Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Distribution and clinical association of plasma soluble ST2 during the development of type 2 diabetes

Ya-Hui Lin [a], Rong-Cheng Zhang [b], Li-Bo Hou [c], Kai-Juan Wang [a], Zhong-Ni Ye [a], Tao Huang [a], Jian Zhang [b], Xi Chen [a], Jin-Suo Kang [a,*]

[a] State Key Laboratory of Cardiovascular Disease, Clinical Laboratory Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[b] State Key Laboratory of Cardiovascular Disease, Heart Failure Center Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[c] State Key Laboratory of Cardiovascular Disease, National Cardiovascular Bio-bank Centre, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

ARTICLE INFO

Article history:
Received 12 August 2015
Received in revised form
12 May 2016
Accepted 6 June 2016
Available online 18 June 2016

Keywords:
sST2
Type 2 diabetes
Prediabetes
Atherosclerosis

ABSTRACT

Aim: ST2 plays important roles in diabetes and cardiovascular diseases. However, the distribution and changes in plasma soluble ST2 during the development of type 2 diabetes remain unclear.

Methods: In the present study, 525 subjects were recruited and divided into three groups: normal, prediabetic and diabetic subjects. The sST2 levels of all subjects were measured using a high-sensitivity assay.

Results: sST2 levels were modestly but significantly elevated in patients with diabetes (26.1 ng/ml) compared with normal subjects (19.3 ng/ml, $P < 0.001$) and persons with prediabetes (20.3 ng/ml, $P < 0.001$). The third and fourth quartiles (21.3 and 29.1 ng/ml, respectively) of the sST2 levels were associated with a 2.31- and 4.00-fold increased risk of having diabetes. With the prediabetic group as a reference population, patients with sST2 levels in the fourth quartiles had a higher increased risk of having diabetes mellitus (odds ratios = 2.19, $P < 0.05$). Furthermore, each SD log sST2 was associated with a 1.57-fold increased risk of atherosclerosis when all relevant variables was added to the multivariable logistic regression models. 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 levels.

Conclusion: Elevated sST2 levels were not only associated with metabolic characteristics of diabetes but also with a significantly increased risk of having diabetes.

* *Corresponding author at:* 167 Beilishilu, Beijing 100037, China. Fax: +86 10 88396217.
E-mail address: kangjinsuofuwai@sina.com (J.-S. Kang).

http://dx.doi.org/10.1016/j.diabres.2016.06.006
0168-8227/

1. Introduction

ST2 (suppression of tumorigenicity 2) is an interleukin 1 receptor-like 1 (IL1RL-1). Membrane-bound ST2 activates the transcription factor nuclear factor-κB (NF-κB) and the mitogen-activated protein kinase (MAPK) pathway via interaction with interleukin 33 (IL-33) that is secreted by necrotic cells. Ultimately, IL-33/ST2L signaling leads to the production of inflammatory factors and a Th2 immune response [1,2]. Truncated soluble ST2 (sST2), a decoy receptor of IL-33, is detectable in circulating blood and modulates the IL-33/ST2L signaling pathway. Thus far, publications have reported that the IL-33/ST2L signaling pathway has multiple biological effects and participates in the pathogenesis of several diseases. Plasma soluble ST2 is associated with cardiac disease, cancer, immune diseases and diabetes [3].

Type 2 diabetes is the most important chronic metabolic disorder and threatens public health worldwide [4]. Many causes play important roles in the pathogenesis of diabetes mellitus, including genetic and environmental factors [5]. In obese and diabetic mouse models, IL-33 reduced the level of fasting plasma glucose and increased glucose and insulin tolerance [6]. In clinical cohorts, patients with type 2 diabetes had high levels of circulating sST2 [7–11]. However, the distribution and changes in plasma soluble ST2 levels during the development of type 2 diabetes remain unclear. The prediction of conversion from prediabetes to diabetes and diabetic complication risks in the general population are a major challenge. Furthermore, prolonged high blood sugar levels lead to a fourfold increased risk of cardiovascular diseases and cause a greater overall coronary plaque burden [12,13].

Therefore, we investigated circulating ST2 levels in three groups: normal glucose, prediabetes and type 2 diabetes patients. Furthermore, the relationship between soluble ST2 and chronic diabetic complications was assessed after the subjects were stratified according to atherosclerosis.

2. Methods

2.1. Study sample

All 525 subjects were recruited from routine outpatients of Fu Wai Hospital in China from May to July 2014. The exclusion criteria included age <35 y or >75 y, heart failure, serious arrhythmia, valvular heart disease, malignancy, autoimmune disease and surgery in the previous month. According to the American Diabetes Association Standards of Medical Care in Diabetes [14], type 2 diabetes is defined as fasting plasma glucose (FPG) ⩾ 7.0 mmol/L, 2-h glucose tolerance test (GTT) ⩾ 11.0 mmol/L, hemoglobin A1c test (HbA1c) ⩾ 6.5% or currently taking medication for diabetes mellitus. Prediabetes is defined as FPG 5.5–6.9 mmol/L, 2-h GTT 7.7–10.9 mmol/L, HbA1c test 5.7–6.4% and without any diabetes medications. Normal blood glucose levels were defined as FPG < 5.5 mmol/L, 2-h GTT < 7.7 mmol/L, HbA1c test <5.7% and without any diabetes medications. The carotid and coronary arteries of all subjects were ascertained using color Doppler ultrasound, coronary computerized tomography angiography (CTA) or selective coronary angiography [15,16]. These images of coronary and carotid arteries were blindly reviewed by a pair of experienced vascular specialists.

This study complied with the declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee of Fu Wai Hospital. All participants reported that they were of Han ethnicity and provided written informed consent.

2.2. Data collection

Each eligible subject underwent a clinical examination. A medical history and status of cigarette smoking and alcohol consumption were collected using a standardized questionnaire. All subjects underwent a standard 12-lead ECG. The clinical chemistry analysis of the serum was performed at the clinical laboratory of Fu Wai Hospital on an Olympus AU5400 Automatic Analyzer (Olympus Ltd., Tokyo, Japan.). Peripheral blood samples were analyzed with an automated Sysmex XN-20 hematology analyzer system (Sysmex Corporation, Kobe, Japan).

2.3. Measurement of plasma soluble ST2

Participants provided a morning fasting blood sample that was isolated within 60 min of sample acquisition and stored immediately at −80 °C until sST2 measurement. We measured sST2 in EDTA-anticoagulated plasma using a highly sensitive ELISA (Presage® ST2 assay, Critical Diagnostics) following the product instructions [17].

2.4. Statistical analysis

We used descriptive statistics to obtain the characteristics of each group. Means (SDs), medians and quartiles are presented for continuous variables and percentages for categorical variables. sST2 concentrations were log-transformed before analysis, due to non-normality of distribution. Linear regression models were used to determine the correlates of ST2 and covariates. Logistic regression models were used to identify the association of sST2 and glucose tolerance status. In the multivariate regression analysis, all the variables which were significant in the univariate analysis were added to the regression models. All P values were two tailed, with values <0.05 considered statistically significant.

3. Results

3.1. Clinical characteristics of subjects

Baseline characteristics of the 525 subjects are summarized in Table S1. Significant differences were not observed for age and gender among the three groups. As expected, fasting blood glucose levels were gradually increased in normal, prediabetic and diabetic patients. The clinical characteristics of the normal and prediabetes groups were similar across most factors, except for the fasting blood glucose level and BMI. However, indicators for blood lipids and liver and renal function were significantly higher in patients with diabetes mellitus than in the other two groups.