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Increased plasma DPP4 activities predict new-onset hyperglycemia in Chinese over a four-year period: Possible associations with inflammation

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ABSTRACT

Objective. DPP4, a novel proinflammatory cytokine, is involved in the inflammatory process through its interaction with the IGF-II/M6P receptor. Our objective was to determine whether DPP4 acts as a link between low-grade chronic inflammation and hyperglycemia.

Design and methods. A prospective cohort study was conducted with 486 adults (177 men and 309 women) aged 18 to 70 years without hyperglycemia examined in 2007 (baseline) and 2011 (follow-up). Circulating DPP4 activity, IGF-II/M6P receptor, and inflammatory markers were measured at baseline and four years later.

Results. After a four-year follow-up period, 111 individuals developed hyperglycemia (71 prediabetes and 40 type 2 diabetes). According to the multiple linear regression analysis, the baseline DPP4 activity was an independent predictor of an increase in the IGF-II/M6P receptor, inflammatory markers, and insulin resistance over the four-year period (all $P < 0.05$).
In the multivariable-adjusted models, the odds ratio (OR) for incident hyperglycemia comparing the highest and lowest quartiles of DPP4 activity was 2.90 (95% CI 1.47–5.73) after adjustment for confounding risk factors ($P = 0.002$). The incidence of hyperglycemia because of DPP4 activity increased by 9.47%. Furthermore, the plasma DPP4 activity significantly improved the area under the ROC curve for predicting new-onset hyperglycemia based on the information from the baseline levels of the risk factors ($P = 0.036$).

Conclusions. DPP4 activity is an important predictor of the onset of insulin resistance and hyperglycemia in apparently healthy Chinese. This finding may have important implications for understanding the proinflammatory role of DPP-4 in the development and pathogenesis of hyperglycemia.

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Abbreviations: DPP4, dipeptidyl peptidase-4; VAT, visceral adipose tissue; HOMA-IR, homeostasis model assessment of insulin resistance; IAUC, insulin area under-curve; hs-CRP, C-reactive protein; IL-6, interleukin-6; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, isolated impaired glucose tolerance; OGTT, oral glucose tolerance test; BMI, body mass index; WHR, waist/hip ratio; IGF-II/M6P-R, insulin-like growth factor II/mannose 6-phosphate receptor; SBP, systolic blood pressure; DBP, diastolic blood pressure; PAR, population attributable risk; ROC, receiver operating characteristic.

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1. Introduction

Chronic subclinical inflammation is hypothesized to be involved in the pathogenesis of hyperglycemia [1]. A number of prospective studies [2–4] have demonstrated an association between high levels of inflammation and the development of hyperglycemia. Despite numerous reports of inflammatory markers that predict the development of hyperglycemia, the metabolic signaling pathways linking inflammation to hyperglycemia are less well understood.

Dipeptidyl peptidase-4 (DPP4) or T-cell activation antigen CD26 (EC 3.4.14.5.) is a serine protease found on the apical surface of a variety of cells. It has a catalytic activity that removes N-terminal dipeptides with alanine or proline at the penultimate position of various peptide substrates, including chemokines and inflammatory cytokines. In addition to its membrane form, DPP4 exists in the plasma as a soluble form, sCD26, which is the extracellular domain of the molecule predicted to be cleaved from the cell surface [5]. DPP4 occurs in organs, including the lung, spleen, liver, kidney, intestines, endothelial cells, bone marrow and blood cells, in both rodents and humans [5–7]. In addition, recent data suggest that DPP4, as an important proinflammatory cytokine, can also be released from adipose tissue [8]. Consistent with its wide distribution, DPP4 exerts pleiotropic effects on glucose metabolism, gut motility, appetite regulation, inflammation, and immune system function though its peptidase activity [9].

Previous studies showed that DPP4 enhances T-cell maturation and migration, cytokine secretion, and activation of cytotoxic T cells via an interleukin-12-dependent mechanism [10]. In addition, soluble DPP4 binds to insulin-like growth factor II/mannose 6-phosphate receptor (IGF-II/M6P-R) and is taken up by CD14 positive monocytes, increasing their antigen presenting activity and T-cell proliferation [11]. Shirakawa et al. [12] reported that M1 macrophages and T cells were increased in the visceral adipose tissue (VAT) of diet-induced diabetic mice and that CD26/DPP4 inhibition prevented both the infiltration of those cells into the VAT and diet-induced adipose tissue inflammation. These findings suggest that DPP4 may be involved in the development of tissue inflammation in the body. Because key pathophysiological changes in hyperglycemia include chronic low-grade inflammation, we hypothesize that DPP4 activity may play an important role in promoting hyperglycemia through its proinflammatory actions. However, the majority of previous observations arise from cross-sectional studies and focus on the protein level of DPP4, and until recently, little has been known about circulating DPP4 activity as a predictor of hyperglycemia as a result of its proinflammatory actions.

Therefore, we studied the possible link between low-grade chronic inflammation and hyperglycemia by determining whether fasting plasma DPP4 activity in a population of Chinese patients predicts the development of hyperglycemia. In our study, we used the homeostasis model assessment of insulin resistance (HOMA-IR), Matsuda index, and insulin area under-curve (IAUC) for the analysis of insulin resistance, and the disposition index for integrated β cell function. In addition, high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were used to estimate the degree of inflammation.

2. Methods and procedures

2.1. Population

The study population consisted of both men and women, aged 18–70 years, who participated in the China National Diabetes and Metabolic Disorders Study [13], a 4-year follow-up study that aims to clarify the prevalence and development of type 2 diabetes and metabolic disorders. The subjects are volunteers from 2 health examination centers in Sichuan province. The Medical Research Ethics Committee of the China–Japan Friendship Hospital (2 Cherry Park Street, Chaoyang District, Beijing 100029, China) reviewed and approved the present study. Written informed consent was obtained from each participant prior to data collection. This study was registered on the Chinese clinical trial registry (#TR-CCH-Chi CTR-CCH-00000361).

The final sample size for the present analysis was 486 adults (177 men and 309 women) without hyperglycemia at baseline [fasting plasma glucose (FPG) < 6.1 mmol/L, and 2-h post oral glucose tolerance test plasma glucose (2 h-PG) < 7.8 mmol/L] [14]. The inclusion criteria were as follows: [1] age between 18 and 70 years old; and [2] long-term residence (≥5 years) in China's Sichuan province. The exclusion criteria were as follows: [1] all subjects with a past history of hyperglycemia [including isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), IFG plus IGT, or type 2 diabetes] or diagnosis of hyperglycemia at baseline during screening; [2] use of drugs to control blood glucose, blood pressure, and blood lipids; [3] subjects deprived of personal safety and the presence of any chronic diseases, including stroke and myocardial infarction. Other heart, liver, renal and respiratory dysfunctions were excluded as progression of these in any stage may hinder our study; [4] pregnant subjects and subjects with malignancy; [5] subjects who refused to undergo blood analysis and answer the questionnaire form at two successive follow-ups; and [6] subjects with incomplete data.

2.2. Clinical measurements

A standard questionnaire was administered by trained staff to the participants to record the demographic characteristics and life style risk factors [15]. Blood pressure, body weight, height, waist and hip circumference, body mass index (BMI), and waist/hip ratio (WHR) were measured and calculated using standard methods as previously described [13]. The participants were instructed to maintain their usual physical activity and diet for at least 3 days before undergoing an oral glucose tolerance test (OGTT). After an overnight fast ≥10 h, venous blood samples were collected to measure the FPG, fasting insulin, blood lipids, including TC, TG, LDL-C, and HDL-C, hs-CRP, IL-6, IGF-II/M6P-R and DPP4 activity. Blood samples were also drawn at 30 and 120 min after a 75 g glucose load to measure the glucose and insulin concentrations. The demographic characteristics, life style risk factors, anthropometric parameters and venous blood samples were collected or determined at baseline and four years later.

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