for future frailty risk and policy. *Nat Aging*. (2021) 1:295–308. doi: 10.1038/s43587-021-00044-4
43. Bureau UC, editor. *The Older Population in the United States: 2019*. US Census Bureau: International Database (2019). Available online at: https://www.census.gov/data/tables/2019/demo/age-and-sex/2019-older-population.html (accessed April 29, 2020).
44. Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD, Lainscak M. Cachexia as a major public health problem: frequent, costly, and deadly. *J Cachexia Sarcopenia Muscle*. (2013) 4:173–8. doi: 10.1007/s13539-013-0105-
45. Imamura. K, Ashida H, Ishikawa T, Fujii M. Human major psoas muscle and sacrospinalis muscle in relation to age: a study by computed tomography. *J Gerontol*. (1983) 38:678–81. doi: 10.1093/geronj/38.6.678
46. Welle S, Thornton C, Jozefowicz R, Statt M. Myofibrillar protein synthesis in young and old men. *Am J Physiol*. (1993) 264:E693–8. doi: 10.1152/ajpendo.1993.264.5.E693
47. Cheng S, Degens H, Evans M, Cheng SM, Selänne H, Rittweger J, et al. What makes a 97-year-old man cycle 5,000 km a year? *Gerontology*. (2016) 62:508–12. doi: 10.1159/000443390
48. Olivieri F, Ahtiainen M, Lazzarini R, Pöllänen E, Capri M, Lorenzi M, et al. Hormone replacement therapy enhances IGF-1 signaling in skeletal muscle by diminishing miR-182 and miR-223 expressions: a study on postmenopausal monozygotic twin pairs. *Aging Cell*. (2014) 13:850–61. doi: 10.1111/acel.12245
49. Degens H. The role of systemic inflammation in age-related muscle weakness and wasting. *Scand J Med Sci Sports*. (2010) 20:28–38. doi: 10.1111/j.1600-0838-2009-01018-x

50. Degens H, Always SE. Control of muscle size during disuse, disease, and aging. *Int J Sports Med*. (2006) 27:94–9. doi: 10.1055/s-2005-837571
51. Wullems JA, Verschueren SM, Degens H, Morse CI, Onambélé GL. A review of the assessment and prevalence of sedentarism in older adults, its physiology/health impact and non-exercise mobility counter-measures. *Biogerontology*. (2016) 17:547–65. doi: 10.1007/s10522-016-9640-1
52. Berg HE, Larsson L, Tesch PA. Lower limb skeletal muscle function after 6 wk of bed rest. *J App Physiol*. (1997) 82:182–8. doi: 10.1152/jappl.1997.82.1.182
53. Larsson L, Li X, Berg HE, Frontera WR. Effects of removal of weight-bearing function on contractility and myosin isoform composition in single human skeletal muscle cells. *Pflügers Arch*. (1996) 432:320–8. doi: 10.1007/s004240050139
54. Millward DJ. Macronutrient intakes as determinants of dietary protein and amino acid adequacy. *J Nutr*. (2004) 134(Suppl. 6):1588S−96. doi: 10.1093/jn/134.6.1588S
55. Calloway DH, Spector H. Nitrogen balance as related to caloric and protein intake in active young men. *Am J Clin Nutr*. (1954) 2:405–12. doi: 10.1093/ajcn/2.6.405
56. Munro HN. Energy and protein intakes as determinants of nitrogen balance. *Kidney Int*. (1978) 14:313–6. doi: 10.1038/ki.1978.129
57. Carbone JW, McClung JP, Pasiakos SM. Recent advances in the characterization of skeletal muscle and whole-body protein responses to dietary protein and exercise during negative energy balance. *Adv Nutr*. (2019) 10:70–9. doi: 10.1093/advances/nmy087
58. Inoue G, Fujita Y, Niiyama Y. Studies on protein requirements of young men fed egg protein and rice protein with excess and maintenance energy intakes. *J Nutr*. (1973) 103:1673. doi: 10.1093/jn/103.12.1673
59. Iyengar A, Narasinga Rao BS. Effect of varying energy and protein intake on nitrogen balance in adults engaged in heavy manual labour. *Br J Nutr*. (1979) 41:19.
60. Motil KJ, Bier DM, Matthews DE, Burke JF, Young VR. Whole body leucine and lysine metabolism studied with (1-13C) -leucine and (α−15N) -lysine: Response in healthy young men given excess energy intakes. *Metabolism*. (1981) 30:783.
61. Bier DM, Motil KJ, Matthews DE, Burke JF, Young VR. Energy intake and whole body protein dynamics in man. *Prog Clin Biol Res*. (1981) 61:161–80.
62. Duenhas MR, Draibe SA, Avesani CM, Sesso R, Cuppari L. Influence of renal function on spontaneous dietary intake and on nutritional status of chronic renal insufficiency patients. *Eur J Clin Nutr*. (2003) 57:1473–8. doi: 10.1038/sj.ejcn.1601713
63. Carrero JJ, Zawada AM, Wolf M, Stuard S, Canaud B, Gauly A, et al. Evolution of body composition and wasting indicators by time of day of haemodialysis. *Nephrol Dial Transplant*. (2021) 36:346–54. doi: 10.1093/ndt/gfaa253
64. Slomovitz LA, Monteon FJ, Grosvenor M, Laodlaw SA, Kopple JD. Effect of energy intake on nutritional status in maintenance hemodialysis patients. *Kidney Int*. (1989) 35:704–11.
65. Cuppari L, Avesani CMJ. Energy requirements in patients with chronic kidney disease. *J Ren Nutr*. (2004) 14:121–6. doi: 10.1053/j.jrn.2004.04.001
66. Ikizler TA, Wingard RL, Sun M, Harvell J, Parker RA, Hakim RMJ. Increased energy expenditure in hemodialysis patients. *J Am Soc Nephrol*. (1996) 7:2646–53.
67. Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. *Am J Clin Nutr*. (2005) 82:801–5. doi: 10.1093/ajcn/82.4.801
68. Shah A, Bross R, Shapiro BB, Morrison G, Kopple JD. Dietary energy requirements in relatively healthy maintenance hemodialysis patients estimated from long-term metabolic studies. *Am J Clin Nutr*. (2016) 103:757–−65. doi: 10.3945/ajcn.115.112995
69. Gorissen SHM, Burd NA, Hamer HM, Gijsen AP, Groen BB, van Loon LJC. Carbohydrate coingestion delays dietary protein digestion and absorption but does not modulate postprandial muscle protein accretion. *J Clin Endocrinol Metab*. (2014) 99:2250–8. doi: 10.1210/jc.2013-3970
70. Elliot TA, Cree MG, Sanford AP, Wolfe RR, Tipton KD. Milk ingestion stimulates net muscle protein synthesis following resistance exercise. *Med Sci Sports Exerc*. (2006) 238:667–74. doi: 10.1249/01.mss.0000210190.64458.25
71. van Vliet S, Shy EL, Abou Sawan S, Beals JW, West DW, Skinner SK, et al. Consumption of whole eggs promotes greater stimulation of postexercise muscle protein synthesis than consumption of isonitrogenous amounts of egg whites in young men. *Am J Clin Nutr*. (2017) 106:1401–12. doi: 10.3945/ajcn.117.159855
72. Hammond KM, Impey SG, Currell K, Mitchell N, Shepherd SO, Jeromson S, et al. Postexercise high-fat feeding suppresses p70S6K1 activity in human skeletal muscle. *Med Sci Sports Exerc*. (2016) 48:2108–17. doi: 10.1249/MSS.0000000000001009
73. Stephens FB, Chee C, Wall BT, Murton AJ, Shannon CE, van Loon LJC, et al. Lipid-induced insulin resistance is associated with an impaired skeletal muscle protein synthetic response to amino acid ingestion in healthy young men. *Diabetes*. (2015) 64:1615–20. doi: 10.2337/db14-0961
74. Reeds PJ, Fuller MF, Nicholson BA. Metabolic basis for energy expenditure with particular regard to protein. In: Garrow JS, Halliday D, editors. *Substrate and Energy Metabolism in Man*. London: J. Libbey (1985). p. 46–57.
75. Welle S, Nair KS. Relationship of resting metabolic rate to body composition and protein turnover. *Am J Physiol*. (1990) 258:E990–8.
76. Garibotto G, Barreca A, Sofia A, Russo R, Fiorini F, Cappelli G, et al. Effects of growth hormone on leptin metabolism and energy expenditure in hemodialysis patients with protein-calorie malnutrition. *J Am Soc Nephrol*. (2000) 11:2106–13. doi: 10.1681/ASN.V11112106
77. Hoffer LJ. Human protein and amino acid requirements. *JPEN J Parenter Enteral Nutr*. (2016) 40:460–74. doi: 10.1177/0148607115624084
78. Tessari P, Cecchet D, Cosma A, Puricelli L, Millioni R, Vedovato M, et al. Insulin resistance of amino acid and protein metabolism in type 2 diabetes. *Clin Nutr*. (2011) 30:267–72. doi: 10.1016/j.clunu.2011.02.009
79. Workeneh B, Bajaj M. The regulation of muscle protein turnover in diabetes. *Int J Biochem Cell Biol*. (2013) 45:2239–44. doi: 10.1016/j.biocel.2013.06.028
80. De Cosmo S, Viazzi F, Pacilli A, Giorda C, Ceriello A, Gentile G, et al. Achievement of therapeutic targets in patients with diabetes and chronic kidney disease: insights from the Associazione Medici Diabetologi Annals initiative. *Nephrol Dial Transaplant*. (2015) 30:1526–33. doi: 10.1093/ndt/gfv101
81. Pupim LB, Heimbürger O, Qureshi AR, Ikizler TA, Stenvinkel P. Accelerated lean body mass loss in incident chronic dialysis patients with diabetes mellitus. *Kidney Int*. (2005) 68:2368–74. doi: 10.1111/j.1523-1755.2005.00699.x
82. Izzo A, Massimino E, Riccardi G, Della Pepa G. A narrative review on sarcopenia in type 2 diabetes mellitus: prevalence and associated factors. *Nutrients*. (2021) 13:183. doi: 10.3390/nu13010183
83. Siew ED, Ikizler TA. Insulin resistance and protein energy metabolism in patients with advanced chronic kidney disease. *Semin Dial*. (2010) 23:378–82. doi: 10.1111/j.1525-139X.2010.00763.x
84. Zanetti M, Barazzoni R, Kiwanka E, Vettore M, Vedovato M, Tessari P. Accelerated whole-body protein catabolism in subjects with type 2 Diabetes Mellitus and albuminuria. *PLoS ONE*. (2020) 15:e0243638. doi: 10.1371/journal.pone.0243638
85. Vanholder R, Ringoir S. Infectious morbidity and defects of phagocytic function in end-stage renal disease: A review. *J Am Soc Nephrol*. (1993) 22:149–56. doi: 10.1681/ASN.V391541
86. Vaziri ND, Pahl MV, Crum A, Norris K. Effect of uremia on structure and function of immune system. *J Ren Nutr*. (2012) 22:149–56. doi: 10.1053/j.jrn.2011.10.020
87. Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int*. (2000) 58:1758–64. doi: 10.1111/j.1523-1755.2000.00337.x
88. Peerapornratana S, Priyanka P, Wang S, Smith A, Singbartl K, Palevsky PM, et al. Sepsis-associated acute kidney disease. *Kidney Int Rep*. (2020) 5:839–50. doi: 10.1016/j.ekir.2020.03.005
89. Ottonello L, Gnerre P, Bertolotto M, Mancini M, Dapino P, Russo R, et al. Leptin as a uremic toxin interferes with neutrophil chemotaxis. *J Am Soc Nephrol*. (2004) 15:2366–72. doi: 10.1097/01.ASN.0000139321.98029.40

90. Bradley D, Shantaram D, Smith A, Hsueh WA. Adipose tissue T regulatory cells: implications for health and disease. *Adv exp Med Biol.* (2021) 1278:125–39. doi: 10.1007/978-981-15-6407-9_8
91. Kaneki M. Metabolic inflammatory complex in sepsis: septic cachexia as a novel potential therapeutic target. *Shock.* (2017) 48:600–9. doi: 10.1097/SHK.0000000000000906
92. Chen F, Zou L, Brittney W, Chao W. Targeting toll-like receptors in sepsis - from bench to clinical trials. *Antiox Redox Signal.* (2021). doi: 10.1089/ars.2021.0005. [Epub ahead of print].
93. Kashani B, Zandi Z, Pourbagheri-Sigaroodi A, Bashash D, Ghaffari SH. The role of toll-like receptor 4 (TLR4) in cancer progression: A possible therapeutic target? *J Cell Physiol.* (2021) 236:4121–37. doi: 10.1002/jcp.30166
94. Garibotto G, Picciotto D, Saio M, Esposito P, Verzola D. Muscle protein turnover and low-protein diets in patients with chronic kidney disease. *Nephrol Dial Transplant.* (2020) 35:741–51. doi: 10.1093/ndt/gfaa072
95. Kleger GR, Turgay M, Imoberdorf R. et al. Acute metabolic acidosis decreases muscle protein synthesis but not albumin synthesis in humans. *Am J Kidney Dis.* (2001) 38:1199–207. doi: 10.1053/ajkd.2001.29215
96. Caso G, Garlick BA, Casella GA, Savary D, Garlick P. Acute metabolic acidosis inhibits muscle protein synthesis in rats. *Am J Physiol Endocrinol Metab.* (2004) 287:E90–6. doi: 10.1152/ajpendo.00387.2003
97. Ballmer PE, McNurlan MA, Hulter HN, et al. Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans. *J Clin Invest.* (1995) 95:39–45.
98. Lofberg E, Gutierrez A, Anderstam B, Wernerman J, Bergstrom J, Price SR, et al. Effect of bicarbonate on muscle protein in patients receiving hemodialysis. *Am J Kidney Dis.* (2006) 48:419–29. doi: 10.1053/j.ajkd.2006.05.029
99. Ikizler TA, Pupim LB, Brouillette JR, Levenhagen DK, Farmer K, Hakim M, et al. Hemodialysis stimulates muscle and whole body protein loss and alters substrate oxidation. *Am J Physiol Endocrinol Metab.* (2002) 282:E107–16. doi: 10.1152/ajpendo.2002.282.1.E107
100. Raj DS, Zager P, Shah VO, Dominic EA, Adeniyi O, Blandon P, et al. Protein turnover and amino acid transport kinetics in end-stage renal disease. *Am J Physiol Endocrinol Metab.* (2004) 286:E136–44. doi: 10.1152/ajpendo.00352.2003
101. Garibotto G, Bonanni A, Verzola D. Effect of kidney failure and hemodialysis on protein and amino acid metabolism. *Curr Op Clin Nutr Metab Care.* (2012) 15:78–84. doi: 10.1097/MCO.0b013e32834d9df6
102. Hendriks FK, Kooman JP, van Loon LJ. Dietary protein interventions to improve nutritional status in end-stage renal disease patients undergoing hemodialysis. *Curr Opp Clin Nutr Metab Care.* (2021) 24:79–87. doi: 10.1097/MCO.0000000000000703
103. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM. Amino acid and albumin losses during hemodialysis. *Kidney Int.* (1994) 46:830–7. doi: 10.1038/ki.1994.339
104. Garibotto G, Fiorini F, Sala MR, Marchelli M, Verzola D, Rossi D, et al. Amino acid loss with polyethersulfone. *Contrib Neprhol.* (2003) 138:59–67. doi: 10.1159/000067387
105. Hendriks FK, Smeets JSJ, Broers NJH, van Kranenburg JMX, van der Sande FM, Kooman JP, et al. End-stage renal disease patients lose a substantial amount of amino acids during hemodialysis. *J Nutr.* (2020) 150:1160–6. doi: 10.1093/jn/nxaa010
106. Kalantar-Zadeh K, Ficociello LH, Bazzanella J, Mullon C, Anger MS. Slipping through the pores: hypoalbuminemia and albumin loss during hemodialysis. *Int J Nephrol Renov Dis.* (2021) 14:11–21. doi: 10.2147/IJNRD.S291348
107. Van Gelder MK, Abrahams AC, Joles JA, Kaysen GA, Gerritsen KGF. Albumin handling in different hemodialysis modalities. *Nephrol Dial Transaplant.* (2018) 33:906–13. doi: 10.1093/ndt/gfx191
108. Boivin MA, Battah SI, Dominic EA, Kalantar-Zadeh K, Ferrando A, Tzamaloukas H, et al. Activation of caspase-3 in the skeletal muscle during haemodialysis. *Eur J Clin Invest.* (2010) 40:903–10. doi: 10.1111/j.1365-2362.2010.02347.x
109. Gutierrez A, Alvestrand A, Wahren J, Bergström J. Effect of *in vivo* contact between blood and dialysis membranes on protein catabolism in humans. *Kidney Int.* (1990) 38:487–94. doi: 10.1038/ki.1990.230
110. Mares J, Thongboonkerd V, Tuma Z, Moravec J, Matejovic M. Specific adsorption of some complement activation proteins to polysulfone dialysis membranes during hemodialysis. *Kidney Int.* (2009) 76:404–13. doi: 10.1038/ki.2009.138
111. Mares J, Richtrova P, Hricinova A, Tuma Z, Moravec J, Lysak D, et al. Proteomic profiling of blood-dialyzer interactome reveals involvement of lectin complement pathway in hemodialysis-induced inflammatory response. *Proteomics Clin Appl.* (2010) 4:829–38. doi: 10.1002/prca.201000031
112. Ekdahl KN, Soveri I, Hilborn J, Fellström B, Nillson B. Cardiovascular disease in haemodialysis: role of the intravascular innate immune system. *Nat Rev Nephrol.* (2017) 13:285–96. doi: 10.1038/nrneph.2017.17
113. Kopple JD, Blumenkrantz MJ, Jones MR, Moran JK, Coburn JW. Plasma amino acid levels and amino acid losses during continuous ambulatory peritoneal dialysis. *Am J Clin Nutr.* (1982) 36:395–402. doi: 10.1093/ajcn/36.3.395
114. Krediet RT, Zuyderhoudt FM, Boeschoten EW, Arisz. L. Peritoneal permeability to proteins in diabetic and non-diabetic continuous ambulatory peritoneal dialysis patients. *Nephron.* (1986) 42:133.e40. doi: 10.1159/000183652
115. Westra WM, Kopple JD, Krediet RT, Appell M, Mehrotra R. Dietary protein requirements and dialysate protein losses in chronic peritoneal dialysis patients. *Perit Dial Int.* (2007) 27:192–5. doi: 10.1177/089686080702700217
116. Kittiskulnam P, Chuengsaman P, Kanjanabuch T, Katesomboon S, Tungsanga S, Tiskajornsiri K, et al. Protein-energy wasting and mortality risk prediction among peritoneal dialysis patients. *J Ren Nutr.* (2021) 25:S1051–2276. doi: 10.1053/j.jrn.2020.11.007
117. Melo TL, Meireles MS, Kamimura MA, Cuppari L. Concurrent validity of an appetite questionnaire in peritoneal dialysis. *Perit Dial Int.* (2020) 40:41–6. doi: 10.1177/0896860819879878
118. Garibotto G, Sofia A, Canepa A, Saffioti S, Sacco P, Sala M, et al. Acute effects of peritoneal dialysis with dialysates containing dextrose or dextrose and amino acids on muscle protein turnover in patients with chronic renal failure. *J Am Soc Nephrol.* (2001) 12:557–67. doi: 10.1681/ASN.V123557
119. Gordon BS, Kelleher AR, Kimball SC. Regulation of muscle protein synthesis and the effects of catabolic states. *Int J Biochem Cell Biol.* (2013) 45:2147–57. doi: 10.1016/j.biocel.2013.05.039
120. Bammens B, Verbeke K, Vanrenterghem Y, Evenpoel P. Evidence for impaired assimilation of protein in chronic renal failure. *Kidney Intern.* (2003) 64:2196–203. doi: 10.1046/j.1523-1755.2003.00314.x
121. Chen Y, Sood S, McIntire K, Roth R, Rabkin R. Leucine-stimulated mTOR signaling is partly attenuated in skeletal muscle of chronically uremic rats. *Am J Physiol Endocrinol Metab.* (2011) 301:E873–81. doi: 10.1152/ajpendo.00068.2011
122. Chen Y, Biada J, Sood S, Rabkin R. Uremia attenuates growth hormone-stimulated insulin-like growth factor-1 expression, a process worsened by inflammation. *Kidney Int.* (2010) 78:89–95. doi: 10.1038/ki.2010.85
123. Sood S, Chen Y, McIntire K, Rabkin R. Acute acidosis attenuates leucine stimulated signal transduction and muscle protein synthesis in rat skeletal muscle. *Am J Nephrol.* (2014) 40:362–70. doi: 10.1159/000366524
124. Deferrari G, Garibotto G, Robaudo C, Sala M, Tizianello A. Splanchnic exchange of amino acids after amino acid ingestion in patients with chronic renal insufficiency. *Am J Clin Nutr.* (1988) 48:72–83. doi: 10.1093/ajcn/48.1.72
125. Garibotto G, Deferrari G, Robaudo C, Saffioti S, Paoletti E, Pontremoli R, et al. Effects of a protein meal on blood amino acid profile in patients with chronic renal failure. *Nephron.* (1993) 64:216–25. doi: 10.1159/000187317
126. Garibotto G, Deferrari G, Robaudo C, Saffiotti S, Sofia A, Russo R, et al. Disposal of exogenous amino acids by muscle in patients with chronic renal failure. *Am J Clin Nutr.* (1995) 62:136–42. doi: 10.1093/ajcn/62.1.136
127. Castellino P, Solini A, Luzi L, Barr JG, Smith DJ, Petrides A, et al. Glucose and amino acid metabolism in chronic renal failure: effect of insulin and amino acids. *Am J Physiol.* (1992) 262:F168–76. doi: 10.1152/ajprenal.1992.262.2.F168

128. Garibotto G, Sofia A, Russo R, Paoletti E, Bonanni A, Parodi E, et al. Insulin sensitivity of muscle protein metabolism is altered in patients with chronic kidney disease and metabolic acidosis. *Kidney Int*. (2015) 88:1419–26. doi: 10.1038/ki.2015.247
129. van Vliet S, Skinner SK, Beals JW, Pagni BA, Fang HY, Ulanov AV, et al. Dysregulated handling of dietary protein and muscle protein synthesis after mixed-meal ingestion in maintenance hemodialysis patients. *Kidney Int Rep*. (2018) 3:1403–15. doi: 10.1016/j.ekir.2018.08.001
130. Draicchio F, van Vliet S, Ancu O, Paluska SA, Wilund K, Mickute M, et al. Integrin-associated ILK and PINCH1 protein content are reduced in skeletal muscle of maintenance haemodialysis patients. *J Physiol.* (2020) 598:5701–16. doi: 10.1113/JP280441
131. Cheema B, Abas H, Smith B, O'Sullivan A, Chan M, Patwardhan A, et al. Progressive exercise for anabolism in kidney disease (PEAK): a randomized, controlled trial of resistance training during hemodialysis. *J Am Soc Nephrol*. (2007) 18:1594–601. doi: 10.1681/ASN.2006121329
132. Molsted S, Harrison AP, Eidemak I, Andersen JL. The effects of high-load strength training with protein- or nonprotein-containing nutritional supplementation in patients undergoing dialysis. *J Ren Nutr*. (2013) 23:132–40. doi: 10.1053/j.jrn.2012.06.007
133. Robinson MJ, Burd NA, Breen L, Rerecich T, Yang Y, Hector J, et al. Dose-dependent responses of myofibrillar protein synthesis with beef ingestion are enhanced with resistance exercise in middle-aged men. *Appl Physiol Nutr Metab*. (2013) 38:120–5. doi: 10.1139/apnm-2012-0092
134. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney*. (2020) 76(3 Suppl 1):S1–107. doi: 10.1053/j.ajkd.2020.05.006
135. Kistler BM, Moore LW, Benner D, Biruete A, Boaz M, Brunori G, et al. The international society of renal nutrition and metabolism commentary on the national kidney foundation and academy of nutrition and dietetics KDOQI clinical practice guideline for nutrition in chronic kidney disease. *J Ren Nutr*. (2021) 31:116–20. doi: 10.1053/j.jrn.2020.05.002
136. FAOSTAT. *Food Balance Sheets*. Ottawa, ON: FAOSTAT (2009).
137. Kalantar-Zadeh K, Joshi S, Schlueter R, Cooke J, Brown-Tortorici A, Donnelly M, et al. Plant-dominant low-protein diet for conservative management of chronic kidney disease. *Nutrients*. (2020) 12:1931. doi: 10.3390/nu12071931
138. St-Jules DE, Goldfarb DS, Popp CJ, Pompeii ML, Liebman SE. Managing protein-energy wasting in hemodialysis patients: A comparison of animal- and plant-based protein foods. *Semin Dial*. (2019) 32:41–6. doi: 10.1111/sdi.12737
139. Letourneau P, Bataille S, Chauveau P, Fouque D, Koppe L. Source and composition in amino acid of dietary proteins in the primary prevention and treatment of CKD. *Nutrients*. (2020) 12:3892. doi: 10.3390/nu12123892
140. González-Ortiz A, Xu H, Acevedo SR, Avesani CM, Lindholm B, Rotter C, et al. Nutritional status, hyperkalaemia and attainment of energy/protein intake targets in haemodialysis patients following plant-based diets: a longitudinal cohort study. *Nephrol Dial Transplant*. (2021) 36:681–8. doi: 10.1093/ndt/gfaa194
141. Verzola D, Picciotto D, Saio M, Aimasso F, Bruzzone F, Sukkar GS, et al. Low protein diets and plant-based low protein diets: do they meet protein requirements of patients with chronic kidney disease? *Nutrients*. (2020) 13:83. doi: 10.3390/nu13010083
142. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. (2004) 15:2208–18. doi: 10.1097/01.ASN.0000133041.27682.A2
143. Yamamoto S, Bieber BA, Komaba H, Hanafusa N, Kitabayashi H, Nomura T, et al. Medical director practice of advising increased dietary protein intake in hemodialysis patients with hyperphosphatemia: associations with mortality in the dialysis outcomes and practice patterns study. *J Ren Nutr*. (2021). doi: 10.1053/j.jrn.2021.02.007. [Epub ahead of print].
144. Fotiadou E, Panagiotis IG, Chourdakis M, Zebekakis P, Liakopoulos V. Eating during the hemodialysis session: a practice improving nutritional status or a risk factor for intradialytic hypotension and reduced dialysis adequacy? *Nutrients*. (2020) 12:1703. doi: 10.3390/nu12061703
145. Pupim LB, Majchrzak KM, Flakoll PJ, Ikizler TA. Intradialytic oral nutrition improves protein homeostasis in chronic hemodialysis patients with deranged nutritional status. *Am J Physiol Endocrinol Metab*. (2003) 17:3149–57. doi: 10.1681/ASN.2006040413
146. Struijk-Wielinga G, Romijn M, Neelemaat F, ter Wee P, Weijs P. Providing in-between meals during dialysis treatment contributes to an adequate protein and energy intake in hemodialysis patients: a non-randomized intervention study. *Mathews J Nutr Diet*. (2016) 1:1–8.
147. Mouillot T, Filancia A, Boirie Y, Brindisi MC, Hafnaoui N, Van Wymelbeke V, et al. Hemodialysis affects wanting and spontaneous intake of protein-rich foods in chronic kidney disease patients. *J Ren Nutr*. (2020) 25:S1051–2276(20)30138–2. doi: 10.1053/j.jrn.2020.05.006
148. Veeneman JM, Kingman HA, Boer TS, Stellard F, De Jong PE, Reijngoud DJ, et al. Protein intake during hemodialysis maintains a positive whole body protein balance in chronic hemodialysis patients. *Am J Physiol Endocrinol Metab*. (2003) 284:E954–65. doi: 10.1152/ajpendo.00264.2002
149. Kistler BM, Benner D, Burrowes JD, Campbell KL, Fouque D, Garibotto G, et al. Eating during hemodialysis treatment: a consensus statement from the international society of renal nutrition and metabolism. *J Ren Nutr*. (2018) 28:4–12. doi: 10.1053/j.jrn.2017.10.003
150. Flakoll PJ, Brouillette JR, Levenhagen DK, Hakim RM, Ikizler TA. Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients *J Clin Invest*. (2002) 110:483–92. doi: 10.1172/JCI15449
151. Anderson J, Peterson K, Bourne D, Boundy E. Effectiveness of intradialytic parenteral nutrition in treating protein-energy wasting in hemodialysis: a rapid systematic review. *J Ren Nutr*. (2019) 29:361–9. doi: 10.1053/j.jrn.2018.11.009
152. Cano NJM, Fouque D, Roth H, Aparicio M, Azar R, Canaud B, et al. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. *J Am Soc Nephrol*. (2007) 18:2583–91. doi: 10.1681/ASN.2007020184
153. Deleaval P, Luaire B, Laffay P, Jambut-Cadon D, Stauss-Grabo M, Canaud B, et al. Short-term effects of branched-chain amino acids-enriched dialysis fluid on branched-chain amino acids plasma level and mass balance: a randomized cross-over study. *Ren Nutr*. (2020) 30:61–8. doi: 10.1053/j.jrn.2019.03.079
154. Chan W. Chronic kidney disease and nutrition support. *Nutr Clin Pract*. (2021) 36:312–30. doi: 10.1002/ncp.10658
155. Canepa A, Carrea A, Menoni S, Verrina E, Trivelli A, Gusmano R, et al. Acute effects of simultaneous intraperitoneal infusion of glucose and amino acids. *Kidney Int*. (2001) 59:1967–73. doi: 10.1046/j.1523-1755.2001.0590051967.x
156. Ikizler T, Cano NJ, Franch H, Fouque D, Himmelfarb J, Zadeh KK, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int*. (2013) 84:1096–107. doi: 10.1038/ki.2013.147
157. Tjiong HL, van den Berg JW, Wattimena JL, Rietveld T, van Dijk LJ, van der Wiel AM, et al. Dialysate as food: combined amino acid and glucose dialysate improves protein anabolism in renal failure patients on automated peritoneal dialysis. *J Am Soc Nephrol*. (2005) 16:1486–93. doi: 10.1681/ASN.2004050402
158. Malgorzewicz S, Galezowska G, Cieszynska-Semenowicz M, Ratajczyk J, Wolska L, Rutkowski P, et al. Amino acid profile after oral nutritional supplementation in hemodialysis patients with protein-energy wasting. *Nutrition*. (2019) 57:231–6. doi: 10.1016/j.nut.2018.06.013
159. Pokkrong L, Bancha, Samitti C, Paramat T, Ouppatham S. Effectiveness of renal-specific oral nutritional supplements compared with diet counseling in malnourished hemodialysis patients. *Int Urol Nephrol*. (2021) 53:1675–87. doi: 10.1007/s11255-020-02768-5
160. Mah JY, Choy SW, Roberts MA, Desai AM, Corken M, Gwini SM, et al. Oral protein-based supplements versus placebo or no treatment for people with chronic kidney disease requiring dialysis. *Cochrane Database Syst Rev*. (2020) 5:CD012616. doi: 10.1002/14651858.CD012616.pub2
161. Liu PJ, Ma F, Wang QY, He SL. The effects of oral nutritional supplements in patients with maintenance dialysis therapy: A systematic review and metaanalysis of randomized clinical trials. *PLoS ONE*. (2018) 13:e0203706. doi: 10.1371/journal.pone.0203706

162. Koppe L, Cassani de Oliveira M, Fouque D. Ketoacid analogues supplementation in chronic kidney disease and future perspectives. *Nutrients*. (2019) 11:2071. doi: 10.3390/nu11092071
163. Garibotto G, Sofia A, Parodi EL, Ansaldo F, Bonanni A, Picciotto D, et al. Effects of Low-protein, and supplemented very low-protein diets, on muscle protein turnover in patients with CKD. *Kidney Int Rep*. (2018) 3:701–10. doi: 10.1016/j.ekir.2018.01.003
164. Chen HY, Sun CY, Lee CC, Wu W, Chen YC, Lin YH, et al. Ketoanalogue supplements reduce mortality in patients with pre-dialysis advanced diabetic kidney disease: A nationwide population-based study. *Clin Nutr*. (2021) 40:4149–60. doi: 10.1016/j.clnu.2021.01.045
165. Wang DT, Lu L, Shi Y, Geng ZB, Yin Y, Wang M, et al. Supplementation of ketoacids contributes to the up-regulation of the Wnt7a/Akt/p70S6K pathway and the down-regulation of apoptotic and ubiquitin-proteasome systems in the muscle of 5/6 nephrectomised rats. *Br J Nutr*. (2014) 111:1536–48. doi: 10.1017/S0007114513004091
166. Wang D, Wei L, Yang Y, Liu H. Dietary supplementation with ketoacids protects against CKD-induced oxidative damage and mitochondrial dysfunction in skeletal muscle of 5/6 nephrectomised rats. *Skelet Muscle*. (2018) 8:18. doi: 10.1186/s13395-018-0164-z
167. Walejko JM, Cristopher BA, Crown SB, Zhang GF, Pickar-Oliver A, Yoneshiro K, et al. Branched-chain α-ketoacids are preferentially reaminated and activate protein synthesis in the heart. *Nat Commun*. (2021) 12:1680. doi: 10.1038/s41467-021-21962-2
168. Garibotto G, Verzola D, Vettore M, Tessari P. The contribution of muscle, kidney, and splanchnic tissues to leucine transamination in humans. *Can J Physiol Pharmacol*. (2018) 96:382–7. doi: 10.1139/cjpp-2017-0439
169. Tessari P, Garibotto G, Inchiostro S, Robaudo C, Saffioti S, Vettore M, et al. Kidney, splanchnic, and leg protein turnover in humans. Insight from leucine and phenylalanine kinetics. *J Clin Invest*. (1996) 98:1481–92. doi: 10.1172/JCI118937
170. Escobar J, Frank JW, Suryawan A, Nguyen HV, Van Horn CG, Hutson SM. Leucine TA, α-ketoisocaproic acid. but not norleucine, stimulate skeletal muscle protein synthesis in neonatal pigs. *J Nutr*. (2010) 140:1418–24. doi: 10.3945/jn.110.123042
171. Fuchs CJ, Hermans WJH, Holwerda AM, Smeets JSJ, Senden JM, van Kranenburg J, et al. Branched-chain amino acid and branched-chain ketoacid ingestion increases muscle protein synthesis rates *in vivo* in older adults: A double-blind, randomized trial. *Am J Clin Nutr*. (2019) 110:862–72. doi: 10.1093/ajcn/nqz120
172. Li HL, Li H, Cao YF, Qi Y, Wangm WQ, Liu SQ, et al. Effects of keto acid supplements on Chinese patients receiving maintenance hemodialysis: a prospective, randomized, controlled, single-center clinical study. *Chin Med J (Engl)*. (2020) 133:9–16. doi: 10.1097/CM9.0000000000000578
173. Bronas UG. Exercise training and reduction of cardiovascular disease risk factors in patients with chronic kidney disease. *Adv Chronic Kidney Dis*. (2009) 16:449–58. doi: 10.1053/j.ackd.2009.07.005
174. Koh KP, Fassett RG, Sharman JE, Coombes JS, Williams AD. Effect of intradialytic versus home-based aerobic exercise training on physical function and vascular parameters in hemodialysis patients: a randomized pilot study. *Am J Kidney Dis*. (2010) 55:88–99. doi: 10.1053/j.ajkd.2009.09.025
175. Kouidi E, Grekas D, Deligiannis A. Effects of exercise training on noninvasive cardiac measures in patients undergoing long-term hemodialysis: a randomized controlled trial. *Am J Kidney Dis*. (2009) 54:511–52. doi: 10.1053/j.ajkd.2009.03.009
176. Kopple JD, Wang H, Casaburi R, Fournier M, Lewis MI, Taylor W, et al. Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle. *J Am Soc Nephrol*. (2007) 18:2975–86. doi: 10.1681/ASN.2006070794
177. Chan D, Cheema BS. Progressive resistance training in end-stage renal disease: systematic review. *Am J Nephrol*. (2016) 44:32–45. doi: 10.1159/000446847
178. Sheng K, Zhang P, Chen L, Cheng J, Wu C, Chen J. Intradialytic exercise in hemodialysis patients: a systematic review and meta-analysis. *Am J Nephrol*. (2014) 40:478–90. doi: 10.1159/000368722
179. Cheema BS, Smith BC, Singh MA. A rationale for intradialytic exercise training as standard clinical practice in ESRD. *Am J Kidney Dis*. (2005) 45:912–6. doi: 10.1053/j.ajkd.2005.01.030
180. Koufaki P, Greenwood S, Painter P, Mercer T. The BASES expert statement on exercise therapy for people with chronic kidney disease. *J Sports Sci*. (2015) 33:1902–7. doi: 10.1080/02640414.2015.1017733
181. Smart NA, Williams AD, Levinger I, Seling S, Howden E, et al. Exercise & Sports Science Australia (ESSA) position statement on exercise and chronic kidney disease. *J Sci Med Sport*. (2013) 16:406–11. doi: 10.1016/j.jsams.2013.01.005
182. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis*. (2012) 45(4 Suppl 3):S1–153. doi: 10.1053/j.ajkd.2005.01.019
183. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The physical activity guidelines for Americans. *JAMA*. (2018) 320:2020–8. doi: 10.1001/jama.2018.14854
184. Clarkson MJ, Bennett PN, Fraser SF, Warmington SA. Exercise interventions for improving objective physical function in patients with end-stage kidney disease on dialysis: a systematic review and meta-analysis. *Am J Physiol Renal Physiol*. (2019) 316:F856–72. doi: 10.1152/ajprenal.00317.2018
185. Wilund KR, Viana JL, Perez LM. A critical review of exercise training in hemodialysis patients: personalized activity prescriptions are needed. *Exerc Sport Sci Rev*. (2020) 48:28–39. doi: 10.1249/JES.0000000000000209
186. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in patients on dialysis: a multicenter, randomized clinical trial. *J Am Soc Nephrol*. (2017) 28:1259–68. doi: 10.1681/ASN.2016030378
187. Exel AL, Lima PS, Urtado CB, Dibai-Filho AV, Vilanova CL, Sabino EFP, et al. Effectiveness of a resistance exercise program for lower limbs in chronic renal patients on hemodialysis: A randomized controlled trial. *Hemodial Int*. (2021). doi: 10.1111/hdi.12918. [Epub ahead of print].
188. Salhab N, Karavetian M, Kooman J, Fiaccadori E, El Khoury CF. Effects of intradialytic aerobic exercise on hemodialysis patients: a systematic review and meta-analysis. *J Nephrol*. (2019) 32:549–66. doi: 10.1007/s40620-018-00565-z
189. Pu J, Jiang Z, Wu W, Li L, Zhang L, Li Q, et al. Efficacy and safety of intradialytic exercise in haemodialysis patients: a systematic review and meta-analysis. *BMJ Open*. (2019) 9:e020633. doi: 10.1136/bmjopen-2017-020633
190. Matsuzawa R, Hoshi K, Yoneki K, Harada M, Watanabe T, Shimoda T, et al. Exercise training in elderly people undergoing hemodialysis: a systematic review and meta-analysis. *Kidney Int Rep*. (2017) 2:1096–110. doi: 10.1016/j.ekir.2017.06.008
191. Tentori F, Elder SJ, Thumma J, Pisoni RL, Bommer J, Fissell RB, et al. Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. *Nephrol Dial Transplant*. (2010) 25:3050–62. doi: 10.1093/ndt/gfq138
192. Labib M, Bohm C, MacRae JM, Paul N, Bennett PN, Wilund K, et al. An international delphi survey on exercise priorities in CKD. *Kidney Int Rep*. (2020) 6:657–68. doi: 10.1016/j.ekir.2020.12.001
193. Breen L, Phillips SM. Skeletal muscle protein metabolism in the elderly: Interventions to counteract the 'anabolic resistance' of ageing. *Nutr Metab (Lond)*. (2011) 8:68. doi: 10.1186/1743-7075-8-68
194. Majchrzak KM, Pupim LB, Flakoll PJ, Ikizler TA. Resistance exercise augments the acute anabolic effects of intradialytic oral nutritional supplementation. *Nephrol Dial Transplant*. (2008) 23:1362–9. doi: 10.1093/ndt/gfm773
195. Dong J, Sundell MB, Pupim LB, Wu P, Shintani A, Ikizler TA. The effect of resistance exercise to augment long-term benefits of intradialytic oral nutritional supplementation in chronic hemodialysis patients. *J Ren Nutr*. (2010) 21:149–59. doi: 10.1053/j.jrn.2010.03.004
196. Alemany MA, Ortiz VO, Olvera SG, Guerrero IG, Esquivel GA, Quintanilla GC. The effects of resistance exercise and oral nutritional supplementation during hemodialysis on indicators of nutritional status and quality

of life. *Nephrol Dial Transplant.* (2016) 31:1712–20. doi: 10.1093/ndt/gfw297
197. Jeong JH, Biruete A, Tomayko EJ, Wu PT, Fitschen P, Chung HR, et al. Results from the randomized controlled IHOPE trial suggest no effects of oral protein supplementation and exercise training on physical function in hemodialysis patients. *Kidney Int.* (2019) 96:777–76. doi: 10.1016/j.kint.2019.03.018
198. Engelen MPKJ, Deutz NEP. Is β-hydroxy-methylbutyrate an effective anabolic agent to improve outcome in older diseased populations? *Curr Opin Clin Nutr Metab.* (2018) 21:207–13. doi: 10.1097/MCO.0000000000000459
199. Marshall RN, Smeuninx B, Morgan T, Breen L. Nutritional strategies to offset disuse-induced skeletal muscle atrophy and anabolic resistance in older adults: from whole-foods to isolated ingredients. *Nutrients.* (2020) 12:1533. doi: 10.3390/nu12051533
200. Oktaviana J, Zanker J, Vogrin S, Duque G. The effect of β-Hydroxy-β-Methylbutyrate (HMB) on sarcopenia and functional frailty in older persons: a systematic review. *J Nutr Health Aging.* (2019) 23:145–50. doi: 10.1007/s12603-018-1153-y
201. Din US, Brook MS, Selby A, Quinlan J, Boereboom C, Abdulla H, et al. A double-blind placebo controlled trial into the impacts of HMB supplementation and exercise on free-living muscle protein synthesis, muscle mass and function, in older adults. *Clin Nutr.* (2019) 38:2071–8. doi: 10.1016/j.clnu.2018.09.025
202. Fitschen PJ, Biruete A, Jeong J, Wilund KR. Efficacy of beta-hydroxy-beta-methylbutyrate supplementation in maintenance hemodialysis patients. *Hemodial Int.* (2017) 21:107–16. doi: 10.1111/hdi.12440
203. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr.* (1991) 54:438–63. doi: 10.1093/ajcn/54.3.438
204. Lalia AZ, Dasari S, Robinson MM, Abid H, Morse DM, Klaus KA, et al. Influence of omega-3 fatty acids on skeletal muscle protein metabolism and mitochondrial bioenergetics in older adults. *Aging (Albany NY).* (2017) 9:1096–29. doi: 10.18632/aging.101210
205. Smith GI, Atherton P, Reeds DN, Mohammed BS, Rankin D, Rennie MJ, et al. Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial. *Am Clin Nutr.* (2011) 93:402–12. doi: 10.3945/ajcn.110.005611
206. McGlory C, Calder PC, Nunes EA. The influence of omega-3 fatty acids on skeletal muscle protein turnover in health, disuse, and disease. *Front Nutr.* (2019) 6:144. doi: 10.3389/fnut.2019.00144
207. Deger SM, Hung AM, Ellis CD, Booker C, Bian A, Chen G, et al. High dose omega-3 fatty acid administration and skeletal muscle protein turnover in maintenance hemodialysis patients. *Clin J Am Soc Nephrol.* (2016) 7:1227–35. doi: 10.2215/CJN.04150415
208. Rondanelli M, Perna S, Riva A, Petrangolini G, Di Paolo E, Gasparri C. Effects of n-3 EPA and DHA supplementation on fat free mass and physical performance in elderly. A systematic review and meta-analysis of randomized clinical trial. *Mech Ageing Dev.* (2021) 196:111476. doi: 10.1016/j.mad.2021.111476
209. Bello AK, Stenvinkel P, Lin M, Hemmelgarn B, Thadhani R, Klarenbach S, et al. Serum testosterone levels and clinical outcomes in male hemodialysis patients. *Am J Kidney Dis.* (2014) 63:268–75. doi: 10.1053/j.ajkd.2013.06.010
210. Cigarrán S, Pousa M, Castro MJ, González B, Martínez A, Barril G, et al. Endogenous testosterone, muscle strength, and fat-free mass in men with chronic kidney disease. *J Ren Nutr.* (2013) 23:e89–95. doi: 10.1053/j.jrn.2012.08.007
211. Garibotto G, Esposito P, Picciotto D, Verzola D. Testosterone disorders and male hypogonadism in kidney disease. *Sem Nephrol.* (2021) 41:114–25. doi: 10.1016/j.semnephrol.2021.03.006
212. Chiang JM, Kaysen GA, Segal M, Chertow GM, Delgado C, Jphansen KL. Low testosterone is associated with frailty, muscle wasting, and physical dysfunction among men receiving hemodialysis: a longitudinal analysis. *Nephrol Dial Transpl.* (2019) 34:802–10. doi: 10.1093/ndt/gfy252
213. Florini JR, Ewton DZ, Coolican SA. Growth hormone and the insulin-like growth factor system in myogenesis. *Endocr Rev.* (1996) 17:481–17. doi: 10.1210/edrv-17-5-481
214. Kostyo JL. Rapid effects of growth hormone on amino acid transport and protein synthesis. *Ann N Y Acad Sci.* (1968) 148:389–407. doi: 10.1111/j.1749-6632.1968.tb20365.x
215. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, et al. Effects of human growth hormone in men over 60 years old. *N Engl J Med.* (1990) 323:1–6. doi: 10.1056/NEJM199007053230101
216. Rucker K, de Sá L, Arbex A. Growth hormone replacement therapy in patients without adult growth hormone deficiency: What answers do we have so far? *Health.* (2017) 9:799–810. doi: 10.4236/health.2017.95057
217. Drube J, Wan M, Bonhuis M, Wühl E, Bacchetta J, Santos F, et al. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. *Nat Rev Nephrol.* (2019) 15:577–89. doi: 10.1038/s41581-019-0161-4
218. Foster BJ, Shultsemel BS, Wetzsteon RJ, Thayu M, Foerster DL. Association of chronic kidney disease with muscle deficits in children. *J Am Soc Nephrol.* (2010) 22:377–86. doi: 10.1681/ASN.2010060603
219. Garibotto G, Barreca A, Russo R, Sofia A, Araghi P, Cesarone A, et al. Effects of recombinant human growth hormone on muscle protein turnover in malnourished hemodialysis patients. *J Clin Invest.* (1997) 99:97–105. doi: 10.1172/JCI119139
220. Iglesias P, Diez JJ, Fernandez-Reyes MJ, Aguilera A, Burgues S, Martinez-Ara J, et al. Recombinant human growth hormone therapy in malnourished dialysis patients: A randomized controlled study. *Am J Kidney Dis.* (1998) 32:454–4=63. doi: 10.1053/ajkd.1998.v32.pm9740162
221. Hansen TB, Gram J, Jensen PB, Kristiansen JH, Ekelund B, Christiansen JS, et al. Influence of growth hormone on whole body and regional soft tissue composition in adult patients on hemodialysis. A double-blind, randomized, placebo-controlled study. *Clin Nephrol.* (2000) 53:99–107.
222. Kopple JD, Cheung AK, Christiansen JS, Djurhuus CB, Nahas ME, Rasmussen BF, et al. OPPORTUNITY^{TM}: a randomized clinical trial of growth hormone on outcome in hemodialysis patients. *Clin J Am Soc Nephrol.* (2008) 3:1741–51. doi: 10.2215/CJN.027606
223. Eghbali-Fatourechi G, Khosla S, Sanyal A, Boyle WJ, Lacey L, Riggs BL. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. *J Clin Invest.* (2003) 111:1221–30. doi: 10.1172/JCI17215
224. Kirk B, Zanker J, Duque GJ. Osteosarcopenia: epidemiology, diagnosis, and treatment-facts and numbers. *J Cachexia Sarcopenia Muscle.* (2020) 11:609–18. doi: 10.1002/jcsm.12567
225. Genant HK, Libanati C, Engelke K, Zanchetta JR, Høiseth A, Yuen K, et al. Improvements in hip trabecular, subcortical, and cortical density and mass in postmenopausal women with osteoporosis treated with denosumab. *Bone.* (2013) 56:482–8. doi: 10.1016/j.bone.2013.07.011
226. Phu S, Bani Hassan E, Vogrin S, Kirk B, Duque G. Effect of denosumab on falls, muscle strength, and function in community-dwelling older adults. *J Am Geriatr Soc.* (2019) 67:2660–1. doi: 10.1111/jgs.16165
227. Lee D, Goldberg AL. Muscle wasting in fasting requires activation of NF-κB and inhibition of AKT/mechanistic target of rapamycin (mTOR) by the protein acetylase, GCN5. *J Biol Chem.* (2015) 290:30269–79. doi: 10.1074/jbc.M115.685164
228. Bonnet N, Bourgoin L, Biver E, Douni E, Ferrari S. RANKL inhibition improves muscle strength and insulin sensitivity and restores bone mass. *J Clin Invest.* (2019) 129:3214–23. doi: 10.1172/JCI125915
229. Janssen HCJP, Samson MM, Verhaar JJH. Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr.* (2002) 75:611–5. doi: 10.1093/ajcn/75.4.611
230. Christian M, Kuan Minn Cha G, So B, Tsang M, Chen J, Houweling J, et al. Mice with myocyte deletion of vitamin D receptor have sarcopenia and impaired muscle function. *J Cachexia Sarcopenia Muscle.* (2019) 10:1228–40. doi: 10.1002/jcsm.12460
231. Molina P, Carrero JJ, Bover J, Chauveau P, Mazzaferro S, Torres PU. European Renal Nutrition (ERN) and Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Working Groups of the European Renal Association-European Dialysis Transplant Association (ERA-EDTA).

Vitamin D, a modulator of musculoskeletal health in chronic kidney disease. *J Cachexia Sarcopenia Muscle*. (2017) 8:686–701. doi: 10.1002/jcsm.12218

232. Sabatino A, Cuppari L, Stenvinkel P, Lindholm B, Avesani C. Sarcopenia in chronic kidney disease: what have we learned so far? *J Nephrol.* (2020). doi: 10.1007/s40620-020-00840-y. [Epub ahead of print].
233. van Vliet S, Fappi A, Reeds DN, Mittendorfer B. No independent or combined effects of vitamin D and conjugated linoleic acids on muscle MPS in older adults: a randomized, double-blind, placebo-controlled clinical trial. *Am J Clin Nutr.* (2020) 112:1382–9. doi: 10.1093/ajcn/nqaa240
234. Deane C, Wilkinson DJ, Phillips BE, Smith K, Etheridge T, Atherton PJ. "Nutraceuticals" in relation to human skeletal muscle and exercise. *Am J Physiol Endocrinol Metab.* (2017) 312:E282–99. doi: 10.1152/ajpendo.00230.2016
235. Riechman SE, Andrews RD, Maclean DA, Sheather S. Statins and dietary and serum cholesterol are associated with increased lean mass following resistance training. *J Gerontol A Biol Sci Med Sci.* (2007) 62:1164–71. doi: 10.1093/gerona/62.10.1164
236. Verzola D, Barisione C, Picciotto D, Garibotto G, Koppe L. Emerging role of myostatin and its inhibition in the setting of chronic kidney disease. *Kidney Int.* (2019) 295:506–17. doi: 10.1016/j.kint.2018.10.010

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Nutrition

REVIEW
published: 16 August 2021
doi: 10.3389/fnut.2021.697523

Estimation of Muscle Mass in the Integrated Assessment of Patients on Hemodialysis

Alice Sabatino[1], *Natascha J. H. Broers*[2,3], *Frank M. van der Sande*[2,3], *Marc H. Hemmelder*[2,3], *Enrico Fiaccadori*[1] *and Jeroen P. Kooman*[2,3]*

[1] *Nephrology Unit, Department of Medicine and Surgery, Parma University Hospital, University of Parma, Parma, Italy,*
[2] *Division on Nephrology, Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, Netherlands,*
[3] *NUTRIM School of Nutrition and Translational Research in Metabolism, CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, Netherlands*

Assessment of muscle mass (MM) or its proxies, lean tissue mass (LTM) or fat-free mass (FFM), is an integral part of the diagnosis of protein-energy wasting (PEW) and sarcopenia in patients on hemodialysis (HD). Both sarcopenia and PEW are related to a loss of functionality and also increased morbidity and mortality in this patient population. However, loss of MM is a part of a wider spectrum, including inflammation and fluid overload. As both sarcopenia and PEW are amendable to treatment, estimation of MM regularly is therefore of major clinical relevance. Whereas, computer-assisted tomography (CT) or dual-energy X-ray absorptiometry (DXA) is considered a reference method, it is unsuitable as a method for routine clinical monitoring. In this review, different bedside methods to estimate MM or its proxies in patients on HD will be discussed, with emphasis on biochemical methods, simplified creatinine index (SCI), bioimpedance spectroscopy (BIS), and muscle ultrasound (US). Body composition parameters of all methods are related to the outcome and appear relevant in clinical practice. The US is the only parameter by which muscle dimensions are measured. BIS and SCI are also dependent on either theoretical assumptions or the use of population-specific regression equations. Potential caveats of the methods are that SCI can be influenced by residual renal function, BIS can be influenced by fluid overload, although the latter may be circumvented by the use of a three-compartment model, and that muscle US reflects regional and not whole body MM. In conclusion, both SCI and BIS as well as muscle US are all valuable methods that can be applied for bedside nutritional assessment in patients on HD and appear suitable for routine follow-up. The choice for either method depends on local preferences. However, estimation of MM or its proxies should always be part of a multidimensional assessment of the patient followed by a personalized treatment strategy.

Keywords: ultrasound, bioimpedance, sarcopenia, hemodialysis, creatinine index

OPEN ACCESS

Edited by:
Michele Barone,
University of Bari Aldo Moro, Italy

Reviewed by:
Leigh C. Ward,
The University of Queensland, Australia
Calvin Lloyd Cole,
University of Rochester, United States

***Correspondence:**
Jeroen P. Kooman
Jeroen.kooman@mumc.nl

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *19 April 2021*
Accepted: *16 July 2021*
Published: *16 August 2021*

Citation:
Sabatino A, Broers NJH, van der Sande FM, Hemmelder MH, Fiaccadori E and Kooman JP (2021) Estimation of Muscle Mass in the Integrated Assessment of Patients on Hemodialysis. Front. Nutr. 8:697523. doi: 10.3389/fnut.2021.697523

INTRODUCTION

Assessment of nutritional state is of high relevance in patients on hemodialysis (HD). This given the relation between protein-energy wasting (PEW), a condition characterized by reduced body stores of protein and energy fuels characteristic of patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD), and mortality (1), and since abnormalities in the nutritional state may be amenable to therapeutic intervention (2). Muscle wasting in patients on HD can be due to

multiple factors including insufficient dietary intake and a loss of nutrients through the dialysate, or an increased muscle breakdown due to inflammation or metabolic acidosis (3). Measurement of muscle mass (MM), or its proxies lean tissue mass (LTM) or fat-free mass (FFM), is an integral part of the assessment of the nutritional state, as well as in the diagnosis of sarcopenia. Sarcopenia is characterized by reduced MM and strength and is frequently observed in the elderly, but can also happen earlier as a consequence of chronic conditions, such as CKD/ESKD and patients on HD (3–5). Malnutrition as well as sarcopenia are part of a spectrum including impaired functional status, low physical activity, low quality of life, and frailty (6–8), and they are the important components of the premature aging phenomenon in this patient population (9). Next to this, inflammation and fluid overload were also found to be related to a decrease in LTM and intracellular water (ICW) (8, 10). Thus, loss of MM is a central part of the multimorbid spectrum of patients on HD, and should be interpreted in view of both its consequences as well as in the context of potentially amendable underlying factors. The aim of this short review is to give a concise overview of instrumental methods that can be used on a daily clinical basis in patients on HD, and their use in the context of a multidimensional assessment in these patients will be discussed.

CLINICAL SYNDROMES ASSOCIATED WITH A LOSS OF MM

Loss of MM or its proxies is included in various syndromes related to the nutritional and functional status of the patient on HD, as summarized in **Table 1**. Except frailty, in which only a reduction in muscle strength is a parameter, a reduction of MM or FFM is included in the diagnostic criteria of other syndromes, such as PEW, cachexia, and sarcopenia. These partly, but not entirely, overlapping syndromes (3, 11) are part of a wide spectrum of nutritional and functional abnormalities in patients on HD, although an important common denominator appears to be tissue loss (11). Importantly, one of the criteria for the definition of PEW, also referred to as kidney cachexia, is an increase in inflammatory parameters (4, 12). In contrast, inflammation is not included in the diagnostic criteria of sarcopenia (13). This division is relevant, as the pathophysiology and also possibly the clinical approach to a patient on HD with a pure "sarcopenic" phenotype may differ from that of a patient with a "cachectic" phenotype (14). Furthermore, patients can have both an increase in fat mass and a decline in MM (15), an entity also known as sarcopenic obesity, which is prevalent in patients on HD, although its relation with the outcome is yet uncertain (16, 17). The development of sarcopenic obesity is not captured by the estimation of changes in body weight or body mass index (BMI) (18).

The assessment of body composition is complicated by the fact that various parameters are used to express (loss) of MM or LBM. For instance, LBM, FFM, and MM are not equivalent, although they are often used as interchangeable surrogates. FFM, as the name suggests, is the total body mass except for the body fat, and it includes LBM and bone mineral tissue. The LBM, in turn, is composed of the total body water, appendicular skeletal muscle mass (ASMM), and the fat-free mass of organs. Since different techniques measure different compartments, the identification of the body compartment of interest, along with the availability of the method, must precede the choice of the method of assessment. As an example, some available techniques, such as bioelectrical impedance analysis (BIA), assess body composition by dividing the body into two compartments (2-C), the FFM, which conceptually includes all non-fat tissue and the fat mass (FM) (19). While other methods, such as dual-energy X-ray absorptiometry (DXA) and one application of bioelectrical impedance spectroscopy (BIS), divides the body into three compartments (3C). DXA assesses LBM, which includes total body protein and total body water (TBW), but excludes bone and fat mass (20, 21) (**Figure 1**). On the other hand, 3C-BIS assess a "normohydrated" LTM, which reflects a compartment that is separate from adipose tissue mass (ATM; fat mass and adipose water) and a virtual "overhydration" compartment, but that includes bone mineral tissue (8) (**Figure 1**), as will be discussed later in more detail.

These specific examples show that although all entities reflect comparable physiological dimensions, they are not interchangeable. FFM assessed by a 2-C model can be different from LTM assessed by a 3-C model (22). Thus, parameters obtained by a specific method cannot be used interchangeably with comparable parameters assessed by different methodologies. In addition, ideally, reference values should also be developed for specific techniques, devices, and populations. As this may not always be feasible, it is important to have these caveats in mind when assessing literature on body composition in patients on kidney replacement therapy (KRT).

BEDSIDE TECHNOLOGY FOR THE ASSESSMENT OF MM

For the assessment of MM or its proxies, various options are available. Computer-assisted tomography (CT) or MRI are considered gold standard methods but are impractical to be used on a routine basis (13, 23). DXA is generally considered a reference method to estimate LBM as well as ASMM in guidelines (13) but may be difficult to perform frequently in clinical practice. Furthermore, because DXA assumes a hydration ratio with LBM of 0.73 (24), results can be influenced by severe fluid overload (25). Still, DXA, when routinely available, provides important information on changes in body composition on HD and might also serve as a calibration for bedside methods.

Various methods are available to assess MM or LBM in patients which can be used on a routine basis in patients on KRT. These can be conceptually divided into methods that indirectly estimate body composition (such as bioimpedance or anthropometry), biochemical methods (based on creatinine kinetics), and methods that measure muscle dimensions at an anatomical level [MRI, CT, or ultrasound (US)]. Anthropometry is a time-honored method that is also included in the original diagnostic criteria for PEW (4). When performed by a skilled

TABLE 1 | Categories of assessment for the diagnosis of different syndromes related to the nutritional and functional status of patients.

Criteria	Malnutrition ESPEN	Malnutrition GLIM	PEW	Cachexia	Sarcopenia	Frailty
Weight loss/BMI	+	+	+	+		+
Muscle mass/FFM/LTM	+	+	+	+	+	
Muscle strength					+	+
Functional performance					+	+
Fatigue/exhaustion						+
Biochemical markers			+	+		
Etiology		+				

BMI, body mass index; FFM, fat free mass; LTM, lean tissue mass; PEW, protein energy wasting.

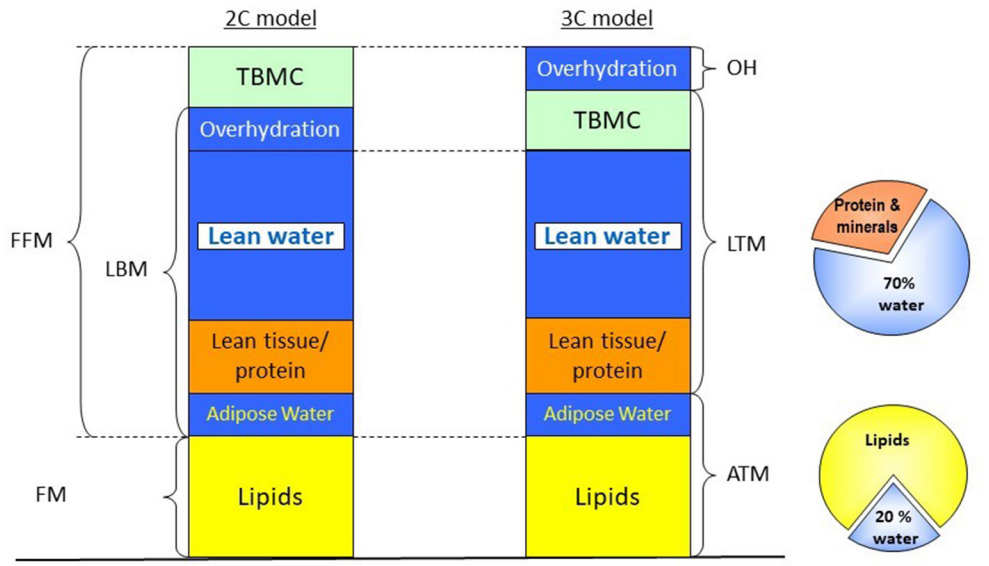

FIGURE 1 | Different body compartment models based on BIA, BIS, and DXA. In the BIA approach, a two-compartment model is applied, dividing the body in FFM, which includes bone mineral tissue, total body water, skeletal muscle and visceral proteins, and FM. Both DXA and three-compartment BIS apply a three-compartment approach; however, in the case of DXA, bone mineral density is removed from the FFM, and LBM is measured instead, while in the case of BIS, a virtual "overhydration" compartment is calculated as the difference between measured and expected ECW, providing information on ATM and a normohydrate LTM, which includes bone mineral tissue. ATM, adipose tissue mass; BIA, bioelectrical impedance analysis; BIS, bioelectrical impedance spectroscopy; DXA, dual-energy X-ray absorptiometry; FFM, fat-free mass; FM, fat mass; LBM, lean body mass; LTM, lean tissue mass; OH, overhydration; TBMC, total body mineral content. Modified from Broers et al. (22) with permission.

investigator it was able to predict a reduction in MM with an accuracy comparable with instrumental methods (16). However, the emphasis of the present article is on biochemical and technological tools in the assessment of body composition.

Bioelectrical Impedance

Although the theoretical backgrounds of BIA are complex and discussed in excellent reviews (26, 27), in general, this method measures the opposition (impedance) of the body or a body segment to an alternating current. The impedance (Z) is a composite of the resistance to this flow, which is related to TBW, and reactance (Xc) is related to the capacitance of the cellular membrane. With the single-frequency (SF) approach, FFM and ASMM are estimated using population-derived regression equations, including Z or R, measured at 50 kHz as the resistance index H^2/R50 along with anthropometric parameters, sex, and age (27). With SF-BIA, also ASMM can be estimated using regression equations (27, 28).

The multifrequency (MF) approach delivers different frequencies that vary from 5 to 1,000 kHz, and depending on the method it can use only several frequencies or, in the case of BIS, broadband of frequencies within this range. The lower the frequency, the more the difficulty with which it has to pass across the cell, passing only at the extracellular water (ECW) at frequencies < than 1 kHz and not through the ICW, with higher frequencies it passes through both, with TBW being measured at frequencies > 5,000 kHz. For technical reasons, measurements at very low and very high frequencies are not possible; however, with BIS, the resistance at zero (Ro) and infinity (R ∞) are extrapolated by applying a Cole-Cole plot to predict ECW and TBW (27). In classic 2C-models of SF-BIA and MF-BIA, FFM is subsequently calculated from TBW, assuming fractional

hydration of 0.73 (29). A drawback of this method, which divides the body into two compartments, is that the excess of ECW due to fluid overload is added to the TBW which can subsequently result in an overestimation of FFM (25) (**Figure 1**). In the case of BIS, Moissl et al. developed a model for the assessment of ECW, ICW, and TBW using Hanai mixture theory adjusted for BMI, which showed good agreement with dilution methods (30). Chamney et al. further developed the so-called 3C-model, which assumes fixed hydration of LTM and ATM, and divides the body in normohydrate LTM and ATM, and a virtual "overhydration" (OH) compartment (31).

With regard to the estimation of body composition, a definite superiority of either approach has not yet been proven. Donadio et al. found a slightly lower prediction error for FFM with SF-BIA as compared with an MF-BIA using a two-compartment approach, with a highly significant correlation of both methods with DXA (32). Another study observed a stronger relation between FFM estimated by MF-BIA and creatinine kinetics as compared with SF-BIA (33). Raimann et al. found a slightly improved estimation of ICW with the SF method, and conversely, improved estimation of ECW with BIS. With regard to the detection of changes in ECW, MF-BIA was found to have a higher precision (34, 35). On the other hand, ASMM predicted by the Sergi equation using SF-BIA showed high accuracy in predicting sarcopenia with DXA as the reference method (16); however, this equation with the form: ASMM (kg) $= -3.964 + (0.227^{*}$[height (cm)]^2/R]) + (0.095*weight) + (1.384*sex) + (0.064*Xc), was primarily validated in an elderly Caucasian population (36).

With the 3C BIS method, estimation of body composition is based on a theoretical approach without the use of population-specific regression equations. Lean tissue index (LTI), which corresponds to LTM, divided by height^2, below the 10th percentile of a healthy age-matched reference population was independently related to outcome in most, but not all studies (8, 15, 37, 38). Still, in a meta-analysis including over 15,000 patients, a low LTI was associated with increased mortality [Hazard ratio 1.53 (95% CI: 1.41–1.64)] (39). Especially, the combination of a low LTI and fat tissue index (FTI, the height^2-normalized ATM) appears to be associated with increased mortality risk (15).

However, in several studies, despite reasonable agreement at a population level, relatively wide limits of agreement were observed between body compartments assessed by 3C-BIS and reference techniques, such as DXA (40, 41). To some degree, these differences may be explained by the fact that even the reference method is not free of errors. Indeed, the excess ECW with overhydration is added to the LBM compartment with DXA, but not with the 3C-BIS approach (8). Also, it should be taken into account that ATM assessed by 3C-BIS includes intra adipose water, unlike FM measured by DXA. Using ASMM measured by DXA as the reference method, LTM measured by whole-body BIS was able to predict sarcopenia with acceptable accuracy (mean AUC 0.79 for females and 0.77 for males) (16); however, it should be noted that in the current EWGSOP2 guidelines, cut-off values based on the 3C-BIS model were not yet included in the definition, while the Sergi equation based on SF BIA was advocated for standardization (13). However, in the case of tissue edema, these estimations may be less reliable in patients on HD. To standardize measurements and avoid this kind of problem, the recent KDOQI guidelines on nutrition in CKD recommends that BIA/BIS should be performed at least 30 min after the HD session to allow for the distribution of body fluids (42). Still, in the case of 3C-BIS, measurements of ATM and normohydrated LTM were slightly (0.77 and 0.40 kg, respectively) affected by the timing of measurements (43), whereas predialytic fluid status was more consistently related to the outcome as compared with postdialytic measurements (44).

An alternative approach is the construction of a vector plotting R and Xc at 50 kHz within tolerance ellipses of a healthy population. The advantage of this method is that results are displayed without the need for underlying theoretical assumptions or population-based equations (28). A potential disadvantage is that the direct translation of the findings into constructs such as sarcopenia, fluid overload, and PEW may be more difficult as compared with a numerical approach.

To summarize, whereas various BIA approaches can be used to assess body composition in dialysis patients, it must be kept in mind that estimations are dependent on population-specific regression equations or theoretical assumptions regarding the conversion from bioelectrical signals to estimations of body water compartments. Measurements obtained with a specific device or method can therefore not be used interchangeably (45), even with regard to raw parameters such as Z, Xc, and R (46). It is important to acknowledge that as long as a device is correctly calibrated, the magnitude of the differences are small and generally within the precision of the specifications of the manufacturer. Whereas, a definite superiority of a specific BIA methodology for estimations of body composition has not been proven, in our view, the 3-C model holds the advantage that it also provides a separate estimation of fluid status in a single measurement, whereas it has shown high-construct validity in predicting outcome in large datasets.

Biochemical Methods: The Creatinine Index

Serum creatinine is a breakdown product of creatine phosphate in muscle tissue that was found to be strongly related to LBM assessed by DXA in patients on HD (47). Serum creatinine is inversely related to mortality in patients on renal replacement therapy (48); however, serum creatinine in patients on HD is also dependent on dialysis adequacy. Therefore, the concept of creatinine index (CI) was developed (49). CI was found to be an independent predictor of outcome in patients with HD (50). However, as creatinine kinetics may be complicated to use in routine clinical practice, a simplified form [simplified creatinine index (SCI)] was developed, which was also found to be related to the outcome (51). SCI (mg/kg/d) is calculated according to the formula 16.21 + 1.12* [1 if male; 0 if female]−0.06*age (years) −0.08*spKt/V urea + 0.009*predialytic serum creatinine (μmol/l). Also, LTI derived from SCI was strongly related to LTI assessed by BIS, although the mean BIS-derived value was 4.7 kg lower than the SCI-estimated value (51). SCI is easy to apply in clinical practice as only routinely gathered data that are already present in electronic health records (EHR) are needed,

with the advantage that longitudinal trends can be tracked easily. Indeed, SCI declined 6 months before death, potentially serving as an early warning sign (51). However, a potential pitfall in the follow-up of the SCI is changes in residual renal function, which may independently affect serum creatinine values apart from muscle mass, as well as changes in dietary intake (42). Serum creatinine is also a parameter included in the nutritional component score (NCS), an aggregate score that also consists of routinely captured parameters interdialytic weight gain, serum phosphate, serum albumin, and normalized protein catabolic rate (nPCR). The use of this score, which was shown to decline 1–2 months before hospitalization and also up to 6 months before death (52, 53), allows for the interpretation of changes in parameters like interdialytic weight gain (IDWG) and serum phosphate, which have a bidirectional relationship with the outcome (54). Whereas, a decrease in these parameters is usually regarded as a positive sign given their detrimental effect on the cardiovascular status of the patient, a sharp decline in IDWG and serum phosphate can also be a sign of impending malnutrition and adverse outcomes when accompanied by a decrease in the other nutritional parameters (52).

To Summarize, following trends in biochemical indices derived from EHR can aid in the early detection of changes in nutritional state and MM, whereas changes in serum creatinine or SCI cannot replace validated questionnaires to establish the risk for sarcopenia (55), they can aid in case finding given the fact that they can be performed on a frequent and routine basis with the potential for automated processing of the findings.

Muscle Ultrasound

Recently, regional muscle US has been applied in patients with kidney disease for the assessment and monitoring of skeletal muscle. Its major advantages, compared to other imaging techniques, are represented by lower cost, portability, lack of radiation exposure, and the possibility to be applied by non-specialized staff (56–58). In comparison to other bedside techniques, such as anthropometry, US allows real-time visualization of the target structure, allowing for the assessment of muscle size (thickness and area) and/or quality, through echogenicity, which provides information about the presence of inflammation, fibrosis, and adipose infiltration (59). Its portability is of particular interest in the CKD research setting and clinical practice since patients can be evaluated during HD session or outpatient visits.

Quadriceps muscle US has been studied extensively in patients with renal disease. In the available research, two muscles were most frequently studied, the quadriceps rectus femoris (RF) and vastus intermedius (VI), in two different points, the midpoint, and at the border of the lower third and upper two-thirds between the anterior superior iliac spine and the upper pole of the patella (**Figure 2**) (56, 57, 60–62). Abundant contact gel to avoid any pressure is needed to prevent muscle deformation. Regarding the accuracy and reproducibility of the method, its reliability has been tested in critically ill patients with acute kidney injury (AKI), showing excellent intraclass correlation coefficients (ICC) for inter- and intra-operator comparisons, as well as for measurements performed before and after HD (56).

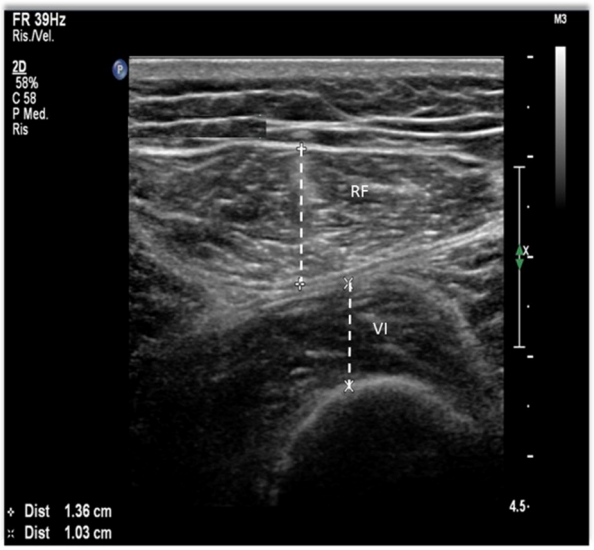

FIGURE 2 | Quadriceps muscle ultrasound (US) methodology. The points of interest correspond to the midpoint and the lower third between the anterior superior iliac spine (ASIS) and the upper pole of the patella. Using a B-mode ultrasound with a linear transducer, we obtain the image on the right. Rectus femoris (RF) and vastus intermedius (VI) thickness, a measure on the inner edge of the muscle.

In the same clinical setting, US assessment of quadriceps muscle has also been validated against CT (60), showing small and non-significant differential and proportional bias in comparison with CT (60). Also in patients with AKI, US was successfully used to monitor the quadriceps muscle in the first 5 days of stay in the intensive care unit, being able to identify early muscle loss (63). In non-acutely ill patients, US was performed in patients on HD before and after the dialysis session to assess whether the presence of fluid overload or the rapid fluid shifts caused by the treatment could influence measurements (57). No differences were found between measurements performed before and after dialysis, and the correlation between measurements was very high, ranging from 0.91 to 0.95 (57), showing that muscle US is not influenced by fluid overload. Also in the outpatient setting, the assessment of muscle cross-sectional area (CSA) was validated using CT in patients with CKD and not on HD (61). In another study, RF-CSA was assessed before and after 12 weeks of resistance exercise in patients with CKD not on HD, showing a high correlation with MRI at baseline and follow-up, and moderate positive association observed between changes in RF-CSA by US and quadriceps volume by MRI following exercise training (64).

More recently, studies investigating the role of quadriceps muscle US in identifying patients with PEW or sarcopenia have been published. Sabatino et al. (57) used the PEW cutoffs for BMI and albumin to stratify patients on chronic HD in two groups and found that in the multivariable analysis patients with lower BMI had lower muscle thickness, whereas no difference was found between patients with serum albumin

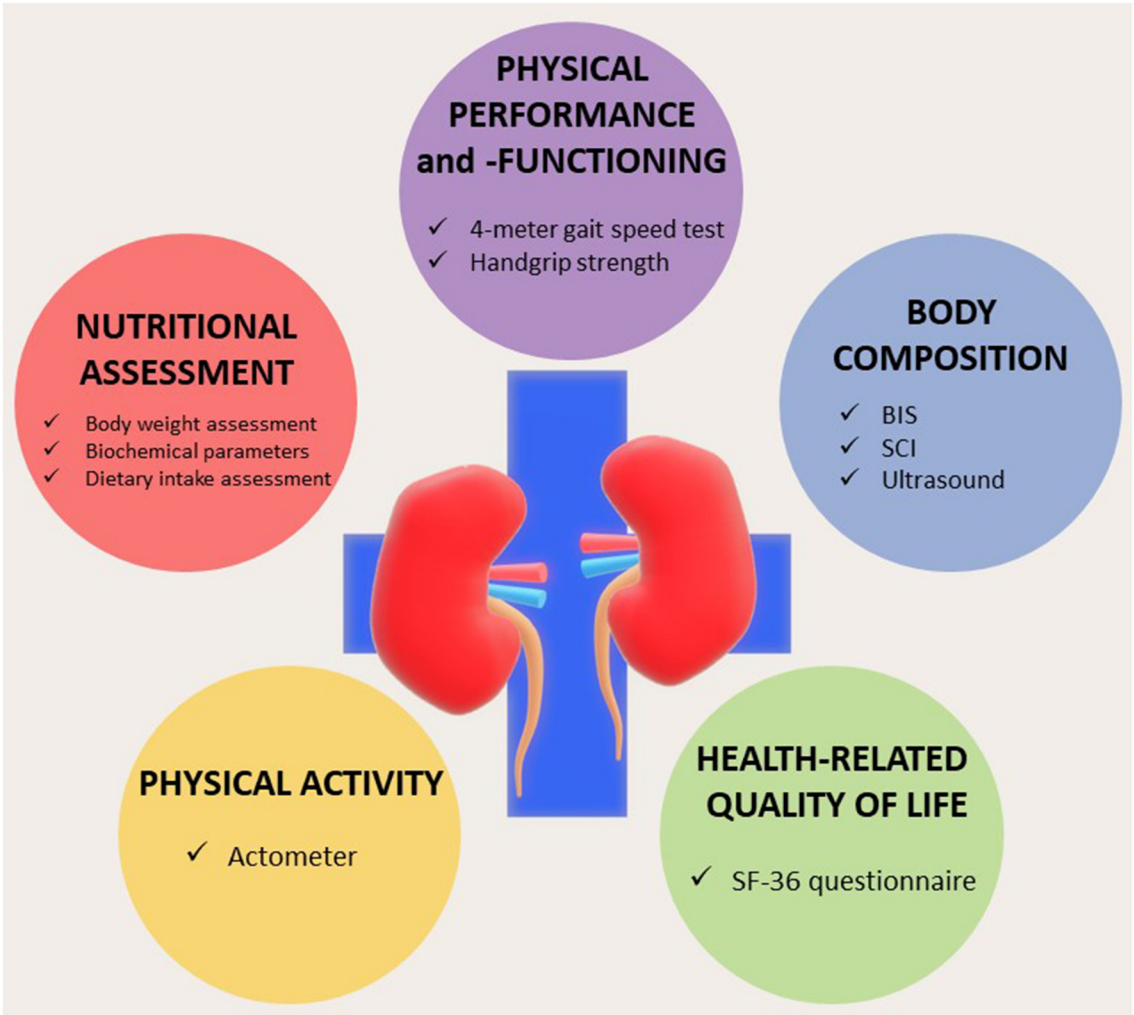

FIGURE 3 | Dashboard summarizing the integrated nutritional assessment of patients with chronic kidney disease (CKD)/end-stage kidney disease (ESKD). BIS, bioelectrical impedance spectroscopy; SCI, simplified creatinine index. Modified from Broers et al. (8) under Creative Commons.

below or above the reference value (57). A similar analysis was performed using the malnutrition inflammation score (MIS), an internationally recognized tool to assess malnutrition and predict outcomes in patients on HD, and found that patients with worse scores ($\geq$ 6) had lower RF and VI thickness (57). In another study, quadriceps CSA cut-offs have been derived using receiver-operation characteristic curves based on the presence or absence of PEW in a Malaysian population (62). In that study, patients diagnosed with PEW had significantly lower RF and VI thickness and RF CSA in comparison with well-nourished patients, and the area under the curve (AUC) for RF CSA was high (men = 0.74, 95% CI: 0.66–0.82 and women = 0.82, 95% CI: 0.73–0.91, both $p < 0.001$). In addition, the correlation between US and LTI by BIS ranged from moderate to high (0.28–0.52) depending on the measurement site, with a higher correlation for RF thickness and CSA in comparison to VI.

Despite such encouraging results, more work is needed before assuming muscle US as a reference method for the diagnosis of sarcopenia. Studies defining reference values derived from healthy subjects from populations with different ethnic backgrounds should be performed to allow the early identification of patients with low MM. However, considering its validity, reliability, and sensitivity in detecting changes in skeletal muscle, its use as a tool for the monitoring of the regional muscularity of a patient could be recommended.

The Role of Estimation of MM in the Integrated Functional Assessment of Patients on KRT

Assessment of MM or its derivatives achieves its full potential in combination with other parameters. As shown in **Table 1**, with a relatively limited battery of measurements, various clinical

syndromes such as PEW, sarcopenia, and frailty can be easily diagnosed. For the diagnosis of sarcopenia, it should be combined with an assessment of muscle strength, for instance, handgrip strength (HGS), and in case of a positive diagnosis, with a measure of physical function such as the 4 m gait speed test (13). HGS and the gait speed tests are easy to perform even in a routine clinical setting. Muscle quantity and strength, though interrelated (22), are not equivalent. Muscle strength appears to be a more powerful predictor for the outcome as compared to MM (65). Furthermore, following renal transplantation, we observed a profound increase in HGS without a significant increase in LTM (66).

Which bedside test should be used for the assessment of MM/FFM/LBM depends on local preferences and availability. In the case of 3C-BIS, information on body composition as well as the fluid overload is combined in a single measurement. Muscle ultrasound may be superior to BIS in the diagnosis of skeletal muscle depletion, but reference values need to be defined in larger populations, whereas a trained investigator is necessary. A possibility is to use SCI or BIS for case finding, followed by the US for a more precise estimate of MM depletion.

A diagnosis of PEW or sarcopenia should be combined with an estimate of potentially modifiable factors such as dietary intake and physical activity, for example, by performing actimetry regularly. Also, impaired physical activity, nutritional status, and physical performance should be interpreted given its relation with a low-health-related QoL (7, 67), which is especially important as these factors are often amenable to therapeutic intervention. Lastly, complications that are frequently associated with loss of MM, such as inflammation and fluid overload, should be assessed. A proposal for an integrated assessment, preferably summarized in an easily interpretable dashboard, is illustrated in **Figure 3**. Such a dashboard could be the basis for a personalized approach. For instance, a patient with a low LTI or MM and reduced muscle strength with adequate nutritional intake and absence of inflammation (a "sarcopenic" phenotype), but with low physical activity may primarily benefit from both aerobic as well as resistance training (68). In addition, activity trackers or smartphone applications may provide the patient with feedback on his/her physical activity patterns.

On the other side of the spectrum, a patient with a "cachectic" phenotype, with inflammation, and reduced protein intake, will primarily benefit from a search into the cause of inflammation and targeted nutritional intervention. Participation in an active rehabilitation program will be much more difficult for this patient, although interventions such as neuromuscular electrical stimulation may be beneficial (69). In addition, the risk of fluid overload may be increased in this patient, which may only be resolved by an increase in dialysis time due to the altered distribution between the interstitial and intravascular compartment (70).

In conclusion, a reduction in MM is an important determinant of various clinical syndromes in patients on dialysis, which are related to increased morbidity and mortality but also potentially amenable to therapeutic intervention. Whereas, different bedside methods can be used to assess MM or its proxies in patients on dialysis, it is important to maintain a critical view of their relative advantages and potential pitfalls. Assessment of MM should be part of a multidimensional approach and a personalized treatment strategy.

AUTHOR CONTRIBUTIONS

AS and JK conceived the paper. NB, FS, MH, and EF contributed to and reviewed the paper. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Moreau-Gaudry X, Jean G, Genet L, Lataillade D, Legrand E, Kuentz F, et al. A simple protein-energy wasting score predicts survival in maintenance hemodialysis patients. *J Ren Nutr.* (2014) 24:395–400. doi: 10.1053/j.jrn.2014.06.008
2. Sabatino A, Piotti G, Cosola C, Gandolfini I, Kooman JP, Fiaccadori E. Dietary protein and nutritional supplements in conventional hemodialysis. *Semin Dial.* (2018) 34:583–91. doi: 10.1111/sdi.12730
3. Sabatino A, Cuppari L, Stenvinkel P, Lindholm B, Avesani CM. Sarcopenia in chronic kidney disease: what have we learned so far? *J Nephrol.* (2020). doi: 10.1007/s40620-020-00840-y. [Epub ahead of print].
4. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* (2008) 73:391–8. doi: 10.1038/sj.ki.5002585
5. Noce A, Marrone G, Ottaviani E, Guerriero C, Di Daniele F, Pietroboni Zaitseva A, et al. Uremic sarcopenia and its possible nutritional approach. *Nutrients.* (2021) 13:147. doi: 10.3390/nu13010147
6. Kim JC, Kalantar-Zadeh K, Kopple JD. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J Am Soc Nephrol.* (2013) 24:337–51. doi: 10.1681/ASN.2012010047
7. Gadaen RJR, Kooman JP, Cornelis T, van der Sande FM, Winkens BJ, Broers NJH. The effects of chronic dialysis on physical status, quality of life, and arterial stiffness: a longitudinal study in prevalent dialysis patients. *Nephron.* (2021) 145:44–54. doi: 10.1159/000510624
8. Broers NJH, Canaud B, Dekker MJE, van der Sande FM, Stuard S, Wabel P, et al. Three compartment bioimpedance spectroscopy in the nutritional assessment and the outcome of patients with advanced or end stage kidney disease: what have we learned so far? *Hemodial Int.* (2020) 24:148–61. doi: 10.1111/hdi.12812
9. Kooman JP, Kotanko P, Schols AM, Shiels PG, Stenvinkel P. Chronic kidney disease and premature ageing. *Nat Rev Nephrol.* (2014) 10:732–42. doi: 10.1038/nrneph.2014.185
10. Gracia-Iguacel C, Gonzalez-Parra E, Mahillo I, Ortiz A. Low intracellular water, overhydration, and mortality in hemodialysis patients. *J Clin Med.* (2020) 9:3616. doi: 10.3390/jcm9113616
11. Gingrich A, Volkert D, Kiesswetter E, Thomanek M, Bach S, Sieber CC, et al. Prevalence and overlap of sarcopenia, frailty, cachexia and malnutrition in older medical inpatients. *BMC Geriatr.* (2019) 19:120. doi: 10.1186/s12877-019-1115-1
12. McKeaveney C, Slee A, Adamson G, Davenport A, Farrington K, Fouque D, et al. Using a generic definition of cachexia in patients with kidney disease receiving haemodialysis: a longitudinal (pilot) study. *Nephrol Dial Transplant.* (2020). doi: 10.1093/ndt/gfaa174. [Epub ahead of print].
13. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. the extended Group for: Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* (2019) 48:16–31. doi: 10.1093/ageing/afy169

14. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options - a mini-review. *Gerontology.* (2014) 60:294–305. doi: 10.1159/000356760
15. Marcelli D, Usvyat LA, Kotanko P, Bayh I, Canaud B, Etter M, et al. Body composition and survival in dialysis patients: results from an international cohort study. *Clin J Am Soc Nephrol.* (2015) 10:1192–200. doi: 10.2215/CJN.08550814
16. Bellafronte NT, Sizoto GR, Vega-Piris L, Chiarello PG, Cuadrado GB. Bedside measures for diagnosis of low muscle mass, sarcopenia, obesity, and sarcopenic obesity in patients with chronic kidney disease under non-dialysis-dependent, dialysis dependent and kidney transplant therapy. *PLoS ONE.* (2020) 15:e0242671 doi: 10.1371/journal.pone.0242671
17. Malhotra R, Deger SM, Salat H, Bian A, Stewart TG, Booker C, et al. Sarcopenic obesity definitions by body composition and mortality in the hemodialysis patients. *J Ren Nutr.* (2017) 27:84–90. doi: 10.1053/j.jrn.2016.09.010
18. Marcelli D, Brand K, Ponce P, Milkowski A, Marelli C, Ok E, et al. Longitudinal changes in body composition in patients after initiation of hemodialysis therapy: results from an international cohort. *J Ren Nutr.* (2016) 26:72–80. doi: 10.1053/j.jrn.2015.10.001
19. Franssen FM, Rutten EP, Groenen MT, Vanfleteren LE, Wouters EF, Spruit MA. New reference values for body composition by bioelectrical impedance analysis in the general population: results from the UK Biobank. *J Am Med Dir Assoc.* (2014) 15:448 e1-6. doi: 10.1016/j.jamda.2014.03.012
20. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. *J Parenter Enteral Nutr.* (2014) 38:940–53. doi: 10.1177/0148607114550189
21. Mundi MS, Patel JJ, Martindale R. Body composition technology: implications for the ICU. *Nutr Clin Pract.* (2019) 34:48–58. doi: 10.1002/ncp.10230
22. Broers NJ, Martens RJ, Cornelis T, Diederen NM, Wabel P, van der Sande FM, et al. Body composition in dialysis patients: a functional assessment of bioimpedance using different prediction models. *J Ren Nutr.* (2015) 25:121–8. doi: 10.1053/j.jrn.2014.08.007
23. Sabatino A, D'Alessandro C, Regolisti G, di Mario F, Guglielmi G, Bazzocchi A, et al. Muscle mass assessment in renal disease: the role of imaging techniques. *Quant Imaging Med Surg.* (2020) 10:1672–86. doi: 10.21037/qims.2020.03.05
24. Salamone LM, Fuerst T, Visser M, Kern M, Lang T, Dockrell M, et al. Measurement of fat mass using DEXA: a validation study in elderly adults. *J Appl Physiol.* (2000) 89:345–52. doi: 10.1152/jappl.2000.89.1.345
25. Konings CJ, Kooman JP, Schonck M, van Kreel B, Heidendal GA, Cheriex EC, et al. Influence of fluid status on techniques used to assess body composition in peritoneal dialysis patients. *Perit Dial Int.* (2003) 23:184–90. doi: 10.1177/089686080302300215
26. Kotanko P, Levin NW, Zhu F. Current state of bioimpedance technologies in dialysis. *Nephrol Dial Transplant.* (2008) 23:808–12. doi: 10.1093/ndt/gfm889
27. Khalil SF, Mohktar MS, Ibrahim F. The theory and fundamentals of bioimpedance analysis in clinical status monitoring and diagnosis of diseases. *Sensors.* (2014) 14:10895–928. doi: 10.3390/s140610895
28. Lukaski HC. Evolution of bioimpedance: a circuitous journey from estimation of physiological function to assessment of body composition and a return to clinical research. *Eur J Clin Nutr.* (2013) 67(Suppl. 1):S2–9 doi: 10.1038/ejcn.2012.149
29. Molfino A, Don BR, Kaysen GA. Comparison of bioimpedance and dual-energy x-ray absorptiometry for measurement of fat mass in hemodialysis patients. *Nephron Clin Pract.* (2012) 122:127–33 doi: 10.1159/000350817
30. Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, et al. Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas.* (2006) 27:921–33. doi: 10.1088/0967-3334/27/9/012
31. Chamney PW, Wabel P, Moissl UM, Muller MJ, Bosy-Westphal A, Korth O, et al. A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr.* (2007) 85:80–9. doi: 10.1093/ajcn/85.1.80
32. Donadio C, Halim AB, Caprio F, Grassi G, Khedr B, Mazzantini M. Single- and multi-frequency bioelectrical impedance analyses to analyse body composition in maintenance haemodialysis patients: comparison with dual-energy x-ray absorptiometry. *Physiol Meas.* (2008) 29:S517–24 doi: 10.1088/0967-3334/29/6/S43
33. Donadio C, Consani C, Ardini M, Bernabini G, Caprio F, Grassi G, et al. Estimate of body water compartments and of body composition in maintenance hemodialysis patients: comparison of single and multifrequency bioimpedance analysis. *J Ren Nutr.* (2005) 15:332–44. doi: 10.1016/j.jrn.2005.04.001
34. Raimann JG, Abbas SR, Liu L, Zhu F, Larive B, Kotanko P, et al. Agreement of single- and multi-frequency bioimpedance measurements in hemodialysis patients: an ancillary study of the frequent hemodialysis network daily trial. *Nephron Clin Pract.* (2014) 128:115–26. doi: 10.1159/000366447
35. Raimann JG, Zhu F, Wang J, Thijssen S, Kuhlmann MK, Kotanko P, et al. Comparison of fluid volume estimates in chronic hemodialysis patients by bioimpedance, direct isotopic, dilution methods. *Kidney Int.* (2014) 85:898–908. doi: 10.1038/ki.2013.358
36. Sergi G, De Rui M, Veronese N, Bolzetta F, Berton L, Carraro S, et al. Assessing appendicular skeletal muscle mass with bioelectrical impedance analysis in free-living Caucasian older adults. *Clin Nutr.* (2015) 34:667–73. doi: 10.1016/j.clnu.2014.07.010
37. Dekker MJE, Konings C, Canaud B, van der Sande FM, Stuard S, Raimann JG, et al. Interactions between malnutrition, inflammation, and fluid overload and their associations with survival in prevalent hemodialysis patients. *J Ren Nutr.* (2018) 28:435–44. doi: 10.1053/j.jrn.2018.06.005
38. Wu B, Yan C, Zhang S, Ge Y, Xu X, Wang Y, et al. Comparative performance of body composition parameters in prediction of death in hospitalized patients on maintenance hemodialysis: a cohort study. *Sci Rep.* (2020) 10:10199. doi: 10.1038/s41598-020-67019-0
39. Hwang SD, Lee JH, Lee SW, Kim JK, Kim MJ, Song JH. Risk of overhydration and low lean tissue index as measured using a body composition monitor in patients on hemodialysis: a systemic review and meta-analysis. *Ren Fail.* (2018) 40:51–59. doi: 10.1080/0886022X.2017.1419963
40. Zhou Y, Hoglund P, Clyne N. Comparison of DEXA and bioimpedance for body composition measurements in nondialysis patients with CKD. *J Ren Nutr.* (2019) 29:33–8. doi: 10.1053/j.jrn.2018.05.003
41. Lim PS, Chen CH, Zhu F, Kotanko P, Jeng Y, Hu CY, et al. Validating body fat assessment by bioelectric impedance spectroscopy in Taiwanese hemodialysis patients. *J Ren Nutr.* (2017) 27:37–44. doi: 10.1053/j.jrn.2016.08.003
42. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis.* (2020) 76(3 Suppl. 1):S1–107. doi: 10.1053/j.ajkd.2020.05.006
43. Keane DF, Baxter P, Lindley E, Moissl U, Pavitt S, Rhodes L, et al. The body composition monitor: a flexible tool for routine fluid management across the haemodialysis population. *Biomed Phys Eng Exp.* (2017) 3:035017. doi: 10.1088/2057-1976/aa6f45
44. Dekker M, Konings C, Canaud B, Carioni P, Guinsburg A, Madero M, et al. Pre-dialysis fluid status, pre-dialysis systolic blood pressure and outcome in prevalent haemodialysis patients: results of an international cohort study on behalf of the MONDO initiative. *Nephrol Dial Transplant.* (2018) 33:2027–34. doi: 10.1093/ndt/gfy095
45. Sheean P, Gonzalez MC, Prado CM, McKeever L, Hall AM, Braunschweig CA. American society for parenteral and enteral nutrition clinical guidelines: the validity of body composition assessment in clinical populations. *J Parenter Enteral Nutr.* (2020) 44:12–43. doi: 10.1002/jpen.1669
46. Silva AM, Matias CN, Nunes CL, Santos DA, Marini E, Lukaski HC, et al. Lack of agreement of in vivo raw bioimpedance measurements obtained from two single and multi-frequency bioelectrical impedance devices. *Eur J Clin Nutr.* (2019) 73:1077–83. doi: 10.1038/s41430-018-0355-z
47. Patel SS, Molnar MZ, Tayek JA, Ix JH, Noori N, Benner D, et al. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. *J Cachexia Sarcopenia Muscle.* (2013) 4:19–29. doi: 10.1007/s13539-012-0079-1
48. Park J, Mehrotra R, Rhee CM, Molnar MZ, Lukowsky LR, Patel SS, et al. Serum creatinine level, a surrogate of muscle mass, predicts mortality in peritoneal dialysis patients. *Nephrol Dial Transplant.* (2013) 28:2146–55. doi: 10.1093/ndt/gft213
49. Canaud B, Granger Vallee A, Molinari N, Chenine L, Leray-Moragues H, Rodriguez A, et al. Creatinine index as a surrogate of lean body mass derived from urea Kt/V, pre-dialysis serum levels and anthropometric

characteristics of haemodialysis patients. *PLoS ONE.* (2014) 9:e93286 doi: 10.1371/journal.pone.0093286
50. Terrier N, Jaussent I, Dupuy AM, Morena M, Delcourt C, Chalabi L, et al. Creatinine index and transthyretin as additive predictors of mortality in haemodialysis patients. *Nephrol Dial Transplant.* (2008) 23:345–53. doi: 10.1093/ndt/gfm573
51. Canaud B, Ye X, Usvyat L, Kooman J, van der Sande F, Raimann J, et al. Clinical and predictive value of simplified creatinine index used as muscle mass surrogate in end-stage kidney disease haemodialysis patients-results from the international MONitoring Dialysis Outcome initiative. *Nephrol Dial Transplant.* (2020) 35:2161–71. doi: 10.1093/ndt/gfaa098
52. Ye X, Dekker MJE, Maddux FW, Kotanko P, Konings C, Raimann JG, et al. Dynamics of nutritional competence in the last year before death in a large cohort of US hemodialysis patients. *J Ren Nutr.* (2017) 27:412–20. doi: 10.1053/j.jrn.2017.06.006
53. Thijssen S, Wong MM, Usvyat LA, Xiao Q, Kotanko P, Maddux FW. Nutritional competence and resilience among hemodialysis patients in the setting of dialysis initiation and hospitalization. *Clin J Am Soc Nephrol.* (2015) 10:1593–601. doi: 10.2215/CJN.08430814
54. Ye X, Kooman JP, van der Sande FM, Raimann JG, Usvyat LA, Wang Y, et al. Relationship between serum phosphate levels and survival in chronic hemodialysis patients: interactions with age, malnutrition and inflammation. *Clin Kidney J.* (2021) 14:348–57. doi: 10.1093/ckj/sfz143
55. Beaudart C, McCloskey E, Bruyere O, Cesari M, Rolland Y, Rizzoli R, et al. Sarcopenia in daily practice: assessment and management. *BMC Geriatr.* (2016) 16:170. doi: 10.1186/s12877-016-0349-4
56. Sabatino A, Regolisti G, Bozzoli L, Fani F, Antoniotti R, Maggiore U, et al. Reliability of bedside ultrasound for measurement of quadriceps muscle thickness in critically ill patients with acute kidney injury. *Clin Nutr.* (2017) 36:1710–15. doi: 10.1016/j.clnu.2016.09.029
57. Sabatino A, Regolisti G, Delsante M, Di Motta T, Cantarelli C, Pioli S, et al. Noninvasive evaluation of muscle mass by ultrasonography of quadriceps femoris muscle in end-stage renal disease patients on hemodialysis. *Clin Nutr.* (2019) 38:1232–9. doi: 10.1016/j.clnu.2018.05.004
58. Connolly B, MacBean V, Crowley C, Lunt A, Moxham J, Rafferty GF, et al. Ultrasound for the assessment of peripheral skeletal muscle architecture in critical illness: a systematic review. *Crit Care Med.* (2015) 43:897–905. doi: 10.1097/CCM.0000000000000821
59. Ticinesi A, Meschi T, Narici MV, Lauretani F, Maggio M. Muscle ultrasound and sarcopenia in older individuals: a clinical perspective. *J Am Med Dir Assoc.* (2017) 18:290–300. doi: 10.1016/j.jamda.2016.11.013
60. Sabatino A, di Mario F, Ciuni A, Palumbo A, Peyronel F, Maggiore U, et al. Validation by CT scan of quadriceps muscle ultrasound in acute kidney injury. *J Nephrol.* (2020) 33:109–17. doi: 10.1007/s40620-019-00659-2
61. Souza VA, Oliveira D, Cupolilo EN, Miranda CS, Colugnati FAB, Mansur HN, et al. Rectus femoris muscle mass evaluation by ultrasound: facilitating sarcopenia diagnosis in pre-dialysis chronic kidney disease stages. *Clinics.* (2018) 73:e392. doi: 10.6061/clinics/2018/e392
62. Sahathevan S, Khor B, Singh B, Sabatino A, Fiaccadori E, Daud Z, et al. Association of ultrasound-derived metrics of the quadriceps muscle with protein energy wasting in hemodialysis patients: a multicenter cross-sectional study. *Nutrients.* (2020) 12:3597. doi: 10.3390/nu12113597
63. Sabatino A, Maggiore U, Regolisti G, Rossi GM, Di Mario F, Gentile M, et al. Ultrasound for non-invasive assessment and monitoring of quadriceps muscle thickness in critically ill patients with acute kidney injury. *Front Nutr.* (2021) 8:622823. doi: 10.3389/fnut.2021.622823
64. Gould D, Watson E, Wilkinson T, Wormleighton J, Xenophontos S, Viana J, et al. Ultrasound assessment of muscle mass in response to exercise training in chronic kidney disease: a comparison with MRI. *J Cachexia Sarcopenia Muscle.* (2019) 10. doi: 10.1002/jcsm.12429
65. Isoyama N, Qureshi AR, Avesani CM, Lindholm B, Barany P, Heimburger O, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. *Clin J Am Soc Nephrol.* (2014) 9:1720–8. doi: 10.2215/CJN.10261013
66. Broers NJH, Fung TY, Kooman JP, Christiaans MHL. Living-donor transplantation leads to a major improvement in physical functioning: an observational study on the impact on potential donors and their recipients. *BMC Nephrol.* (2019) 20:109. doi: 10.1186/s12882-019-1299-9
67. Broers NJ, Usvyat LA, Kooman JP, van der Sande FM, Lacson E Jr, Kotanko P, et al. Quality of life in dialysis patients: a retrospective cohort study. *Nephron.* (2015) 130:105–12. doi: 10.1159/000430814
68. Huang M, Lv A, Wang J, Xu N, Ma G, Zhai Z, et al. Exercise training and outcomes in hemodialysis patients: systematic review and meta-analysis. *Am J Nephrol.* (2019) 50:240–54. doi: 10.1159/000502447
69. Dirks ML, Hansen D, Van Assche A, Dendale P, Van Loon JL. Neuromuscular electrical stimulation prevents muscle wasting in critically ill comatose patients. *Clin Sci.* (2015) 128:357–65. doi: 10.1042/CS20140447
70. John B, Tan BK, Dainty S, Spanel P, Smith D, Davies SJ. Plasma volume, albumin, and fluid status in peritoneal dialysis patients. *Clin J Am Soc Nephrol.* (2010) 5:1463–70. doi: 10.2215/CJN.09411209

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Nutrition

ORIGINAL RESEARCH
published: 17 September 2021
doi: 10.3389/fnut.2021.721941

Malnutrition and Sarcopenia Combined Increases the Risk for Mortality in Older Adults on Hemodialysis

Catarina Macedo[1], *Teresa F. Amaral*[1], *Juliana Rodrigues*[2], *Fernanda Santin*[2] *and Carla Maria Avesani*[2,3]*

[1] *Faculty of Nutrition and Food Science, University of Porto, Porto, Portugal,* [2] *Graduation Program in Food, Nutrition and Health, Nutrition Institute, Rio de Janeiro State University, Rio de Janeiro, Brazil,* [3] *Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden*

Aim: Sarcopenia and malnutrition are highly prevalent in older adults undergoing hemodialysis (HD) and are associated with negative outcomes. This study aimed to evaluate the role of sarcopenia and malnutrition combined on the nutritional markers, quality of life, and survival in a cohort of older adults on chronic HD.

Methods: This was an observational, longitudinal, and multicenter study including 170 patients on HD aged >60 years. Nutritional status was assessed by 7-point-subjective global assessment (7p-SGA), body composition (anthropometry and bioelectrical impedance), and appendicular skeletal muscle mass (Baumgartner's prediction equation). Quality of life was assessed by KDQoL-SF. The cutoffs for low muscle mass and low muscle strength established by the 2019 European Working group on sarcopenia for Older People (EWGSOP) were used for the diagnosis of sarcopenia. Individuals with a 7p-SGA score ≤5 were considered malnourished, individuals with low strength or low muscle mass were pre-sarcopenic, and those with low muscle mass and low muscle strength combined as sarcopenic. The sample was divided into four groups: sarcopenia and malnutrition; sarcopenia and no-malnutrition; no-sarcopenia with malnutrition; and no-sarcopenia and no-malnutrition. Follow-up for survival lasted 23.5 (12.2; 34.4) months.

Results: Pre-sarcopenia, sarcopenia, and malnutrition were present in 35.3, 14.1, and 58.8% of the patients, respectively. The frequency of malnutrition in the group of patients with sarcopenia was not significantly higher than in the patients without sarcopenia (66.7 vs. 51.2%; $p = 0.12$). When comparing groups according to the occurrence of sarcopenia and malnutrition, the sarcopenia and malnutrition group were older and presented significantly lower BMI, calf circumference, body fat, phase angle, body cell mass, and mid-arm muscle circumference. In the survival analysis, the group with sarcopenia and malnutrition showed a higher hazard ratio 2.99 (95% CI: 1.23: 7.25) for mortality when compared to a group with no-sarcopenia and no-malnutrition.

OPEN ACCESS

Edited by:
Nada Rotovnik Kozjek, Institute of Oncology Ljubljana, Slovenia

Reviewed by:
Neha Bakshi, University of Delhi, India
Maria Montserrat Diaz Pedrosa, State University of Maringá, Brazil

***Correspondence:**
Carla Maria Avesani
carla.avesani@ki.se

Specialty section:
This article was submitted to Clinical Nutrition, a section of the journal Frontiers in Nutrition

Received: *07 June 2021*
Accepted: *20 August 2021*
Published: *17 September 2021*

Citation:
Macedo C, Amaral TF, Rodrigues J, Santin F and Avesani CM (2021) Malnutrition and Sarcopenia Combined Increases the Risk for Mortality in Older Adults on Hemodialysis. Front. Nutr. 8:721941. doi: 10.3389/fnut.2021.721941

Conclusion: Older adults on HD with sarcopenia and malnutrition combined showed worse nutritional parameters, quality of life, and higher mortality risk. In addition, malnutrition can be present even in patients without sarcopenia. These findings highlight the importance of complete nutritional assessment in patients on dialysis.

Keywords: chronic kidney disease, hemodialysis, malnutrition, older adults, mortality

INTRODUCTION

Chronic kidney disease (CKD) has been recognized as one of the main and most prevalent public health problems worldwide. In fact, in 2017 it was estimated that 1.2 million of people died from CKD with an increase of 41% in the global mortality rate between 1990 and 2017 (1). The global prevalence of CKD is of 9.1% (1), which is similar to the CKD prevalence reported of 8.9% in Brazil in 2015 (2). The main factors justifying this increase in CKD are related to the population aging and to the increase in the prevalence of hypertension, diabetes mellitus, and obesity, which are knows as the main risk factors for the development of CKD (1).

The stages of CKD evolve as the glomerular filtration rate decreases and the clinical condition worsens, requiring renal replacement therapy in the later stages of the disease, with hemodialysis (HD) being one of the therapeutic options. If, on the one hand, HD enables patients with CKD to live, on the other hand, it can contribute to the development of nutritional disturbances malnutrition, sarcopenia, and frailty. Among these patients on HD, malnutrition and sarcopenia stand out due to their high prevalence in dialyzed patients (3).

According to the sarcopenia consensus from the European Working Group on Sarcopenia for Older People (EWGSOP2), sarcopenia is defined as a progressive and generalized skeletal muscle disorder characterized by the occurrence of low muscle strength and low quality or quantity of muscle mass (4). The coexistence of both conditions constitutes the confirmatory criteria for the diagnosis of sarcopenia. Particularly in CKD, sarcopenia has multicausal etiology, with factors that overlap with traditional factors of sarcopenia in the elderly (5). According to a group of experts from the International Society of Renal Nutrition and Metabolism (ISRNM), malnutrition is characterized by multiple changes caused by a set of factors that lead to an increase in protein catabolism, thus leading to a negative protein balance (6). Sarcopenia and malnutrition are highly prevalent in patients on HD, with the former varying from 51 to 68% and the latter varying from 3.9 to 63.3%, depending on the detection method, disease stage, type of treatment, age, and cutoff points used (7). Both conditions are associated with adverse outcomes, including not only decreased quality of life and functionality, but also increased susceptibility to infection, high hospitalization rates, healthcare costs, morbidity, and mortality (8, 9).

Moreover, data from the United States shows that 40% of end-stage patients were over 65 years in 2013, and projections for 2030 indicate that this proportion will increase to 55–61% (10). Given the fast increase in the prevalence of older adults on dialysis in the recent decades, and the effect of senescence on decreasing skeletal muscle mass, the assessment of the outcomes of malnutrition and sarcopenia in patients undergoing chronic HD is of major relevance. Importantly, research has shown that early intervention in these patients increases the quality of life and reduces mortality (11). However, the diagnosis and monitoring of malnutrition and sarcopenia in dialyzed patients is not yet carried routinely out in many dialysis clinics, hindering the early intervention for these two conditions. Although it is well-known that malnutrition and sarcopenia are related to higher mortality risk, we now investigate the effect of these two conditions combined on markers of nutritional status, clinical condition, quality of life, and on mortality.

METHODS

Study Protocol

This is an observational, longitudinal, and multicenter study including 170 patients under HD treated in six dialysis units in Brazil. A detailed description of the methodology can be found elsewhere (8). All participants were included from March 2010 to February 2014 and were followed for mortality events up to 36 months. Patients who changed dialysis modality or were transferred to other dialysis units or had kidney transplantation were censored.

Patients

Patients were eligible for inclusion if aged over 60 years, undergoing HD for at least 3 months, three times per week, with each session lasting 3.5–4 h. The exclusion criteria comprised patients using a wheelchair, with amputated limbs and with HIV, cancer, and Alzheimer's and Parkinson's diseases. The study was approved by the Ethics and Research Committee of Rio de Janeiro State University, Brazil registered with protocol number 039.3.2011, and a written informed consent was obtained from all patients before their admission in the study.

Methods

At baseline, all participants had the nutritional status assessed by the 7-point-subjective global assessment (7p-SGA) translated to Portuguese (12), by anthropometric measurements [body weight, height, midarm circumference, triceps skinfold (SKF) thickness, and hip and calf circumference], bioelectrical impedance (BIA), and handgrip strength (HGS) after 30–60 min the dialysis session in a midweek dialysis day to minimize the influence of fluids overload on body composition (13). SKFs were measured using an SKF caliper (Lange, Cambridge Scientific Industries, Cambridge, MD, USA), following the Lohman's Protocol (14).

Body fat was estimated by BIA (Biodynamics® 450; Biodynamics Corporation, Seattle, WA, USA) with the patient in a supine position after 5 min of rest. The measurements of body weight, height, resistance, and reactance were entered in the software Fluid & Nutrition version 3.0 (RJL body composition analyzer) to obtain body fat and phase angle. The study from Heo et al. (15) that evaluated body composition by BIA in non-CKD individuals was used to classify obesity, by using body fat percentage above 32.3% for men and above 44.1% for women. The arm contrary to the arteriovenous fistula was used for the assessment of arm circumference, triceps SKF, and HGS. Muscle strength was measured by a mechanical handgrip dynamometer (Baseline, Fabrication Enterprises, Inc, Elmsford, NY, USA). The highest value of three measurements was taken, with arms along the body after a voice command asking to use the maximal force in the dynamometer. The midarm muscle circumference (MAMC) was calculated using the Frisancho equation (16). The standard values of MAMC and triceps SKF were calculated by the equation: (measured value/value on P50 from NHANES III) × 100 (9).

The 7p-SGA was applied by experienced renal dietitians. The nutritional status of a patient was classified as well-nourished when the 7p-SGA score was equal to 7 and 6 and, as malnourished when the 7p-SGA score ≤5 (12).

The Baumgartner's prediction equation (17) was used to estimate appendicular skeletal muscle mass (ASM):

$$\mathbf{ASM\ (kg) = 0.2487\ (weight, kg) + 0.0483\ (height, cm) - 0.1584\ (hip\ circumference, cm) + 0.0732\ [HGS, kgf\ (kilogram\ force)\ ] + 2.5843\ (male) + 5.8828}\ (17)$$

A previous study, conducted by our research group and which included patients on HD, showed that this equation had good agreement with the ASM assessed by dual-energy X-ray absorptiometry (DXA) with an intraclass coefficient correlation (ICC) of 0.92 (95% CI: 0.86–0.95) (9). The ASM was divided by the square height (m) for calculation of the ASM index (ASMI).

The laboratorial measurements were performed before the dialysis session and included assessment of serum albumin (bromocresol green method), high-sensitive C-reactive protein (hs-CRP; by nephelometry), and 25 hydroxyvitamin D [(25 (OH) D); by chemiluminescence immunoassay]. Serum urea was assessed before and after dialysis session for calculation of the urea Kt/V according to the formula of Daugirdas (18) from a midweek dialysis session.

Quality of life was assessed using the Short Form 1.3 questionnaire (KDQoL-SF) (19), which was applied during the dialysis session in 154 patients from the total sample (170 patients). The reason for a smaller sample having data on quality of life is that this assessment did not start at the beginning of the data collection.

For sarcopenia diagnosis, the cutoffs for low muscle mass and low muscle strength established by the 2019 EWGSOP (4) were used. Low muscle strength was considered when HGS was <27 kilogram force (kgf) for men and <16 kgf for women and low muscle mass was considered when the ASMI was <7.0 kg/m^2 for male and <5.5 kg/m^2 for female (4). Patients were considered with pre-sarcopenia when presenting only one of the muscle abnormalities, that is, low muscle mass or low muscle strength and with sarcopenia when both conditions were present.

The patients were classified into four groups considering the presence of malnutrition, pre-sarcopenia, and sarcopenia:

- Group sarcopenia and malnutrition ($n = 56$): Comprised by patients with positive criteria for sarcopenia/pre-sarcopenia and for malnutrition (7p-SGA score ≤ 5).
- Group sarcopenia and no-malnutrition ($n = 28$): Comprised by patients with positive criteria for sarcopenia/pre-sarcopenia, but without criteria for malnutrition (7p-SGA score = 6 and 7).
- Group no-sarcopenia with malnutrition ($n = 44$): Comprised by patients without criteria for sarcopenia/pre-sarcopenia, but with positive criteria for malnutrition (7p-SGA score ≤ 5).
- Group no-sarcopenia and no-malnutrition ($n = 42$): Comprised by patients without criteria for sarcopenia/pre-sarcopenia and for malnutrition (7p-SGA score = 6 and 7).

Statistical Analysis

The Shapiro–Wilk test was applied to test normality. Categorical variables are described as absolute number and percentage and continuous variables as mean and SD or as median and interquartile range, as appropriate. The comparisons of the variables among the groups of sarcopenia and malnutrition were performed using the chi-square test for categorical variables, and one-way ANOVA or Kruskal–Wallis tests for continuous variables, as appropriate. The Bonferroni test was used to verify the differences among the groups for the variables presenting normal distribution.

The comparisons between the survival and deceased groups were done by chi-square test, independent *t*-test, or Mann–Whitney test, as appropriate. The survival analyses were performed by the Kaplan–Meier graphic using the log-rank test to compare the survival curves among the sarcopenia and malnutrition groups. The Cox's proportional risk model adjusted for gender, age, and hs-CRP was used to assess the hazard ratio for mortality, using the no-sarcopenia and well-nourished group as reference. The value of $p < 0.05$ will be used for statistical significance. All analyses will be performed using the SPSS software version 27 (IBM Corp. Released 2015, Armonk, NY, USA).

RESULTS

Table 1 shows the main characteristic of the studied sample comprised of older adults on chronic HD. In general, the mean age was around 70.6 years, the majority of the sample was comprised of males, and the urea Kt/V was indicative of adequate dialysis. The mean BMI, calf circumference, standard triceps SKF, and MAMC indicated adequate nutritional status according to cutoffs stablished for non-CKD individuals, which are well-accepted for use in patients with CKD (20). However, when the

TABLE 1 | Main demographic, nutritional, and clinical characteristics of older adults on hemodialysis.

	Results (n = 170)
Age (years)	70.6 ± 7.2
Male (*n*; %)	111 (65.3)
Dialysis length (years)	2.9 (1.3; 5.6)
Urea Kt/V	1.5 (1.3; 1.6)
Diabetes (*n*; %)	44 (37.7)
BMI (kg/m^2)	25.4 ± 4.5
Pre-sarcopenia (*n*; %)	60 (35.3)
Sarcopenia (*n*; %)	24 (14.1)
No sarcopenia (*n*; %)	86 (50.6)
Standard triceps skinfold thickness (%)	102.5 (72.7; 142.1)
Standard Midarm muscle circumference (%)	98.1 ± 14.7
Calf circumference (cm)	
Male	34.5 ± 3.9
Female	33.3 ± 3.5
Malnutrition (*n*; %)	100 (58.8)
Body fat (%)	
Male	27.5 ± 7.0
Female	37.7 ± 5.3
Phase angle (°)	
Male	5.5 ± 1.3
Female	5.3 ± 1.2
Body cellular mass (kg)	
Male	22.1 ± 4.8
Female	17.0 ± 3.6
Appendicular skeletal muscle mass index (kg/m^2)	
Male	7.48 ± 0.77
Female	4.60 ± 0.81
Pre-sarcopenia (*n*; %)	
Low HGS	38 (22.4)
Low ASMI	22 (12.9)
Total	60 (35.3)
Albumin (g/dl)	3.9 ± 0.4
Hemoglobin (mg/dl)	11.3 ± 1.6
Hematocrit (%)	34.4 ± 5.0
S Creatinine (mg/dl)	8.7 ± 2.8
S Urea (mg/dl)	138 ± 39.5
PTH (mg/dl)	223 (101; 402)
25(OH)D (ng/ml)	19.2 (12.7; 27.1)
hs-CRP (mg/dl)	0.42 (0.2; 1.1)

BMI, body mass index; hs-CRP, high-sensitive C-reactive protein; 25(OH)D, 25-hydroxyvitamin D; PTH, parathormone.

Data described as absolute values and its percentage for categorical variables; as mean ± SD as or as median and interquartile range for continuous variables according to the variable's distribution. Malnutrition defined as 7p-SGA ≤ 5.

Pre-sarcopenia defined as either low muscle mass (appendicular skeletal muscle mass index below 7 kg/m^2 for male and below 5.5 kg/m^2 for female) or low muscle strength (handgrip strength below 27 kgf for male and below 16 kgf for female). Sarcopenia was defined by the concomitant condition of low muscle mass and low muscle strength.

nutritional status was assessed by 7p-SGA, 58.8% of the sample had a score ≤5, indicating malnutrition. As for body composition assessed by BIA, the mean ± SD values for body fat percentage showed that 26.7% of male and 7% of female were obese when applying the cutoffs suggested by Heo et al. (15). When assessing the presence of sarcopenia, about one-third of the sample had either low muscle mass or low muscle strength, here defined as pre-sarcopenia, whereas 14.1% had both conditions combined, defined as sarcopenia, and 50.6% had no signs of low muscle mass or low muscle strength. The laboratory exams were compatible to that observed for patients on dialysis treatment, and the mean serum albumin was within the acceptable values to patients with CKD (>3.8 mg/dl) (21).

Considering that the presence of two nutritional disturbances—malnutrition and sarcopenia were investigated, we evaluated whether the frequency of malnutrition differed among the sarcopenia groups. **Figure 1** shows the frequency of patients with malnutrition (assessed as 7p-SGA ≤ 5) in the groups stratified as sarcopenia, pre-sarcopenia, and no-sarcopenia. As can be observed, the prevalence of patients with malnutrition did not differ among the sarcopenia groups, indicating that malnutrition was present even in the group of no-sarcopenia. We then expanded our analysis by exploring the role that these two conditions combined (sarcopenia and malnutrition) have on other nutritional markers, clinical condition, quality of life, and mortality events.

Table 2 shows the comparison of demographic, nutritional, clinical characteristics and quality of life among the groups classified by the presence of sarcopenia and malnutrition. Age and the percentage of males differed significantly among the groups, with the age higher in the group sarcopenia and malnutrition while male gender had higher prevalence in the group sarcopenia and no-malnutrition. Except for serum albumin that did not differ among the groups, the other nutritional markers differed significantly, indicating worse nutritional status in the group sarcopenia and malnutrition as compared to the group no-sarcopenia and no-malnutrition. Regarding clinical condition, the urea Kt/V and 25(OH)D differed among the groups, being the group sarcopenia and malnutrition presenting higher Kt/V and lower 25(OH)D as compared to the group no-sarcopenia and no-malnutrition. Regarding the domains related to the quality of life, most of them did not differ among the groups. Those that showed significant differences were quality of social interaction, role physical, social function, and SF12 mental composite with the group no-sarcopenia and no-malnutrition showing better scores when compared to the remaining groups. After 23.5 (12.2; 34.4) months of follow-up (median and interquartile ranges), there were 62 events of death. The group of deceased patients was older, with higher Kt/V and hs-CRP as compared to the patients who survived (**Table 3**).

The survival analysis showed that there was a significant difference in the survival curves among the groups, being the group combining both conditions (sarcopenia and malnutrition) the one with lower survival rate (**Figure 2**, Kaplan–Meier; log-rank test, $p = 0.019$). This finding was confirmed in the Cox regression analysis adjusted for age, gender, and hs-CRP, where the group with sarcopenia and malnutrition had a hazard ratio of 2.99 (95% CI: 1.23: 7.25) as compared to the reference group no-sarcopenia and no-malnutrition (**Table 4**).

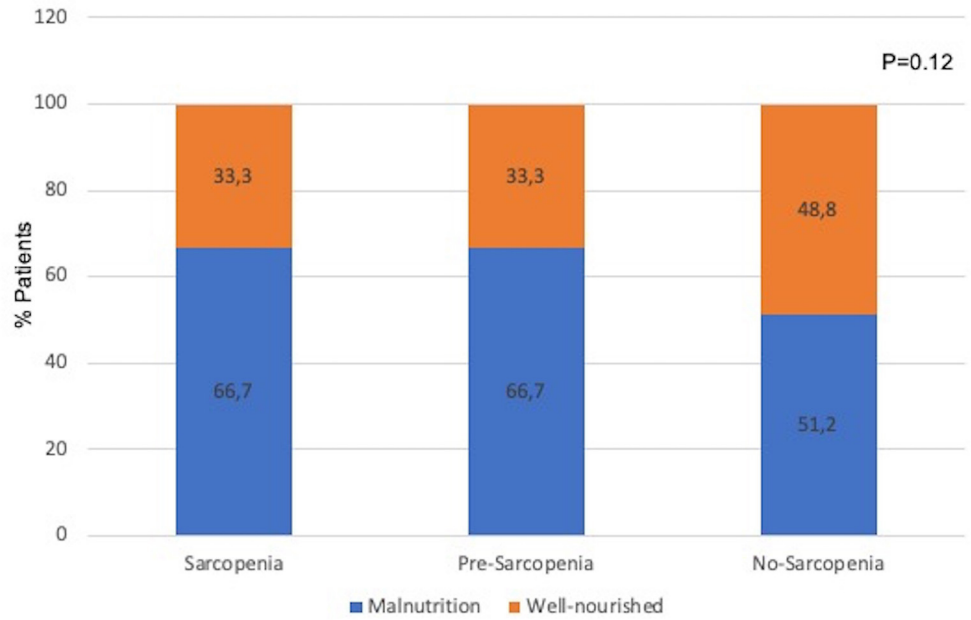

FIGURE 1 | Prevalence of malnutrition (assessed by 7p-SGA) in groups classified as sarcopenia, pre-sarcopenia, and no-sarcopenia. Differences among groups were tested by chi-square test.

DISCUSSION

In this study, we aimed to evaluate the role of sarcopenia and malnutrition on the nutritional markers and survival in a cohort of older adults on chronic HD. Malnutrition (diagnosed by 7p-SGA) was present in 58.8%, which was similar to that found by Cianciaruso et al. (22) where 51% of older adults (>65 years) in HD and peritoneal dialysis had malnutrition assessed by SGA. Moreover, in a meta-analysis aiming to describe the prevalence of malnutrition in patients with CKD (assessed by SGA or malnutrition inflammation score), it was shown that the 25–75th percentile ranges of malnutrition among studies on dialyzed patients was 28–54% (3). Therefore, our findings on the presence of malnutrition are somehow higher than that from previous studies, most likely due to the inclusion of only older adults on HD.

Markers of muscle abnormality, such as low muscle strength or low muscle mass, named as pre-sarcopenia in the current study, were present in 35.3% of the patients, a percentage similar to that found by Isoyama et al. in incident dialyzed patients (39% of the patients with either low muscle strength or low muscle mass) (23). Moreover, we found that sarcopenia (diagnosed by the concomitance of low muscle mass and low muscle strength) was present in 14.1% of the patients, a frequency lower to that from previous studies in dialysis patients (20–40%) (23–25). This discrepancy is most likely due to the diagnostic methods used and the cutoffs applied for the diagnose of low muscle mass and low muscle strength in patients on HD, as previously shown by Lamarca et al. (7). In addition, these divergent results, when comparing with findings from other studies, can also be explained by different characteristics from the studied sample, such as the CKD stage, dialysis modality, presence of comorbidities, and the mean age of the sample (5).

Furthermore, we identified that among the groups stratified by sarcopenia status, 66.7% of the patients from the group sarcopenia had also malnutrition (**Figure 2**). In another study including older adults (>65 years) with CKD stages 3b to 5 not on dialysis, 52% of the patients with sarcopenia were diagnosed with protein energy wasting (PEW) using the diagnostic criteria from the ISRNM (26). In incident dialysis patients, 64.7% of the patients with sarcopenia had malnutrition diagnosed by SGA (23). The similar frequency of sarcopenia and malnutrition combined found in our study and in the aforementioned ones underlines that these nutritional disturbance can coexist, and a careful assessment for both conditions should be performed in patients on HD.

Surprisingly, when comparing the frequency of malnutrition among the sarcopenia groups (**Figure 1**), 51.2% of the patients in the group no-sarcopenia had malnutrition, a proportion not different from that observed in the groups sarcopenia and pre-sarcopenia. Similarly, in two previous studies including either patients with CKD stages 3b−5 or before the start of dialysis therapy, 14–20% of the patients with no-sarcopenia had malnutrition (23, 26). In other words, the absence of sarcopenia does not exclude the existence of malnutrition. This finding highlights that although sarcopenia and malnutrition share some common criteria, these are different nutritional abnormalities, and the investigation of both is crucial. In the current study, malnutrition was diagnosed by 7p-SGA, which

TABLE 2 | Comparisons of demographic, nutritional, clinical characteristics, and quality of life of older adults on hemodialysis according to the groups sarcopenia and malnutrition.

	Sarcopenia and malnutrition (*n* = 56; 33%)	**Sarcopenia and no-malnutrition (*n* = 28; 16.5%)**	**No-sarcopenia and malnutrition (*n* = 44; 25.8%)**	**No-sarcopenia and no-malnutrition (*n* = 42; 24.7%)**	***p****
Age (years)	73.2 ± 8.0[a]	72.4 ± 7.9[a,c]	69.3 ± 6.0[b,c]	67.4 ± 5.4[b,d]	<0.001
Male (*n*; %)	34 (60.7)	24 (85.7)	23 (52.3)	30 (71.4)	0.02
Dialysis length (years)	3.01 (1.66; 5.60)	2.96 (1.37; 6.32)	2.08 (0.93; 5;87)	3.15 (1.24; 5.60)	0.67
Urea Kt/V	1.51 (1.40; 1.70)	1.34 (1.22; 1.71)	1.47 (1.30; 1.63)	1.41 (1.28; 1.53)	0.04
Diabetes (*n*; %)	14 (25)	12 (42.8)	24 (54.5)	14 (33.3)	0.06
BMI (kg/m^2)	23.6 ± 4.7[a]	25.0 ± 3.3[a,c]	25.9 ± 4.6[b,c]	27.7 ± 3.9[b,d]	<0.001
Standard triceps skinfold thickness (%)	89.5 (63.6; 125.7)	110.1 (91.4; 175.7)	96.15 (72.1; 121.2)	134.4 (96.5; 169.1)	<0.001
Standard midarm muscle circumference (%)	93.6 ± 13.4[a]	94.0 ± 13.2[a,c]	100.9 ± 16.7[a,b,c]	103.9 ± 12.7[b]	0.001
Calf circumference (cm)	32.6 ± 3.4[a]	33.7 ± 2.3[a]	33.6 ± 4.6[a]	36.6 ± 2.9[b]	<0.001
Body fat %	28.5 ± 7.8[a]	30.0 ± 8.5[a,b]	32.3 ± 8.2[a,b]	33.9 ± 7.3[b]	0.007
Phase angle (°)	4.9 ± 1.2[a]	5.2 ± 0.9[a,c]	5.4 ± 0.9[a,b,c]	6.2 ± 1.4[b]	<0.001
Body cellular mass (kg)	17.7 ± 4.3[a]	20.0 ± 3.8[b]	19.2 ± 3.8[a,b]	24.2 ± 5.0[c]	<0.001
Appendicular skeletal muscle mass index (kg/m^2)	6.42 ± 1.1[a]	7.03 ± 0.83[a,b,c]	6.99 ± 0.96[b]	7.56 ± 0.94[c]	<0.001
Albumin (g/dl)	3.83 ± 0.41	3.98 ± 0.40	3.92 ± 0.41	3.91 ± 0.41	0.44
Hemoglobin (mg/dl)	11.3 ± 1.9	11.2 ± 1.7	11.2 ± 1.3	11.4 ± 1.5	0.96
Hematocrit (%)	34.6 ± 6.0	34.3 ± 5.2	34.0 ± 4.1	34.4 ± 4.5	0.94
S Creatinine (mg/dl)	8.5 ± 2.4	8.9 ± 2.9	8.2 ± 2.8	9.4 ± 3.1	0.24
S Urea (mg/dl)	130.6 ± 41.7	150.8 ± 40.9	137.2 ± 37.2	140.4 ± 36.7	0.16
PTH (mg/dl)	165.3 (59.6; 331.6)	218.3 (111.6; 454.1)	262.3 (106.6; 442.8)	256 (171.2; 402.6)	0.23
25(OH)D (ng/ml)	17.5 (11.7; 30.1)	14.7 (10.5; 21.4)	18.0 (13.5; 25.4)	25.7 (19.0; 34.0)	0.001
hs-CRP (mg/dl)	0.37 (0.20; 1.23)	0.26 (0.09; 0.69)	0.52 (0.26; 1.18)	0.52 (0.22; 1.15)	0.19
Quality-of-life domains					
Symptom problem list	75.1 ± 16.8	74.5 ± 21.6	67.7 ± 24.0	75.6 ± 18.4	0.24
Effects of kidney disease	68.7 (50.0; 84.4)	71.9 (40.6; 90.6)	59.4 (42.2; 78.1)	75.0 (66.7; 91.7)	0.38
Burden of kidney disease	37.5 (18.8; 56.3)	50.0 (18.8; 75.0)	25.0 (12.5; 50.0)	50.0 (25.0; 68.8)	0.10
Work status	50.0 (0.0; 50.0)	50.0 (0.0; 50.0)	50.0 (0.0; 50.0)	50.0 (0.0; 100.0)	0.83
Cognitive function	80.4 ± 21.0	78.3 ± 26.4	75.9 ± 25.8	83.5 ± 19.4	0.50
Quality of social interaction	81.5 ± 17.9[a]	77.1 ± 20.4[a]	70.7 ± 24.0[a,b]	82.8 ± 19.2[a,c]	0.03
Sexual function	95.8 ± 10.2	85.9 ± 14.5	77.3 ± 26.8	84.2 ± 19.7	0.50
Sleep	65.0 (47.5; 83.8)	57.5 (35.0; 75.0)	57.5 (46.3; 70.0)	72.5 (52.5; 81.3)	0.08
Social support	100.0 (66.7; 100.0)	83.3 (66.7; 100.0)	100.0 (66.7; 100.0)	100.0 (66.7; 100.0)	0.78
Dialysis staff encouragement	75.0 (56.3; 93.8)	87.5 (75.0; 100.0)	100.0 (75.0; 100.0)	87.5 (75.0; 100.0)	0.07
Overall health	60.0 (50.0; 100.0)	50.0 (50.0; 100.0)	60.0 (50.0; 85.0)	60.0 (50.0; 80.0)	0.61
Patient satisfaction	68.4 ± 19.3	75.4 ± 21.2	72.4 ± 21.6	71.9 ± 20.2	0.56
Physical functioning	45.0 (22.5; 80.0)	50.0 (25.0; 70.0)	40.0 (25.0; 70.0)	55.0 (40.0.75.0)	0.21
Role physical	50.0 (0.0; 75.0)	50.0 (0.0; 100.0)	0.0 (0.0; 62.5)	50.0 (25.0; 100.0)	0.009
Pain	62.5 (45.0; 90.0)	70.0 (45.0; 90.0)	55.0 (22.5; 95.0)	67.5 (45.0; 100.0)	0.43
General health	60.0 (30.0; 70.0)	50.0 (35.0; 75.0)	50.0 (32.5; 62.5)	65.0 (40.0; 82.5)	0.15
Emotional well-being	76.0 (52.0; 92.0)	84.0 (60.0; 96.0)	68.0 (42.0; 90.0)	80.0 (64.0; 92.0)	0.18
Role emotional	33.3 (0.0; 100.0)	66.7 (0.0; 100.0)	33.3 (0.0; 66.7)	66.7 (33.3; 100.0)	0.09
Social function	62.5 (37.5; 100.0)	87.5 (62.5; 100.0)	62.5 (25.0; 87.5)	75.0 (62.5; 100.0)	0.04
Energy fatigue	55.0 (32.5; 75.0)	60.0 (40.0; 80.0)	45.0 (32.5; 75.0)	65.0 (42.5; 80.0)	0.27
SF12 Physical composite	37.9 (31.1; 45.8)	36.4 (32.3; 45.3)	36.5 (26.2; 46.5)	40.6 (35.1; 47.2)	0.22
SF12 Mental Composite	44.9 ± 11.1[a]	50.3 ± 13.5[a,b]	44.3 ± 12.3[a]	50.5 ± 10.1[b]	0.02

NA, non-applicable; hs-CRP, high-sensitive C-reactive protein; 25(OH)D, 25(OH)D, 25-hydroxyvitamin D; PTH, parathormone. Quality of life was evaluated in a subgroup of 154 patients (n = 49, n = 23, n = 41, and n = 41, respectively in the four groups). Data described as absolute values and its percentage for categorical variables; as mean ± SD as or as median and interquartile range for continuous variables according to the variable's distribution.

**Chi-square or one-way ANOVA or Kruskal–Wallis test, as appropriate. The Bonferroni post-hoc test for ANOVA $p \leq 0.05$: Significant differences among the groups are signed by the different superscript letters.*

TABLE 3 | Comparison of older adult patients on hemodialysis according to the group alive and deceased ($n = 170$).

	Alive ($n = 108$)	Deceased ($n = 62$)	p*
Male	71 (65.7)	40 (64.5)	0.87
Age (years)	69.6 ± 6.7	72.5 ± 7.8	0.013
Kt/V	1.42 ± 0.3	1.60 ± 0.5	0.002
hs-CRP	0.34 (0.18; 0.82)	0.58 (0.27; 1.48)	0.004
Dialysis length (years)	2.9 (1.2; 5.4)	2.9 (1.3; 6.0)	0.68

hs-CRP, high-sensitive C-reactive protein.
**The t-test; chi-square test, or Mann–Whitney test, as appropriate.*

evaluate several domains of nutritional status (involuntary loss of body weight, food intake, gastrointestinal symptoms, poor appetite, functional status, comorbidities, and physical exam for subcutaneous fat and muscle loss) (27). Therefore, it provides a broad assessment of nutritional status including aspects not included in the criteria for sarcopenia diagnosis. This likely explains the reason why individuals in the group no-sarcopenia had malnutrition when diagnosed by 7p-SGA. Adding to these findings, we also demonstrated, as expected, that when sarcopenia and malnutrition occurred concomitantly (group sarcopenia and malnutrition), all parameters of nutritional status, except for albumin, were worse when compared with the group no-sarcopenia and no-malnutrition. The non-difference in serum albumin among the groups of sarcopenia and malnutrition corroborates the findings from Gama-Axelsson et al. (28) The authors reported that in prevalent dialyzed patients, serum albumin correlated poorly with markers of nutritional status, including SGA score and body composition parameters, but it was significantly correlated with hs-CRP (28). Altogether, this is aligned with the statement from the updated guidelines in nutrition and CKD from the NKF-KDOQI that albumin is a predictor of hospitalization and mortality, and not a marker of nutritional status (29).

It was interesting to note that within the sarcopenia and malnutrition group, the mean values of body fat markers, such as BMI, percentage of body fat, and standard triceps SKFs were within the normal range for non-CKD individuals (15, 30, 31). Similarly, Lee et al. (32) also observed in a group of older adults on HD that patients with low gait speed and low HGS combined had BMI within the normal range. Additionally, in the study from Ren et al. (24), no significant differences were found between no-sarcopenia and sarcopenia in relation to anthropometric indexes, namely TSF, BMI, MAC, and MAMC. The remaining markers of nutritional status differed among the groups stratified as malnutrition and sarcopenia status, being this difference more marked between the group sarcopenia and malnutrition and group no-sarcopenia and no-malnutrition. Among those, the phase angle, which is not much explored in patients on HD, could discriminate adequately the nutritional status in the four studied groups. In our study, the phase angle differed mainly between the sarcopenic and malnourished group and the group no-sarcopenia and no-malnutrition. This finding is in agreement with studies in non-elderly adults on HD, where the phase angle also differed significantly between malnourished and non-malnourished groups (24, 33, 34). Therefore, one marker of nutritional status should not be used alone to evaluate nutritional status, but rather a combination of markers can be used, as in fact stated in the guideline for nutrition and CKD from the NKF-KDOQI (29).

Regarding quality of life, the domains most affected were social interaction, role physical, social function, and SF12 mental composite, which had worse scores in the group sarcopenia and malnutrition. We are not aware of studies in patients with CKD evaluating the role of sarcopenia and malnutrition combined on quality-of-life domains, but in a previous study from our group, we showed that patients on HD with low muscle strength had worse quality-of-life domains than that of the group with low muscle mass (9). Moreover, in another study including patients on dialysis, malnutrition was associated with worse quality of life (35–37) and with the presence of depression and sleep disorders (35).

Finally, when evaluating survival, we found that the mortality risk of the groups with sarcopenia and malnutrition was close to three times higher than the group without any of these abnormalities. As far as we are concerned, there are no previous studies assessing the role of malnutrition and sarcopenia combined in older adults on HD, but studies in older adults hospitalized without CKD, showed that older adults with combined sarcopenia and malnutrition had a risk for mortality of close to five times higher when compared to the group with none of these nutritional disturbances (38). In patients on dialysis, previous studies have consistently shown that malnutrition (36, 39), sarcopenia (25), and low muscle strength (23, 32, 40) were associated with increased mortality.

Some limitations and strengths of this study can be listed. As a limitation, the observational study design can impair the identification of a causality–effect association. Second, the relatively small sample size can underpower the comparison among the sarcopenia and malnutrition groups, though statistical differences were already listed with this sample size. Third, the lack of robust methods to estimate muscle mass can hinder muscle abnormalities related to muscle mass. As positive aspects, we consider the originality of evaluating the concomitance of malnutrition and sarcopenia in elderly patients on HD, and the relationship of these conditions with quality of life and survival. In addition, although the methods used to evaluate muscle mass could be influenced by the variation in the hydration status, all measurements were performed after the dialysis session to minimize the influence of fluid retention. In addition, since these are the methods used in the routine care of dialysis clinics and also recommended by the updated guidelines in nutrition and CKD from NKF/KDOQI (29), our findings can be used to support a nutritional assessment with methods that are suitable for the routine use.

In conclusion, patients on HD aged 60 years and older who have sarcopenia and malnutrition showed worse nutritional parameters, quality-of-life domains, and higher mortality risk. In addition, we reported that malnutrition can occur in patients without sarcopenia, and that the body fat markers within the normality range can occur concomitantly with

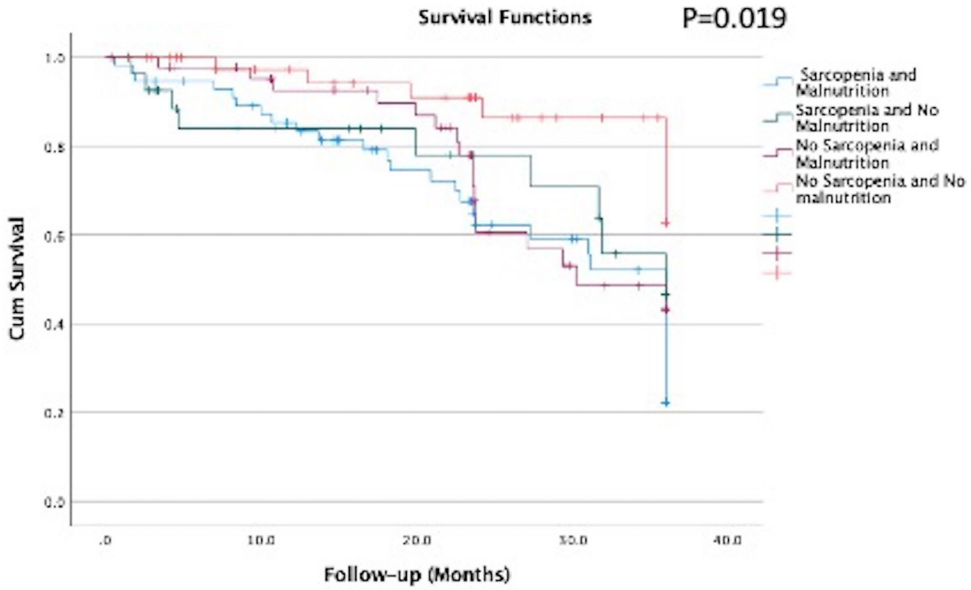

FIGURE 2 | Survival curves according to the groups with sarcopenia and malnutrition of elderly patients on hemodialysis ($n = 170$).

TABLE 4 | Risk for mortality events, expressed as hazard ratio* according to the combination of group with sarcopenia and malnutrition in older adults undergoing maintenance hemodialysis ($n = 170$).

		95% CI		
	Hazard ratio*	**Lower**	**Upper**	***p*-value**
Male	0.44	0.24	0.83	0.01
Age (years)	1.02	0.96	1.06	0.27
hs-CRP (mg/dl)	1.35	2.00	1.58	0.03
No-sarcopenia + no-malnutrition (reference group) ($n = 42$)				
Sarcopenia + no-malnutrition ($n = 28$)	2.65	0.86	7.05	0.09
No-Sarcopenia + malnutrition ($n = 44$)	2.43	0.97	6.05	0.06
Sarcopenia + malnutrition ($n = 56$)	2.99	1.23	7.25	0.03

hs-CRP, high-sensitive C-reactive protein.
**Cox's proportional risk model.*

malnutrition and sarcopenia. Altogether, these findings highlight the importance of complete nutritional assessment in older patients on dialysis. Further studies to better understand the role of these abnormalities in the health of older adults undergoing maintenance HD are needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will not be made available by the authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics and Research Committee of Rio de Janeiro State University, Brazil. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CM and TA analyzed and interpreted the data, drafted the article, and gave final approval of the submitted version. JR and FS acquired the data, critically revised the important intellectual content, and gave final approval of the submitted version. CA conceived and designed the study, acquired, analyzed, interpreted the data, drafted the article, critically revised the important intellectual content, and gave final approval of the submitted version. All authors contributed to the article and approved the submitted version.

FUNDING

This research received two grants from Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ; Grant Numbers: E-26/111.653/2010 and E-26/103.209/2011).

ACKNOWLEDGMENTS

The authors would like to thank Renata Lemos Fetter, Fernanda Guedes Bigogno, Fernando Lamarca, Juliana Giglio, and Ana Lucia Mendes Pereira who helped during the data collection and also thank Sergio Franco Laboratory for the laboratorial analysis.

REFERENCES

1. Collaboration GCKD. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* (2020) 395:709–33. doi: 10.1016/S0140-6736(20)30045-3
2. Barreto SM, Ladeira RM, Duncan BB, Schmidt MI, Lopes AA, Benseñor IM, et al. Chronic kidney disease among adult participants of the ELSA-Brasil cohort: association with race and socioeconomic position. *J Epidemiol Community Health.* (2016) 70:380–9. doi: 10.1136/jech-2015-205834
3. Carrero JJ, Thomas F, Nagy K, Arogundade F, Avesani CM, Chan M, et al. Global prevalence of protein-energy wasting in kidney disease: a meta-analysis of contemporary observational studies from the international society of renal nutrition and metabolism. *J Ren Nutr.* (2018) 28:380–92. doi: 10.1053/j.jrn.2018.08.006
4. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* (2019) 48:16–31. doi: 10.1093/ageing/afz046
5. Sabatino A, Cuppari L, Stenvinkel P, Lindholm B, Avesani CM. Sarcopenia in chronic kidney disease: what have we learned so far? *J Nephrol.* (2020) 34:1347–72. doi: 10.1007/s40620-020-00840-y
6. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr.* (2013) 23:77–90. doi: 10.1053/j.jrn.2013.01.001
7. Lamarca F, Carrero JJ, Rodrigues JC, Bigogno FG, Fetter RL, Avesani CM. Prevalence of sarcopenia in elderly maintenance hemodialysis patients: the impact of different diagnostic criteria. *J Nutr Health Aging.* (2014) 18:710–7. doi: 10.1007/s12603-014-0505-5
8. Rodrigues J, Santin F, Brito F, Lindholm B, Stenvinkel P, Avesani CM. Nutritional status of older patients on hemodialysis: which nutritional markers can best predict clinical outcomes? *Nutrition.* (2019) 65:113–9. doi: 10.1016/j.nut.2019.03.002
9. Giglio J, Kamimura MA, Lamarca F, Rodrigues J, Santin F, Avesani CM. Association of sarcopenia with nutritional parameters, quality of life, hospitalization, and mortality rates of elderly patients on hemodialysis. *J Ren Nutr.* (2018) 28:197–207. doi: 10.1053/j.jrn.2017.12.003
10. McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD incidence and prevalence in the United States through 2030. *J Am Soc Nephrol.* (2019) 30:127–35. doi: 10.1681/ASN.2018050531
11. Wingard RL, Pupim LB, Krishnan M, Shintani A, Ikizler TA, Hakim RM. Early intervention improves mortality and hospitalization rates in incident hemodialysis patients: RightStart program. *Clin J Am Soc Nephrol.* (2007) 2:1170–5. doi: 10.2215/CJN.04261206
12. Fetter RL, Bigogno FG, de Oliveira FG, Avesani CM. Cross-cultural adaptation to Portuguese of tools for assessing the nutritional status of patients on dialysis. *J Bras Nefrol.* (2014) 36:176–85. doi: 10.5935/0101-2800.20140028
13. Carrero JJ, Johansen KL, Lindholm B, Stenvinkel P, Cuppari L, Avesani CM. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. *Kidney Int.* (2016) 90:53–66. doi: 10.1016/j.kint.2016.02.025
14. Lohman TG. *Advances in Body Composition Assessment*. Champaign, IL: Human Kinetics Publishers. (1992).
15. Heo M, Faith MS, Pietrobelli A, Heymsfield SB. Percentage of body fat cutoffs by sex, age, and race-ethnicity in the US adult population from NHANES 1999-2004. *Am J Clin Nutr.* (2012) 95:594–602. doi: 10.3945/ajcn.111.025171
16. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr.* (1981) 34:2540–5. doi: 10.1093/ajcn/34.11.2540
17. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol.* (1998) 147:755–63. doi: 10.1093/oxfordjournals.aje.a009520
18. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol.* (1993) 4:1205–13. doi: 10.1681/ASN.V451205
19. Duarte PS, Ciconelli RM, Sesso R. Cultural adaptation and validation of the "Kidney Disease and Quality of Life–Short Form (KDQOL-SF 13)" in Brazil. *Braz J Med Biol Res.* (2005) 38:261–70. doi: 10.1590/S0100-879X2005000200015
20. Fouque D, Vennegoor M, ter Wee P, Wanner C, Basci A, Canaud B, et al. EBPG guideline on nutrition. *Nephrol Dial Transplant.* (2007) 22(Suppl.2):ii45–87. doi: 10.1093/ndt/gfm020
21. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* (2008) 73:391–8. doi: 10.1038/sj.ki.5002585
22. Cianciaruso B, Brunori G, Traverso G, Panarello G, Enia G, Strippoli P, et al. Nutritional status in the elderly patient with uraemia. *Nephrol Dial Transplant.* (1995) 10(Suppl.6):65–8. doi: 10.1093/ndt/10.supp6.65
23. Isoyama N, Qureshi AR, Avesani CM, Lindholm B, Bàràny P, Heimbürger O, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. *Clin J Am Soc Nephrol.* (2014) 9:1720–8. doi: 10.2215/CJN.10261013
24. Ren H, Gong D, Jia F, Xu B, Liu Z. Sarcopenia in patients undergoing maintenance hemodialysis: incidence rate, risk factors and its effect on survival risk. *Ren Fail.* (2016) 38:364–71. doi: 10.3109/0886022X.2015.1132173
25. Mori K, Nishide K, Okuno S, Shoji T, Emoto M, Tsuda A, et al. Impact of diabetes on sarcopenia and mortality in patients undergoing hemodialysis. *BMC Nephrol.* (2019) 20:105. doi: 10.1186/s12882-019-1271-8
26. Vettoretti S, Caldiroli L, Armelloni S, Ferrari C, Cesari M, Messa P. Sarcopenia is associated with malnutrition but not with systemic inflammation in older persons with advanced CKD. *Nutrients.* (2019) 11:61378. doi: 10.3390/nu11061378
27. Steiber A, Leon JB, Secker D, McCarthy M, McCann L, Serra M, et al. Multicenter study of the validity and reliability of subjective global assessment in the hemodialysis population. *J Ren Nutr.* (2007) 17:336–42. doi: 10.1053/j.jrn.2007.05.004
28. Gama-Axelsson T, Heimbürger O, Stenvinkel P, Bárány P, Lindholm B, Qureshi AR. Serum albumin as predictor of nutritional status in patients with ESRD. *Clin J Am Soc Nephrol.* (2012) 7:1446–53. doi: 10.2215/CJN.10251011
29. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis.* (2020) 76(3Suppl.1):S1–107. doi: 10.1053/j.ajkd.2020.05.006
30. Lipschitz DA. Screening for nutritional status in the elderly. *Prim Care.* (1994) 21:55–67. doi: 10.1016/S0095-4543(21)00452-8
31. Landi F, Onder G, Russo A, Liperoti R, Tosato M, Martone AM, et al. Calf circumference, frailty and physical performance among older adults living in the community. *Clin Nutr.* (2014) 33:539–44. doi: 10.1016/j.clnu.2013.07.013
32. Lee YH, Kim JS, Jung SW, Hwang HS, Moon JY, Jeong KH, et al. Gait speed and handgrip strength as predictors of all-cause mortality and cardiovascular events in hemodialysis patients. *BMC Nephrol.* (2020) 21:166. doi: 10.1186/s12882-020-01831-8
33. Tan RS, Liang DH, Liu Y, Zhong XS, Zhang DS, Ma J. Bioelectrical impedance analysis-derived phase angle predicts protein-energy wasting in maintenance hemodialysis patients. *J Ren Nutr.* (2019) 29:295–301. doi: 10.1053/j.jrn.2018.09.001

34. Guida B, Maro MD, Lauro MD, Lauro TD, Trio R, Santillo M, et al. Identification of sarcopenia and dynapenia in CKD predialysis patients with EGWSOP2 criteria: an observational, cross-sectional study. *Nutrition.* (2020) 78:110815. doi: 10.1016/j.nut.2020.110815
35. Bilgic A, Akgul A, Sezer S, Arat Z, Ozdemir FN, Haberal M. Nutritional status and depression, sleep disorder, and quality of life in hemodialysis patients. *J Ren Nutr.* (2007) 17:381–8. doi: 10.1053/j.jrn.2007.08.008
36. Rambod M, Bross R, Zitterkoph J, Benner D, Pithia J, Colman S, et al. Association of Malnutrition-Inflammation Score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. *Am J Kidney Dis.* (2009) 53:298–309. doi: 10.1053/j.ajkd.2008.09.018
37. Günalay S, Öztürk YK, Akar H, Mergen H. The relationship between malnutrition and quality of life in haemodialysis and peritoneal dialysis patients. *Rev Assoc Med Bras.* (1992). (2018) 64:845–52. doi: 10.1590/1806-9282.64.09.845
38. Hu X, Zhang L, Wang H, Hao Q, Dong B, Yang M. Malnutrition-sarcopenia syndrome predicts mortality in hospitalized older patients. *Sci Rep.* (2017) 7:3171. doi: 10.1038/s41598-017-03388-3
39. Ho LC, Wang HH, Peng YS, Chiang CK, Huang JW, Hung KY, et al. Clinical utility of malnutrition-inflammation score in maintenance hemodialysis patients: focus on identifying the best cut-off point. *Am J Nephrol.* (2008) 28:840–6. doi: 10.1159/000137684
40. Kittiskulnam P, Chertow GM, Carrero JJ, Delgado C, Kaysen GA, Johansen KL. Sarcopenia and its individual criteria are associated, in part, with mortality among patients on hemodialysis. *Kidney Int.* (2017) 92:238–47. doi: 10.1016/j.kint.2017.01.024

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership