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Serum Cystatin C levels increase with increasing visceral fat area in patients with type 2 diabetes mellitus

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The present study aimed to explore the association between serum cystatin C (Cys-C) levels and visceral fat area (VFA) in patients with type 2 diabetes mellitus (T2DM). A total of 208 previously diagnosed T2DM patients who visited our hospital from September 2019 to December 2021 were included and divided into three groups based on tertiles of Cys-C levels, namely, Groups C1, C2, and C3. The clinical data of the subjects were collected, biochemical parameters such as Cys-C levels were determined, and bioelectrical impedance analysis was applied to determine the VFA and subcutaneous fat area (SFA). The VFA in Group C1 was lower than that in Groups C2 and C3 (all $P < 0.05$), with no significant difference in VFA between Groups C2 and C3 ($P > 0.05$). Spearman's correlation analysis revealed that the serum Cys-C level was positively correlated with age, VFA, SFA, insulin resistance index, waist circumference, body mass index, systolic blood pressure, serum creatinine level, and blood uric acid level (r = 0.543, 0.353, 0.168, 0.148, 0.365, 0.264, 0.25, 0.497, and 0.155, respectively; $P < 0.05$) and negatively correlated with glycated haemoglobin levels (r = -0.175, $P < 0.05$). Univariate linear regression analysis revealed that VFA was positively correlated with the Cys-C level ($\beta = 0.002$, 95% CI = 0.001–0.003, $P < 0.05$), with an increase of 0.002 mg/L in the Cys-C level for each 1 cm^2 increase in VFA. Further multivariate linear regression analysis was performed with the serum Cys-C level as the dependent variable and age, VFA, SFA, insulin resistance (HOMA-IR), WC, BMI, SBP, Cr, UA, and HbA1c as the independent variables. The results suggested that VFA was positively correlated with serum Cys-C level ($\beta = 0.001$, 95% CI = 0.000–0.002, $P < 0.05$), with serum Cys-C levels increasing by 0.001 mg/L for every 1 cm^2 increase in VFA. Using a VFA ≥ 100 cm^2 as the criterion for visceral obesity, ROC analysis revealed that the Cys-C level was a better predictor of visceral obesity, with an area under the ROC curve (AUC) of 0.701 (95% CI = 0.631–0.771, $P < 0.05$), an optimal cut-off of 0.905 mg/L, and a sensitivity and specificity of 58.3% and 75.2%, respectively. The results suggested that the serum Cys-C level was correlated with the VFA in patients with T2DM and that Cys-C may play a vital role in T2DM patients with visceral obesity.

Keyword Type 2 Diabetes Mellitus; Cystatin C; Visceral Fat Area; Association

The incidence of diabetes mellitus has been increasing annually with economic development and the improvement of individuals' living standards. On December 6, 2021, the International Diabetes Federation released the Global Diabetes Atlas. Five hundred thirty-seven million adults aged > 20–79 years suffer from diabetes[1]. Notably, long-term poor glycaemic control may lead to a series of complications, such as atherosclerotic cardiovascular and cerebrovascular diseases, which can seriously affect the quality of life of patients and thus increase the burden on society and families[2]. Obesity is closely related to the onset of type 2 diabetes mellitus (T2DM), with 90% of T2DM patients having varying degrees of overweight or obese[3]. Obesity-induced inflammation is a crucial driver of insulin resistance and T2DM[4]. Cystatin C, an important cysteine protease inhibitor, is considered a better indicator of renal function than creatinine due to its constant secretion rate[5]. Cys-C is also associated with inflammation[4]. On the other hand, diabetes mellitus, its complications, and diabetes-associated disorders such

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as hypertension, hepatosteatosis, obesity, and metabolic syndrome are associated with inflammation[6,7]. Thus, studying Cys-C in diabetes mellitus patients is logical.

Previous studies have demonstrated a correlation between Cys-C levels and body mass index (BMI) in non-diabetic populations[8–10]. However limited research has been conducted on the relationship between Cys-C levels and overweight or obesity in individuals with T2DM. Moreover, studies on T2DM patients have assessed obesity based on BMI[11,12]. However, the conventional measure of obesity using BMI may not effectively distinguish between fat mass, muscle mass, and bone mass[13,14] and is, therefore not a good measure of overall obesity[15]. Visceral fat is a particular abdominal fat that is hidden deep in the abdomen and surrounds visceral organs; thus, the VFA can well reflect body fat and visceral fat content ≥ 100 cm^2 is currently used to determine visceral obesity[16]. CT and MRI are recognised as the gold standards for determining VFA. However, the wide application of CT and MRI is limited due to many factors, such as radiation exposure, high cost, and complex equipment and operation. Recently, bioimpedance analysis (BIA), due to its advantages of simple operation, lack of radiation, low cost, etc., has become a good alternative to CT for the assessment of body composition[17]. Given the limitations of using BMI to assess obesity and the potential importance of cystatin C in T2DM, this study assessed visceral fat content by VFA to evaluate the cross-sectional relationship between VFA and serum Cys-C levels among patients with T2DM. This study aimed to further investigate the significance of Cys-C as a potential serological marker of visceral obesity and to provide a foundation for prevention and treatment studies of T2DM combined with overweight or obesity.

Materials and methods

Participants

This was a cross-sectional observational study, and all patients were screened according to this study's inclusion and exclusion criteria. Patients previously diagnosed with T2DM who attended Suzhou Municipal Hospital from September 2019 to December 2021 and met the diagnostic criteria recommended by the most recent American Diabetes Association guidelines were selected[18]. Patients aged 18–70 years were included in this study. The exclusion criteria were patients with type 1 diabetes mellitus and other types of diabetes, diabetic ketoacidosis, diabetic hyperosmolar syndrome, renal insufficiency (a glomerular filtration rate (GFR) < 90 mL/min/1.73 m^2), or hepatic insufficiency (transaminases > 120 U/L); pregnant and lactating women; patients with abnormal thyroid function; patients receiving glucocorticoid treatment; and patients with other diseases of the immune system. This study was approved by the Ethics Committee of Suzhou Municipal Hospital, and all study subjects understood the study's objective and signed the informed written consent form. A total of 208 patients were ultimately enrolled, and all patients who met the inclusion criteria for this study were divided into three groups, Groups C1, C2, and C3, according to Cys-C tertile (C1: ≤ 33.3%, C2: 33.3%-66.7%, and C3: 66.7%-100%).

Data collection and laboratory measurements

(1) Recording of basic patient data: Patients' medical histories were collected, and sex, age, height, weight, and waist circumference were also recorded to calculate BMI. Systolic and diastolic blood pressure were measured three times during quiet rest to obtain the mean values. (2) Determination of the serum Cys-C concentration and other biochemical indices: The test instrument used was a Hitachi H7600 automatic biochemical analyser, and the Cys-C reagent was obtained from Beijing Leadman Biochemistry Co., Ltd. The intra-assay coefficients of variation (CVs) were 2.0%-3%, and the inter-assay CVs were 3.6%-7.9%. All patients fasted for at least 8 h, and blood was collected from the elbow vein in the early morning during fasting. Cys-C levels were measured by immunoturbidimetric assay, and triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), creatinine (Cr), uric acid (UA), fasting blood glucose (FBG), glycated haemoglobin (HbA1c), and fasting insulin (FINS) levels were determined simultaneously. Homeostasis model assessment for HOMA-IR was calculated as follows: HOMA-IR = fasting insulin × fasting glucose ÷ 22.5. (3) VFA and SFA were measured using an Omron DUALSCAN HDS-2000, and the measurements were performed according to the manufacturer's instructions. (4) Patients were divided into three groups, namely, Groups C1, C2, and C3, based on Cys-C tertile.

Statistical analysis

Data were statistically analysed using SPSS 25.0 statistical software, and GraphPad Prism 8.0 was used to plot the data. The normality of the data was evaluated with the Kolmogorov–Smirnov test. Normally distributed continuous variables are expressed as the mean ± standard deviation, for which one-way analysis of variance (ANOVA) was used for intergroup comparisons. Nonnormally distributed data are expressed as medians (interquartile ranges), for which nonparametric tests were used for intergroup comparisons. Correlation analysis between Cys-C levels and other variables was performed using Spearman's rank correlation. Univariate linear regression analysis was used to analyse the correlation between Cys-C levels and VFA. Further multivariate linear regression analysis was performed with the serum Cys-C level as the dependent variable and variables with statistically significant differences in the univariate linear regression analysis as the independent variables. Receiver Operating Characteristic curves were used to evaluate the predictive role of Cys-C levels for visceral obesity. A difference of $P < 0.05$ was considered to indicate statistical significance.

Ethical approval

All procedures performed in this study were conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Suzhou Municipal Hospital (No. KL901503).

Results

General data characteristics

A total of 208 patients were enrolled, including 102 males and 106 females, with a mean age of 52.3 ± 13.7 years. The patients were divided into three groups based on Cys-C tertile, namely, Groups C1, C2, and C3 (0.78 and 0.97 mg/L), with 70 subjects (32/38) in Group C1 (Cys-C level ≤ 0.78 mg/L), 66 subjects (30/36) in Group C2 (0.78 < Cys-C level < 0.97 mg/L), and 72 subjects (40/32) in Group C3 (Cys-C level ≥ 0.97 mg/L). One-way ANOVA suggested significant differences in age, VFA, WC, BMI, SBP, Cr, HbA1c, TC, and LDL-C among the three groups ($P < 0.05$). The clinical and biochemical data of each group are shown in Table 1.

Intergroup comparison of VFA at different serum Cys-C levels

The VFA in each group was measured, and statistically significant differences were identified ($P < 0.05$). The VFA levels in Group C2 (93.81 ± 31.85 cm^2) and Group C3 (105.40 ± 34.78 cm^2) were significantly greater than those in Group C1 (80.26 ± 39.38 cm^2). There was no significant difference in VFA between the C2 and C3 groups ($P > 0.05$). See Fig. 1.

Correlation analysis of Cys-C levels with various indicators

Serum Cys-C levels were positively correlated with age, VFA, SFA, HOMA-IR, WC, BMI, SBP, Cr, and UA (r = 0.543, 0.353, 0.168, 0.148, 0.365, 0.264, 0.25, 0.497, 0.155, $P < 0.05$) and negatively correlated with HbA1c (r = -0.175, $P < 0.05$) in T2DM patients. Serum Cys-C were not found to correlate with sex (male = 0, female = 1), TG, TC, HDL-C, LDL-C, FBG, and DBP ($P > 0.05$), as shown in Table 2.

Linear trend of serum

Cys-C levels and each index and linear regression analysis with the Cys-C level as the dependent variable A linear trend test was performed for the association between the serum Cys-C level and each index. Group C1 was used as a reference group, and an increasing trend was observed for VFA, SFA, HOMA-IR, BMI, WC, age, SBP, Cr, and UA, while a decreasing trend was observed for HbA1c levels ($P < 0.05$).

Univariate linear regression analysis was performed with the serum Cys-C level as the dependent variable and various indicators as the independent variables. The results suggested that age, VFA, SFA, HOMA-IR, WC, BMI, SBP, Cr levels, UA levels, and HbA1c levels were all influencing factors of Cys-C levels according to univariate linear regression analysis (all $P < 0.05$). VFA was positively correlated with Cys-C levels ($\beta = 0.002$, 95% CI = 0.001–0.003, $P < 0.05$), with an increase of 0.002 mg/L in the Cys-C level for each 1 cm^2 increase in VFA, as shown in Table 3.

Further multivariate linear regression analysis was performed with the serum Cys-C level as the dependent variable and variables with statistically significant differences in the univariate linear regression analysis as the independent variables, namely, age, VFA, SFA, HOMA-IR, WC, BMI, SBP, Cr levels, UA levels, and HbA1c levels.

Variables	C1	C2	C3	*P*	ALL
Age (years)	44.7 ± 12.2	51.7 ± 13.5[a]	60.0 ± 11.6[ab]	< 0.001	52.3 ± 13.7
Sex (M/F)	(32/38)	(30/36)	(40/32)	0.441	(102/106)
VFA (cm^2)	80. 3 ± 39. 4	9 3.8 ± 31.9[a]	105. 4 ± 3 4.8[ab]	< 0.001	93.3 ± 36.9
SFA (cm^2)	167.0 ± 64.9	182.4 ± 55.2	187.7 ± 57.3[a]	0.1	179.0 ± 59.7
WC(cm)	86.6 ± 10.5	91.2 ± 8.7[a]	94.4 ± 8.3[ab]	0.003	90.8 ± 9.7
BMI (kg/m^2)	24.3 ± 3.7	25.2 ± 3.0	26.2 ± 3.5[a]	< 0.001	25.2 ± 5.6
FBG (mmol/L)	8.18 ± 3.04	8.24 ± 2.93	8.44 ± 3.95	0.894	8.29 ± 3.33
SBP (mm/Hg)	129.4 ± 17.0	135.8 ± 19.7[a]	137.3 ± 17.3[a]	0.024	134.2 ± 18.2
DBP (mm/Hg)	79.5 ± 10.9	81.3 ± 11.4	77.4 ± 9.6	0.093	79.4 ± 10.7
Cr (umol/L)	49.1 ± 12.1	56.4 ± 11.0[a]	62.7 ± 10.[ab]	< 0.001	56.1 ± 12.5
UA (umol/L)	310.0 ± 92.6	320.0 ± 84.2	329.2 ± 80.2	0.415	319.8 ± 85.8
Cys-C (mg/L)	0.69 ± 0.0 7	0.88 ± 0.05[a]	1.13 ± 0.15[ab]	< 0.001	0.9 ± 0.21
HbA1c (%) HOMA-IR	9.7 ± 2.7 45.35 ± 20.06	9.9 ± 2.3 48.83 ± 16.94	8.7 ± 2.0[ab] 49.06 ± 17.99	0.009 0.893	9.4 ± 2.4 47.74 ± 18.39
TG (mmol/L)	1.92 ± 1.41	1.88 ± 1.06	1.96 ± 2.27	0.953	1.92 ± 1.67
TC (mmol/L)	4.64 ± 1.32	4.82 ± 0.99	4.31 ± 1.10[a]	0.031	4.58 ± 1.16
HDL (mmol/L)	1.14 (0.97, 1.36)	1.07 (0.93, 1.25)	1.14 (0.93, 1.33)	0.581	1.13 (0.95, 1.31)
LDL-C (mmol/L)	2.97 ± 1.16	3.19 ± 0.94	2.63 ± 0.9[ab]	0.002	2.94 ± 1.02

Table 1. Clinical and biochemical characteristics according to the level of Cys-C [mean ± SD, M (quartile)]. *SFA* subcutaneous fat area, *BMI* body mass index, *HOMA-IR* homeostasis model assessment-insulin resistance, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *UA* uric acid, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Cr* creatinine, *WC* waist circumference, *SFA* subcutaneous fat area, *cystatin C* Cys-C, *FBG* fasting blood glucose; vs. C1. [a]$P < 0.05$; vs. C2, [b]$P < 0.05$.

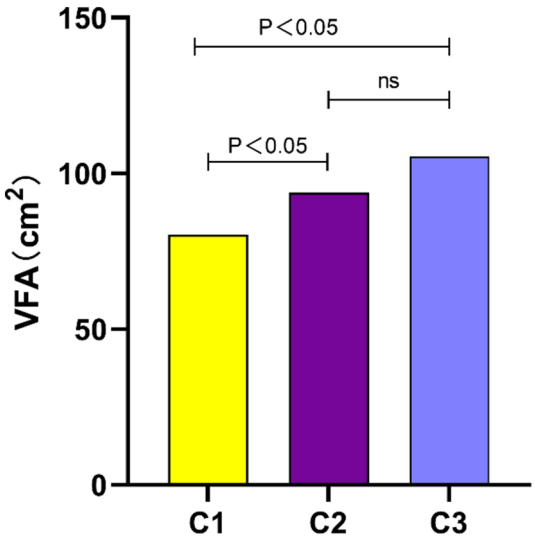

Figure 1. VFA in Group C1, Group C2 and Group C3.

Variables	*r*	*P*
Age (years)	0.543	< 0.001
Sex (M/F)	− 0.081	0.243
VFA (cm^2)	0.353	< 0.001
SFA (cm^2)	0.168	0.015
HOMA-IR	0.148	0.033
WC (cm)	0.365	< 0.001
BMI (kg/m^2)	0.264	< 0.001
FBG (mmol/L)	− 0.047	0.505
SBP (mm/Hg)	0.25	< 0.001
DBP (mm/Hg)	− 0.071	0.306
Cr (umol/L)	0.497	< 0.001
UA (umol/L)	0.155	0.025
HbA1c (%)	− 0.175	0.011
TG (mmol/L)	0.001	0.989
TC (mmol/L)	− 0.043	0.536
HDL-C (mmol/L)	− 0.027	0.699
LDL-C (mmol/L)	− 0.109	0.117

Table 2. Correlation analysis between Cys-C levels and other variables.

The results showed that VFA was positively correlated with the serum Cys-C level ($\beta = 0.001$, 95% *CI* 0.000–0.002, $P < 0.05$), with an increase of 0.001 mg/L in the serum Cys-C level per 1 cm^2 increase in VFA, as shown in Table 4.

Predictive role of Cys-C levels in visceral obesity

Using a VFA ≥ 100 cm^2 as the criterion for visceral obesity, ROC analysis revealed that the Cys-C level was a better predictor of visceral obesity, with an area under the ROC curve (AUC) of 0.701 (95% CI = 0.631–0.771, P < 0.05), an optimal cut-off of 0.905 mg/L, and a sensitivity and specificity of 58.3% and 75.2%, respectively. See Fig. 2.

Discussion

To our knowledge, this is the first study to compare serum Cys-C levels in patients with T2DM combined with visceral obesity. While previous studies have indicated a correlation between cystatin C levels and BMI, these studies primarily focused on non-diabetic populations and used BMI to measure obesity. In this study, T2DM patients were divided into three groups based on their serum Cys-C levels to explore the correlation between the serum Cys-C level and VFA, and the results showed that the Cys-C level was positively associated with the VFA ($r = 0.353$, $P < 0.05$). Variables were included in the multivariate linear regression model, and the Cys-C level was found to be positively correlated with the VFA after adjusting for age, SFA, HOMA-IR, WC, BMI, SBP, Cr levels, UA levels, and HbA1c levels.

Indicators		Cys-C		
	β	*t*	*P*	*95% CI*
Age (years)	0.008	8.158	0.000	0.006–0.009
Sex (M/F)	− 0.038	− 1.304	0.194	− 0.096–0.020
VFA (cm^2)	0.002	5.479	0.000	0.001–0.003
SFA (cm^2)	0.001	2.295	0.023	0.000–0.001
HOMA-IR	0.002	2.301	0.022	0.000–0.003
WC (cm)	0.008	5.677	0.000	0.005–0.011
BMI (kg/m^2)	0.017	4.220	0.000	0.009–0.025
FBG (mmol/L)	− 0.003	− 0.645	0.520	− 0.012–0.006
SBP (mm/Hg)	0.002	3.094	0.002	0.001–0.004
DBP (mm/Hg)	− 0.002	− 1.312	0.191	− 0.005–0.001
Cr (umol/L)	0.018	7.285	0.000	0.006–0.010
UA (umol/L)	0.000	2.330	0.021	0.000–0.001
HbA1c (%)	− 0.015	-2.382	0.018	− 0.027- -0.003
TG (mmol/L)	0.011	1.191	0.235	− 0.007–0.028
TC (mmol/L)	− 0.017	-1.378	0.170	− 0.042–0.008
HDL-C (mmol/L)	− 0.028	− 0.603	0.547	− 0.118–0.063
LDL-C (mmol/L)	− 0.028	− 2.209	0.081	− 0.059- -0.003

Table 3. Univariate linear regression analysis of Cys-C levels with various indicators.

Variables	*β*	*t*	*P*	*95% CI*
Age (years)	0.007	7.094	0.000	0.005–0.008
VFA(cm^2)	0.001	2.216	0.028	0.000–0.002
SFA(cm^2)	0.000	− 1.406	0.161	− 0.001–0.000
WC (cm)	0.000	0.067	0.947	− 0.005–0.005
BMI (kg/m^2)	0.013	1.810	0.072	− 0.001–0.027
SBP (mm/Hg)	− 0.001	− 0.752	0.453	− 0.002–0.001
UA (umol/L)	0.000	1.166	0.245	0.000–0.000
Cr (umol/l)	0.004	4.254	0.000	0.002–0.006
HbA1c (%)	− 0.003	− 0.516	0.606	− 0.013–0.007

Table 4. Multivariate linear regression analysis of the Cys-C level as the dependent variable in patients with type 2 diabetes.

Cystatin C, an endogenous cathepsin inhibitor produced by almost all organs, is cleared only by glomerular filtration and is also completely metabolised and catabolised after reabsorption in the proximal convoluted tubule. Therefore, the blood concentration of Cys-C is determined by glomerular filtration and is considered to be an ideal biomarker of the glomerular filtration rate compared to the serum creatinine level[19]. Recent studies have shown Cys-C to be closely related to the onset of atherosclerosis[20]. Moreover, Cys-C is also a favourable prognostic indicator for cardiovascular diseases such as acute and chronic heart failure and myocardial infarction[21,22]. Cys-C is closely related to tumour infiltration and development and can be used as a prognostic indicator, especially for head and neck tumours as well as gastrointestinal tumours[23].

Numerous studies have suggested that the serum Cys-C level is an independent risk factor for diabetic retinopathy, carotid atherosclerosis, and diabetic peripheral neuropathy in T2DM patients[24–26]. In addition, Cys-C may be associated with the development of diabetes mellitus in obese patients[12]. Insulin resistance is an essential pathogenesis of T2DM. Although the exact mechanism underlying the development of insulin resistance is not fully understood, insulin resistance is often associated with obesity, and visceral lipids play an essential role in the development of insulin resistance[27]. The results of this study suggested that the serum Cys-C level was positively correlated with the insulin resistance index in T2DM patients ($r = 0.148$, $P < 0.05$). However, the exact mechanism by which Cys-C causes insulin resistance remains unclear. It is speculated that Cys-C may be involved in the development of T2DM through fat deposition caused by insulin resistance. However, some studies have suggested that Cys-C may be a protective factor against obesity and that its elevation inhibits cathepsins and thus attenuates increased adipose tissue. Therefore, the actual pathophysiological role of Cys-C needs to be further elucidated[28].

Obesity is a significant risk factor for many metabolic syndromes, such as diabetes, hypertension, hyperlipidemia, and cardiovascular diseases. It increases the risk of the onset of these diseases by three to four times. A study by Jhatta et al.[11] revealed that serum Cys-C levels were significantly greater in patients with T2DM combined with obesity than in patients with T2DM or obesity alone. Mahajan et al.[29] investigated 100 healthy people aged 17 years and older and reported that serum Cys-C levels increased with increasing BMI in all subjects.

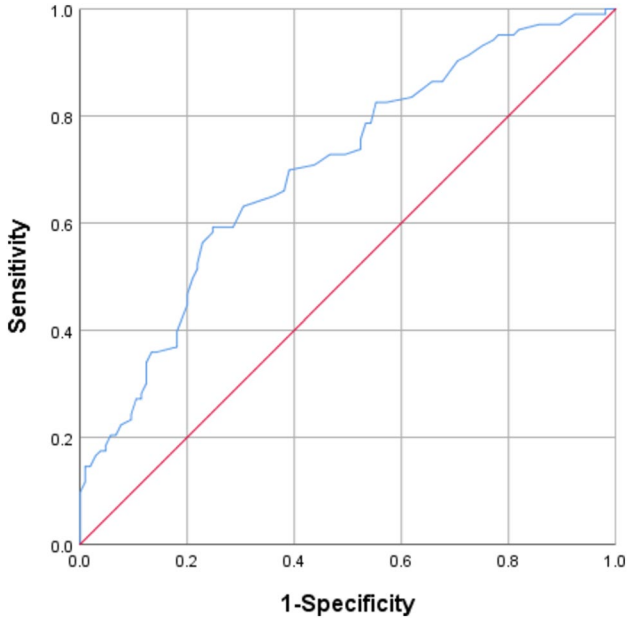

Figure 2. ROC curve for the prediction of visceral obesity by Cys-C levels.

Furthermore, Alaje et al.[30] reported higher serum Cys-C levels in obese subjects than in nonobese subjects. In contrast, the study by Schuck et al. revealed no association between serum Cys-C levels and BMI[31]. The reason for this discrepancy was considered to be that the study population consisted of patients with chronic kidney disease. In this study, we found that serum cystatin C levels were positively correlated with VFA, and ROC analysis showed that Cys-C was a better predictor of visceral obesity and that cystatin C may be a predictor of insulin resistance and visceral fat obesity.

Compared to previous studies, this study used visceral fat, which provides a more realistic representation of lipid deposition in the body. The direct interaction between serum Cys-C and adipose tissue may occur because adipose tissue produces a large number of bioactive molecules, including Cys-C, which are also highly expressed in adipose tissue, especially white adipose tissue, in obese subjects[4,32]. However, some studies have shown that elevated Cys-C may inhibit adipose tissue synthesis by inhibiting cathepsin, thereby alleviating the inflammatory response caused by obesity[12]. The pathophysiological mechanism involved requires further clarification. Moreover, this study revealed that Cys-C levels were positively correlated with systolic blood pressure and were a significant predictor of vascular sclerosis[20]. The mechanism through which Cys-C leads to elevated blood pressure may be related to atherosclerosis.

This study has several limitations. The small sample size and single-centre cross-sectional observational design could not reveal whether the decrease in VFA was followed by a decrease in the serum Cys-C level.

Conclusions

In conclusion, this study investigated the correlation between serum Cys-C levels and VFA in T2DM patients and revealed that the serum Cys-C level was positively correlated with the VFA. However, the specific mechanism of the interaction between the serum Cys-C level and VFA has not been determined. In clinical work, serum Cys-C levels in patients with T2DM may be an early serological marker for obesity-related complications such as cardiovascular and metabolic diseases. Screening for Cys-C levels could help identify T2DM patients who are more prone to visceral obesity, thereby enabling more effective prevention and management strategies for obesity. In patients with T2DM, visceral fat should be strictly controlled, as it is essential to delay the onset of vascular complications. Moreover, further expansion of the study population is needed in future studies to confirm the role of Cys-C in T2DM combined with visceral obesity and to determine whether aggressive weight loss in patients with T2DM is associated with a reduction in Cys-C levels. This study provides new insights into the prevention, treatment, and understanding of pathophysiological mechanisms in T2DM patients with visceral obesity.

Data availability

The clinical data of the population used to support the findings of this study are available from the corresponding author upon request.

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Author contributions

G.X.C., X.C., and L.C. participated in the design of the study. G.X.C., Q.S., Y.W., and Q.W. collected the samples. G.X.C. and X.C. performed the statistical analysis. L.C. helped in interpreting the results. All authors drafted, read, and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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