Can J Diabetes 43 (2019) 415–420

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

# The Relationship Between Increased Ratio of Visceral-to-Subcutaneous Fat Area and Renal Outcome in Chinese Adults With Type 2 Diabetes and Diabetic Kidney Disease

Yiting Wang PhD [1]; Feng Chen BA [1]; Jiali Wang PhD; Tingli Wang PhD; Junlin Zhang MA; Qianqian Han PhD; Yucheng Wu MA; Rui Zhang PhD; Fang Liu MD, PhD *

*Division of Nephrology, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China*

**Key Messages**

- Abdominal obesity is associated with body mass index and hyperlipemia. This study revealed strong correlations between the ratio of visceral-to-subcutaneous fat area and C-reactive protein.
- An increased ratio of visceral-to-subcutaneous fat area is a risk factor for diabetes and hypertension. This study revealed abdominal fat to be associated with renal outcomes in patients with diabetic kidney disease.

ARTICLE INFO

*Article history:*
Received 10 April 2018
Received in revised form
9 July 2018
Accepted 22 August 2018

*Keywords:*
abdominal obesity
diabetic kidney disease
subcutaneous fat area
type 2 diabetes
visceral fat area

ABSTRACT

*Objective:* Abdominal obesity is a risk factor of diabetes and hypertension. The aim of this study was to investigate the association between excessive abdominal fat and renal outcomes in patients with type 2 diabetes and diabetic kidney disease.
*Methods:* Thirty-five patients with type 2 diabetes and diabetic kidney disease who were followed up on for at least 1 year were enrolled. Visceral fat area and subcutaneous fat area were assessed by computed tomography to evaluate the degree of abdominal fat. Patients were divided into 2 groups. Patients in group 1 had a ratio of visceral fat area to subcutaneous fat area (V/S ratio) $<0.70$ (n=16), and those in group 2 had a V/S ratio $\geq 0.70$ (n=19) according to the second quartile. Renal outcome was defined as end-stage renal disease and initiation of renal replacement therapy.
*Results:* At baseline, patients with a high V/S ratio had higher levels of triglycerides (p=0.060) and C-reactive protein (p=0.028), but lower high-density lipoprotein cholesterol levels (p=0.006). Strong correlations between V/S ratio and C-reactive protein (r=0.521, p=0.015) and high-density lipoprotein cholesterol (r=−0.576, $p<0.001$) were observed. Univariate Cox regression indicated the higher the V/S ratio, the greater the risk for a poor renal outcome (hazard ratio, 3.536; 95% confidence interval, 1.140 to 10.960; p=0.029). However, multivariate Cox analysis demonstrated that a higher V/S ratio was not an independent risk factor for progression to end-stage renal disease (hazard ratio, 2.212; 95% confidence interval, 0.543 to 9.005; p=0.268) when adjustments were made for important clinical variables.
*Conclusion:* The V/S ratio was positively correlated with C-reactive protein and high-density lipoprotein cholesterol. The higher V/S ratio was associated with a greater risk for progression to end-stage renal disease, although it did not emerge as an independent predictor of diabetic kidney disease progression.


*Mots clés :*
obésité abdominale
néphropathie diabétique
surface de graisse sous-cutanée
diabète de type 2
surface de graisse viscérale

RÉSUMÉ

*Objectif :* L'obésité abdominale est le facteur de risque du diabète et de l'hypertension. L'objectif de la présente étude était d'examiner l'association entre l'excès de graisse abdominale et les issues de la maladie rénale chez les patients atteints de diabète de type 2 et de néphropathie diabétique.

* Address for correspondence: Fang Liu MD, PhD, Division of Nephrology, West China Hospital of Sichuan University, No. 37, Guoxue Alley, Chengdu, Sichuan Province 610041, China.
*E-mail address:* liufangfh@163.com
[1] Co-first authors.

1499-2671/
https://doi.org/10.1016/j.jcjd.2018.08.199

*Méthodes :* Trente-cinq patients atteints de diabète de type 2 et de néphropathie diabétique qui avaient un suivi d'au moins 1 année étaient inscrits à l'étude. Nous avons évalué la surface de graisse viscérale et la surface de graisse sous-cutanée par tomodensitométrie pour obtenir le taux de graisse abdominale. Nous avons réparti les patients en 2 groupes. Les patients du groupe 1 avaient un ratio de la surface de graisse viscérale par rapport à la surface de graisse sous-cutanée (ratio V/S)<0,70 (n=16), et ceux du groupe 2 avaient un ratio V/S≥0,70 (n=19) en fonction du deuxième quartile. Nous avons défini les issues de la maladie rénale par l'insuffisance rénale en phase terminale et la mise en place d'un traitement de suppléance de l'insuffisance rénale.

*Résultats :* Au début, les patients qui avaient un ratio V/S élevé avaient des concentrations plus élevées de triglycérides (p=0,060) et de protéine C réactive (p=0,028), mais ils avaient des concentrations plus faibles de cholestérol à lipoprotéines de haute densité (p=0,006). Nous avons observé de fortes corrélations entre le ratio V/S et les concentrations de la protéine C réactive (r=0,521, p=0,015) et du cholestérol à lipoprotéines de haute densité (r=-0,576, $p$<0,001). L'analyse de régression univariée selon le modèle de Cox indiquait le ratio V/S plus élevé, plus le risque d'une issue médiocre de la maladie rénale était grand (rapport de risque, 3,536; intervalle de confiance à 95 %, 1,140 to 10,960; p=0,029). Toutefois, l'analyse multivariée selon le modèle de Cox démontrait qu'un ratio V/S plus élevé n'était pas un facteur de risque indépendant de la progression vers l'insuffisance rénale en phase terminale (rapport de risque, 2,212; intervalle de confiance à 95 %, 0,543-9,005; p=0,268) après ajustements en fonction de variables cliniques importantes.

*Conclusion :* Le ratio V/S corrélait de manière positive avec les concentrations de la protéine C réactive et du cholestérol à lipoprotéines de haute densité. Le ratio V/S plus élevé était associé à un risque plus grand de progression vers l'insuffisance rénale en phase terminale, bien qu'il ne fût pas considéré comme un prédicteur indépendant de la progression de la néphropathie diabétique.



## Introduction

Diabetic kidney disease (DKD) is one of the most devastating microvascular complications of diabetes and develops in approximately 40% of patients with type 2 diabetes (1). The past few decades have witnessed a marked increase in the prevalence of DKD, which has been the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESRD) in the world (2–4). The management of common risk factors, such as hyperglycemia, hyperlipidemia and hypertension, has reduced the rates of incident diabetic cardiovascular complications over recent years, although there seems to be limited effect on the prevalence of DKD (2). Given the huge health-care burden related to DKD, there has been much interest in identifying more risk factors and underlying mechanisms for this common diabetic microvascular complication.

Recent epidemiologic studies indicate that obesity is a substantial risk factor for CKD (5,6). Abdominal obesity and visceral fat have been identified as playing pivotal roles in regulating various adipokines and cytokines involved in kidney injury (7). However, body mass index (BMI) is no longer an optimal measurement of abdominal obesity or visceral fat area (VFA) because decreased BMI may be associated with not only reduced VFA but also muscle mass wasting, which is common in patients with CKD (8,9). Therefore, computed tomography (CT) is regarded as the gold standard for assessing VFA and subcutaneous fat area (SFA) (10).

Several studies have revealed that Asian people are susceptible to type 2 diabetes and cardiovascular disease (11). The speculation is that Asian individuals are more predisposed to accumulate visceral fat relative to subcutaneous fat than white individuals (12,13). In contrast, SFA has been found to be inversely associated with atherosclerosis, and it might provide some protection against metabolic diseases (14,15). Actually, the ratio of VFA to SFA (V/S ratio) has been proposed to be a better predictor of atherosclerosis and cardiovascular events in patients with type 2 diabetes than VFA or SFA alone (16,17). However, it remains largely unclear whether an increased V/S ratio in patients with type 2 diabetes and DKD is associated with accelerated disease progression, or a worse renal outcome. In this study, we aimed to explore the relationship between a V/S ratio measured by CT and renal outcome in 35 patients with type 2 diabetes and DKD who were followed up on for at least 1 year.

## Methods

### *Study design and patients*

Patients with type 2 diabetes who had persistent proteinuria (albumin-to-creatinine ratio >30 mg/g and/or proteinuria >0.5 g/24 h) and/or a decreased estimated glomerular filtration rate (eGFR) (<60 mL/min per 1.73 $m^2$) for more than 3 months were included in a retrospective cohort study. The protocol of the study was approved by the ethics committee of West China Hospital of Sichuan University and conducted based on the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. Patients with eGFR <15 mL/min per 1.73 $m^2$, those who were diagnosed with nondiabetic kidney disease or cancer, those who were receiving dialysis and pregnant women were excluded from the study. All of the patients were followed up on for at least 1 year. DKD confirmed by renal biopsy was defined according to a standard in a previous study published in 2015 by An et al (18) and was diagnosed by at least 2 renal pathologists and/or nephrologists according to Tervaert's classification (19). The diagnosis of type 2 diabetes and DKD was based on guidelines from the American Diabetes Association in 2018. The study endpoint was defined by the presence of ESRD or initiation of renal replacement therapy.

### *Measurement of abdominal adipose fat area*

Standard abdominal CT scans were performed, and all the images were analyzed using a 3D Slicer (http://www.slicer.org). The average area from the 3 levels, ranging from L2 to L5, was calculated to reduce noise and errors. The data was collected from the medical records of patients.

### *Clinical, biochemical and pathologic characteristics*

The clinical information was obtained from medical records and included age; sex; body weight; height; duration of diabetes; and measurements of systolic/diastolic blood pressure, fasting blood glucose, glycated hemoglobin, 24 h protein excretion, albumin-to-creatinine ratio (measured for 32 patients), serum creatinine, eGFR, serum albumin, uric acid, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL)

cholesterol, C-reactive protein and interleukin-6 (IL-6). BMI was calculated as weight in kilograms per square meter of height (kg/m$^2$), and eGFR was calculated according to the Modification of Diet in Renal Disease equation. Smoking history was divided into current smoker and non–current smoker groups.

Sixteen patients had biopsy-confirmed DKD. Each renal biopsy specimen was routinely examined by light microscopy, immunofluorescence and electron microscopy. The pathologic classification was assessed based on the criteria established by the Renal Pathology Society in 2010 (19).

All data were collected on the date closest to the day on which adipose fat distribution was assessed by CT.

### *Statistical analysis*

Statistical analyses were performed using SPSS software 22.0 (IBM Corporation, Armonk, New York). The Shapiro-Wilk test was done for all parameters to check the normality. Variables that follow a normal distribution are presented as means with standard deviations, and other variables are presented as medians with ranges. The Student *t* test or the Mann-Whitney test was performed as appropriate to analyze differences in continuous variables. Categorical variables were expressed as counts and ratios, and the differences in proportions were analyzed using the chi-square test. The association between the variables was observed by using the Spearman correlation. Renal outcomes were compared by using the log-rank test and demonstrated by the Kaplan-Meier curves method. The relationship between V/S ratio and renal outcome was assessed using Cox regression. Multivariate Cox analysis was applied to pinpoint the independent risk factors related to prognosis. A 2-sided p value $<0.05$ was regarded as statistically significant.

## Results

### *Baseline of clinical characteristics*

A total of 35 patients with DKD (mean age, 57.71±9.70 years; 66% male) were enrolled in the study and divided into 2 groups according to the second quartile (0.70) of the V/S ratio. The clinical characteristics of the 2 groups at baseline are shown in Table 1. Patients in group 1 had a V/S ratio $<0.70$ (n=16), and patients in group 2 had a V/S ratio $\geq 0.70$ (n=19). Compared with patients in group 1, those in group 2 had higher values for VFA (105.30 [93.15 to 186.24] cm$^2$ vs. 76.58 [47.36 to 107.30] cm$^2$, p=0.036), triglycerides (2.61±2.28 vs. 1.59±0.76 mmol/L, p=0.060) and C-reactive protein (3.500 [2.718 to 11.10] mg/L vs. 2.320 [1.325 to 3.425] mg/L, p=0.028), but lower HDL cholesterol levels (1.00±0.27 vs. 1.38±0.47 mmol/L, p=0.006). There were no significant differences in age, sex, BMI, serum albumin, SFA, smoking history, duration of diabetes, fasting blood glucose, diabetic retinopathy, blood pressure, total cholesterol, low-density lipoprotein cholesterol or IL-6. The renal prognosis of the 2 groups were comparable (Table 1).

### *Correlation between V/S ratio and clinical variables*

Correlation analysis revealed strong correlations between V/S ratio and C-reactive protein (r=0.521, p=0.015) and between V/S ratio and HDL cholesterol (r=−0.576, p<0.001). However, no significant correlation was observed between the V/S ratio and BMI, triglycerides or IL-6 (Figure 1).

### *The V/S ratio and renal outcome*

During the median follow-up period of 14 months (range, 12 to 32 months), 20 patients (57%) reached the endpoint; 8 of them were in the group with the lower V/S ratio and 12 of them were in the group with the higher V/S ratio. Kaplan-Meier survival analysis (log-rank test) indicated that the renal prognosis was significantly poorer in patients with the higher V/S ratio (p=0.021). The mean estimated renal survival time was 43.78±5.29 months in group 1 and 22.21±3.86 months in group 2 (Figure 2).

In addition, risk factors of renal outcome were analyzed by Cox regression, which revealed that a higher V/S ratio (hazard ratio [HR], 3.536; 95% confidence interval [CI], 1.140 to 10.960; p=0.029] contributed to a poorer renal prognosis. Moreover, increased serum

**Table 1**
Clinical characteristics at baseline according to the ratio of visceral fat area to subcutaneous fat area

| Variables | V/S ratio | | | p value |
|---|---|---|---|---|
| | All (n=35) | Group 1 (n=16) | Group 2 (n=19) | |
| Age (years) | 57.71±9.70 | 57.25±9.38 | 58.10±10.21 | 0.799 |
| Sex, n (% male) | 23 (66) | 9 (56) | 14 (73) | 0.313 |
| Visceral fat area (cm$^2$) | 96.30 (60.20–126.35) | 76.58 (47.36–107.30) | 105.30 (93.15–186.24) | 0.036 |
| Subcutaneous fat area (cm$^2$) | 131.10 (96.30–196.3) | 161.20 (111.70–216.2) | 117.20 (87.80–160.10) | 0.088 |
| Body mass index (kg/m$^2$) | 25.49±3.64 | 25.62±2.81 | 25.38±4.30 | 0.847 |
| Duration of diabetes (months) | 96 (48–156) | 84 (48–144) | 120 (60–168) | 0.851 |
| Diabetic retinopathy, n (%) | 17 (49) | 7 (44) | 10 (52) | 0.746 |
| Fasting blood glucose (mmol/L) | 8.64±5.18 | 8.95±5.96 | 8.35±4.06 | 0.744 |
| Glycated hemoglobin (%) | 6.92±1.54 | 7.11±1.64 | 6.76±1.48 | 0.514 |
| Smoking, n (%) | 11 (29) | 5 (28) | 6 (31) | 0.728 |
| SBP (mmHg) | 141.97±22.32 | 145.93±20.22 | 138.63±23.96 | 0.342 |
| DBP (mmHg) | 81.09±12.08 | 82.68±12.05 | 79.73±12.27 | 0.480 |
| Hypertension, n (%) | 31 (89) | 15 (94) | 16 (84) | 0.604 |
| Initial proteinuria (g/d) | 3.39 (1.9–5.31) | 2.86 (0.97–8.08) | 3.39 (1.45–4.60) | 0.393 |
| ACr (mg/g) | 2608.50±1885.99 | 2914.80±1911.48 | 2350.55±1876.25 | 0.386 |
| Serum creatinine (μL/L) | 168.01±113.95 | 170.23±108.99 | 166.13±120.91 | 0.918 |
| eGFR (mL/min/1.73 m$^2$) | 49.81±30.66 | 47.87±31.08 | 53.58±30.46 | 0.592 |
| Serum albumin (g/L) | 36.50±14.53 | 32.91±8.06 | 39.52±17.98 | 0.184 |
| Uric acid (mmol/L) | 406.70±81.17 | 409.33±101.70 | 404.50±61.76 | 0.864 |
| Triglycerides (mmol/L) | 2.14±1.81 | 1.59±0.76 | 2.61±2.28 | 0.060 |
| Total cholesterol (mmol/L) | 4.51±1.27 | 4.71±1.26 | 4.35±1.28 | 0.405 |
| LDL cholesterol (mmol/L) | 2.50±0.89 | 2.76±0.97 | 2.28±0.79 | 0.114 |
| HDL cholesterol (mmol/L) | 1.17±0.41 | 1.38±0.47 | 1.00±0.27 | 0.006 |
| C-reactive protein (mg/L) | 3.225 (1.668–4.650) | 2.320 (1.325–3.425) | 3.500 (2.718–11.10) | 0.028 |
| IL-6 (pg/mL) | 4.320 (1.900–10.81) | 4.450 (1.800–11.07) | 4.320 (1.850–11.21) | 0.825 |

*Note.* Data presented as mean ± SD or median (range).
*ACr*, albumin to creatinine ratio; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *HDL*, high-density lipoprotein; *IL-6*, interleukin-6; *LDL*, low-density lipoprotein; *SBP*, systolic blood pressure; *V/S ratio*, ratio of visceral fat area to subcutaneous fat area.

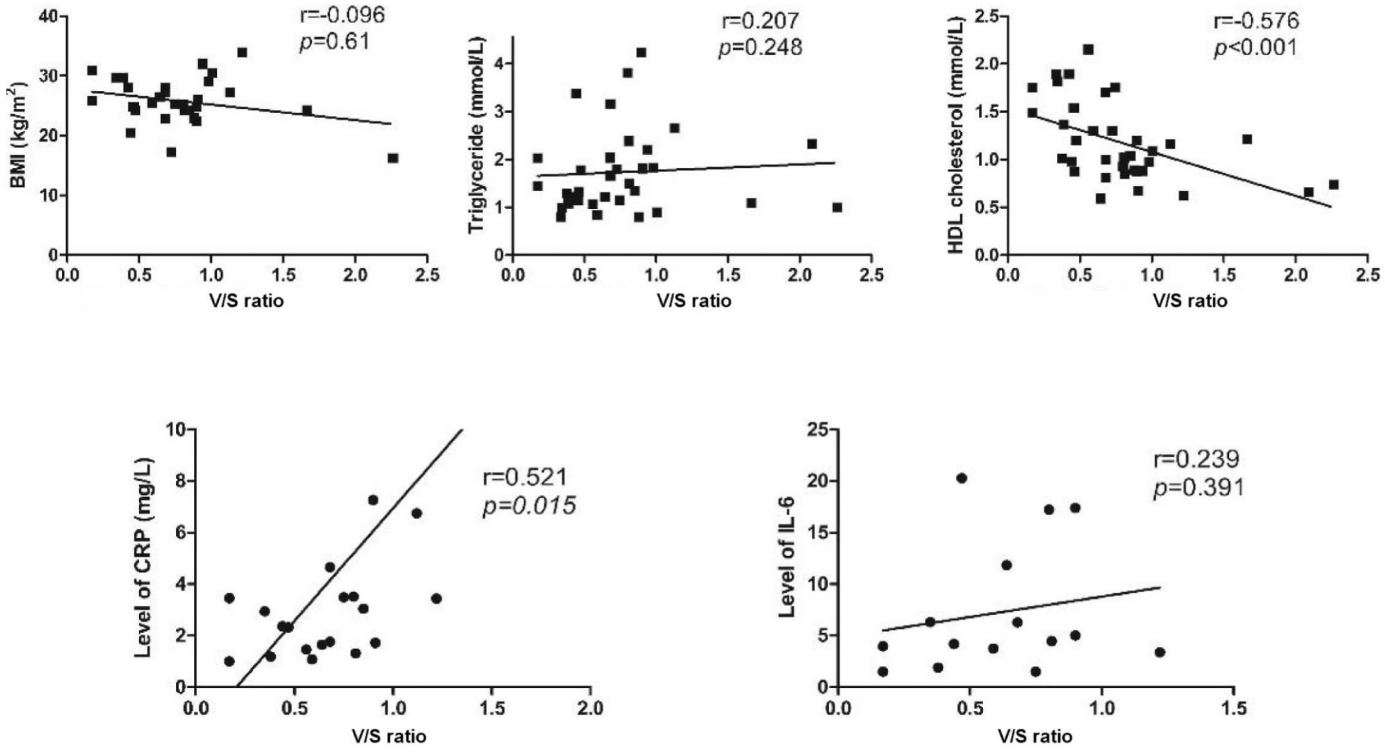


**Figure 1.** Correlation analysis between V/S ratio and clinical variables. Spearman analysis showed strong correlations between V/S ratio and CRP and V/S ratio and high-density lipoprotein cholesterol. No correlation was observed between V/S ratio and body mass index, triglycerides, or interleukin-6. *BMI*, body mass index; *CRP*, C-reactive protein; *HDL*, high-density lipoprotein; *IL-6*, interleukin-6; *V/S ratio*, ratio of visceral fat area to subcutaneous fat area.

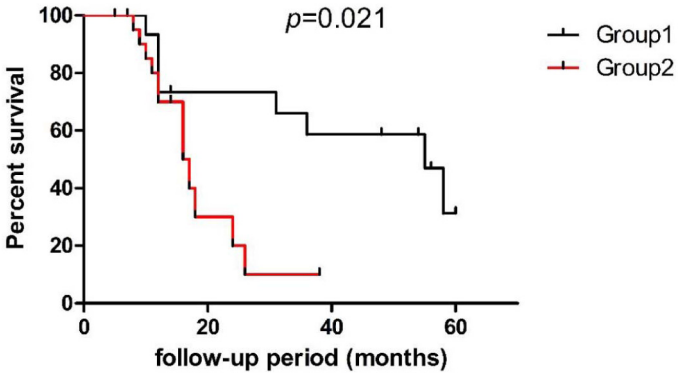


**Figure 2.** Kaplan-Meier survival curve to the endpoint according to the second quartile of the V/S ratio. V/S ratio represents the ratio of visceral fat area to subcutaneous fat area. Group 1 included patients with a V/S ratio <0.70; group 2 included others. A log-rank test was used to calculate p values.

creatinine (HR, 1.007; 95% CI, 1.003 to 1.011; p<0.01) and reduced eGFR (HR, 0.950; 95% CI, 0.918 to 0.984; p=0.004) were risk factors for progression to ESRD. However, when adjusted for age, sex, initial proteinuria, serum creatinine, eGFR and serum albumin, a higher V/S ratio was no longer indicated as an independent risk factor for a poor renal outcome (HR, 2.212; 95% CI, 0.543 to 9.005; p<0.268) (Table 2).

## Discussion

The results of the present retrospective study show, for the first time, that an increased V/S ratio is a potential risk factor for progression to ESRD in patients with DKD. A higher V/S ratio was found to be associated with decreased HDL cholesterol and increased C-reactive protein. Additionally, univariate Cox analysis revealed that increased V/S ratio was responsible for the poorer outcomes of patients with DKD. However, the multivariate Cox analysis demonstrated that a higher V/S ratio is not an independent risk factor when adjustments for confounding clinical variables are made.

According to the World Health Organization, more than 1.9 billion adults aged ≥18 years were identified as overweight in 2014 (http://www.who.int/mediacentre/factsheets/fs311/en). The physiological function of adipose tissue is energy storage and mobilization, and adipose tissue is also important in the endocrine and immune systems. However, growing evidence has demonstrated that adipokines, complements and some other inflammatory factors are increased in obese people in the form of acute-phase proteins and are mainly regulated by IL-1 and IL-6 (20–22). The low-grade inflammatory state mediated by obesity is regarded as a major risk factor for type 2 diabetes, hypertension and dyslipidemia (23–25). Moreover, excess adipose tissue, particularly visceral fat, releases a wide array of adipokines, as well as pathogenic signaling cytokines, which exert modulatory effects on nonadipose organs including the kidney (7,26,27). Because of these profound effects on the kidney, adipose tissue plays an important role in various kidney diseases, including focal segmental glomerulosclerosis, acute kidney injury, sepsis-associated kidney injury and CKD (7).

The interactions of excessive visceral fat with the kidney are mainly involved in inflammatory and fibrotic processes. The level of proinflammatory macrophages and inflammatory cytokines within adipose tissue increases with obesity, leading to a low-grade subclinical inflammatory state. The elevated adiponectin level in a patient with advanced CKD is associated with increased mortality independent of BMI. The effect might be attributed to lipopolysaccharide-induced inflammation and tubular damage (28). Leptin is an important cytokine secreted by adipose tissue to regulate appetite and energy expenditure; however, hyperleptinemia was relevant with CKD independent of BMI (29,30).

**Table 2**
Risks for renal endpoint determined by univariate/multivariate Cox hazard analysis

| | Univariate model | | | Multivariate model | | |
|---|---|---|---|---|---|---|
| Variables | HR | 95% CI | p value | HR | 95% CI | p value |
| Age | 1.029 | 0.972–1.088 | 0.326 | 0.989 | 0.934–1.047 | 0.692 |
| Sex | 1.085 | 0.376–3.132 | 0.881 | 1.004 | 0.188–5.783 | 0.961 |
| High V/S ratio | 3.536 | 1.140–10.960 | 0.029 | 2.212 | 0.543–9.005 | 0.268 |
| Initial proteinuria | 0.978 | 0.875–1.094 | 0.700 | 0.896 | 0.724–1.109 | 0.312 |
| Serum creatinine | 1.007 | 1.003–1.011 | <0.01 | 1.000 | 0.990–1.011 | 0.971 |
| eGFR | 0.950 | 0.918–0.984 | 0.004 | 0.947 | 0.896–1.001 | 0.052 |
| Serum albumin | 1.022 | 0.986–1.060 | 0.239 | 1.021 | 0.985–1.057 | 0.255 |
| Visceral fat area (>100 $cm^2$) | 1.073 | 0.362–3.178 | 0.899 | | | |
| Duration of diabetes | 1.004 | 0.999–1.009 | 0.160 | — | — | — |
| Diabetic retinopathy | 2.144 | 0.728–6.141 | 0.196 | — | — | — |
| Glycated hemoglobin | 0.925 | 0.662–1.292 | 0.647 | — | — | — |
| Smoking | 1.205 | 0.388–3.738 | 0.747 | — | — | — |
| Hypertension | 1.270 | 0.287–5.615 | 0.753 | — | — | — |
| Triglycerides | 1.031 | 0.775–1.372 | 0.833 | — | — | — |
| HDL cholesterol | 0.496 | 0.145–1.705 | 0.266 | — | — | — |
| C-reactive protein | 1.026 | 0.988–1.065 | 0.181 | | | |

*Note*: Renal endpoint is defined as the time patients initially received renal replacement therapy. The V/S ratio was analyzed as a continuous variable.
*CI,* confidence interval; *eGFR,* estimated glomerular filtration rate; *HDL,* high-density lipoprotein; *HR,* hazard ratio; *V/S ratio,* ratio of visceral fat area to subcutaneous fat area.

Multiple pathologic signaling pathways mediated by leptin are involved in kidney injury (31,32). Moreover, the expression of transforming growth factor-β1, type IV collagen and fibronectin in mesangial cells and the glomerulus were increased when leptin was administrated in vivo or in vitro (33–35). The dysfunction of the renin-angiotensin system also plays a critical role in the incidence and progression of DKD in addition to the effect of hypertension. In addition to the liver, adipose tissue produces approximately one-third of the circulating angiotensinogen (AGT) (36,37). In vivo, plasma AGT was increased by targeting adipocyte overexpression of AGT in mice with systemic deletion of AGT (38,39). Circulating AGT further converts to active angiotensin II, which binds to its type 1 receptor on the kidney and promotes inflammation infiltration (40). One of the antagonists of type 1 receptors, losartan, was found to reduce visceral fat and decrease inflammation in the kidneys in mice fed a high-fat diet (41). In summary, multiple established pathologic pathways of DKD can be activated by excess adipose tissue.

Although BMI has been widely used as an indicator of excess adipose tissue, it does not provide a precise measurement of visceral fat accumulation, especially for patients with CKD in whom muscle mass wasting is common (8,42–44). Therefore, CT is considered the gold standard for direct measurement of VFA and SFA (10). Various distributions of adipose tissue display distinct physiological traits; unlike VFA, SFA has properties that identify it as a protective fat depot (7,45). When the effects of VFA and SFA are considered together, a large body of evidence indicates that the V/S ratio is a better predictor of metabolic disorders and cardiovascular risk (16,46). Results of a recent study indicate that an increased V/S ratio is an independent predictor of incident or recurrent cardiovascular events in patients with type 2 diabetes (17). However, the criteria to define visceral obesity by means of the V/S ratio have not been established yet. Therefore, we used the second quartile of the ratio (0.70) as a cutoff value and determined that a higher V/S ratio is associated with a poorer renal outcome.

Bariatric surgery will decrease abdominal fat effectively. Moreover, a healthy lifestyle that includes more exercise and a low-fat diet is also beneficial. The best evidence-based therapy for DKD is renin-angiotensin system–blocking medication, which could also reduce injuries to the kidney caused by excess fat. The overlapping pathophysiology for abdominal fat and DKD implies the need for an overlapping treatment strategy.

The present study has several limitations. First, because this was a retrospective study, selection bias might exist. Second, the sample size was small, mainly because of the high cost of CT. Third, the follow-up period was relatively short. Twenty patients (57%) reached the endpoint during a median of 14 months. Fourth, there is no definite cutoff V/S ratio to define abdominal obesity. Additional studies to investigate the underlying mechanism are required. Moreover, a larger sample of patients with DKD and longer follow-up period are necessary to shed light on the association between abnormal adipose tissue and the prognosis of DKD.

In conclusion, the results of the present study demonstrate that decreased levels of HDL cholesterol and increased levels of C-reactive protein are concomitant with the higher V/S ratio.

## Funding

This study was supported by Grant 81670662 from the National Natural Science Foundation of China.

## Author Disclosures

Conflicts of interest: None.

## Author Contributions

YW and FC collected the data and wrote the manuscript. JW, TW, JZ, QH, YW, RZ, and FL were involved in performing the CT scans and revised the manuscript.

## References

1. Doshi SM, Friedman AN. Diagnosis and management of type 2 diabetic kidney disease. Clin J Am Soc Nephrol 2017;12:1366–73.
2. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med 2014;370:1514–23.
3. Liu Z. Nephrology in China. Nat Rev Nephrol 2013;9:523–8.
4. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. JAMA 2016;316:602–10.
5. Kramer HJ, Saranathan A, Luke A, et al. Increasing body mass index and obesity in the incident ESRD population. J Am Soc Nephrol 2006;17:1453–9.
6. Vivante A, Golan E, Tzur D, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Arch Intern Med 2012;172:1644–50.

7. Zhu Q, Scherer PE. Immunologic and endocrine functions of adipose tissue: Implications for kidney disease. Nat Rev Nephrol 2017;14:105–20.
8. 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 Dial Transplant 2016;31:1070–7.
9. Oliveira EA, Cheung WW, Toma KG, Mak RH. Muscle wasting in chronic kidney disease. Pediatr Nephrol 2018;33:789–98.
10. Jensen MD, Kanaley JA, Reed JE, Sheedy PF. Measurement of abdominal and visceral fat with computed tomography and dual-energy x-ray absorptiometry. Am J Clin Nutr 1995;61:274.
11. Consultation WE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–63.
12. Park YW, Allison DB, Heymsfield SB, Gallagher D. Larger amounts of visceral adipose tissue in Asian Americans. Obes Res 2001;9:381–7.
13. Tanaka S, Horimai C, Katsukawa F. Ethnic differences in abdominal visceral fat accumulation between Japanese, African-Americans, and Caucasians: A meta-analysis. Acta Diabetol 2003;40:s302–4.
14. Narumi H, Yoshida K, Hashimoto N, et al. Increased subcutaneous fat accumulation has a protective role against subclinical atherosclerosis in asymptomatic subjects undergoing general health screening. Int J Cardiol 2009;135:150–5.
15. Yang X, Smith U. Adipose tissue distribution and risk of metabolic disease: Does thiazolidinedione-induced adipose tissue redistribution provide a clue to the answer? Diabetologia 2007;50:1127–39.
16. Katsuyama H, Kawaguchi A, Yanai H. Not visceral fat area but the ratio of visceral to subcutaneous fat area is significantly correlated with the marker for atherosclerosis in obese subjects. Int J Cardiol 2015;179:112–3.
17. Fukuda T, Bouchi R, Takeuchi T, et al. Ratio of visceral-to-subcutaneous fat area predicts cardiovascular events in patients with type 2 diabetes. J Diabetes Investig 2018;9:396–402.
18. An Y, Xu F, Le W, et al. Renal histologic changes and the outcome in patients with diabetic nephropathy. Nephrol Dial Transplant 2015;30:257–66.
19. Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol 2010;21:556–63.
20. Barbu A, Hamad OA, Lind L, Ekdahl KN, Nilsson B. The role of complement factor C3 in lipid metabolism. Mol Immunol 2015;67:101–7.
21. Zhang J, Wang Y, Zhang R, et al. Implication of decreased serum complement 3 in patients with diabetic nephropathy. Acta Diabetol 2018;55:31–9.
22. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97.
23. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. J Epidemiol Community Health 2000;54:596–602.
24. Kang YS. Obesity associated hypertension: New insights into mechanism. Electrolyte Blood Press 2013;11:46.
25. Misra A, Shrivastava U. Obesity and dyslipidemia in South Asians. Nutrients 2013;5(7):2708–33.
26. Wisse BE. The inflammatory syndrome: The role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004;15:2792–800.
27. Juge-Aubry CE, Somm E, Pernin A, et al. Adipose tissue is a regulated source of interleukin-10. Cytokine 2005;29:270–4.
28. Perri A, Vizza D, Lupinacci S, et al. Adiponectin secreted by tubular renal cells during LPS exposure worsens the cellular inflammatory damage. J Nephrol 2016;29:185–94.
29. Shankar A, Syamala S, Xiao J, Muntner P. Relationship between plasma leptin level and chronic kidney disease. Int J Nephrol 2012;2012:1–6.
30. Lim CC, Teo BW, Tai ES, et al. Elevated serum leptin, adiponectin and leptin to adiponectin ratio is associated with chronic kidney disease in Asian adults. PLoS ONE 2015;10:e0122009.
31. Alhasson F, Das S, Chandrashekaran V, et al. High circulatory leptin mediated NOX-2 promotes kidney inflammation in nonalcoholic fatty liver disease via MiR21-dependent mesangial cell activation. Free Radical Biol Med 2016;100:S51.
32. Dattaroy D, Pourhoseini S, Das S, et al. Micro-RNA 21 inhibition of SMAD7 enhances fibrogenesis via leptin-mediated NADPH oxidase in experimental and human nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 2015;308:G298–312.
33. Wolf G, Hamann A, Han DC, et al. Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: Potential role in glomerulosclerosis [see comments]. Kidney Int 1999;56:860–72.
34. Cui W, Maimaitiyiming H, Qi X, Norman H, Wang S. Thrombospondin 1 mediates renal dysfunction in a mouse model of high-fat diet-induced obesity. Am J Physiol Renal Physiol 2013;305:F871–80.
35. Kümpers P, Gueler F, Rong S, et al. Leptin is a coactivator of TGF-β in unilateral ureteral obstructive kidney disease. Am J Physiol Renal Physiol 2007;293:F1355–62.
36. Yvan-Charvet L, Quignard-Boulange A. Role of adipose tissue renin-angiotensin system in metabolic and inflammatory diseases associated with obesity. Kidney Int 2011;79:162–8.
37. Yiannikouris F, Karounos M, Charnigo R, et al. Adipocyte-specific deficiency of angiotensinogen decreases plasma angiotensinogen concentration and systolic blood pressure in mice. Am J Physiol Regul Integr Comp Physiol 2012;302:R244–51.
38. Kihara M, Umemura S, Sumida Y, et al. Genetic deficiency of angiotensinogen produces an impaired urine concentrating ability in mice. Kidney Int 1998;53:548–55.
39. Massiera F, Bloch-Faure M, Ceiler D, et al. Adipose angiotensinogen is involved in adipose tissue growth and blood pressure regulation. FASEB J 2001;15:2727–9.
40. Guo H, Li H, Wang B, et al. Protective effects of glucagon-like peptide-1 analog on renal tubular injury in mice on high-fat diet. Cell Physiol Biochem 2017;41:1113–24.
41. Ma LJ, Corsa BA, Zhou J, et al. Angiotensin type 1 receptor modulates macrophage polarization and renal injury in obesity. Am J Physiol Renal Physiol 2011;300:F1203–13.
42. Okorodudu DO, Jumean MF, Montori VM, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: A systematic review and meta-analysis. Int J Obes (Lond) 2010;34:791–9.
43. Gomez-Ambrosi J, Silva C, Galofre JC, et al. Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. Int J Obes (Lond) 2012;36:286–94.
44. Javed A, Jumean M, Murad MH, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity in children and adolescents: A systematic review and meta-analysis. Pediatr Obes 2015;10:234–44.
45. Porter SA, Massaro JM, Hoffmann U, et al. Abdominal subcutaneous adipose tissue: A protective fat depot? Diabetes Care 2009;32:1068–75.
46. Pisitsak C, Lee JGH, Boyd JH, et al. Increased ratio of visceral to subcutaneous adipose tissue in septic patients is associated with adverse outcome. Crit Care Med 2016;44:1966–73.