Observational Study

Medicine®

OPEN

Soluble ST2 is associated with increased carotid intima-media thickness in patients with type 2 diabetes mellitus

A case-control study

Xiaolei Hu, MD, PhD[a,*], Hengyan Zhang, BS[a], Yuan Song, MS[a], Qingqing Yang, MS[a], Langen Zhuang, MD, PhD[a], Guoxi Jin, MS[a], Shirong Zhang, MS[b], Weihua Sun, MS[a], Zhaoming Shi, MS[a]

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 2 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% CI, 0.084–0.311, $P < .01$), FPG level ($\beta = 0.302$, 95% CI, 0.162–0.442, $P < .01$) and HbA1c level ($\beta = 0.296$, 95% CI, 0.165–0.426, $P < .01$) and negatively correlated with HDL level ($\beta = -0.153$, 95% CI, −0.259 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.[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.[2,3] Compared with subjects without diabetes, patients with T2DM have a twofold higher risk of cardiovascular disease events.[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

Editor: Gaurav Malhotra.

This work was supported by grants from the National Nature Science Foundation of China (Grant No. 81770803); the Project of Training and studying domestic or abroad for Excellent Youth Scholars and Key Teacher in Higher Education Institutions, Anhui Province (Grant No. gxgwfx2019028); the Science and Technology Development Foundation of Bengbu Medical College (Grant No. BYKF1832).

No conflict of interest has been declared by the authors.

[a] *Department of Endocrinology,* [b] *Laboratory of the Endocrinology Department, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui, China.*

[*] *Correspondence: Xiaolei Hu, Department of Endocrinology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui, China, 287 Changhuai Road, Bengbu, Anhui, China (e-mail: caesar80@163.com).*

How to cite this article: Hu X, Zhang H, Song Y, Yang Q, Zhuang L, Jin G, Zhang S, Sun W, Shi Z. Soluble ST2 is associated with increased carotid intima-media thickness in patients with type 2 diabetes mellitus: A case-control study. Medicine 2020;99:5(e18940).

Received: 19 September 2019 / Received in final form: 5 December 2019 / Accepted: 30 December 2019

http://dx.doi.org/10.1097/MD.0000000000018940

subclinical organ damage.[5] A growing number of studies have demonstrated that CIMT can not only predict cardiovascular risk in the general population,[6,7] but also be associated with other vascular disease such as stroke.[8] Recently, in patients with T2DM, CIMT has also been reported as a predictor of adverse cardiovascular outcomes.[9]

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.[10–12] The ST2V and ST2LV isoforms are the results of alternate splicing of ST2.[11,12] sST2 is a free form of membrane-bound ST2, which is found on the surface of Th2 cells, mast cells, and basophil granulocytes.[13] 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 (Fig. 1).[14,15] 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.[16–22] 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.[23] A study in ApoE-deficient mice found that ST2 did not impact the development of atherosclerosis.[24]

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,[25] 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,[26] 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) [= (kg/m^2)]. WC was

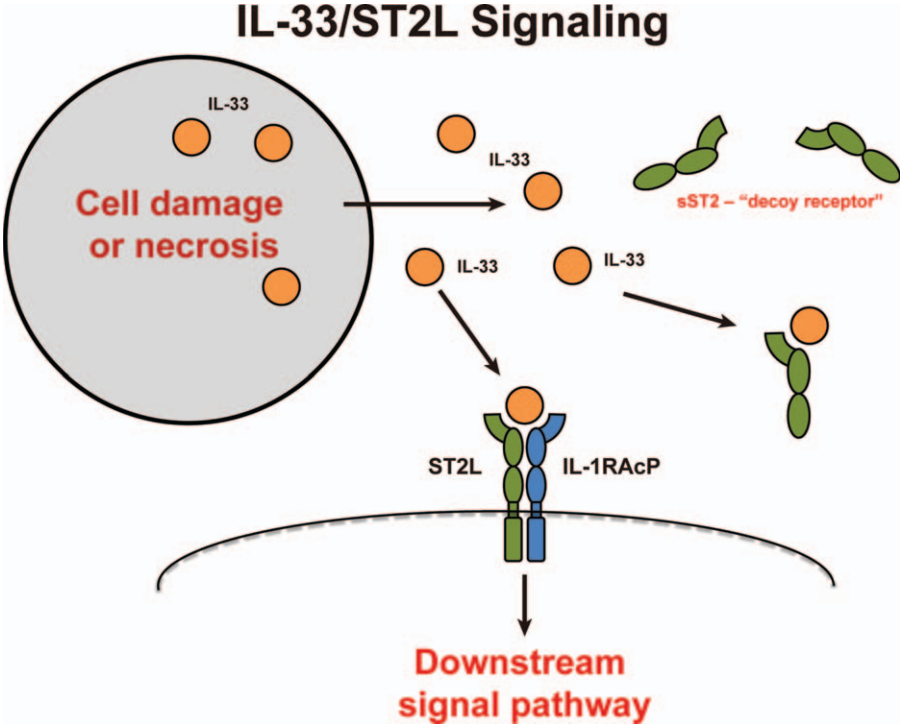

Figure 1. Interleukin-33/ST2L signaling. Due to cell damage or necrosis, the release of full-length IL-33 (active IL-33) can activate the heterodimeric ST2L/IL-1RAcP complex on a variety of immune cells or can be neutralized by sST2, which acts as a "decoy" receptor for IL-33.

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.[27] Briefly, fasting blood samples were obtained after a 10-hour fast by venepuncture of the large antecubital veins. Then, the samples were centrifuged at 2500 rpm 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.[28] In brief, all carotid ultrasound measurements were performed on a color Doppler ultrasound (IU 22, Philips, Amsterdam, Netherlands) with a 10 MHz 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	$P = .037^{\Delta}$
Male sex (%)	33.7%	32.7%	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 ± 1.45**	9.93 ± 1.89$^{**,\#\#}$	$P < .001$
HbA1c (%)	5.42 ± 0.37	9.29 ± 2.09**	10.25 ± 2.32$^{**,\#\#}$	$P < .001$
BMI (kg/m^2)	24.2 ± 3.2	25.3 ± 3.0	25.9 ± 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 ± 0.90	4.82 ± 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	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.

ALT = alanine aminotransferase, AST = aspartic transaminase, BMI = body mass index, BUN = blood urea nitrogen, DBP = diastolic blood pressure, FBG = fasting blood glucose, HbA1c = glycosylated 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.

** $P < .01$.

* $P < .05$, vs NC group.

$^{\#\#}$ $P < .01$.

$^{\#}$ $P < .05$, vs NCIMT group.

$^{\Delta}$ Student *t* test, vs NCIMT group.

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).

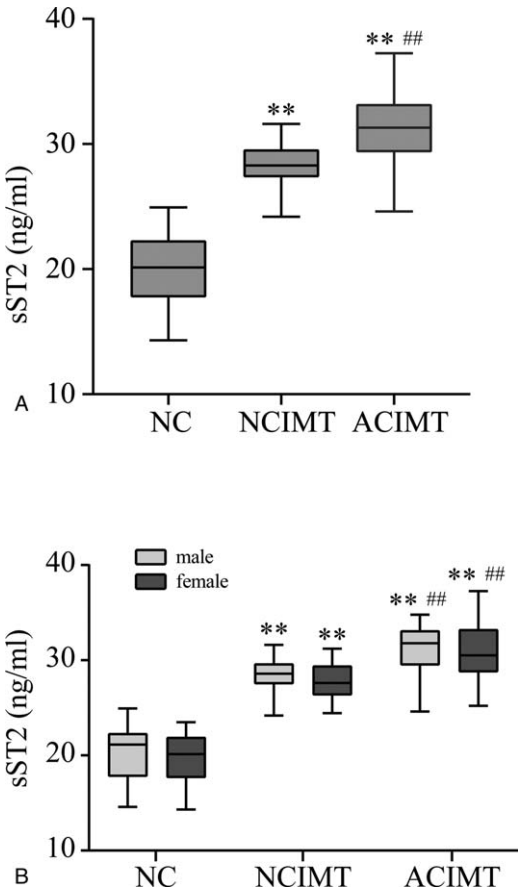

Figure 2. The sST2 levels (ng/ml) of the different groups. Each box represents the median and upper/lower quartiles, with the whiskers showing the 25th and 75th percentiles. A: the sST2 levels of the 3 groups. B: the sST2 level in each group by sex. $^{**}P < 0.01$, vs NC group; $^{\#\#}P < 0.01$, vs NCIMT group; ACIMT = abnormal carotid intima-media thickness, NC = normal control, NCIMT = normal carotid intima-media thickness.

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% CI, 0.084–0.311, $P < .01$), FPG level ($\beta = 0.302$, 95% CI, 0.162–0.442, $P < .01$) and HbA1c ($\beta = 0.296$, 95% CI, 0.165–0.426, $P < .01$) and negatively correlated with HDL level ($\beta = -0.153$, 95% CI, −0.259 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

Associations between sST2 level and clinical parameters.

Variable	r	P
Gender	−0.070	.353
Current smoking	0.531	.000
Age (years)	0.157	.033
FBG (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
TC (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 (μmol/L)	−0.011	.884
BUN	0.025	.739
UA (μmol/L)	−0.101	.178

ALT = alanine aminotransferase, AST = aspartic transaminase, BMI = body mass index, BUN = blood urea nitrogen, DBP = diastolic blood pressure, FBG = fasting blood glucose, HbA1c = glycosylated 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.

Table 3

Risk factors for sST2 in participants.

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 = glycosylated hemoglobin A1c, HDL = high density lipoprotein.

factors for increased CIMT. To see the results more easily, some continuous variables were converted to categorical variables according to the Chinese guidelines,[26,29] 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 = 6.701, 95% CI, 1.353–33.185, $P < .05$), 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.

Table 4

Risk Factors for increased CIMT in Patients of T2DM.

Risk factors	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	0.734–1.402	.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	1.106–2.481	.014

FBG = fasting blood glucose, HbA1c = glycosylated haemoglobin A1c, HDL = high density lipoprotein, LDL = low density lipoprotein, SBP = systolic blood pressure, TG = triglyceride.

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 yet 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

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.[23] 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.[22] In a recent prospective cohort study, the results indicated that increased level of sST2 was a predictor of a lower survival rate in acute coronary syndrome patients.[21] All patients in our study were sorted by CIMT, which is an early indicator of atherosclerosis. Thus, 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.[36] 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.[37] Finally, because sST2 acts as a decoy receptor binding to IL33, 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, Zhaoming Shi collected the data. Xiaolei Hu and Guoxi Jin conducted the statistical analysis. Shirong Zhang detected specimens.

References

[1] Peters A. Epidemiology: air pollution and mortality from diabetes mellitus. Nat Rev Endocrinol 2012;8:706–7.

[2] Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007;115:1544–50.

[3] Beckman JA, Paneni F, Cosentino F, et al. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Eur Heart J 2013;34:2444–52.

[4] Sarwar N, Gao P, et al. Emerging Risk Factors CDiabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–22.

[5] Lorenz MW, Price JF, Robertson C, et al. Carotid intima-media thickness progression and risk of vascular events in people with diabetes: results from the PROG-IMT collaboration. Diabetes Care 2015;38:1921–9.

[6] Polak JF, Pencina MJ, Pencina KM, et al. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med 2011;365:213–21.

[7] Baldassarre D, Hamsten A, Veglia F, et al. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study. J Am Coll Cardiol 2012;60:1489–99.

[8] Jain J, Lathia T, Gupta OP, et al. Carotid intima-media thickness and apolipoproteins in patients of ischemic stroke in a rural hospital setting in central India: a cross-sectional study. J Neurosci Rural Pract 2012;3:21–7.

[9] Katakami N, Mita T, Gosho M, et al. Clinical utility of carotid ultrasonography in the prediction of cardiovascular events in patients with diabetes: a combined analysis of data obtained in five longitudinal studies. J Atheroscler Thromb 2018;25:1053–66.

[10] Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov 2008;7:827–40.

[11] Tominaga S, Kuroiwa K, Tago K, et al. Presence and expression of a novel variant form of ST2 gene product in human leukemic cell line UT-7/GM. Biochem Biophys Res Commun 1999;264:14–8.

[12] Iwahana H, Hayakawa M, Kuroiwa K, et al. Molecular cloning of the chicken ST2 gene and a novel variant form of the ST2 gene product, ST2LV. Biochim Biophys Acta 2004;1681:1–4.

[13] Samuelsson M, Dereke J, Svensson MK, et al. on the behalf of the DSg. Soluble plasma proteins ST2 and CD163 as early biomarkers of nephropathy in Swedish patients with diabetes, 15-34 years of age: a prospective cohort study. Diabetol Metab Synd 2017;9:41.

[14] Bandara G, Beaven MA, Olivera A, et al. Activated mast cells synthesize and release soluble ST2-a decoy receptor for IL-33. Eur J Immunol 2015;45:3034–44.

[15] Mueller T, Jaffe AS. Soluble ST2–analytical considerations. Am J Cardiol 2015;115(7 Suppl):8B–21B.

[16] van Vark LC, Lesman-Leegte I, Baart SJ, et al. Prognostic Value of Serial ST2 Measurements in Patients With Acute Heart Failure. J Am Coll Cardiol 2017;70:2378–88.

[17] Shen J, Shang Q, Wong CK, et al. IL-33 and soluble ST2 levels as novel predictors for remission and progression of carotid plaque in early rheumatoid arthritis: A prospective study. Sem Arthrit Rheum 2015;45:18–27.

[18] Du LX, Wang YQ, Hua GQ, et al. IL-33/ST2 pathway as a rational therapeutic target for CNS diseases. Neuroscience 2018;369:222–30.

[19] Sun Z, Chang B, Gao M, et al. IL-33-ST2 axis in liver disease: progression and challenge. Mediators Inflamm 2017;2017:5314213.

[20] Chen WY, Li LC, Yang JL. Emerging roles of IL-33/ST2 axis in renal diseases. Int J Mol Sci 2017;18:

[21] Jha D, Goenka L, Ramamoorthy T, et al. Prognostic role of soluble ST2 in acute coronary syndrome with diabetes. Eur J Clin Invest 2018;48: e12994.

[22] Lin YH, Zhang RC, Hou LB, et al. Distribution and clinical association of plasma soluble ST2 during the development of type 2 diabetes. Diabetes Res Clin Pract 2016;118:140–5.

[23] Miller AM, Purves D, McConnachie A, et al. Soluble ST2 associates with diabetes but not established cardiovascular risk factors: a new inflammatory pathway of relevance to diabetes? PloS One 2012;7: e47830.

[24] Martin P, Palmer G, Rodriguez E, et al. Atherosclerosis severity is not affected by a deficiency in IL-33/ST2 signaling. Immun Inflamm Dis 2015;3:239–46.

[25] Chinese Diabetes SocietyChina guideline for type 2 diabetes (2013 edition). Chin J Endocrinol Metab 2014;30:893–942.

[26] Writing Group of 2010 Chinese Guidelines for the Management of Hypertension2010 Chinese guidelines for the management of hypertension. Chin J Cardiol 2011;39:579–616.

[27] Hu X, Hua Y, Shi Z, et al. Association of serum 25-hydroxy vitamin D and osteocalcin levels with non-alcoholic fatty liver disease. Int J Clin Exp Med 2016;9:22750–7.

[28] Zhou M, Hu X, Sun W, et al. Relationship between serum semaphorin 3a and carotid intima-media thickness in patients with type 2 diabetes mellitus. Chin J Diabetes 2018;26:479–83.

[29] Joint committee issued Chinese guideline for the management of dyslipidemia2016 Chinese guideline for the management of dyslipidemia in adults. Chin J Gen Practition 2017;16:15–35.

[30] Sibal L, Agarwal SC, Home PD. Carotid intima-media thickness as a surrogate marker of cardiovascular disease in diabetes. Diabetes Metab Syndr Obes 2011;4:23–34.

[31] Cardoso CRL, Salles GC, Leite NC, et al. Prognostic impact of carotid intima-media thickness and carotid plaques on the development of micro- and macrovascular complications in individuals with type 2 diabetes: the Rio de Janeiro type 2 diabetes cohort study. Cardiovasc Diabetol 2019;18:2.
[32] Zhang Y, Feng H, Wei Z. Association between IL-18 and carotid intima-media thickness in patients with type II diabetic nephropathy. Med Sci Monit 2017;23:470–8.
[33] Fousteris E, Melidonis A, Panoutsopoulos G, et al. Toll/interleukin-1 receptor member ST2 exhibits higher soluble levels in type 2 diabetes, especially when accompanied with left ventricular diastolic dysfunction. Cardiovasc Diabetol 2011;10:101.
[34] Miller AM, Asquith DL, Hueber AJ, et al. Interleukin-33 induces protective effects in adipose tissue inflammation during obesity in mice. Circ Res 2010;107:650–8.
[35] Kearley J, Silver JS, Sanden C, et al. Cigarette smoke silences innate lymphoid cell function and facilitates an exacerbated type I interleukin-33-dependent response to infection. Immunity 2015;42: 566–79.
[36] Hu L. Correlation of plasma EMP, NF-κB and IMT in patients with type 2 diabetes. HeBei: HeBei North University, 2014.
[37] Sanada S, Hakuno D, Higgins LJ, et al. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest 2007;117:1538–49.