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Predictive value of serum soluble corin in the risk of hyperglycemia: A population-based prospective cohort study in China

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ABSTRACT

Background: Serum soluble corin has been suggested to be associated with hyperglycemia by cross-sectional study. However, the prospective relationship between them remains unclear, and whether lipid component influences the relationship between them has not yet been studied.

Methods: A total of 1961 participants who were free from hyperglycemia were enrolled at baseline in 2010. The serum soluble corin concentrations were measured at baseline and all participants were followed up for hyperglycemia in 2014.

Results: The association between serum soluble corin and hyperglycemia incidence was appreciably modified by high density lipoprotein cholesterol (HDL-C) ($P_{interaction}$ = 0.04). Elevated serum soluble corin was associated with the risk of hyperglycemia only in the HDL-C ≥1.04 mmol/l subgroup rather than all participants. In participants with HDL-C ≥1.04 mmol/l, the adjusted odds ratio (95% CU) of hyperglycemia associated with the fourth quartiles of corin was 1.78 (1.08–2.94) compared with the lowest quartile of serum soluble corin, and there was a positive linear dose-response relationship between them (P for linearity < 0.01). The ordinal analysis showed an association between serum soluble corin and hyperglycemia severity (adjusted OR, 1.81; 95% CI, 1.10–2.99; P_{trend} = 0.02, when 2 extreme quartiles were compared). The addition of serum soluble corin to conventional risk factors improved risk prediction for hyperglycemia (net reclassification index: 0.16; integrated discrimination improvement: 0.01) in participants with HDL-C ≥1.04 mmol/l.

Conclusion: Serum soluble corin might be a valuable biomarker in prediction of future hyperglycemia in population with HDL-C ≥1.04 mmol/l, suggesting that corin might play a potential role in glucose metabolism.

1. Introduction

Corin is a type II transmembrane serine protease highly expressed in the heart, where it converts natriuretic peptides from inactive precursors to mature active forms [1,2]. In the past decade, accumulating evidence has demonstrated that corin plays critical roles in the regulation of salt-water balance, blood pressure, and cardiac function [3]. Recently, it was found that corin could be shed from the cardiomyocyte surface through corin autocleavage and metalloproteinase-mediated hydrolysis, and shed corin molecules which entered the circulation was detectable [4]. Circulating soluble corin has the same activity as the membrane-bound corin [5] and it has been reported to be associated with many diseases, such as hypertension [6], preeclampsia [7], obesity [8], and dyslipidemia [9].

In many large cross-sectional or prospective studies, low plasma atrial natriuretic peptide (ANP) concentration and B-type natriuretic peptide (BNP) concentration are both demonstrated to be able to predict development of future diabetes and glucose progression over time [10–12], but the reliable detection of plasma ANP or BNP concentration is challenged by its short half-life [13,14]. Our previous study [15] found a significantly positive association between serum soluble corin and hyperglycemia, indicating that it was possible for corin to play a potential role in glucose metabolism. However, a prospective relationship between serum soluble corin and hyperglycemia cannot be inferred in our previous study because it was a cross-sectional study design. To date, there is no prospective cohort study to confirm the

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relationship between them. In addition, our previous study also found that serum soluble corin was positively associated with dyslipidemia [9]. Given the close relationship between serum soluble corin and dyslipidemia, whether the association between serum soluble corin and hyperglycemia is modified by certain lipid components because of a potential interaction between lipids and serum soluble corin needs to be further elucidated. In order to improve identification of those at risk of hyperglycemia and improve prevention of hyperglycemia, we aimed to examine the association between serum soluble corin and the risk of hyperglycemia in general population and by blood lipid components subgroups based on a prospective cohort study in China.

2. Methods

2.1. Study participants

The baseline investigation was conducted from January to May 2010. Details on the design and baseline data collection have been described elsewhere [8]. Briefly, from the total 20 urban communities and 19 rural villages in a traditional but economically developed district of Suzhou, 4 urban communities and 4 rural villages were selected as the research fields via multiphase cluster random sampling. A total of 3061 eligible residents aged ≥30 y above lived in the study fields. Among them, 563 people were excluded because they refused to participate, or had cardiovascular diseases or parathyroid diseases, or failed to provide blood sample. Finally, a total of 2498 people (men: 962, women: 1536) aged from 30 to 80 y were investigated for their baseline data and baseline fasting plasma glucose (FPG) test. Among 2498 people, 386 people were excluded because of hyperglycemia, 2112 participants were followed up in 2014. 151 participants were lost to follow-up and the follow-up rate was 92.9%. Finally, a total of 1961 participants were included in the present study (Supplemental data, Fig. 1). Most baseline characteristics were balanced between participants who attended the follow-up and those who did not attend the follow-up (Supplemental data, Table 1). This study was approved by the Soochow University Ethics Committee. Written informed consent was obtained from all study participants.

2.2. Data collection

Trained staffs interviewed participants using a standard questionnaire in Chinese language to obtain information on demographic characteristics, medical history, and lifestyle risk factors. Cigarette smoking was defined as having smoked at least 1 cigarette per day for 1 year or more and reported current smoking [8,16]. Alcohol consumption was defined as consuming any type of alcohol beverage at least once per week during the last 3 y [8,17]. Body weight and height were measured using a regularly calibrated stadiometer and balance-beam scale with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured at the level of 1 cm above the umbilicus. Three consecutive blood pressure (BP) measurements were taken for each participant while participants were seated using a standard mercury sphygmomanometer. The mean of these three BP measurements was used for data analysis.

Blood samples were collected in EDTA-containing tubes by venipuncture and immediately centrifuged at 4 °C in the morning after a requested overnight fast (at least 8 h). All plasma and serum samples were frozen at −80 °C until laboratory testing. Total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and FPG were measured for all participants by Hitachi 7020 chemical analyzer using commercial reagents. The cut-off points of blood lipid components were defined as 6.22 mmol/l for TC, 2.26 mmol/l for TG, 4.14 mmol/l for LDL-C and 1.04 mmol/l for HDL-C according to Chinese guidelines on the prevention and treatment of dyslipidemia in adults [18].

2.3. Serum soluble corin measurement

Soluble corin was reported to be stable in blood samples frozen at −80 °C after several cycles of freezing and thawing [19]. Quantikine human corin immunoassay (R&D Systems) was used to test soluble corin concentration in serum samples and the gradient concentrations of corin standard were 4800, 2400, 1200, 600, 300, 150, 75 and 0 pg/ml. A standard curve was constructed according to these eight corin standard levels and from which serum soluble corin concentrations of unknown samples were determined. Intra- and interassay CVs were < 2.7% and 6.3%, respectively.

2.4. Follow-up and outcome assessment

Trained staffs interviewed either the participants or their relatives (if participants were dead or unable to communicate) and completed a medical status questionnaire. If a participant or their relatives reported that diabetes occurred during the period from baseline survey to follow up, the staffs contacted the subject's general practitioner and reviewed hospital records or death certificate to confirm. Moreover, we obtained the blood samples of all participants who attended the follow-up by venipuncture in the morning after a requested overnight fast (at least 8 h). FPG level at the follow-up was also measured with the use of the enzymatic assay. In our study, hyperglycemia was defined as FPG ≥6.1 mmol/l or self-reported history of physician-diagnosed diabetes [20].

2.5. Statistical analysis

Circulating corin was reported to be varied by sex but not age [21], so all participants were divided into four groups according to the quartiles of serum corin distributed in men and women, respectively. The quartile cutoff values of serum soluble corin were 1750.6, 2102.9, and 2552.6 pg/ml in men and 1277.2, 1504.6, and 1755.9 pg/ml in women, respectively. Baseline characteristics were presented and compared among the four groups. Tests for linear trend were performed using covariance analysis for continuous variables, and chi-square trend analysis for categorical variables. Multivariate logistic regression analyses were performed to assess the association between baseline serum soluble corin levels and subsequent hyperglycemia incidence. Odds ratios and 95% CI were calculated for upper quartiles of serum soluble corin with the lowest quartile as a reference both in all participants and in different lipid profile subgroups. Trends for the ORs of hyperglycemia across corin quartiles were determined, having corin quartile as an ordinal variable. The effect of serum soluble corin on hyperglycemia severity (none, pre-diabetes, diabetes) was analyzed using ordinal logistic regression models. The potential covariates such as age, sex, cigarette smoking, alcohol drinking, systolic BP, BMI, FPG, and the other three lipid levels at baseline were included in the multivariate model. Interactions between lipid profile and serum soluble corin on the risk of hyperglycemia were tested in the models with interaction terms by the likelihood ratio test, adjusting for the aforementioned covariates.

Furthermore, in the significant interaction lipid-level subgroups, we used a logistic regression model with restricted cubic splines to evaluate the pattern and magnitude of the association between baseline serum soluble corin levels and the risk of hyperglycemia, with four knots placed at the 5th, 35th, 65th, and 95th percentiles of corin [22]. In addition, continuous net reclassification index (NRI) and integrated discrimination improvement (IDI) were used to evaluate the incremental predictive value of serum soluble corin levels in the risk of hyperglycemia beyond conventional risk factors [23]. All P values were 2 tailed, and a $P < 0.05$ was used. Statistical analysis was conducted with SAS statistical software (ver 9.4).