Relationship of visceral and subcutaneous adiposity with renal function in people with type 2 diabetes mellitus

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Abstract

Background. Obesity and diabetes mellitus (DM) are established risk factors for the development of chronic kidney disease. Visceral adiposity (VAT) and subcutaneous adiposity (SAT) may be associated with the differential metabolic risk. Our study was performed to determine whether VAT or SAT was associated with the decrease of renal function in people with type 2 DM.

Methods. Nine hundred and twenty-nine people with type 2 DM and who had undergone abdominal computed tomography assessment of the SAT and VAT areas were included. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault equation and the Modification of Diet in Renal Disease (MDRD) four-variable equation at the time of the assessment of the SAT and VAT areas.

Results. VAT was negatively associated with eGFR using the MDRD equation after adjustment for the clinical variables (β-coefficient = −0.075, P = 0.034), while SAT was not significantly associated with eGFR. There was no significant association between the abdominal adiposity measurements and the eGFR using the Cockcroft–Gault formula. When stratifying the individuals by the body mass index groups, VAT was negatively associated with eGFR by the MDRD equation and the Cockcroft–Gault formula in the overweight and obese subjects after adjustment for the clinical variables, while there was no significant association between the VAT and the eGFR in the normal weight subjects. SAT was not significantly associated with eGFR in the normal weight, overweight and obese subjects.

Conclusions. Our data suggest that VAT may be an additional prognostic factor for the decrease of renal function especially in the overweight or obese subjects with type 2 DM.

Keywords: adiposity; diabetes mellitus; glomerular filtration rate; obesity

Introduction

Chronic kidney disease (CKD) is a significant public health problem, and the incidence and prevalence of CKD are gradually increasing worldwide [1,2]. Obesity is also increasing worldwide, and previous studies have demonstrated that obesity is a risk factor for CKD and end-stage renal disease (ESRD) [3–8]. Central obesity, as estimated by the waist circumference, is more associated with the metabolic risk and cardiovascular risk as compared to the body mass index (BMI) [9,10]. For the association of central obesity with renal function, Elsayed et al. reported that central obesity, as estimated by the waist-to-hip ratio, was associated with the development of decreased kidney function in a generalizable community-based US population [6].

Visceral adiposity (VAT) and subcutaneous adiposity (SAT) may have differential metabolic risks [11]. The visceral fat component is metabolically active and it regulates numerous adipokines and cytokines such as leptin, adiponectin, plasminogen activator-I and vascular endothelial growth factor, which may all be associated with increased cardiometabolic risk, but they may also be associated with the deterioration of renal function [12–15]. A recent study demonstrated that VAT measured by computed tomography (CT) is more strongly associated with an adverse metabolic risk, as compared to that of SAT [16]. As for the differential association between the abdominal fat compartment and CKD, one community-based study showed that both the VAT and the SAT, as measured using CT, were associated with CKD, as defined by only the cystatin C estimating equation, but neither the VAT nor the SAT was associated with CKD, when defined using the creatine-based estimating equation [17].

Diabetes mellitus (DM) is a well-established risk factor for CKD or ESRD. Obesity is more prevalent in people with DM, and obesity may accelerate the deterioration of renal function in people with DM [18,19]. The distribution
of adipose tissue was significantly altered in people with type 2 DM; VAT was greater and SAT was lower in people with type 2 DM than that in the healthy control subjects [20]. The association between the regional distribution of abdominal adiposity and the renal function in people with type 2 DM is not well established.

We hypothesized that VAT would be more associated with the decrease of renal function compared to that of SAT in people with type 2 DM. Examining the influence of the regional distribution of abdominal adiposity on renal function may help to define it as a risk factor for the development or progression of CKD in people with type 2 DM.

Materials and methods

Subjects

From March 2005 to December 2007, 929 patients with type 2 DM and who had undergone abdominal CT for obesity screening at the Bucheon Saint Mary’s Hospital were enrolled in this hospital-based, cross-sectional study. Type 2 DM was diagnosed if (i) the patients had no episodes of ketoacidosis, (ii) they were diagnosed with DM after the age of 40 years and (iii) they had fasting serum C-peptide values 1.0 ng/mL when administered with insulin. The exclusion criteria were missing values for the BMI, serum creatinine or other clinical variables. The study protocol was approved by the local ethical committee, and this study was conducted according to the principles of the Declaration of Helsinki.

Measurements of the visceral fat area and subcutaneous fat area

Measurements of the cross-sectional abdominal visceral and subcutaneous fat areas by CT (Somatom plus 4, Siemens, Germany) were performed using an established protocol [21]. The subjects were placed supine with their feet first in the scanner and a cross-sectional scan at 10-mm thickness centred at the level of the intervertebral space between the fourth and fifth lumbar vertebrae was obtained using a radiograph of the skeleton as a reference to establish the position of the scans to the nearest millimetre. The boundaries of the subcutaneous and visceral fat areas were defined by tracing their contours on the scans, and the adipose tissue areas were calculated by computing the fat area surfaces with an attenuation range of -190 to -30 Hounsfield units. The visceral fat area was measured within the region by outlining the circumference of the abdominal cavity. The total fat area was measured in the region by outlining the circumference of the abdominal wall. The subcutaneous fat area was calculated by subtracting the visceral fat area from the total fat area. The measurements were done by one radiologist who was blinded to the subjects’ clinical and laboratory data. We tested the intra-observer reproducibility. VAT and SAT of the scan on a subset of 50 randomly selected subjects were repeatedly measured by the radiologist. The intraclass correlation coefficients for VAT and SAT were 0.991 and 0.981, respectively. For the inter-observer reproducibility, previous studies reported that the measurement of VAT and SAT is reproducible between observers [16,22].

Clinical information and laboratory data

The clinical information was assessed from the written and electronic medical records, and this information included medical history, current medications and laboratory data. The collected data included age, gender, BMI, systolic and diastolic blood pressures, duration of diabetes, serum creatinine, haemoglobin and albumin levels, total cholesterol and high-density lipoprotein (HDL) cholesterol levels, triglyceride and serum uric acid levels, urinary albumin excretion rate (AER), homeostasis model for insulin resistance (HOMA-IR) score, lipoprotein (a) and high-sensitivity C-reactive protein levels and estimated glomerular filtration rate (eGFR). The urine AER was assessed via 24-h urine collection. The BMI was calculated as weight (kg)/height (m²). The blood pressure was measured twice, 5 min apart, using a random zero sphygmomanometer with the patient seated after 10 min of rest. The HOMA-IR (%) index of insulin resistance score was calculated by the standard formula [23].

To estimate the GFR, we calculated it using both the Cockcroft–Gault equation and the Modification of Diet in Renal Disease (MDRD) four-variable equation at the time of CT scanning. The Cockcroft–Gault formula was calculated as \[ \frac{140 - \text{age (years)}}{72 \times \text{weight (kg)}} \times 0.85 \text{ if female} \] and it was standardized for the body surface area using the Dubois formula. The MDRD formula was calculated as \[ 186 \times \text{serum creatinine (mg/dL)}^{1.154} \times \text{age (years)^{-0.203}} \times 1.212 \text{ if black} \times 0.742 \text{ if female} \] [25].

Statistics

The data for continuous variables with a normal distribution are presented as means ± SDs, and the data for continuous variables without a normal distribution are presented as medians with interquartile ranges. Pearson correlation coefficients were used to assess the simple correlation between the clinical parameters and the eGFR. Multivariate linear regression analysis was used to determine the association between the adiposity measurements, including total fat area, visceral fat area and subcutaneous fat area with eGFR after adjustment for age, gender, duration of diabetes, systolic and diastolic blood pressures, serum triglyceride, HOMA-IR score, level of uric acid and urinary albumin excretion. To determine whether the abdominal fat distribution was related to eGFR in the normal weight, overweight and obese subjects, the association of abdominal adiposity measurements with eGFR was assessed by linear regression analysis separately for the normal weight (BMI 15.0-24.9 kg/m²), overweight (BMI 25.0-29.9 kg/m²) and obese (BMI > 29.9 kg/m²) subjects with adjusting for age, gender, duration of diabetes, systolic and diastolic blood pressures, serum triglyceride, HOMA-IR score, level of uric acid and urinary albumin excretion. P-values < 0.05 were considered statistically significant. The statistical analyses were performed using SPSS 15.0 software (Chicago, IL, USA).

Results

Patients’ characteristics

Table 1 shows the clinical characteristics of the enrolled patients. Overall, 488 women and 441 men with type 2 DM were available for analysis. Their mean age was 55 years old. The mean total fat area was 282 ± 121 cm². The mean visceral fat area was 122 ± 61 cm², and the mean subcutaneous fat area was 159 ± 81 cm². The age and gender-adjusted correlation between the visceral fat area and the subcutaneous fat area was 0.60 (P < 0.001). The mean BMI was 25.2 ± 3.9 kg/m². The age and gender-adjusted correlations of the total fat area with the BMI, the visceral fat area with the BMI and the subcutaneous fat area with the BMI were 0.80, 0.69 and 0.72, respectively (P < 0.001). The mean eGFR calculated by the MDRD equation was 95 ± 27 mL/min/1.73 m², and the mean eGFR by the Cockcroft–Gault formula was 93 ± 30 mL/min/1.73 m².

Association of abdominal adiposity measurements with eGFR

Table 2 shows the univariate and multivariate regression analyses for the association of abdominal adiposity with eGFR by the MDRD equation and the Cockcroft–Gault formula. On the univariate analysis, the visceral fat area was negatively correlated with eGFR using the MDRD equation (r = -0.158; P = < 0.001), while the total fat and subcutaneous fat areas were not correlated with eGFR using the MDRD equation. The total fat area, visceral fat area and subcutaneous fat area were not correlated with
Values are expressed as means ± SDs, medians (interquartile range) or n (%). eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index.

eGFR using the Cockcroft–Gault formula. On the multivariate analysis of the association between the abdominal adiposity measurements and the eGFR using the MDRD equation, the visceral fat area was negatively associated with eGFR after adjustment for age, gender, duration of diabetes, systolic and diastolic blood pressures, serum triglyceride, HOMA-IR score, uric acid level and urinary albumin excretion (β-coefficient = −0.075, P = 0.034), while the total fat area and subcutaneous fat area were not significantly associated with eGFR. There was no significant association in the analysis between the abdominal adiposity measurements and the eGFR using the Cockcroft–Gault formula.

Table 3. Total, visceral and subcutaneous adiposity in the normal weight (BMI 15.0–24.9 kg/m²), overweight (BMI 25–25.9 kg/m²) and obese (BMI > 29.9 kg/m²) subjects with type 2 diabetes

Table 2. Univariate and multivariate linear regression analyses for the association of abdominal adiposity with eGFR by the MDRD equation and the Cockcroft–Gault formula

Table 1. Clinical characteristics of the patients

Clinical characteristics Value (n = 929)

Age, years 55 ± 13
Male, n (%) 441 (47.5)
Total fat, cm² 282 ± 121
Visceral fat, cm² 122 ± 61
Subcutaneous fat, cm² 159 ± 81
BMI, kg/m² 25.2 ± 3.9
Obese, BMI > 29.9, n (%) 97 (10.4)
Systolic blood pressure, mm Hg 130 ± 16
Diastolic blood pressure, mm Hg 77 ± 11
Duration of diabetes, months 64 ± 83
Serum creatinine, mg/dL 0.8 ± 0.2
eGFR by MDRD equation, mL/min/1.73 m² 95 ± 27
eGFR by Cockcroft–Gault formula, mL/min/1.73 m² 93 ± 30
Haemoglobin, g/dL 13.6 ± 1.9
Serum albumin, g/dL 4.3 ± 0.3
Serum total cholesterol, mg/dL 188 ± 45
Serum triglyceride, mg/dL 175 ± 119
Serum HDL, mg/dL 51 ± 16
Serum uric acid, mg/dL 4.6 ± 1.5
Urinary albumin excretion, μg/min 49 ± 150
Haemoglobin A1c 8.9 ± 2.4
HOMA-IR 3.7 ± 2.5
Lipoprotein (a), (IU/L) 171 (47–398)
hs-CRP, mg/dL 1.5 ± 5.2

Adapted for age, sex, duration of diabetes, systolic blood pressure, diastolic blood pressure, serum triglyceride, HOMA-IR, uric acid and urinary albumin excretion.

Discussion

In most of the previous studies that focused on the association between VAT and renal function, VAT was measured...
using the waist-to-hip ratio or the waist circumference. However, because of the inability of the waist-to-hip ratio or the waist circumference to represent the abdominal fat compartment such as VAT or SAT, imaging such as CT or magnetic resonance imaging (MRI) is required for determining the differential association between the abdominal fat compartment and the clinical outcomes. Studies using imaging such as CT or MRI for assessing the differential association between the abdominal fat compartment and renal function are rare. In our cross-sectional study, CT was used to measure VAT and SAT in people with type 2 DM and we found that VAT was negatively associated with eGFR using the MDRD equation after adjustment for the clinical variables, while SAT was not associated with eGFR. However, there was no significant association of VAT and SAT with eGFR using the Cockcroft–Gault formula. When stratifying the individuals by the BMI groups, VAT was negatively associated with eGFR by the MDRD equation and the Cockcroft–Gault formula in the overweight and obese subjects, but not in the normal weight subjects. Furthermore, SAT was not significantly associated with eGFR in the normal weight, overweight and obese subjects. These findings suggest that VAT, but not SAT, may be able to predict the decrease of renal function especially in the overweight or obese subjects with type 2 DM.

Table 4. Multiple regression analysis for the association of abdominal adiposity with eGFR in the normal weight, overweight and obese subjects with type 2 diabetes

<table>
<thead>
<tr>
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<th>eGFR by MDRD equation, mL/min/1.73 m²</th>
<th>eGFR by CG formula, mL/min/1.73 m²</th>
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<tbody>
<tr>
<td></td>
<td>β-coefficient</td>
<td>P-value</td>
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<tr>
<td>Normal weight (n= 473)</td>
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<tr>
<td>Total fat, cm²</td>
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<tr>
<td>Visceral fat, cm²</td>
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<tr>
<td>Subcutaneous fat, cm²</td>
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<td>Overweight (n= 359)</td>
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<td>Visceral fat, cm²</td>
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<td>Subcutaneous fat, cm²</td>
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<tr>
<td>Obese (n= 97)</td>
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<td>Visceral fat, cm²</td>
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<tr>
<td>Subcutaneous fat, cm²</td>
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<td>0.964</td>
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eGFR, estimated glomerular filtration rate; BMI, body mass index; CG, Cockcroft–Gault.

Adjusted for age, duration of diabetes, systolic blood pressure, diastolic blood pressure, serum triglyceride, HOMA-IR, uric acid and urinary albumin excretion.

Fig. 1. Association of visceral adiposity and eGFR calculated by the MDRD equation (A) and the Cockcroft–Gault formula (B) in the normal weight, overweight and obese subjects with type 2 diabetes.
The visceral fat component is metabolically active and it regulates numerous adipokines and cytokines such as leptin, adiponectin, plasminogen activator-1 and vascular endothelial growth factor, which may be associated with renal dysfunction [12–16]. A previous community-based study reported that both VAT and SAT were associated with CKD as defined by the cystatin C estimating equation [17], which is inconsistent with the result of our study. This discrepancy may be due to the differences of the study designs or the populations of the studies. In our study, only subjects with type 2 DM were recruited while the previous study was a community-based study and the percentage of the subjects with DM was 8.6%. Type 2 DM is a strong risk factor for CKD and obesity may accelerate the deterioration of renal function especially in subjects with DM [18,19]. The amount of VAT is higher and the amount of SAT is lower in people with type 2 DM than that in people with normal glucose tolerance [20,26]. Furthermore, VAT, but not SAT, has a significant negative impact on glycaemic control through a decrease in peripheral insulin sensitivity in type 2 DM [27], which may be associated with renal dysfunction especially in the subjects with type 2 DM.

In our study, VAT was negatively associated with eGFR in the overweight and obese subjects, but not in the normal weight subjects when stratifying the individuals by the BMI groups. It is unclear why VAT was associated with eGFR only in the overweight and obese subjects, but not in the normal weight subjects. A previous study reported that the amount of VAT is associated with the stepwise linear increase of the prevalence of metabolic risk [16]. In our study, the amount of VAT in the normal weight subjects was significantly lower than that of the overweight or obese subjects, and the amount of VAT was more strongly related with the decrease of eGFR in the higher BMI group than that in the lower BMI group (Figure 1). We cautiously supposed that the amount of VAT may not have been enough to decrease the renal function in our study. This finding may support the clinical implication of VAT on the renal function in Caucasians with type 2 DM, whose BMI is higher than that of Asians with type 2 DM [28,29].

Our study has several limitations. Firstly, this was a cross-sectional study; therefore, it is difficult to infer causality between VAT and the deterioration of renal function. Secondly, this study was a single centre study; therefore, the generalizability of our results to other ethnic groups with type 2 DM is uncertain. Thirdly, the validity of the MDRD equation that was used for estimating the GFR is not known for Korean people since the MDRD equation was developed using US white and black participants. However, one study reported that the MDRD equation and the Cockcroft–Gault formula have accuracy and precision with the true GFR, and so two equations can be applied to the subjects within the healthy general Korean population [30]. Therefore, we used both the MDRD equation and the Cockcroft–Gault formula for calculating the eGFR in our study. Finally, other measurements of obesity such as the waist-to-hip ratio or waist circumference were not done, and so the association of various other measurements of obesity with renal function was not analysed.

Despite the above limitations, the present study is the first to investigate the differential association between the abdominal fat compartment and renal function in people with type 2 DM and who have a different regional adipose tissue distribution from those people with normal glucose tolerance.

In conclusion, VAT, but not SAT, was associated with the decrease of eGFR in the overweight or obese subjects with type 2 DM. Our data suggest that VAT might be an additional prognostic factor for decreased renal function in overweight or obese subjects with type 2 DM. Efforts to decrease VAT may be helpful to prevent the development of CKD especially in overweight or obese subjects with type 2 DM.

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Conflict of interest statement. None declared.

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Low glomerular density is a risk factor for progression in idiopathic membranous nephropathy

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Abstract

Background. The adverse histological features predicting a progressive loss of renal function in idiopathic membranous nephropathy (IMN), before the establishment of impaired renal function with advanced glomerulosclerosis and/or interstitial fibrosis, are still poorly understood. The present study examined the relationship between the glomerular density (GD; non-sclerotic glomerular number/renal cortical area of biopsy) and the renal prognosis in IMN patients, especially in those without any apparent renal dysfunction at the time of diagnosis.

Methods. The predictive value of the factors at biopsy, including the GD, on the renal outcome was retrospectively analyzed in the 65 IMN patients with an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73m² (mean, 80 mL/min/1.73m²) at biopsy.

Results. The individual values for GD ranged from 1.6 to 6.5/mm² with 4-fold variation. A lower GD was associated with progression based on a ≥50% reduction in eGFR or reaching to end-stage renal disease. An association between a lower GD and progression was observed, especially in patients with persistent proteinuria of ≥1 g/day at follow-up. In contrast, any patients who achieved proteinuria of <1 g/day at follow-up did not show progression regardless of their GD levels. In addition, among the various clinicopathological factors observed, the GD was the only factor at biopsy that independently predicted the slope of the renal function during the observation periods.

Conclusion. These results suggest that low GD is a plausible risk factor for progression in IMN patients, especially in those that do not achieve a remission of proteinuria during the follow-up.

Keywords: glomerular density; membranous nephropathy; remission; renal biopsy; renal outcome

Introduction

Idiopathic membranous nephropathy (IMN) is the second most common cause of end-stage renal disease (ESRD) in