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ORIGINAL ARTICLE

Visceral obesity in Asian living kidney donors significantly impacts early renal function after donor nephrectomy

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Abstract

Introduction Obesity may be a risk factor for kidney donors to develop reduced renal function. The Framingham heart study suggested that visceral adipose tissue (VAT) confers a more adverse metabolic profile compared with subcutaneous adipose tissue (SAT). Asians tend to have a higher VAT composition and it is unclear if their kidney function is affected differently. We hypothesized that Asian living kidney donors who have visceral obesity are at a higher risk of renal function deterioration 1 year after donation.

Methods Between 2011 and 2014, we retrospectively evaluated data from 73 consecutive patients (52% male; mean age 44.9 ± 11.7 years) before they underwent donor nephrectomy and at their 1 year routine follow-up. VAT and SAT were measured at the level of the umbilicus on pre-operative computerized tomography (CT). Visceral obesity (VO) was defined as a VAT > 100 cm [2] and patients were then further divided and compared in two subgroups: VAT > 100 and < 100 cm [2]. Estimated glomerular filtration rate (eGFR, mL/min per 1.73 m [2]) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation pre-operatively and 1 year post-operatively.

Results Both subgroups had similar baseline kidney function (P = NS) pre-operatively. At the 1 year follow-up, patients with VO experienced a more significant decline of renal function (109 ± 9 to 89 ± 8 mL/min per 1.73 m^2), compared to those without VO (111 ± 12 to 96 ± 11 mL/min per 1.73 m^2, $P = 0.013$). VO was associated with a body mass index (BMI) > 25 kg/m^2 ($P < 0.001$), male gender ($P < 0.001$) and older age at the time of donor nephrectomy (48.0 vs 39.5 years, $P = 0.01$). The presence of hypertension or hyperlipidaemia pre-operatively, choice of surgical approach, and post-operative complication rates, did not differ significantly between the subgroups.

Conclusions Visceral obesity as defined by VAT > 100 cm^2 at the level of the umbilicus on cross-sectional imaging, may have a significant impact on early renal function after donor nephrectomy. Adiposity markers, as measured by cross-sectional CT imaging, may be incorporated into routine pre-operative kidney donor workup.

Keywords Visceral obesity · Obesity · Nephrectomy · Donor · Donor nephrectomy · Transplantation · Chronic kidney disease · CKD · CKD-EPI

Introduction

Obesity, defined by a body mass index (BMI) of at least 30 kg/m^2, is a known risk factor for the development of chronic kidney disease (CKD), and is a growing problem in industrialized countries. Obesity is also closely associated with other comorbidities including cardiovascular disease, diabetes mellitus and hypertension [1, 2].

Many studies in the literature [3, 4] have used BMI as an indicator of the degree to which a patient is overweight, but its utility does not accurately reflect the distribution of adipose tissues among individuals, and also fails to distinguish between visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) compartments. The Multicultural Community Health Assessment Trial (M-CHAT) [5] showed that BMI significantly underestimated VAT in all non-European groups, particularly in the Chinese and South Asian cohorts. VAT has been considered to be the more pathogenic adipose

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compartment, and independently confers a higher risk of metabolic syndrome, hypertension, impaired fasting glucose, and diabetes mellitus than SAT [6].

This problem is accentuated in the Asian population; previous studies have shown that at any given BMI, Asians have a greater amount of body fat and visceral adiposity [7]. For the same BMI, body fat in Asians is higher by 3–5% [8]. Asians also tend to accumulate visceral fat without developing generalized obesity, compared with Caucasian counterparts [9].

In this study, we examined the impact of VAT in an Asian population on early renal function after donor nephrectomy. We hypothesized that, even with a normal BMI and without diabetes, Asian living kidney donors who have visceral obesity are at higher risk of renal function decline 1 year after donation.

Methods

Study population

We performed a retrospective analysis of data obtained from patients who had undergone donor nephrectomy through the National University Centre for Organ Transplantation (NUCOT) clinic in Singapore over 4 years, from January 2011 to December 2014. The data was collected according to an approved institutional review board protocol. Preoperatively, a multi-disciplinary team including transplant surgeons, transplant nephrologists, psychiatrist and medical social worker rigorously assessed all living kidney donors (LKD). Assessment of our LKDs adhered to the Amsterdam Forum [10] and LKDs proceeded to donation after review and approval by the institutional ethics review committee. Donor nephrectomy was performed either using an open technique via a flank incision, or hand-assisted laparoscopic donor nephrectomy (HALDN) technique via a midline handport, or a pure laparoscopic technique with a Pfannenstiel extraction incision as described previously [11, 12]. Postoperatively, all LKDs were initially seen 6 weeks after surgery, then 6 months later, and annually thereafter, unless otherwise clinically indicated.

Our inclusion criteria included at least 1 year of follow-up post donor nephrectomy, patients undergoing pre-operative single-slice CT which included the level of the umbilicus (L4–L5), patients who underwent pre and post-operative eGFR assessment, and 24 h urinary protein collection.

VAT and visceral obesity

VAT was pre-operatively measured using a cross-sectional CT scan obtained at the level of the umbilicus (L4-L5) using the Medical Imaging Interaction Toolkit (MITK) software (German Cancer Research Center, Division of Medical Image Computing, Germany).

Total adipose tissue (TAT), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT) were measured according to a procedure described and validated previously [13–15]. Briefly, the tomographic attenuation of adipose tissue was defined to be between − 50 and − 50 HU. SAT was defined by manual contour tracing, and VAT was calculated by subtracting SAT from TAT (Fig. 1). All the measurements were completed by a single experienced radiologist who was blinded to the clinical details of the subject.

For the purpose of analysis, the patients were then classified into two groups as follows: Viscerally non-obese (VNO) with VAT < 100 cm [2] (Group 1) and Visceral obesity (VO) > 100 cm [2] (Group 2), in accordance with the VAT cutoff prescribed by the Japan Society for the Study of Obesity [16–18] and Hiuge-Shimizu's VACATION-J Study [19].

Renal function assessment

We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to assess renal function in this study. The CKD-EPI equation has been shown to be an appropriate and validated measurement tool in living donors with eGFR levels > 60 mL/min/1.73 m [2], compared to the Modification of Diet in Renal Disease (MDRD) equation [20, 21]. The CKD-EPI equation has also been specifically validated in our local kidney donor population [21] against nuclear glomerular filtration rate. We assessed eGFR preoperatively and at the 1 year follow-up.

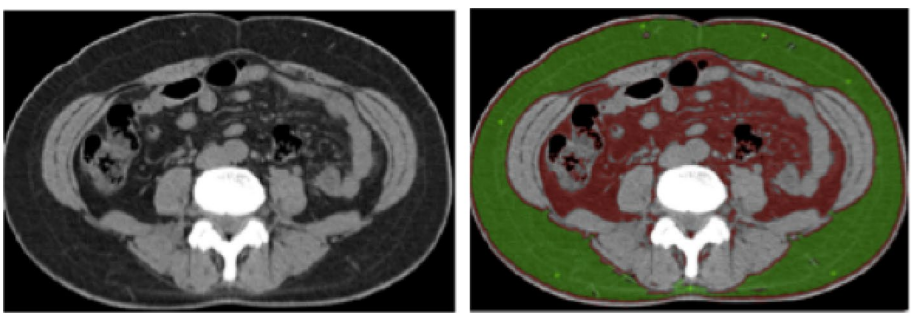

Fig. 1 CT scan at the level of the umbilicus. Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) coloured in red and green, respectively

Statistical analysis

The patients were divided into two groups according to whether they had visceral obesity before surgery (VNO and VO). Demographic and clinical characteristics of the patients were summarized using frequencies and percentages for categorical variables, means and standard deviations for continuous variables which were approximately normally distributed and median and range for continuous variables with skewed distribution. Clinical variables analysed included age, gender, body mass index (BMI), and renal hilar anatomy. Standard hilar anatomy included one renal artery and vein, versus complex anatomy, which included multiple arteries and/or veins. Fisher's exact test, Chi square test, independent two-sample t test and Wilcoxon rank-sum test were used to compare baseline features and post-operative outcomes as appropriate.

All statistical analyses were generated using STATA software, version 11 (StataCorp LP, College Station, TX, USA), assuming a 2-sided test at the conventional 0.05 level of significance.

Results

Baseline demographics

A total of 73 consecutive patients who had undergone donor nephrectomy performed at NUCOT were identified and evaluated for recruitment into this study. There were no missing data as all the donors were compliant to their follow-up outpatient visits and investigations.

The demographics and clinicopathological characteristics of the 73 patients are presented in Tables 1 and 2. There were 43 patients (58.9%) with a VAT < 100 cm^2, the rest were classified as having visceral obesity (41.1%). Visceral obesity was associated with a BMI > 25 kg/m^2 ($p < 0.001$), male gender ($p < 0.001$), and older age (48.0 vs 39.5, $p = 0.003$) at the time of donor nephrectomy.

Importantly, there was no significant difference in eGFR pre-operatively. The 24-h urinary protein levels, renal hilar anatomy, or the presence of comorbidities (controlled hypertension, diabetes mellitus, hyperlipidaemia and smoking history) between the two subgroups were not significantly different as well. This implies both patient groups (VO and VNO) were comparable for conventional risk factors for impaired renal function at baseline before donor nephrectomy.

Surgical outcomes and renal function follow-up

Table 2 presents the perioperative surgical outcomes after nephrectomy. The type of donor nephrectomy (open vs minimally invasive), length of index admission, post-operative complications, and incident diabetes, hypertension, and hyperlipidaemia at 1 year also did not differ significantly between the two subgroups.

Both subgroups demonstrated similar renal function ($p = 0.56$) pre-operatively, but at the 1 year follow-up, patients with VO experienced a greater decline of renal function (109 ± 9 to 89 ± 8 mL/min per 1.73 m^2), compared to those without VO (111 ± 12 to 96 ± 11 mL/min per 1.73 m^2) ($P = 0.013$). This is demonstrated in Table 2. Of note, there was no significant change in BMI at the 1 year follow-up

Table 1 Table comparing baseline demographics and clinical characteristics of VNO vs. VO living kidney donors

Baseline characteristics	VNO (VAT < 100 cm^2) $N = 43$	VO (VAT > 100 cm^2) $N = 30$	P
Mean age (Years ± SD)	40.0 ± 12.6	48.4 ± 9.8	0.002
Female gender, *N* (%)	21 (70)	31 (23)	< 0.001
Race			
Chinese, *N* (%)	30 (69.8)	20(66.7)	0.56
Malay	3 (7.0)	5 (16.7)	
Indian	3 (7.0)	2 (6.6)	
Others	7 (16.2)	3 (10.0)	
Pre-op mean BMI (kg/m2 ± SD)	22.8 ± 2.9	25.1 ± 3.8	< 0.001
Pre-op mean VAT (cm2 ± SD)	149.3 ± 37.2	71.5 ± 22.8	< 0.001
Hypertension, N (%)	8 (18.6)	3 (10.0)	0.31
Hyperlipidaemia, N (%)	9 (20.9)	8 (26.7)	0.56
Diabetes, N (%)	0	0	NS
Smoker/ex-smoker, N (%)	5 (11.6)	3 (10.0)	0.83
Mean pre-op CKD-EPI eGFR (ml/min/1.73m2 ± SD	111.7 ± 12.3	109.4 ± 9.9	0.56
Mean pre-op 24 urinary protein (g/day)	0.08 ± 0.05	0.09 ± 0.05	NS

Table 2 Table comparing perioperative and post-nephrectomy outcomes of VNO vs. VO living kidney donors

Peri and post operative outcomes	VNO (VAT < 100 cm^2) $N=43$	VO (VAT > 100 cm^2) $N=30$	*P*
Surgical approach Open, *N* (%) Minimally invasive, *N* (%)	6 (14%) 37 (86%)	4 (13.3) 26 (86.7)	0.71
Mean 1 year post op mean BMI	24.1 ± 3.4	26.7 ± 2.9	0.31
Length of index admissions (days)	4.4 ± 0.6	4.0 ± 0.9	NS
Perioperative complications—all Clavien (%)	2.3%	3.3%	NS
Incident diabetes 1 year post op	0	0	NS
Incident hypertension 1 year post op	0	0	NS
Incident hyperlipidaemia 1 year post op	9	9	0.35
Mean pre-op CKD-EPI eGFR (ml/min/1.73m^2 ± SD	111.7 ± 12.3	109.4 ± 9.9	0.56
Mean 1 year CKD-EPI eGFR (ml/min/1.73m^2 ± SD)	96.1 ± 11.8	89.7 ± 8.1	0.013
Mean 1 year 24 urinary protein (g/day)	0.09 ± 0.04	0.14 ± 0.02	0.011

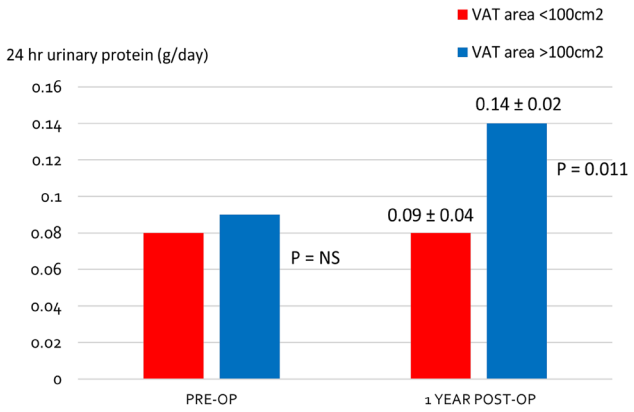

Fig. 2 Figure comparing 24-h urinary protein levels pre-operatively and at 1 year follow-up for VO and NVO living kidney donors

on paired sample *t* test (24.1 ± 3.4 vs 26.7 ± 2.9 kg/m^2, $P=0.31$), which could have potentially implicated the drop in eGFR.

Figure 2 shows that VO patients had significantly more proteinuria than NVO patients after donation, despite comparable levels before donation. Of note, of the 30 patients with VO, nine patients had VAT > 130 cm^2 and all nine patients had clinically significant proteinuria (defined as > 0.2 g/dl) within 1 year after donation.

Discussion

The rate of end-stage renal disease (ESRD) is not negligible; compared with matched healthy non-donors, kidney donors are now known to have an increased risk of ESRD of 30/10,000 over 15 years [22, 23]. This is still a rare event in absolute risk numbers. Importantly, increasing attention is now drawn to risks of living donors to non-ESRD problems and in particular, the impact of mild reduction in GFR donation on donors' subsequent health [24]. Our present study suggested an association between visceral obesity (VAT > 100 cm^2) and the greater decline of renal function 1 year post donor nephrectomy. Both subgroups were very well matched, and both contained non-obese (by BMI definition) healthy group of donors. This was in part due to the stringent workup required at NUCOT to become a kidney donor. The VO group had a mean BMI of 25.1, just shy of what was considered healthy by WHO classification standards. Despite this, we saw a significantly greater decline in eGFR at the 1 year follow-up in the VAT > 100 cm^2 group, relative to the other subgroup VAT < 100 cm^2.

Visceral obesity, irrespective of gender, age and BMI, has been shown to be correlated with cardiovascular risk factors, hypertension, hyperglycaemia, hypertriglyceridaemia and low HDL-cholesterolaemia [25–31]. The pathogenicity of VAT is well evidenced in the literature. The Framingham study [6] suggested that visceral adipose tissue (VAT) has a more adverse metabolic risk profile compared to subcutaneous adipose tissue (SAT). Its mechanism has been postulated to be due to dysfunction of hypertrophied adipocytes. This dysfunction causes an overproduction of plasminogen activator inhibitor type 1 (PAI-1) and tumour necrosis factor alpha (TNF-a), coupled with underproduction of protective adipocytokines like adiponectin [27–29]. This imbalance causes hypersecretion of vasoactive substances, and creates a chronic inflammatory state, which plays a critical role in metabolic syndrome, hyperlipidaemia, insulin resistance, and cardiovascular disease [30–32]. How these factors interact with renal function is unclear and may be more important in Asian patients with greater VO at lower BMI levels.

Compared with the general population where a low eGFR is the result of kidney or systemic disease, in the case for donors, it is a result of nephrectomy. As recommended [24], we tested for proteinuria in our kidney donors to be more

specific on the implications of reduced eGFR at 1 year post donation, to investigate if a statistically significant difference would be clinically meaningful. This study shows that VO patients had significantly more proteinuria than NVO patients after donation, despite comparable normal levels before donation. Of note, of the 30 patients with VO, all nine patients with VAT > 130 cm^2 had clinically significant proteinuria (defined as > 0.2 g/dl) within one year after donation. Kim et al. [33]. were able to suggest this relationship in a recent longitudinal population study, showing how visceral fat was an independent predictor of proteinuria development over a 4-year period. This implies that VO patients may have added hyperfiltrative stress on the remaining kidney after donor nephrectomy.

While it does not mean we discourage donation in LKDs with visceral obesity, we might want to consider closer post donation follow-up for patients in that cohort and to reduce VO after donation. Clinical application of this study's findings for the viscerally obese group could be implemented by means of health education. Health education has been proven to be effective in the literature, and this could be useful as donors are innately driven people. The Amagasaki Visceral Fat Study "Hokenshido", a project included over 3000 patients resulted in the reduction of metabolic syndrome and a reduction in cardiovascular risk factors from 20.8% to 14.4% in men and 3.0% to 1.9% in women over 3 years with proper education and input [34–36]. The project involved physicians and public health nurses identifying people with VO (VAT > 100 cm^2) and these patients received personal counseling, dietary advice regarding eating habits, alcohol intake, exercise and lifestyle behaviour modification. Interestingly, weight loss following obesity surgery in obese Asian patients have been reported by us and others to improve renal function [37].

The authors acknowledge the limitations of the above study. Firstly, this was a retrospective study with a short 1-year follow-up. The authors decided on this timeline as there has not been any other published study investigating the impact of VO on post kidney donation decline of GFR. The authors investigated short-term impact initially (1 year GFR) first before any consideration of any long-term impact. This initial study's finding should therefore be validated by larger scale, multicenter prospective studies with emphasis on the impact of visceral obesity on both short- and long-term post donation renal function. Secondly, the study population is relatively small, and clinicopathological characteristics including CT scan data were evaluated pre-operatively. We did not perform multivariable analysis for possible confounding factors including hypertension, hyperlipidaemia, and smoking status, as we wanted to investigate if visceral obesity was a predictor without a categorial outcome. The impact of other confounders is likely to be small, due to our transplant clinic's stringent selection criteria pre-operatively and strict protocol post-operatively. From the results seen in Table 2, the study population comprised of carefully evaluated living donors with minimal pre-operative comorbidities, both the VO and NVO groups were well matched in terms of controlled hypertension, hyperlipidemia, and smoking history. No one had diabetes.

Although this is a short-term renal function study at 1 year, we believe any impact of post donation renal function should be studied carefully and documented as the implications of a greater short-term eGFR decline can potentially have an impact on long term. Excitingly, more work could identify if VAT > 100 cm^2 pre-operatively is a good biomarker to further stratify our kidney donors in terms of GFR decline after donation. The advantage of pre-operative VAT as a potential biomarker is clear. Measurement of VAT is relatively easy to perform taking on average about 10 min per patient, and takes advantage of routinely performed CT imaging without any additional cost, or any additional radiation exposure to patients. We are looking at longer term follow-up with a prospective group in a multicenter setting.

Author contributions XP: data collection, data collection and analysis, manuscript writing. LYCN: data collection, data analysis. BWT: protocol/project development, data management. AV: protocol/project development, data management, manuscript editing. YSBG: data management, data analysis. CY: data collection, data analysis. LR: data management, data analysis. HYT: protocol/project development, data collection and management, data analysis, manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

Informed consent Informed consent was taken, and the data were collected according to an approved institutional review board protocol (DSRB reference no: 2016/01304).

Human and animal rights No human or animal testing was performed.

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