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Visceral obesity assessed by computed tomography predicts cardiovascular events in chronic kidney disease patients☆

M.A. Kamimura [a,*], J.J. Carrero [b], M.E.F. Canziani [a], R. Watanabe [a], M.M. Lemos [a], L. Cuppari [a]

[a] Division of Nephrology, Federal University of São Paulo, São Paulo, Brazil
[b] Division of Renal Medicine and Baxter Novum, Centre for Molecular Medicine and Centre for Gender Medicine, Karolinska Institutet, Stockholm, Sweden

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KEYWORDS
Visceral obesity;
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Abstract *Background and Aim:* Cardiovascular disease is the leading cause of death among patients with chronic kidney disease (CKD). Although there is emerging evidence that excess visceral fat is associated with a cluster of cardiometabolic abnormalities in these patients, the impact of visceral obesity evaluated by a gold-standard method on future outcomes has not been studied. We aimed to investigate whether visceral obesity assessed by computed tomography was able to predict cardiovascular events in CKD patients.
Methods and Results: We studied 113 nondialyzed CKD patients [60% men; 31% diabetics; age 55.3 ± 11.3 years; body mass index (BMI) 27.2 ± 5.3 kg/m^2; estimated glomerular filtration rate (GFR) 33.7 ± 13.6 ml/min/1.73 m^2]. Visceral and subcutaneous abdominal fat were assessed by computed tomography at L4-L5. Visceral to subcutaneous fat ratio >0.55 (highest tertile cut-off) was defined as visceral obesity. Cardiovascular events including acute myocardial infarction, angina, arrhythmia, uncontrolled blood pressure, stroke and cardiac failure were recorded during 24 months.

Cardiovascular events were 3-fold higher in patients with visceral obesity than in those without visceral obesity. The Kaplan–Meier analysis indicated that patients with visceral obesity had shorter cardiovascular event-free time than those without visceral obesity ($P = 0.021$). In the univariate Cox analysis, visceral obesity was associated with higher risk of cardiovascular events (hazard ratio = 3.4; 95% confidence

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* Corresponding author. Division of Nephrology, Department of Medicine, Federal University of São Paulo, Rua Pedro de Toledo, 282, 04039 000 São Paulo, SP, Brazil. Tel.: +55 11 5572 0530; fax: +55 11 5572 1862.
E-mail address: m.kamimura@uol.com.br (M.A. Kamimura).

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interval = 1.1—10.5; $P = 0.03$). The prognostic power of visceral obesity for cardiovascular events remained significant after adjustments for sex, age, diabetes, previous cardiovascular disease, smoking, sedentary lifestyle, BMI, GFR, hypertension, dyslipidemia and inflammation.

Conclusion: Visceral obesity assessed by computed tomography was a predictor of cardiovascular events in CKD patients.

Introduction

Cardiovascular mortality is up to 20 times higher in chronic kidney disease (CKD) than in the general population [1] accounting for approximately 50% of all deaths [2]. Although a plethora of traditional and nontraditional risk factors have been associated with a high incidence and prevalence of cardiovascular diseases in CKD patients [3], it is noteworthy that the most frequent cardiometabolic risk factors (e.g. hypertension, dyslipidemia, insulin resistance and inflammation) are closely related to obesity, a nutritional disturbance which has gained considerable attention in nephrology during the recent years.

The prevalence of obesity has increased substantially among patients with CKD. Data from the United States Renal Data System (USRDS) demonstrated that 60% of the dialysis population has excess body weight [4]. Although some epidemiological studies have suggested a benefit of obesity on clinical outcomes in CKD patients [5—7], these findings are controversial depending on several factors such as dialysis modality [8], length of follow-up [9,10], ethnicity [11], and the amount of lean body mass [12,13], making difficult the understanding of the real impact of obesity on outcomes in CKD population. The use of BMI as a marker of obesity may be the potential reason for such divergent results [14]. BMI is the most widely used marker of obesity in the general population [15]. However, this index is not able to distinguish body fat and lean body mass besides being influenced by body water disturbances commonly seen in CKD patients. And, importantly, BMI does not discriminate body fat distribution, which would be of relevance considering the known deleterious effect of abdominal obesity. In fact, previous studies have demonstrated that increased visceral fat assessed by the gold-standard methods, such as computed tomography and magnetic resonance, is associated with a cluster of cardiometabolic abnormalities including dyslipidemia, insulin resistance and inflammation in CKD patients [16—21].

A spontaneous accumulation of visceral fat has been described in prospective studies with dialysis patients [22,23]. We previously demonstrated that this occurs early in the course of CKD. By following 87 nondialyzed CKD patients throughout 1 year, we observed that 70% of them increased visceral fat [24]. In the present study, we evaluated for the first time whether visceral obesity, assessed by computed tomography, is able to predict future cardiovascular events in CKD patients.

Methods

Patients

A total of 113 consecutive nondialyzed CKD patients stages 2—4 were recruited from the outpatient clinic of the Nephrology Division, Federal University of São Paulo (São Paulo, Brazil). Recruitment occurred between August 2007 and March 2009. Patients seen in the nephrology clinic for at least 3 months were invited to participate in the study. Exclusion criteria were age below 18 years, chronic use of steroids, and presence of chronic inflammatory disease, active malignancy, human immunodeficiency virus seropositivity and viral hepatitis. The majority of the patients were on regular use of angiotensin-converting enzyme inhibitors (79%) and diuretics (74%). Use of statins was observed in 34% of the patients. Patients were also taking β-blockers (39%), calcium channel blockers (40%), angiotensin receptor blockers (21%), and human recombinant erythropoietin (4%). Thirty-six patients (31%) were using phosphate binders and 6 patients (5%) were taking calcitriol.

This study was reviewed and approved by Ethics Advisory Committee of the Federal University of São Paulo. All patients gave the written informed consent.

Study protocol

In this prospective observational cohort study, all patients underwent clinical history evaluation, laboratory tests and assessment of abdominal adiposity. The occurrence of cardiovascular events (both fatal and non-fatal, including acute myocardial infarction, angina, arrhythmia, uncontrolled blood pressure, stroke and cardiac failure) were recorded during 24 months. All cardiovascular events were reviewed and adjudicated by two physicians in order to ensure consistency of the event diagnosis.

Abdominal computed tomography

Visceral and subcutaneous fat areas were obtained by using computed tomography (Helical Picker PQ 5000 Cleveland, Ohio, USA). All subjects were examined in the supine position with both arms stretched above the head, and slices of 10 mm were measured at the L4-L5 levels. Visceral and subcutaneous fat areas were obtained by delineating and computing the adipose tissue surface using an attenuation range of −150 to −50 Hounsfield units. The area of

each abdominal compartment was measured in square centimeters. The same skilled radiographer performed all measurements. The variability of the computed tomography equipment was 2.5% for visceral fat measurement and 2.3% for subcutaneous fat measurement. Because there is no cut points currently available for defining visceral obesity, we considered it as the ratio of visceral to subcutaneous fat (V/S) ratio higher than 0.55, the upper tertile of distribution in this cohort.

BMI, waist circumference, conicity index and trunk fat

Body mass index (BMI) was calculated as body weight divided by the squared height (kg/m^2). Increased BMI was considered for values equal or higher than 30 kg/m^2, as proposed by the World Health Organization [15]. Waist circumference was measured at the umbilicus level at the end of expiration using a flexible plastic tape while subjects were standing with their weight equally distributed on both feet and the head facing straight forward. The mean of three measurements was used for analysis. Increased waist circumference was considered for values $\geq$88 cm in women and $\geq$102 cm in men, as suggested by the Adult Treatment Panel III guideline [25]. The conicity index was calculated according to the following equation proposed by Valdez [26]: waist circumference/[0.109 $\times$ square root of (weight/height)], and the highest tertile cut-off of 1.35 was used to define an increased conicity index. Finally, trunk fat was assessed by means of dual energy X-ray absorptiometry (DEXA) using a DPX scanner (Lunar Radiation Corporation Madison, WI, USA). Regional measurement of trunk fat compartment was obtained in kg with a minimum radiation of 0.05–1.5 mm during the test. Excess trunk fat was considered for values higher than 14 kg (highest tertile cut-off).

Laboratory tests

Blood samples were drawn after an overnight fast of at least 12 h. Serum creatinine (automated colorimetric method, Jaffe's reaction), high-sensitivity C-reactive protein (immunochemiluminescence kit), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol and triacylglycerol were measured. Dyslipidemia was defined as HDL $<$40 mg/dl, LDL $>$100 mg/dl or triacylglycerol $>$150 mg/dl according to the criteria proposed by the K/DOQI guideline for managing dyslipidemia in CKD [27]. Serum glucose and insulin (immunofluorometric assay) were measured in order to calculate the homeostatic model assessment (HOMA) index as described by Mathews: fasting serum insulin (mU/ml) $\times$ fasting plasma glucose (mmol/l)/22.5 [28]. Aliquots of serum were stored at $-$70 °C for the measurements of adiponectin (Linco Research, USA) and interleukin-6 (BD Biosciences Pharmingen, USA) by using commercially available enzyme-linked immunosorbent assays. Glomerular filtration rate (GFR) was estimated by the simplified equation of the Modification of Diet in Renal Disease Study [29].

Statistical analysis

Data are expressed as mean and standard deviation, median and interquartile range, or percent frequency (proportions), as appropriate. Patients in the upper tertile of visceral to subcutaneous fat ratio were compared to the other two tertiles combined. Comparisons of continuous variables were done by Student's *t*-test and the Mann–Whitney *U* test for normally distributed data and skewed data, respectively. Chi-square test was used for comparisons of proportions. Cardiovascular event-free survival curves were estimated by Kaplan–Meier method and compared by log rank tests. Univariate and multivariate Cox regression analyses were employed to evaluate the predictive power of visceral obesity for cardiovascular events. Associations were described through the hazard ratios (HR) and 95% confidence intervals (CI). *P* values $<$0.05 were considered statistically significant. All analyses were performed using a standard statistical package (SPSS for Windows, version 16, SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics

The average age of the studied patients was 55.3 $\pm$ 11.3 years, 60% were men, 31% had diabetes, 35% had a history of cardiovascular disease, 16% were smokers, and 74% reported a sedentary lifestyle. The majority of the patients were on stage 3 (51%) or stage 4 (43%) of CKD, and the main CKD etiologies were hypertension (27%) and diabetes (24%). The characteristics of the patients according to the presence of visceral obesity are summarized in Table 1. The group with visceral obesity were older, had a higher proportion of men and history of cardiovascular disease. C-reactive protein was higher among patients with visceral obesity. On the other hand, HDL cholesterol and adiponectin were lower in this group. The proportion of smokers and patients with sedentary behavior was similar between the groups. Markers of abdominal adiposity such as waist circumference, conicity index and trunk fat were increased among patients with visceral obesity.

Follow-up data

During the follow-up period (median 24 months; range 1–29 months) 13 cardiovascular events were registered. Three patients died and 20 patients started dialysis. Cardiovascular events were characterized as follow: angina (n = 4), stroke (n = 2), acute myocardial infarction (n = 2), hypertensive emergence (n = 2), arrhythmia (n = 1), transient ischemic attack (n = 1) and cardiac failure (n = 1). Deaths were attributed to acute myocardial infarction (n = 2), pancreatitis (n = 1), and home accident (n = 1). Cardiovascular death was computed as an event. Cardiovascular events were 3-fold higher in patients with visceral obesity (n = 8, 22%) than in patients without visceral obesity (n = 5, 7%) (P = 0.023). The proportion of patients who died or started dialysis did not differ between the groups (P = 0.70 and P = 0.50, respectively).

Table 1 Baseline characteristics of the patients according to the presence of visceral obesity defined as visceral to subcutaneous fat (V/S) ratio > 0.55.

	V/S ≤ 0.55 (n = 76)	V/S > 0.55 (n = 37)	P
Age (y)	52.6 ± 11.2	60.1 ± 10	0.001
Men [n (%)]	35 (46)	33 (89)	<0.001
Diabetes [n (%)]	21 (28)	14 (38)	0.19
History of CVD [n (%)]	20 (26)	20 (54)	0.004
eGFR (ml/min/1.73 m^2)	32.4 ± 13.4	36.2 ± 14	0.17
Stage 3 CKD [n (%)]	36 (47)	22 (60)	0.68
Stage 4 CKD [n (%)]	35 (46)	13 (35)	
Proteinuria (g/day)	0.23 (0—0.76)	0.25 (0—0.80)	0.79
HDL cholesterol (mg/dl)	53 ± 14	46 ± 13	0.02
LDL cholesterol (mg/dl)	102 ± 33	104 ± 20	0.73
Triglycerides (mg/dl)	148 ± 76	173 ± 120	0.17
HOMA index	2.0 (1.1—3.6)	2.5 (1.4—5.2)	0.10
Adiponectin (mg/l)	29.2 ± 7	25.2 ± 7.1	0.006
C-reactive protein (mg/dl)	0.26 (0.10—0.64)	0.39 (0.17—1.02)	0.045
Interleukin-6 (pg/ml)	3.9 (2.1—7.9)	5.7 (3.5—11.8)	0.06
BMI (kg/m^2)	26.6 ± 5.6	28.4 ± 4.4	0.08
Waist circumference (cm)	92 ± 12.7	99.7 ± 9.3	0.002
Conicity index	1.30 ± 0.8	1.35 ± 0.5	0.002
Trunk fat (kg)	11.5 ± 5.6	14 ± 4.1	0.022
V/S ratio	0.30 ± 0.16	1.06 ± 0.56	NA

Values expressed as proportions, mean ± standard deviation or median and interquartile range. Student's independent t-test, Mann—Whitney test or Chi-square test. V/S: visceral to subcutaneous fat; CVD: Cardiovascular disease, eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA: homeostatic model assessment; BMI: body mass index; NA: not applicable.

The group who experienced cardiovascular events during follow-up had a higher proportion of diabetics (62% *vs.* 27%; P = 0.016) than those free of cardiovascular events. Other demographic and laboratory data remained unchanged. Figure 1 depicts a comparison of abdominal adiposity markers according to the occurrence of cardiovascular events. As can be seen, the proportion of patients with visceral obesity was 2-fold higher among patients who experienced cardiovascular events when compared to those free of events (62% *vs.* 29%; P = 0.023). The frequency of

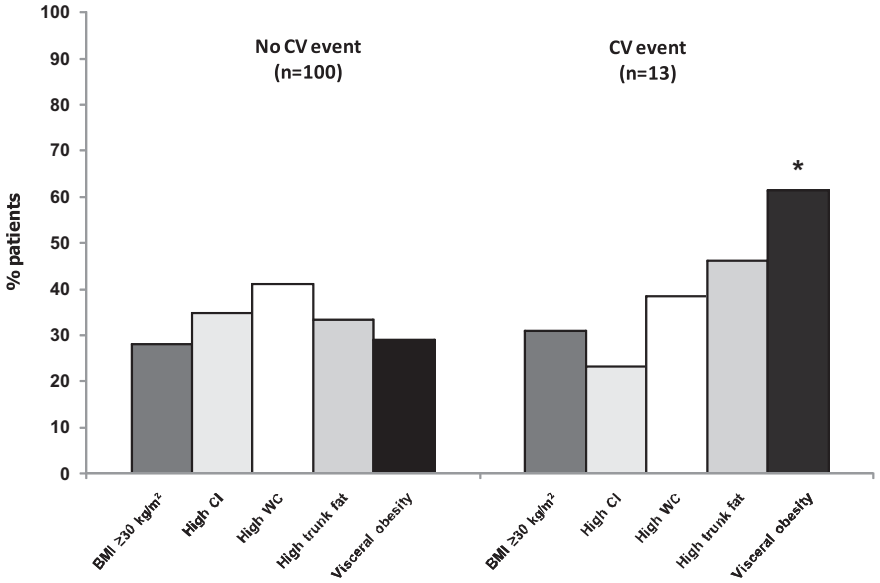

Figure 1 Frequency of body mass index (BMI) ≥30 kg/m^2, increased waist circumference (WC ≥ 88 cm in women and ≥102 cm in men), increased conicity index (CI > 1.35, highest tertile), trunk fat (>14 kg, highest tertile) and visceral obesity (visceral to subcutaneous fat > 0.55, highest tertile) in 113 nondialyzed chronic kidney disease patients according to the occurrence of cardiovascular (CV) event during 24 months of follow-up. *P = 0.023.

increased waist circumference, conicity index, trunk fat and BMI did not differ between the groups. The Kaplan–Meier survival analysis demonstrated that patients with visceral obesity had shorter cardiovascular event-free time as compared to those without visceral obesity (Fig. 2). In the univariate Cox analysis, visceral obesity was associated with higher risk of cardiovascular events. In the multivariate analysis, adjusting for several confounders such as sex, age, diabetes, previous cardiovascular disease, smoking, sedentary lifestyle, BMI, GFR, hypertension, dyslipidemia and inflammation, visceral obesity remained as an independent predictor of cardiovascular events (Table 2). By using the hazard ratio and the observed alpha error of 5% as estimators, the statistic power was 0.98.

Discussion

In the present study, visceral obesity assessed by means of computed tomography was a predictor of cardiovascular events in nondialyzed CKD patients.

Obesity has historically been a mirror of worse health in the general population. Thus, the paradoxical findings in the last years linking a high BMI to a better survival in CKD patients [5–7] have challenged the belief that excess of adiposity is harmful. The most plausible explanation for such paradoxical observation is that a high BMI reflects better overall nutrition and it is not a sensitive marker of abdominal obesity. Accordingly, we observed that a large proportion of patients (59%) with BMI $\geq$ 30 kg/m^2 did not have visceral obesity. This observation is in accordance with the finding by Elsayed et al. who showed that half of their patients with increased BMI had low waist to hip ratio [30]. This elegant study enrolled 1669 patients in the nondialysis stages of CKD and demonstrated that patients in the highest waist to hip ratio group were exposed to a higher risk for myocardial infarction and fatal coronary heart disease. Neither BMI nor waist circumference was associated with higher cardiovascular risk during the 9.3 years of follow-up [30]. In a subsequent study including hemodialysis patients, Postorino et al. reported that patients with increased waist circumference and reduced BMI had the highest risk for all-cause and cardiovascular mortality [31]. A third study supporting the idea that body fat distribution may differently affect outcomes in CKD patients came from Cordeiro et al. who reported that increased conicity index was associated with higher all-cause mortality in 173 hemodialysis patients followed by 41 months [32]. Since the predictive value of conicity index on outcome was abrogated after adjustment for inflammation and protein-energy wasting, the authors suggested that these factors may be within the causal pathway of such association. The current study is the first to illustrate the impact of visceral obesity assessed by a gold-standard method on future clinical events in patients with CKD.

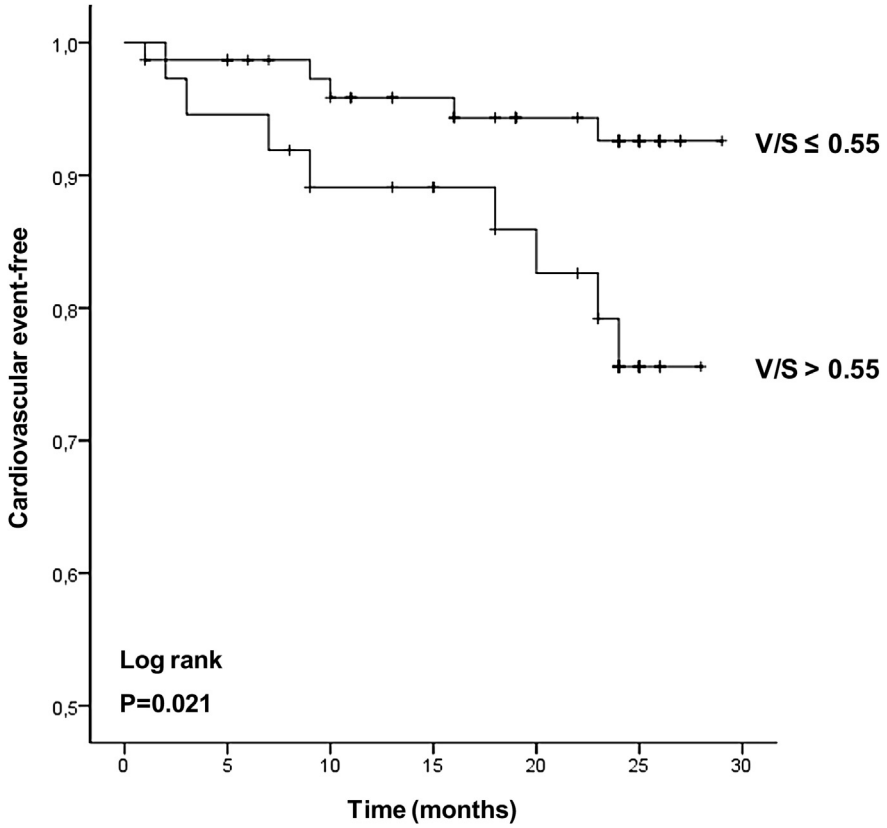

Figure 2 Kaplan–Meier curve analysis in 113 nondialyzed chronic kidney disease patients. The group of patients with visceral obesity, described as the ratio of visceral to subcutaneous fat (V/S) ratio $>$ 0.55 (n = 37), had shorter cardiovascular event-free time in comparison to the group without visceral obesity (n = 76).

Table 2 Prognostic value of visceral obesity in the prediction of cardiovascular events during 24 months of follow-up in 113 nondialyzed chronic kidney disease patients.

	HR	95% CI	*P*
Univariate Cox			
Visceral obesity	3.4	1.1—10.5	0.030
Multivariate Cox			
Model 1	7.0	1.6—30.0	0.009
Model 2	9.4	1.8—49.8	0.009
Model 3	8.8	1.7—46.9	0.010
Model 4	8.7	1.6—46.5	0.011

HR: Hazard ratios; CI: confidence intervals; Model 1: adjusted for sex, age, smoking and sedentary lifestyle; Model 2: Model 1 + history of cardiovascular disease, diabetes and body mass index; Model 3: Model 1 + Model 2 + glomerular filtration rate and hypertension; Model 4: Model 1 + Model 2 + Model 3 + dyslipidemia and C-reactive protein.

Abdominal adiposity by using computed tomography or magnetic resonance has been less explored among patients with CKD. Cross-sectional studies including hemodialysis patients have linked visceral fat accumulation with atherosclerosis, inflammation, insulin resistance, and adypokine dysregulation [16—20,33]. In nondialyzed CKD patients, we have previously demonstrated that visceral fat correlated with parameters of dyslipidemia, insulin resistance and inflammation [21]. In elderly patients with CKD, a recent study showed that both visceral fat and subcutaneous fat were independent determinants of insulin resistance [34]. The pathophysiology of visceral obesity in CKD is not fully understood. Recent studies have evidenced increased expression of proinflammatory cytokines [35,36] and increased immunocompetent cells infiltration [34] in the abdominal fat of CKD patients as compared to healthy controls. Visceral mRNA expression of tumor necrosis factor-α, CD68, adiponectin receptor-1 and monocyte chemoattractant protein-1 were increased in patients with CKD [36], particularly among obese ones [37]. In addition, it was demonstrated that the expression of cytokines was significantly higher in visceral fat tissue compared to subcutaneous fat tissue [37]. However, the contribution of visceral fat tissue in the universe of systemic inflammation in patients with CKD remains to be investigated.

Our finding indicating visceral obesity as an independent and the most important predictor of cardiovascular events in CKD patients supports the notion that identifying a simple surrogate of visceral adiposity is of relevance for the routine care of these patients. We previously demonstrated that waist circumference measurements correlated strongly with visceral fat assessed by computed tomography and with proatherogenic metabolic status in nondialyzed CKD patients [21]. In the present cohort, however, waist circumference as well as conicity index, trunk fat and BMI were not able to predict cardiovascular events, an observation that could be influenced by our relatively small sample size and warrants confirmation. Since waist circumference is a perimeter that embraces visceral and subcutaneous abdominal fat, we could speculate that coexisting effects of both fat depots on cardiovascular events may have blunted the prognostic power of waist circumference. This analogy might be valid for the conicity index, which is based on the waist circumference measurement, and for trunk fat which also represents simultaneously visceral and subcutaneous adiposity. However, this hypothesis has not yet been tested in CKD patients.

The limitation of this study is the relatively small sample size. However, considering the high burden of risk factors that predispose CKD patients to cardiovascular diseases and the lack of understanding on the impact of visceral obesity on future events in these patients, the results of the present study may encourage further investigations on the mechanisms linking abdominal adiposity to cardiovascular injuries.

In conclusion, visceral obesity defined as the increased ratio of visceral to subcutaneous fat was a predictor of cardiovascular events in nondialyzed CKD patients. Strategies are warranted for the early prevention and treatment of visceral obesity in CKD population.

Conflict of interest

None of the authors declare any conflict of interest.

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