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Analyzing body composition in living kidney donors: impact on post-transplant kidney function

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Living donor kidney transplantation boasts superior patient and graft survival rates compared to deceased donor kidney transplantation. However, the impact of living donor body composition (BC) on post-transplant kidney function remains uncertain. In a cohort of 293 living kidney donor-recipients pairs, we utilized linear mixed model analyses, adjusted for time and including a multiplicative interaction term of time with the donor body composition measure, and found no significant associations between any donor BC measure and the annual change in recipient post-transplantation estimated glomerular filtration rate (eGFR) [donor body mass index (BMI): $B=-0.01$, 95%CI -0.13; 0.11, $p=0.88$; donor waist circumference: $B=0.02$, 95%CI -0.02; 0.06, $p=0.38$; donor skeletal muscle index: $B=-0.02$, 95%CI -0.07; 0.04, $p=0.63$; donor skeletal muscle radiation attenuation: $B=-0.002$, 95%CI -0.06; 0.06, $p=0.96$; donor visceral adipose tissue index: $B=-0.001$, 95%CI -0.02; 0.02, $p=0.93$; donor subcutaneous adipose tissue index: $B=-0.001$, 95%CI -0.02; 0.02, $p=0.94$; donor intramuscular adipose tissue index: $B=-0.12$, 95%CI -0.29; 0.06, $p=0.19$; donor total abdominal adipose tissue index: $B=-0.001$, 95%CI -0.01; 0.01, $p=0.89$]. Our study suggests that pre-donation BC does not affect post-transplantation recipient eGFR in donor populations with a BMI below 35 kg/m^2.

KEYWORDS

living donor kidney transplantation, body composition, kidney function, body mass index, computed tomography

Introduction

Kidney transplantation (KT) remains the preferred treatment for patients with end stage kidney disease (ESKD) (1). Although living donor kidney transplantation (LDKT) is less common than deceased donor kidney transplantation (DDKT), it has important advantages in terms of patient and graft survival compared to DDKT (2–4). To ensure the safety and efficacy of LDKT, potential donors undergo a thorough screening process to assess potential risk factors for adverse outcomes of donation. Among these factors, obesity emerges as an important concern due to its association with decreased long-term kidney function through conditions such as hypertension, diabetes, and metabolic syndrome, which can ultimately lead to the development of Chronic Kidney Disease (CKD) and/or ESKD (5, 6). Importantly, donor obesity potentially also impacts recipients (7). KT recipients who receive a kidney from an obese living donor may experience a slight increase in the risk of perioperative complications, delayed graft function and kidney graft loss (6, 8–10). Due to the donor obesity-related health risks for both the donor and the recipient, many centers impose a body mass index (BMI) above 30 kg/m^2 as a relative contra-indication and above 35 kg/m^2 as a hard contra-indication for living kidney donation (11). However, recognizing the inherent limitations of BMI, including its inability to distinguish between muscle mass and fat mass and to differentiate subcutaneous fat from visceral fat, the need of exploring alternative body composition metrics arises. New techniques including radiological imaging have proven to be more precise in measuring different fat and muscle compartments (12). Several KT recipient body composition measures have been linked to adverse post-KT outcomes, resulting in reduced graft function, reduced graft survival and an increased risk of post-KT mortality (13–15). However, little is known about the effect of living kidney donor body composition on post-KT outcomes. An excess of donor fat tissue may have led to direct injury of the donor kidney prior to donation through processes involving increased numbers of adipose-derived molecules and dysregulated metabolites, leading to oxidative stress, inflammation, and kidney fibrosis (16). It may also be possible that, in an effort to meet the increased metabolic demands of the body, hyperfiltration may have occurred prior to donation in overweight or obese donors (17). Glomerular hyperfiltration has been associated with kidney function decline and the development of CKD (18). Transplantation of such a kidney from a donor with a suboptimal body composition type may affect post-transplantation kidney function in the recipient.

Abbreviations: BMI, Body Mass Index; CKD, Chronic Kidney Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DDKT, Deceased Donor Kidney Transplantation; eGFR, Estimated Glomerular Filtration Rate; ESKD, End Stage Kidney Disease; HU, Houndsfield Units; IMAT, Intramuscular Adipose Tissue; IMATi, Intramuscular Adipose Tissue Index; KT, Kidney Transplantation; LDKT, Living Donor Kidney Transplantation; SAT, Subcutaneous Adipose Tissue; SATi, Subcutaneous Adipose Tissue Index; SMA, Skeletal Muscle Area; SMI, Skeletal Muscle Index; TAT, Total Adipose Tissue; TATi, Total Adipose Tissue Index; UMCG, University Medical Center Groningen; VAT, Visceral Adipose Tissue; VATi, Visceral Adipose Tissue Index.

Hence, the goal of this study was to determine the association between living donor body composition, evaluated through conventional measures and computed tomography (CT), and the change in recipient estimated glomerular filtration rate (eGFR) after transplantation. We hypothesized that higher donor BMI, higher waist circumference, and higher values of radiologic adipose tissue measurements are associated with a greater negative change in recipient eGFR after transplantation. Furthermore, we hypothesized that age has an impact on recipient eGFR after transplantation.

Method

Study design and population

In total, 293 pairs of living kidney donors and kidney transplant recipients were included in this study. All transplantations took place between 2002 and 2019 at the University Medical Center Groningen (UMCG, Groningen, the Netherlands). The data were sourced from the TransplantLines Biobank and Cohort Study (ClinicalTrials.gov identifier: NCT03272841), an ongoing, prospective study aiming to assess short- and long-term outcomes in solid organ transplant donors and recipients (19). As part of this study, kidney transplant recipients had their estimated glomerular filtration rate (eGFR) measured at predefined timepoints following transplantation: 3 months, 6 months, 1 year, 2 years, 5 years, 10 years, and then at subsequent five-year intervals.

All solid organ transplantation donors and recipients (aged ≥18 years) were invited to participate and gave written informed consent on enrolment. The study protocol was approved by the local institutional ethical review board (METc 2014/077). All procedures were conducted in accordance with the declaration of Helsinki and declaration of Istanbul. Study-specific exclusion criteria (in addition to those described in the TransplantLines protocol) were the presence of significant interfering artefacts on CT imaging and/or incomplete visualization of the abdominal wall muscles and/or subcutaneous fat tissue on the CT scan.

Data collection

All donors underwent CT imaging as an integral part of the screening protocol for living kidney donation at the UMCG, with the majority (n=292) conducted at the UMCG and one at a non-academic referring hospital in the Netherlands. CT scans were predominantly contrast-enhanced (n=292) (n=2 portal venous phase, n=4 arterial phase, n=286 late phase) and the remaining one was unenhanced. Most scans had a slice thickness of 2 mm (n=284, 97%). Tube voltage ranged from 80-140 kVp (median 100 [IQR 90-100]) and the current varied from 20-455 mAs (mean 89.7 ± 48.1 mAs). For analysis scans at the level of the third lumbar vertebra (L3) were used, which have been shown to correspond with total body mass of skeletal muscle, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) (20). Voxels with densities ranging from -29 to +150 Hounsfield units (HU) indicated muscle tissue and were selected to measure the psoas, paraspinal, and

abdominal wall muscles. The skeletal muscle area (SMA, cm^2) was determined and indexed for donor height^2 (skeletal muscle index, SMI, cm^2/m^2) in accordance with a previous publication by our group (21). Fat tissue, defined by voxels ranging from -190 to -30 HU was assessed for SAT, VAT, and intramuscular adipose tissue (IMAT). Total abdominal adipose tissue (TAT) was calculated as SAT + VAT + IMAT. All adipose tissue measurements were indexed for donor height^2 (m^2) and yielded the subcutaneous adipose tissue index (SATi), visceral adipose tissue index (VATi), intramuscular adipose tissue index (IMATi), and total abdominal adipose tissue index (TATi). All clinical and biochemical parameters were conducted following the protocols outlined in a previous publication (19). eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from 2021 (22).

Statistical analyses

Categorical variables are presented as numbers and percentages and normally distributed continuous variables are presented as a mean ± standard deviation. Linear mixed model analysis was used to investigate possible associations between donor body composition measurements, and recipient post-transplant kidney function over time. This included subgroups of donors with a normal/overweight BMI and high/low intramuscular adipose tissue. Donor body composition measurements were considered fixed effects, as well as their interaction with time (defined as donor body composition measurement * time). The analyses were adjusted for donor age, donor sex, donor pre-donation measured GFR (mGFR) recipient age, and recipient sex, as well as multiplicative interaction terms of these variables with time. The "unstructured" covariance structure was used. The use of "compound symmetry" and "autoregressive" covariance structures did not change the results. Sensitivity analyses were performed in a subset of patients of whom multiple post-transplant eGFR assessments were available. Two-tailed values of p < 0.05 were considered to indicate statistical significance. Statistical analyses were performed using RStudio (PBC, Boston, MA, USA, 2021) and SPSS version 28.0 (IBM, Armonk, USA).

Results

Characteristics of the study population

A total of 293 donor-recipient pairs were included in this study (Table 1). Donor age was 53 ± 11 years and 41% of donors was female. Donor weight was 79.7 ± 12.6 kg, height was 177 ± 10 cm, and BMI was 25.2 ± 3.0 kg/m^2. SMI was 48.3 ± 8.1 cm^2/m^2, TATi was 96.8 ± 39.7 cm^2/m^2, and mGFR at screening for donation was 113.0 ± 22.2 mL/min. Seventy eight donors were classified as being overweight and 70 donors were classified as being within a normal range (Supplementary Table 6). Recipient age at transplantation was 50 ± 13 years, and 42% of recipients were female. Recipient

weight was 81.4 ± 15.6 kg, height was 174 ± 10 cm, and BMI was 26.9 ± 4.6 kg/m^2. The majority of recipients had primary glomerular kidney disease (21.8%), followed by polycystic kidney disease (21.5%), renovascular disease (7.5%), and glomerulonephritis (6.8%). Two hundred and fifty-nine (88.4%) recipients had hypertension prior to transplantation and 41 (14.0%) had pre-existing diabetes mellitus manifested before transplantation. Twenty (6.8%) and 15 (5.2%) experienced delayed graft function and acute rejection, respectively. Supplementary Figure S1 depicts the amount of consecutive post-transplant eGFR measurements per recipient. Median time between transplantation and post-transplant eGFR measurement was 1 year [interquartile range: 0-14 years].

Donor body composition measurements and recipient post-transplantation eGFR

In linear mixed model analyses, adjusted for time and including a multiplicative interaction term of time with the donor body composition measure, no significant associations were found between any donor body composition measure and the annual change in recipient post-transplantation eGFR (donor BMI: B = 0.02, 95%CI -0.10; 0.13, p = 0.79; donor waist circumference: B = 0.01, 95%CI -0.03; 0.05, p = 0.54; donor skeletal muscle index: B = -0.002, 95%CI -0.05; 0.05, p = 0.94; donor skeletal muscle radiation attenuation: B = -0.01, 95%CI -0.06; 0.04, p = 0.65; donor visceral adipose tissue index: B = 0.002, 95%CI -0.01; 0.02, p = 0.76; donor subcutaneous adipose tissue index: B = -0.001, 95%CI -0.02; 0.01, p = 0.87; donor intramuscular adipose tissue index: B = -0.08, 95%CI -0.25; 0.09, p = 0.36; donor total abdominal adipose tissue index: B = 0.00, 95%CI -0.01; 0.01, p = 0.93) (Table 2). Annual change in recipient post-transplantation eGFR was lower in those with a kidney from donors who were overweight and simultaneously had a higher amount of intramuscular adipose tissue compared to those with a kidney from donors who were overweight with a lower amount of intramuscular adipose tissue (B = -1.19, 95%CI -2.29; -0.09, p = 0.04).

Additional adjustments for donor female sex, donor age, donor mGFR, recipient female sex, recipient age, as well as multiplicative interaction terms of these independent variables with time, did not uncover a statistically significant association between donor body composition measurements and annual change in recipient post-transplantation eGFR (Table 3). Neither anthropometric measures of body composition (donor BMI: B = -0.01, 95%CI -0.13; 0.11, p = 0.88; donor waist circumference: B = 0.02, 95%CI -0.02; 0.06, p = 0.38), nor radiologic measures of body composition were associated with recipient post-transplantation eGFR (donor skeletal muscle index: B = -0.02, 95%CI -0.07; 0.04, p = 0.63; donor skeletal muscle radiation attenuation: B = -0.002, 95%CI -0.06; 0.06, p = 0.96; donor visceral adipose tissue index: B = -0.001, 95%CI -0.02; 0.02, p = 0.93; donor subcutaneous adipose tissue index: B = -0.001, 95%CI -0.02; 0.02, p = 0.94; donor intramuscular adipose tissue index: B = -0.12, 95%CI -0.29; 0.06, p = 0.19; donor total abdominal adipose tissue index: B = -0.001, 95%CI -0.01; 0.01, p = 0.89).

TABLE 1 Baseline characteristics of the study population.

Variable	Number (%), mean ± SD or median [IQR]
Number of participants	
Donors	293
Recipients	293
Donor characteristics	
Age (years)	53 ± 11
Women (n, %)	119 (40.6%)
Body composition	
BMI (kg/m^2)	25.2 ± 3.0
Waist circumference (cm)	89.8 ± 9.8
SMI (cm^2/m^2)	48.3 ± 8.1
SMRA (Hounsfield Units)	50.4 ± 6.8
VATi (cm^2/m^2)	39.9 ± 24.1
SATi (cm^2/m^2)	52.6 ± 25.1
IMATi (cm^2/m^2)	4.4 ± 2.2
TATi (cm^2/m^2)	96.8 ± 39.7
mGFR (ml/min)	113.0 ± 22.2
Recipient characteristics	
Age at transplantation (years)	50 ± 13
Women	124 (42.3%)
eGFR follow-up (years)	3.88 ± 1.86
Hypertension	259 (88.4%)
Diabetes Mellitus	41 (14.0%)
BMI (kg/m^2)	26.9 ± 4.6
Etiology of kidney disease	
Primary glomerular disease	64 (21.8%)
Glomerulonephritis	20 (6.8%)
Polycystic kidney disease	63 (21.5%)
Renovascular	22 (7.5%)
Diabetes	15 (5.1%)
Dysplasia	14 (4.8%)
Other/unknown	95 (32.4%)
Cold ischemia time (minutes)*	157 [37.50]
1st warm ischemia time (minutes)	3 [1]
2nd warm ischemia time (minutes)*	40 [12]
Delayed graft function	20 (6.8%)
Acute rejection	15 (5.2%)

*in case of more than one cold ischemia time and/or more than two warm ischemia times, additional minutes were added to the cold ischemia time and 2nd warm ischemia time.

TABLE 2 Time-adjusted linear mixed model analyses of donor body composition measurements and post-transplantation kidney function trajectory.

Donor body composition measurements	Recipient post-transplantation eGFR		
	B	95% CI	p
Donor BMI	0.02	-0.10; 0.13	0.79
Donor waist circumference	0.01	-0.03; 0.05	0.54
Skeletal muscle index	-0.002	-0.05; 0.05	0.94
Skeletal muscle radiation attenuation	-0.01	-0.06; 0.04	0.65
Visceral adipose tissue index	0.002	-0.01; 0.02	0.76
Subcutaneous adipose tissue index	-0.001	-0.02; 0.01	0.87
Intramuscular adipose tissue index	-0.08	-0.25; 0.09	0.36
Total abdominal adipose tissue index	0.00	-0.01; 0.01	0.93

B: annual change in recipient post-transplantation eGFR for every 1-unit increase in body composition measurement.

Higher donor age was consistently significantly associated with lower recipient eGFR, although its interaction with time was not significantly associated with recipient eGFR (Supplementary Tables S1, S2).

Multiple post-transplant eGFR assessments were available for 161 (55%) recipients. Sensitivity analyses with only this subgroup of the study population did not substantially change the results, which are shown in Supplementary Tables 4, 5.

TABLE 3 Adjusted linear mixed model analyses of donor body composition measurements and post-transplantation kidney function trajectory.

Donor body composition measurements	Recipient post-transplantation eGFR		
	B	*95% CI*	*p*
Donor BMI, kg/m^2	-0.01	-0.13; 0.11	0.88
Donor waist circumference, cm	0.02	-0.02; 0.06	0.38
Skeletal muscle index	-0.02	-0.07; 0.04	0.63
Skeletal muscle radiation attenuation	-0.002	-0.06; 0.06	0.96
Visceral adipose tissue index	-0.001	-0.02; 0.02	0.93
Subcutaneous adipose tissue index	-0.001	-0.02; 0.02	0.94
Intramuscular adipose tissue index	-0.12	-0.29; 0.06	0.19
Total abdominal adipose tissue index	-0.001	-0.01; 0.01	0.89

linear mixed models consist of: donor body composition measurement + time (years) + donor female sex + donor age (years) + donor measured glomerular filtration rate (ml/min) + recipient female sex + recipient age (years) + time*body composition measurement + time*donor female sex + time*donor age + time*donor measured glomerular filtration rate + time*recipient female sex + time*recipient age.
B: annual change in recipient post-transplantation eGFR for every 1-unit increase in body composition measurement.

Discussion

We initially hypothesized that higher donor BMI, waist circumference, and radiologic fat tissue measurements are associated with a greater negative change/GFR reduction over time in recipients eGFR after transplantation. However, the results of this study show that, in donors with relatively "normal" body sizes, living kidney donor body composition is not associated with post-transplantation kidney function over time in kidney transplant recipients. Additionally, our findings revealed that annual change in recipient post-transplantation eGFR was lower in those with a kidney from donors who are overweight and simultaneously have a higher amount of intramuscular adipose tissue compared to overweight donors with a lower amount of intramuscular adipose tissue. While donor body composition appears to impact long-term kidney function in the donor, it does not exert a discernible effect on kidney function outcomes for the recipient in this specific study population.

To our knowledge, this is the first study to explore the relationship between living kidney donor body composition and recipient kidney function after living donor kidney transplantation. While this area is relatively unexplored in kidney transplantation, results from other fields of organ transplantation, such as liver transplantation, offer valuable perspectives. For instance, in liver transplantation, high muscle mass and quality in male donors were found to be a protective factor of allograft loss after living donor liver transplantation, while in female donors these factors did not affect allograft loss (23). Similarly, high intramuscular adipose tissue content among living liver donors was identified as an independent risk factor for 6-month graft survival (24). These associations are attributed to the secretion of myokines which influence adipose tissue mass and fat deposition in the liver (25, 26). It is possible that similar mechanisms may influence outcomes in kidney transplantation. Our study suggests that muscle quality in overweight living kidney donors affects recipient kidney function. Further research is needed to explore these potential relationships in kidney transplantation to better understand the underlying biological mechanisms.

In the context of living kidney donation, donor characteristics such as obesity and age have been shown to influence transplant outcomes. A recent systematic review and meta-analysis found that living kidney donor obesity (BMI > 30) affects the incidence of delayed graft function, but not the incidence of acute rejection in recipients (9). Moreover, obese donor recipient pairs were found to be at a higher risk for death censored graft loss, all-cause graft loss, early graft loss and delayed graft function compared to non-obese pairs (27). Other factors such as age also play an evident role in recipient outcomes. Age is not only closely related to body composition but can also independently impact kidney function (28–30). Our study shows that donor age seems to be a determinant of recipient post-transplant kidney function levels, although it was not associated with post-transplantation change in kidney function over time. A meta-analysis showed that one-year serum creatinine was significantly lower in kidney transplant recipients from donors aged <60 years compared to donors aged >60 years (9). Further

exploration of these factors may enhance risk stratification strategies and optimize transplant outcomes, ultimately benefiting both donors and recipients alike.

The clinical implications of our results are multifaceted. Our findings suggest that, in the context of kidney transplantation with a graft from a living donor with a relatively "normal" body size, assessing living donor body composition may not be a critical determinant of post-transplant recipient kidney function. Instead, it may be more important to focus on other donor factors, such as age, to ensure post-transplant success. Obesity has been associated with peri- and postoperative complications such as wound infections, increased surgical blood loss and longer operation time (27). After donation, literature suggests that kidney donor body composition is associated with for example donor (long-term) kidney function, risk of developing end-stage kidney disease, and mortality (28, 31–34). Therefore, assessing and possibly improving donor body composition could still be of interest for the (long-term) health of the kidney donor, although further investigation is necessary to establish this link.

The study's strength lies in its use of both conventional (anthropometric) techniques and radiologic measurements for body composition assessment. However, limitations include the retrospective design of the single center study in The Netherlands, the inability to adjust for race due to population homogeneity, and the exclusion of donors with a pre-donation BMI of $\geq$35 kg/m^2, cautioning against generalizing the results to more diverse populations. Additionally, the absence of standardized normal or cut-off values for body composition indices hampers the comparability of these results with other studies. Therefore, establishing reference values for body composition indices should be a key focus of future research, both for donors and recipients. Nevertheless, the evidence provided supports the notion that transplanting kidneys from living donors with a BMI below 35 kg/m^2 does not appear to affect recipient post-transplant kidney function, encouraging further exploration in larger, more diverse cohorts. In addition, the study not only expands knowledge within the specific context of kidney transplantation but also contributes to the broader field of body composition research by advocating for more comprehensive and sophisticated measurement techniques. This emphasis on methodological improvement holds the potential to enhance the accuracy and applicability of body composition assessments in diverse clinical and research settings and can contribute to better outcomes for both living kidney donors and recipients.

In conclusion, this study, using a combination of anthropometric and radiologic measurements, provides insights into the association between living kidney donor body composition and kidney function in kidney transplant recipients. These results stem from a cohort of living kidney donors with relatively "normal" body sizes, suggesting that in the context of transplanting kidneys from living donors with a BMI below 35 kg/m^2, pre-donation body composition does not affect post-transplantation recipient kidney function. These results invite further investigation in larger, more heterogenous study populations to refine our understanding of these relationships.

Data availability statement

Ethics statement

The studies involving humans were approved by METc, University Medical Center Groningen. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

EQ: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. LW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. GN: Writing – original draft, Writing – review & editing. Ev: Data curation, Writing – original draft, Writing – review & editing. MZ: Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. AV: Writing – original draft, Writing – review & editing. SB: Methodology, Supervision, Writing – original draft, Writing – review & editing. IN: Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. Mv: Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. RP: Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneph.2024.1467669/full#supplementary-material

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