Effect of Visceral, Subcutaneous and Retroperitoneal Adipose Tissue on Renal Function After Living Donor Nephrectomy: A Retrospective Analysis of 69 Cases

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Purpose: Recent studies reported that the presence of metabolic syndrome is closely correlated with impaired kidney function after living donor nephrectomy. Since the measurement of body mass index cannot differentiate the amount of body adipose tissue from total body weight, body mass index is not a reliable parameter for determining metabolic syndrome. In the present study, we investigated the correlation between body adipose tissue and kidney function recovery following living donor nephrectomy.

Materials and Methods: The patients who underwent living kidney donor nephrectomy consequently from July 2016 through December 2017 were enrolled in the study. We preoperatively measured the visceral (VAdT), retroperitoneal (RPAdT), and subcutaneous (SCAdT) adipose tissue volume by a computed tomography scan. Body mass index, adipose tissue measurements, and postoperative estimated glomerular filtration rate (eGFR) were evaluated.

Results: The decrease between preoperative eGFR, and the first day, the first month and the sixth month eGFR after surgery were statistically significant ($P = .001$; $P = .001$; $P = .001$, respectively). The negative correlation between VAdT/SCAdT measurements and changes in eGFR at the first and the sixth postoperative month compared to preoperative eGFR were statistically significant ($P = .049$; $P = .041$, respectively). Additionally, RPAdT measurements and changes in eGFR at the first and the sixth postoperative month compared to preoperative eGFR (decreasing as RPAdT value increased) were statistically significant ($P = .035$; $P = .026$, respectively).

Conclusion: According to a preoperative computed tomography scan, VAdT, RPAdT, and VAdT-to-SAdT ratio can predict impaired kidney function recovery. Furthermore, RPAdT measurement is a new variable to predict the impaired kidney function after living donor nephrectomy.

Keywords: adipose tissue; donor nephrectomy; kidney; metabolic syndrome; retroperitoneal; visceral

INTRODUCTION

Being a kidney donor increases the risk of renal impairment and the possibility of being a chronic kidney disease patient in the future.[1,2] Recent studies showed that the presence of metabolic syndrome is an independent risk factor for the development of chronic kidney disease.[1,3-6] Metabolic syndrome has two main components, increased body mass index (BMI) (obesity) and increased blood pressure (hypertension).

We think the selection of a living kidney donor is a crucial process. Many studies or guidelines have tried to present the best criteria for the selection of the living kidney donors.[7-9] However, none of these studies or guidelines may fully guarantee the safety of the living donor in perioperative or postoperative period. The calculation of BMI gives no idea about the distribution of abdominal adipose tissue or visceral obesity, which have been linked to the risk of microalbuminuria and chronic kidney disease.[1,3,10,11] For this reason, the current living donor selection criteria should be modified. In the present study, we aimed to assess the distribution of abdominal adipose tissue and recovery of kidney function after living kidney donor nephrectomy. Also, this study may show the importance of preoperative evaluation of adipose tissue potentially may lead to getting better outcomes in living donors after donor nephrectomy procedure.

MATERIALS AND METHODS

Selection of donor candidates

All of the kidney donor candidates had detailed blood and urine tests and renal computed tomography (CT) angiography. Candidates who were found to be healthy were considered as kidney donors. Patients with comorbid disease and alcohol and cigarette dependence were not considered as living kidney donor candidates in the institution where the present study was conducted.

Inclusion criteria: The patients who underwent living kidney donor nephrectomy consequently from July 2016 through December 2017 at Istanbul Okan University Hospital and Research Center were enrolled in this observational cohort study.

Exclusion criteria: The patients who had computed tomography angiography at another institution, who did

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Table 1. Spearman Correlation coefficient interpretation guideline

r	Description of strength
0.00 — 0.19	Very weak
0.20 — 0.39	Weak
0.40 — 0.59	Moderate
0.60 — 0.79	Strong
0.80 — 1.00	Very strong

not want to participate in the study protocol, and who had a follow-up period of less than six months were excluded from the study (**Figure 1**).

Surgical procedure

The same two surgeons performed all surgical procedures by using the video-assisted mini-incision technique, which was described and standardized by Choi KH et al.[12]

Evaluation of the individuals: We evaluated routine blood tests, renal CT angiography for all individuals. After laparoscopic kidney donor nephrectomy, routine blood tests were performed until the patients were discharged. Since Choi et al. stated that the time when the renal functions were stabilized in kidney donor patients was six months after surgery, we followed our patients for six-months.[13] We calculated their estimated glomerular filtration rate (GRF) (calculated by using Modification of Diet in Renal Disease Formula, GFR (mL/min/1.73 m2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American))[14] preoperatively, first, and the sixth month of the nephrectomy. Body mass index (BMI) was calculated according to the formula: the bodyweight/ height in meters squared. Patients with BMI $\geq$ 30kg/m^2 were defined as obese.[15] The body surface area was calculated according to the formula described by Mosteller.[16]

Radiologic evaluation

Total intraabdominal and subcutaneous (SCAdT) adipose tissue were measured at the level of the umbilicus using CT axial slice (Optima CT 660, General Electric Medical Systems, Milwaukee, Wisconsin, USA) (**Figure 2**). Total intraabdominal adipose tissue was divided into two part including retroperitoneal adipose tissue (RPAdT) and visceral adipose tissue (VAdT) (Total intraabdominal adipose tissue= VAdT + RPAdT). After the margin of the intraabdominal cavity and subcutaneous soft tissue were delineated on the CT slice, the volumes of total intraabdominal and SCAdT were calculated by a single radiologist (10-year experienced) using CT software (GE AW 4.7 Work Station, Volume and Threshold tools, General Electric Medical Systems, Milwaukee, Wisconsin, USA). This software electronically defines adipose tissue volume by setting the attenuation values for a region of interest within a range of -50 to -250 Hounsfield. RPAdT was calculated in the same way margining border of the retroperitoneal area. The VAdT was calculated by subtracting the RPAdT value from total intraabdominal adipose tissue.

Ethical approval: All procedures performed in studies involving human participants were following the Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was also reviewed and approved by the ethics committee of Istanbul Okan University, Istanbul (No: 104, Date: March 13, 2019). All individuals gave written informed consent

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The suitability of the quantitative data for normal distribution was tested with the Shapiro-Wilk test and graphical analysis. The Kruskal-Wallis test was used for comparison of more than two groups of quantitative variables those were not normally distributed. Bonferroni corrected paired evaluations were used for intra-group comparisons of quantitative variables showing normal distribution, repeated measures analysis of variance, and paired comparisons. Wilcoxon signed-ranks test was used for intra-group comparisons of quantitative variables that were not normally distributed. Spearman correlation analysis was used to evaluate the relationships between quantitative variables (**Table 1**).[17] Statistical significance was accepted as $p < .05$.

RESULTS

Twenty-seven caucasian male, thirty-two caucasian

Table 2. Patients characteristics and adipose volume measurements

Age (year)	Min-Max (Median)	20-71 (44)
	Mean ± SD	44.09 ± 13.54
Gender	Female	32 (54.2%)
	Male	27 (45.8%)
BMI (kg/m2)	Min-Max (Median)	18.6-40.23 (28.2)
	Mean ± SD	28.30 ± 4.44
BSA (m2)	Min-Max (Median)	1.33-2.28 (1.85)
	Mean ± SD	1.86±0.19
Hospitalization time (day)	Min-Max (Median)	2-9 (3)
	Mean ± SD	3.61 ± 1.39
SCAdT (cm3)	Min-Max (Median)	4.58-190.03 (35.98)
	Mean ± SD	54.13 ± 47.42
VAdT (cm3)	Min-Max (Median)	376.89-10368.71 (2923.85)
	Mean ± SD	2846.84 ± 1694.85
RPAdT (cm3)	Min-Max (Median)	39.49-4690.36 (1028.25)
	Mean ± SD	1200.21 ± 879.44
VAdT/SCAdT	Min-Max (Median)	5.79-312.77 (71.41)
	Mean ± SD	84.99 ± 70.13

*BMI: Body mass index, BSA: Body surface area, SCAdT: Subcutaneous adipose tissue, VAdT: Visceral adipose tissue, RPAdT: Retroperitoneal adipose tissue, PAdT: Peritoneal adipose tissue

Table 3. Evaluation of the Relationship Between Changes in eGFR and BMI and Adipose Tissue

			Preoperative-1st day	Preoperative-1st Month	Preoperative-6th month
Donor BMI (kg/m^2)	≥ 30 (Obese) (n=29)	r	0.023	0.038	-0.275
		p	.860	-775	.035*
	<30 (Non-obese) (n=40)	r	0.157	0.023	0.038
		p	.235	.860	.775
SCAdT		r	0.267	0.034	0.189
		p	.041*	.797	.152
VAdT		r	0.097	-0.301	-0.428
		p	.465	.021*	.036*
RPAdT		r	0.122	-0.232	-0.205
		p	.359	.035*	.026*
VAdT/SCAdT		r	-0.099	-0.256	-0.467
		p	.457	.049*	.041*

d = Spearman's correlation coefficient *$p < 0.05$ **$p < 0.01$
eGFR: Estimated glomerular filtration rate. BMI: Body mass index. SCAdT: Subcutaneous adipose tissue. VAdT: Visceral adipose tissue. RPAdT: Retroperitoneal adipose tissue.

female, included to study with a mean age was 44.09 ± 13.54, and follow-up time was six-months. **Table 2** shows patient characteristics and adipose volume measurements.

The relationship between preoperative eGFR and the first day, first month and sixth month eGFR decrement (23.07 ± 23.2 mL/min/m^2, 36.67 ± 14.69 mL/min/m^2, 31.71 ± 13.66 mL/min/m2) were statistically significant (p = .001; p = .001; p = .001, respectively; Bonferroni Test, p <.01) (**Figure 3**).

BMI, VAdT and SCAdT measurements had a statistically significant correlation with each other (p = .035, Pearson correlation, p <.05). Relationship between changes in eGFR and adipose tissue measurements was demonstrated on Table 3. The negative correlation between VAdT/SCAdT measurements and changes in eGFR at the first and the sixth postoperative month compared to preoperative eGFR (decreasing as VAdT/SCAdT value increased) were statistically significant (r = -0.256; p = .049 and r = -0.267; p = .041, respectively). Additionally, RPAdT measurements and changes in eGFR at the first and the sixth postoperative month compared to preoperative eGFR (eGFR decreases as RPAdT value increase) were statistically significant (r = -0.232; p = .035 and r = -0.205; p = .026, respectively). Also, there is a positive correlation between changes in eGRF at the sixth postoperative month in patients with BMI ≥ 30 kg/m^2 (r = 0.275; p = .035). However, no correlation was observed between eGFR changes and BMI in patients with BMI < 30 kg/m^2.

DISCUSSION

We investigated the accuracy of evaluating the fat composition of the kidney donor to predict delayed kidney function, and find out that RPAdT, VAdT, and VAdT-to-SCAdT ratio are significantly associated with an impaired kidney function of the donor patient.

It is well known that metabolic syndrome and its components, obesity, hyperglycemia, and hypertriglyceridemia are closely correlated with impaired kidney function.[18,19] Also, many studies demonstrated that the presence of obesity is linked to impaired postoperative kidney function in kidney donors.[1,3,18,19] Studies from the USA and Sweeden (The Framingham Offspring

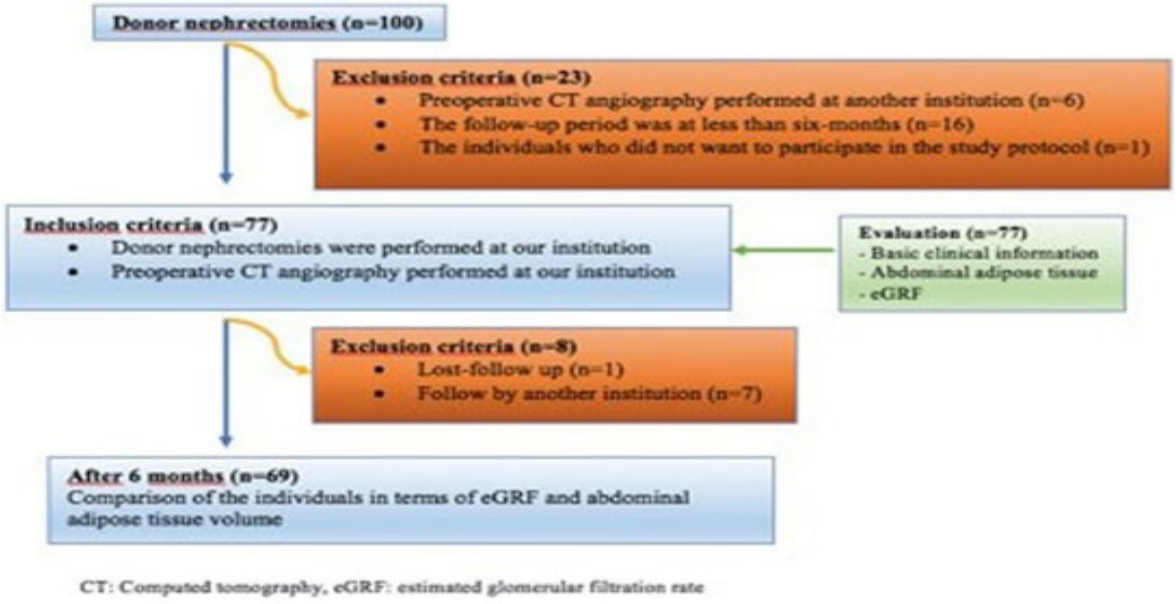

Figure 1. Scheme of the present study

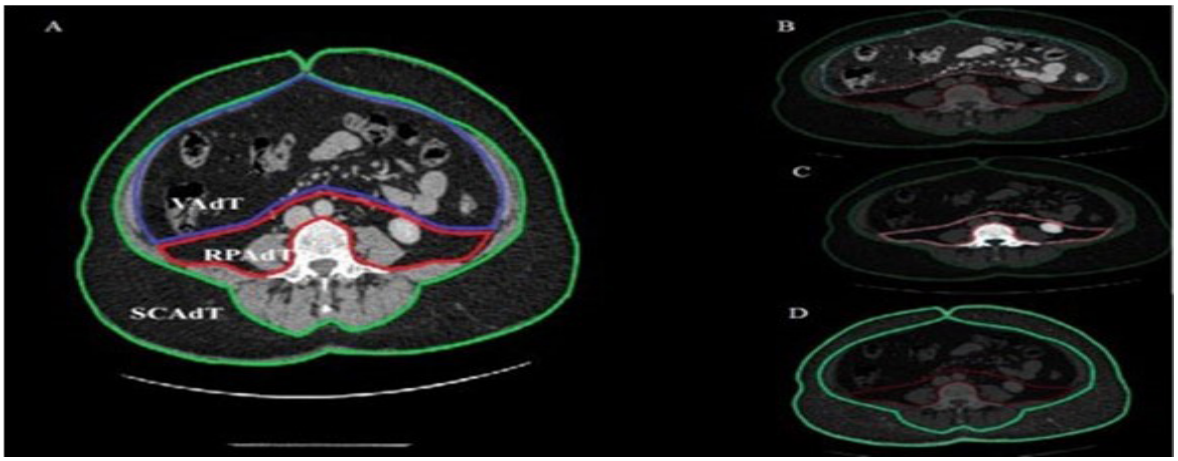

Figure 2. A. Demonstration of SCAdT, VAdT, RPAdT*; **B.** VAdT; **C.** RPAdT; **D.** SCAdT *SCAdT: subcutaneous adipose tissue, VAdT: Visceral adipose tissue, RPAdT: Retroperitoneal adipose tissue

cohort and the Hypertension Detection and Follow-up Program) have revealed that higher BMI is linked with impaired kidney function.[20-22] Locke et al. also showed that obesity was independently associated with an increased risk for ESRD in living kidney donors.[23]

BMI can be easily calculated, and it has been generally used as a reliable anthropometric index of obesity.[24] However, BMI is not a reliable anthropometric measure due to changes in body fluid distribution in patients candidate for kidney transplantation. Moreover, generally accepted BMI norms for determining obesity do not reflect the degree of visceral obesity.[25,26] Additionally, whether visceral obesity quantitatively measured by VAdT, SCAdT, RPAdT, and VAdT-to-SCAdT quotient before the surgery estimate results in living kidney donor have not been well researched.

Numerous studies prove that VAdT has various endocrine, metabolic, and inflammatory roles.[27-30] Many hypotheses have been proposed to explain this enigma of VAdT and metabolic syndrome. The bloodstream of peritoneal and retroperitoneal fatty tissue differs from each other. One idea is that the veins of peritoneal fatty tissue drain into the portal venous system. This drainage may cause an increase in free fatty acid levels in the liver, which may lead to insulin resistance, high triglyceride concentrations, and low HDL cholesterol concentrations.[31,32] Also, Naya et al. demonstrated the increased proinflammatory effect of visceral fat accumulation.[26] Cornier MA et al. showed the role of elevated free fatty acid levels in the portal system, and the endocrine role of adipokines in metabolic syndrome.[33] We think, VAdT analysis ($r = -0.428$; $p = .036$, moderate correlation at sixth month eGFR change, Spearman correlation analysis) might be a more reliable and precise parameter to predict a metabolic syndrome component and the possibility of incoming chronic kidney disease following donor nephrectomy than BMI ($r = -0.275$; $p = .035$; weak correlation at sixth month eGFR change, Spear-

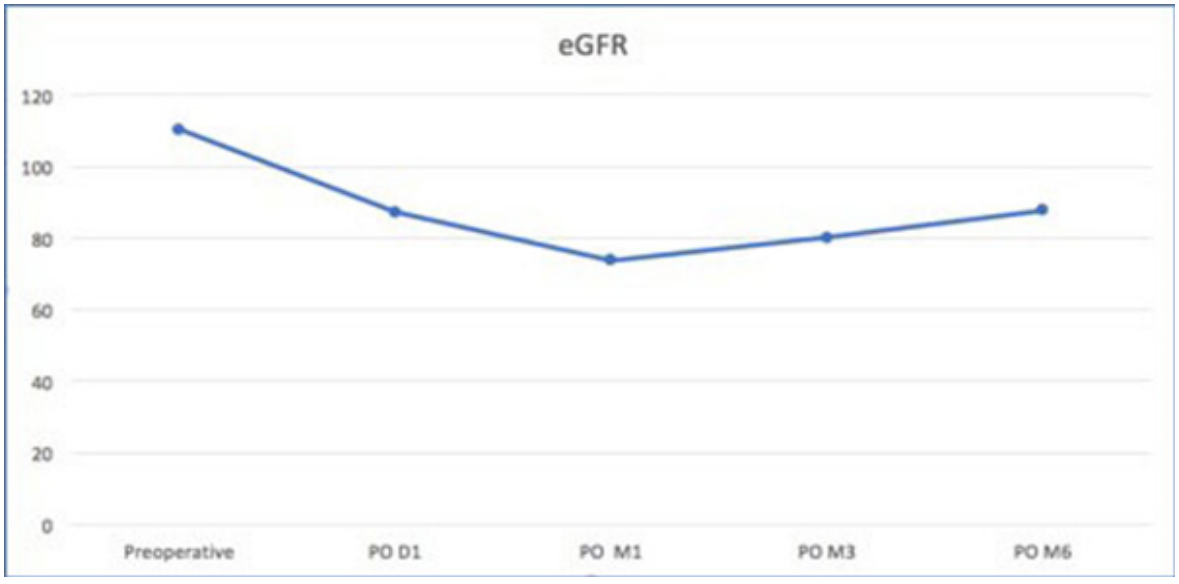

Figure 3. Estimated glomerular filtration rate in preoperative and postoperative period (calculated by using Modification of Diet in Renal Disease Formula, GFR (mL/min/1.73 m^2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American)); PO D: Postoperative Day, PO M: Postoperative Month

man correlation analysis), which is affected by different determinants, including adipose tissue, muscles, bones, body water, and other organs.

Lee et al. showed the importance of visceral and subcutaneous adipose tissue in estimating forthcoming kidney disease in kidney donors.[1] Like the study of Lee et al., we found a negative correlation between eGFR and VAdT/SCAdT ratio (r = -0.467; p = .041; moderate correlation at sixth-month eGFR change, Spearman correlation analysis). Previous studies proved that the VAdT-to-SCAdT ratio is an indicator of visceral obesity.[34] Several studies demonstrated negative outcomes of elevated VAdT-to-SCAdT ratio.[1,3,35,36] Ghigliotti et al. showed the different cytokine synthesis profile of VAdT and SCAdT, and proposed that, although the VAdT has more tendency to produce proinflammatory cytokines such as TNF-α and IL-6, SCAdT has more tendency to produce anti-inflammatory cytokines.[37] We think defining the imbalance between visceral and subcutaneous adipose tissue and the probability of excessive inflammation, which is a known factor for impaired kidney functions, may ease to estimate fort coming delayed kidney function of the donor patient.

Retroperitoneal fat is similar to peritoneal fat, which is associated with metabolic syndrome, and related to inflammation, hypertension, and obesity.[26] Another interesting finding of our study demonstrated that the amount of RPAdT was correlated with the decrease in eGFR after donor nephrectomy (r = -0,205; p = .026, the weak correlation at sixth-month eGFR change, Spearman correlation analysis). Unlike the visceral venous system, the venous system of the retroperitoneal fatty tissue drains into kidney veins or caval venous systems, which leads to a "fatty kidney" which is associated with hypertension. Also, this adipose tissue consists of an increased amount of brown adipose tissue, which has a known interaction with obesity and metabolic syndrome ergo possible cause of delayed kidney function.[38]

Even it has impressive outcomes, this study should be considered in light of several limitations. First, retrospective, single-institution conducted nature, and the limited number of individuals are the main limitations of the present study. Second, the possibility of sampling bias exists in terms of patient inclusion in the study group, because six patients (6%) were excluded from the study protocol, only because they had not undergone preoperative radiological evaluation at another institution. Therefore, there was likely to selection bias in the study. We think performing this research in the prospective form with longer follow-up time would improve the reliability and quality of the study. Moreover, overlooking the comorbidities may be the third limitation of the present study. However, living kidney donors are not drawn from the general population, and they are healthy at baseline. Also, living donors are very carefully screened in preoperative evaluation, and the impact of obesity might be different in these healthier individuals.

CONCLUSIONS

Evaluation of visceral adiposity before donor nephrectomy procedure closely involved with postoperative impaired kidney function in living kidney donors. To improve outcomes of kidney donor after surgery, it is essential to clarify the enigma between visceral adiposity and kidney functions. Also, obesity definition, which is determined only by BMI calculation neglects visceral adiposity. Therefore, the diagnostic criteria for obesity, and accordingly, diagnostic criteria for the metabolic syndrome, should be updated to include visceral adiposity.

CONFLICT OF INTEREST

No conflict of interest of financial ties was declared by the authors.

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