Soluble ST2 is associated with increased carotid intima-media thickness in patients with type 2 diabetes mellitus
A case-control study
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Abstract
Soluble suppression of tumorigenicity 2 (sST2) is a free form of membrane-bound ST2, which is a member of the interleukin-1 receptor family. Previous research has shown that sST2 is associated with diabetes, but cardiovascular risk factors have not been established.

To analyze the relationship between sST2 and carotid intima-media thickness (CIMT) in patients with type 2 diabetes mellitus (T2DM).

After screening, a total of 118 subjects with T2DM were divided into groups according to the measurement of CIMT (normal CIMT (NCIMT), n = 58; abnormal CIMT (ACIMT), n = 60), and 60 healthy subjects (normal control (NC), n = 60) were recruited in this study. CIMT was measured by a color Doppler ultrasound, and sST2 and other metabolic parameters were measured as well.

The median concentration of sST2 was elevated in the ACIMT group (31.30 ng/ml) compared with the NCIMT group (28.29 ng/ml, \(P<.01\)) and the NC group (20.15 ng/ml, \(P<.01\)). After adjustment for age and sex, log sST2 was strongly associated with smoking history (\(\beta=0.197, 95\% \text{CI}, 0.084–0.311, P<.01\)), FPG level (\(\beta=0.302, 95\% \text{CI}, 0.162–0.442, P<.01\)), and HbA1c level (\(\beta=0.296, 95\% \text{CI}, 0.165–0.426, P<.01\)) and negatively correlated with HDL level (\(\beta=–0.153, 95\% \text{CI}, –0.259 \text{ to } –0.046, P<.01\)). Furthermore, sST2 level was a risk factor for increased CIMT in patients with T2DM.

Increased sST2 level not only was associated with indicators of glucose and lipid metabolism but also was a risk factor for increased CIMT in patients with T2DM. Thus, sST2 may be a potential novel marker to assess the progression of diabetic macrovascular complications.

Abbreviations: ACIMT = abnormal CIMT, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BP = blood pressure, BUN = blood urea nitrogen, CIMT = carotid intima-media thickness, DBP = diastolic blood pressure, ELISA = enzyme-linked immunosorbent assay, FPG = fasting plasma glucose, GTT = glucose tolerance test, HbA1c = Glycosylated hemoglobin A1c, HDL = high-density lipoprotein, IL-33 = interleukin 33, LDL = low-density lipoprotein, NC = normal control, NCIMT = normal CIMT, ORs = odds ratios, ROS = reactive oxygen species, SBP = systolic blood pressure, sST2 = soluble suppression of tumorigenicity 2, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides, UA = uric acid, WC = waist circumference.

Keywords: atherosclerosis, cardiovascular disease, carotid intima-media thickness, sST2, type 2 diabetes mellitus

1. Introduction
Diabetes has become the most important chronic non-communicable disease and a threat to human health worldwide.\textsuperscript{[1]} Diabetic macrovascular disease is one of the chronic complications of diabetes, is the main cause of mortality and disability in type 2 diabetes mellitus (T2DM), and is histopathologically characterized by atherosclerosis\textsuperscript{[2,3]} Compared with subjects without diabetes, patients with T2DM have a twofold higher risk of cardiovascular disease events.\textsuperscript{[4]} Therefore, early management of atherosclerosis is necessary to prevent serious diabetic macrovascular disease.

Carotid intima-media thickness (CIMT) is an ultrasound biomarker of atherosclerosis and is considered a marker of...
A growing number of studies have demonstrated that CIMT can not only predict cardiovascular risk in the general population, but also be associated with other vascular disease such as stroke. Recently, in patients with T2DM, CIMT has also been reported as a predictor of adverse cardiovascular outcomes.

Suppression of tumorigenicity 2 (ST2) is a member of the interleukin-1 receptor family whose ligand is interleukin 33 (IL-33) and exists in 4 different isoforms: soluble ST2 (sST2), transmembrane ST2 (ST2L), ST2V, and ST2LV. The ST2V and ST2LV isoforms are the results of alternate splicing of ST2. sST2 is a free form of membrane-bound ST2, which is found on the surface of Th2 cells, mast cells, and basophil granulocytes. Unlike ST2L, sST2 acts as a decoy receptor for IL-33, preventing it from binding to ST2L and thereby reducing the biological effect of IL-33. Previous studies have found that sST2 is associated with various diseases, such as heart failure, rheumatoid arthritis, central nervous system diseases, liver diseases, renal diseases, and diabetes. However, there have been several controversial results. Clinical research has shown that sST2 is associated with diabetes, but cardiovascular risk factors have not been established. A study in ApoE-deficient mice found that ST2 did not impact the development of atherosclerosis.

Therefore, this study aims to analyze the relationships between sST2 and diabetic macrovascular complications after the participants were stratified according to CIMT measurements. The factors influencing CIMT were assessed as well.

2. Method

2.1. Subjects

It is an observational study, all consecutive 142 patients with T2DM were recruited from inpatients of the Department of Endocrinology, the First Affiliated Hospital of Bengbu Medical College, China, from March 2017 to September 2018. T2DM is defined as fasting plasma glucose (FPG) ≥7.0 mmol/L, 2-hour glucose tolerance test (GTT) ≥11.0 mmol/L, or current diagnosis of T2DM. The exclusion criteria included type 1 diabetes mellitus, diabetic ketoacidosis, hyperglycemia and hypertonic state, heart failure, serious arrhythmia, valvular heart disease, malignancy, autoimmune disease, pregnancy, severe liver or kidney dysfunction, acute or chronic infection, and surgery in the previous 6 months. A total of 24 people were removed therein, and the actual effective number was 118. According to the measurement of CIMT, all patients were divided into 2 groups: normal CIMT (NCIMT, n = 60), thickness ≤0.9 mm (35 males and 25 females); and abnormal CIMT (ACIMT, n = 58), thickness >0.9 mm (34 males and 24 females). During the same period, 60 healthy subjects who were recruited from the physical examination center of our hospital were defined as a healthy control group (NC), including 35 males and 25 females. All controls underwent a 75 g OGTT to exclude diabetes and carotid artery color Doppler ultrasound to exclude thickened carotid intima-media.

The protocol for the research project was approved by the Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Bengbu Medical College and conforms to the provisions of the Declaration of Helsinki. All the subjects provided informed consent, and the patient anonymity is preserved within the text of the manuscript.

2.2. Anthropometric measurements

Each subject underwent a physical examination, including measurements of height, weight, waist circumference (WC) and blood pressure (BP). Measurements of weight and height were used to calculate the body mass index (BMI) \( [\text{BMI}] = \frac{[\text{kg}]}{[\text{m}^2]} \). WC was...
measured on the midaxillary line between the lower border of the rib cage and the upper margin of the iliac crest. BP was obtained from the average of 3 measurements made with a standard mercury sphygmomanometer at 3-minute intervals. Furthermore, all the subjects underwent a clinical examination. A medical history and status of cigarette smoking were collected using a questionnaire.

2.3. Laboratory examination

The clinical data were collected as in our previous study. Briefly, fasting blood samples were obtained after a 10-hour fast by venepuncture of the large antecubital veins. Then, the samples were centrifuged at 2500rpm for 10 minutes, resulting in separation of plasma. Finally, the plasma was collected and stored at –80°C until use. FPG was measured by a glucose oxidase method. Glycosylated hemoglobin A1c (HbA1c) was determined using a high-performance liquid chromatographic method (Bio-Rad, Hercules, CA, USA). Circulating sST2 levels were measured from the plasma samples by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (Elabscience Biotechnology Co., Ltd., WuHan, China) according to the manufacturer’s recommendations. The remaining biochemical values were detected by an automatic clinical chemistry analyzer (Beckman Coulter AU5800, CA, USA).

2.4. Ultrasound measurement of CIMT

Detailed ultrasound measuring methods of CIMT were described in our recent research. In brief, all carotid ultrasound measurements were performed on a color Doppler ultrasound (IU 22, Philips, Amsterdam, Netherlands) with a 10MHz linear array transducer by a single experienced sonographer who was unaware of the participants’ data. All subjects lay in a recumbent position without a pillow, hypsokinesis of the head and with the head slightly turned to the opposite side. Moving up gradually from the superior clavicular fossa, bilateral common carotid arteries, bifurcations, and internal carotid arteries were measured. Intima-media thickness is defined as the distance between the intima-lumen interface and the upper layer of the adventitia. The CIMT value of each subject was an average of 6 points’ values.

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables are expressed as the mean ± SD. Skew-distributed continuous variables are expressed as the median with interquartile range or were converted to logarithms for further analysis. Differences between numeric variables were tested with one-way ANOVA for normal distributions or the Kruskal–Wallis test for skewed distributions. Comparative analyses of categorical variables were carried out by the Chi-Squared test. Correlations were tested with Spearman correlation coefficient. Multivariate logistic regression models were used to estimate the odds ratios (ORs) for CIMT. A value of $P < .05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Demographic and clinical characteristics of participants

All participants were divided into 3 groups: healthy control group (NC, n=60), normal CIMT group (NCIMT, n=58), and abnormal CIMT group (ACIMT, n=60). The demographic and clinical characteristics in each group were comparatively analyzed. As shown in Table 1, of the 3 groups, the ACIMT group had the highest proportion of smokers and the oldest average age.

### Table 1

**Demographic and clinical characteristics of participants.**

| Variables                      | NC n=60 | NCIMT n=58 | ACIMT n=60 | $P$ value |
|--------------------------------|---------|------------|------------|-----------|
| Course of diabetes (years)     | 6.7±5.1 | 10.5±6.4   | $P=.003^*$ |           |
| Male sex (%)                   | 33.7%   | 33.7%      | 33.7%      | $P=.999$  |
| Current Smoking (%)            | 11.5%   | 17.3%**    | 71.2%**    | $P<.001$  |
| Age(years)                     | 54.1±13.2 | 49.3±11.7   | 59.3±11.7** | $P<.001$  |
| FBG (mmol/L)                   | 5.15±0.52 | 8.34±4.65** | 9.93±1.89** | $P<.001$  |
| HbA1c (%)                      | 5.42±0.37 | 9.29±2.09** | 10.25±2.32** | $P<.001$  |
| BMI (kg/m²)                    | 24.2±3.2 | 25.3±4.0   | 25.3±3.4   | $P=.015$  |
| WC (cm)                        | 83.0±8.6 | 94.2±11.8** | 97.4±10.3** | $P<.001$  |
| SBP (mmHg)                     | 129±11  | 131±13     | 136±18**   | $P=.004$  |
| DBP (mmHg)                     | 78±10   | 79±9       | 80±11      | $P=.718$  |
| TC (mmol/L)                    | 4.76±0.9 | 4.62±1.48  | 5.08±1.26  | $P=.331$  |
| HDL (mmol/L)                   | 1.38±0.33 | 1.12±0.28** | 0.88±0.17** | $P<.001$  |
| LDL (mmol/L)                   | 2.55±0.69 | 2.63±0.76  | 3.77±1.03** | $P<.001$  |
| TG (mmol/L)                    | 1.46±0.71 | 1.74±1.32  | 2.26±1.48** | $P<.001$  |
| ALT (U/L)                      | 20±12   | 23±15      | 22±15      | $P=.463$  |
| AST (U/L)                      | 21±6    | 24±13      | 21±8       | $P=.181$  |
| Creatinine (µmol/L)            | 60±9    | 60±16      | 65±16      | $P=.075$  |
| BUN (µmol/L)                   | 5.22±1.36 | 5.06±1.17   | 5.49±1.20  | $P=.177$  |
| UA (µmol/L)                    | 301±67  | 271±97     | 302±100   | $P=.110$  |

Data are showed mean ± SD for continuous variables and percentages for categorical variables.

$\ast P<.01$, $\ast\ast P<.001$, $\ast\ast\ast P<.0001$. $\ast\ast\ast\ast P<.00001$. $\ast\ast\ast\ast\ast P<.000001$.
FPG and HbA1c levels increased gradually from the NC to NCIMT to ACIMT group. Other clinical characteristics between the NC and NCIMT groups showed no significant differences, except for WC and high-density lipoprotein (HDL) levels. However, systolic blood pressure (SBP) and indicators for blood lipids, including HDL, low-density lipoprotein (LDL) and triglycerides (TG), were significantly different between the ACIMT group and the other 2 groups. Additionally, BMI and WC were significantly higher in the ACIMT group than in the NCIMT group. Among the 3 groups, significant differences were not observed for sex, diastolic blood pressure (DBP), total cholesterol (TC), or liver or renal function markers, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, blood urea nitrogen (BUN), and uric acid (UA).

3.2. Plasma sST2 levels of different groups

The median concentration of sST2 was elevated in the ACIMT group (31.30 ng/ml) compared with the NCIMT group (28.29 ng/ml, \( P < .01 \)) and the NC group (20.15 ng/ml, \( P < .01 \)) (Fig. 2A). Furthermore, the sST2 concentration in the NCIMT group was also higher than that in the NC group (\( P < .01 \)) (Fig. 2A). Next, sST2 levels were further investigated in the 2 subgroups based on sex because a difference between males and females was previously reported.\(^{22,23}\) Although sST2 levels were higher in males than in females for each group, there were no significant differences (\( P > .05 \)) (Fig. 2B). Additionally, the median sST2 level (31.79 ng/ml) of the male subjects in the ACIMT group was significantly higher than that in the NC (21.13 ng/ml) and NCIMT groups (28.59 ng/ml) (both \( P < .01 \)). Similar results were observed in the female subgroup (30.52 ng/ml vs 17.67 ng/ml and 27.62 ng/ml, both \( P < .01 \)) (Fig. 2B).

3.3. Associations between sST2 level and clinical parameters

Spearman correlation analysis was used to investigate the associations between sST2 and anthropometric and biochemical parameters. The results revealed that sST2 level was positively correlated with smoking history, age, FPG, HbA1c, BMI, WC, SBP, TC, LDL, and TG (\( P < .05 - P < .01 \)), but it was negatively correlated with HDL level (\( P < .01 \)) (Table 2). A multivariate linear regression analysis was performed to further investigate the relationships between plasma sST2 concentration and clinical parameters. Because the sST2 level was skew-distributed and continuous, its logarithm was used in the models along with the variables that had significant differences in univariate analysis. The results are shown in Table 3. After adjusting for age and sex, log sST2 was strongly associated with smoking history (\( \beta = 0.197, 95\% \text{CI}, 0.084-0.311, P < .01 \)), FPG level (\( \beta = 0.302, 95\% \text{CI}, 0.162-0.442, P < .01 \)) and HbA1c (\( \beta = 0.296, 95\% \text{CI}, 0.165-0.426, P < .01 \)) and negatively correlated with HDL level (\( \beta = -0.153, 95\% \text{CI}, -0.259 \text{to} -0.046, P < .01 \)). However, the associations of sST2 with BMI, WC, TC, LDL, and TG were not significant after age and sex were added to the regression models (\( P > .05 \)).

3.4. Analysis of risk factors for increased CIMT in patients with T2DM

Multiple logistic regression analysis was used to evaluate the relationships between CIMT in patients with T2DM and risk

**Table 2**

| Variable                  | \( t \)  | \( P \)  |
|---------------------------|---------|---------|
| Gender                    | -0.070  | .353    |
| Current smoking           | 0.531   | .000    |
| Age (years)               | 0.157   | .033    |
| FPG (mmol/L)              | 0.755   | .000    |
| HbA1c (%)                 | 0.742   | .000    |
| BMI (kg/m\(^2\))          | 0.173   | .021    |
| WC (cm)                   | 0.440   | .000    |
| SBP (mmHg)                | 0.186   | .015    |
| DBP (mmHg)                | 0.094   | .210    |
| TG (mmol/L)               | 0.154   | .040    |
| HDL (mmol/L)              | -0.508  | .000    |
| LDL (mmol/L)              | 0.562   | .000    |
| TG (mmol/L)               | 0.246   | .001    |
| ALT (U/L)                 | 0.030   | .686    |
| AST (U/L)                 | -0.081  | .283    |
| Creatinine (\( \mu \text{mol/L} \))| -0.011 | .084    |
| BUN (\( \mu \text{mol/L} \))| 0.025   | .739    |
| UA (\( \mu \text{mol/L} \))| -0.101  | .178    |

ALT = alanine aminotransferase, AST = aspartic transaminase, BMI = body mass index, BUN = blood urea nitrogen, DBP = diastolic blood pressure, FPG = fasting blood glucose, HbA1c = glycated haemoglobin A1c, HDL = high density lipoprotein, LDL = low density lipoprotein, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, UA = uric acid, WC = waist circumference.
In this study, all participants were stratified according to the Chinese guidelines, including age, SBP, HDL, LDL, and TG. When all relevant variables were added to the multivariable logistic regression models, the results showed that smoking history (OR = 4.625, 95% CI, 1.060–2.145, P < .05), age (OR = 4.625, 95% CI, 1.060–20.180, P < .05), FPG (OR = 2.144, 95% CI 1.300–3.536, P < .01), SBP (OR = 9.945, 95% CI, 1.862–53.130, P < .01), LDL (OR = 5.724, 95% CI, 1.039–31.526, P < .05) and sST2 (OR = 1.645, 95% CI, 1.099–2.462, P < .05) were risk factors for increased CIMT in patients with T2DM, but the HDL level was a protective factor (OR = 8.899, 95% CI, 2.145–36.916, P < .01) (Table 4).

4. Discussion

In this study, all participants were stratified by CIMT, which is different from previous studies related to ST2. The distribution characteristics of plasma sST2 level in subjects with normal blood glucose, patients with T2DM with normal carotid intima-media thickness, and patients with T2DM with increased carotid intima-media thickness were detected. Atherosclerosis is the main pathological feature of diabetic macrovascular complications. CIMT measurement is a safe, noninvasive, relatively inexpensive method that can assist in identifying people with diabetes who are at higher risk of developing macrovascular complications.[30] Therefore, CIMT is a surrogate marker of cardiovascular disease in diabetes.[30,31] Much evidence indicates that when CIMT ≥ 0.9 mm, it will be an important factor not only in the prediction of cardiovascular diseases but also in the assessment of cardiovascular prognosis.[26,32] As a result, we stratified the subjects with a cut-off point of 0.9 mm.

Our results demonstrate that plasma sST2 level was significantly increased in patients with T2DM with increased carotid intima-media thickness compared to the other 2 groups. Furthermore, sST2 level was higher in patients with T2DM than in normal controls. There was no significant difference between males and females, although sST2 level was modestly elevated in males. Furthermore, sST2 level was associated with smoking history, age, FPG, HbA1c, BMI, WC, SBP, TC, LDL, HDL, and TG. Even after adjusting for age and sex, smoking history and the levels of FPG, HbA1c, and HDL were correlated with sST2.

sST2, a decoy receptor for IL-33, has multiple biological effects and participates in the pathogenesis of several diseases, including diabetes.[15,22] In previous studies, Fousteris et al.[33] reported that patients with T2DM exhibited higher sST2 levels compared to healthy controls, and multivariate analysis revealed a significant correlation between glycemic and blood lipid control (HbA1c, HDL) and sST2 level. Miller et al.[23] also reported that after adjusting for age and sex, circulating sST2 level was strongly associated with markers of diabetes, including triglycerides, liver function and glucose but was not correlated with smoking, cholesterol, blood pressure, or atheroma. Recently, Lin et al.[22] found that sST2 level was modestly but significantly elevated in patients with diabetes compared with normal subjects, and after adjustment for age and sex, all markers of liver and renal function, HDL-cholesterol, total cholesterol, and smoking status showed a significant association with sST2 level.

Disorders of glucose and lipid metabolism are important features of diabetes mellitus. The mechanistic link between circulating sST2 and metabolic disorders of diabetes is not fully understood. The IL-33/ST2 signaling pathway may participate in the development of T2DM through inflammatory processes. The evidence of this mechanism is as follows: IL-33 plays a protective role against glucose metabolism and obesity in obese diabetic (ob/ob) mice. ST2 is an IL-33 receptor that upon binding induces Th2 activity and increases Th2 inflammatory responses by inducing chemotaxis in Th2 cells as well as the release of Th2-associated cytokines. Therefore, increased levels of sST2 in diabetes may impair the protective effects of IL-33.[13,23,34] As a result, it is possible that sST2 not only is a biomarker but also is involved in the pathogenesis of diabetes via IL-33 interactions.[23] Furthermore, Kearley et al.[35] indicated that IL-33 is upregulated by cigarette smoke, and ST2 expression was changed in different cells when they were exposed to smoke. This may be the reason that ST2 level was correlated with smoking history in our study.

Interestingly, sST2 did not correlate with biomarkers of hepatic or renal function, which was different from previous studies. This discrepancy between studies may be attributed to differences in the protocols used in each study, such as research subjects, the number of samples, diagnostic criteria of CIMT, duration of diabetes, and statistical methods. Similar to a recent study, there were no significant differences in sST2 levels or classic diabetic risk factors, such as blood lipids and the relevant markers of liver and renal function, between prediabetic subjects and subjects with normal glucose levels.[22] This suggests that the inflammatory response and target-organ damage varies between different stages of diabetes.

In the present study, logistic regression analysis indicated that smoking history; older age; higher FPG, SBP, LDL, and TG; and lower HDL were risk factors for increased carotid intima-media thickness, which was in line with previous studies.[28,30] It is worth noting that sST2 was also a risk factor. Many studies have focused on the relationships between sST2 and cardiovascular

### Table 3

| Risk Factors          | β    | 95% CI             | P   |
|-----------------------|------|--------------------|-----|
| Current smoking (%)   | 0.197| 0.084–0.311        | .001|
| FBG (mmol/L)          | 0.302| 0.162–0.442        | .000|
| HbA1c (%)             | 0.296| 0.165–0.426        | .000|
| HDL (mmol/L)          | −0.153| −0.259–0.046      | .005|

Regression models were fitted with log sST2 as the outcome.

FBG = fasting blood glucose, HbA1c = glycated hemoglobin A1c, HDL = high density lipoprotein.

### Table 4

| Risk Factors for increased CIMT in Patients of T2DM. | OR    | 95% CI             | P   |
|----------------------------------------------------|-------|--------------------|-----|
| Course of diabetes (years)                         | 0.989 | 0.873–1.121        | .866|
| Current smoking (%)                               | 6.701 | 1.353–33.185       | .020|
| Age≥55y                                            | 4.625 | 1.060–20.180       | .042|
| FBG (mmol/L)                                      | 2.144 | 1.300–3.536        | .003|
| HbA1c (%)                                         | 1.015 | 0.739–1.402        | .930|
| SBP≥140 mmHg                                      | 10.014| 1.872–53.572       | .007|
| HDL<1.0 mmol/L                                    | 9.026 | 2.172–37.499       | .003|
| LDL≥4.1 mmol/L                                    | 5.509 | 1.015–29.900       | .048|
| TG≥2.3 mmol/L                                     | 1.190 | 0.291–4.869        | .809|
| sST2 (ng/ml)                                      | 1.657 | 1.160–2.481        | .014|

FBG = fasting blood glucose, HbA1c = glycated hemoglobin A1c, HDL = high density lipoprotein, LDL = low density lipoprotein, SBP = systolic blood pressure, TG = triglyceride.
risk factors, but the results are controversial. A cross-sectional study suggested that sST2 was associated with diabetes but that cardiovascular risk factors have not been established. [21] However, another cross-sectional study from a Chinese population showed that a high level of sST2 significantly increased the risk of atherosclerosis in all subjects. [20] In a recent prospective cohort study, the results indicated that increased level of sST2 could predict atherosclerosis earlier. One plausible explanation is as follows: First, NF-κB is an inflammatory marker that has been implicated in increasing the relative risk of increased CIMT. [16] IL-33-ST2L imparts a protective role by regulating NF-κB activation by acting upon the angiotensin-II or phenylephrine pathway. [21] Furthermore, using the same pathway, IL-33-ST2L also regulates reactive oxygen species (ROS) generation, as an increase in ROS upregulates NF-κB levels. [17] Finally, because sST2 acts as a decoy receptor binding to IL-33, it abrogates this protective benefit, which could lead to increased carotid intima-media thickness in patients with T2DM.

Several limitations in our study should be considered. First, the relatively small size of the study population limits the power of the study. This may partly explain the discrepancies between the previous studies and ours. Second, this is a cross-sectional observational study, which limits our ability to make any causal inference and limits follow up. Third, the data were collected from only 1 site, so the results may not be generalizable to other places. However, this study generates new hypotheses for future investigations, and further large, prospective, multicentric, and follow-up studies are warranted.

5. Conclusion

In the present investigation, we demonstrated that sST2 level was associated with indicators of glucose and lipid metabolism and was a risk factor for increased CIMT in patients with T2DM. Thus, sST2 may be a potential novel marker to assess the progression of diabetic macrovascular complications. Further studies are needed to understand the mechanisms of these associations.

Author contributions

Xiaolei Hu designed the study, wrote and revised the manuscript. Hengyan Zhang, Yuan Song, Qingqing Yang, Langen Zhuang, Weihua Sun, Zhaojing Shi collected the data. Xiaolei Hu and Guoxi Jin conducted the statistical analysis. Shirong Zhang detected specimens.

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