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Postchallenge plasma glucose excursions, carotid intima-media thickness, and risk factors for atherosclerosis in Chinese population with type 2 diabetes

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ABSTRACT

Aims: Isolated hyperglycemia is associated with atherosclerosis in individuals with type 2 diabetes, but the relationship between postchallenge glucose excursion and atherosclerosis is less clear. This study examines the relationships between postchallenge glucose spikes (PGS), carotid intima-media thickness (IMT), and traditional risk factors for atherosclerosis in individuals with type 2 diabetes.

Methods: A total of 474 individuals with type 2 diabetes who were within the highest or lowest IMT distribution quartile were included. The Student's *t*-test, one-way analysis of variance (ANOVA), single variate and multivariate analyses were implemented to study the data. An additional healthy control group ($n = 896$) was selected during routine health examination. They were Han nationality and unrelated to the diabetic patients.

Results: (1) Compared with subjects of healthy control group, the subjects with type 2 diabetes had significantly higher levels of body mass index (BMI), waist-to-hip ratio (WHR), systolic blood pressure, triglyceride, total cholesterol, low density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), 120 min postchallenge glucose (PG120), hemoglobin A1c (HbA1c) and IMT ($P \leq 0.01$) and relatively lower levels of high density lipoprotein cholesterol (HDL-C) ($P \leq 0.05$). (2) According to the IMT which was measured by B-mode ultrasonography, the patients of type 2 diabetes could be divided into two subgroups: one was the subgroup of IMT $\geq P_{75}$ and another was the subgroup of IMT $\leq P_{25}$. Compared with subjects of IMT $\geq P_{25}$ subgroup, subjects being in the IMT $\geq P_{75}$ subgroup exhibited significantly increased age, WHR, diabetes duration, systolic blood pressure, total cholesterol, triglyceride, LDL-C, and significantly decreased HDL-C levels. And among all the plasma glucose variables, except for FPG and PG30, all the other variables (include PG60, PG120, PG180, PGS, HbA1C, under area curve of glucose) showed a significant increase in the IMT $\geq P_{75}$ subgroup. (3) A multivariate logistic regression analysis was performed to establish which were independently related with carotid IMT, and the results showed the PGS was identified as the strongest determinant of IMT from all the atherosclerosis risk factors. (4) PGS is significantly correlated to a variety of atherosclerosis risk factors.

Conclusions: This study identified several important associations between PGS and known risk factors for atherosclerosis and suggested that PGS is independently related to carotid IMT. Wide postchallenge glucose excursions may contribute to the development of atherosclerosis in individuals with type 2 diabetes, independent of other risk factors.

1. Introduction

Cardiovascular and cerebrovascular complications are the leading cause of death in type 2 diabetes mellitus (DM). Even when adjusted for conventional risk factors, diabetic individuals still exhibit a two- to fourfold increased risk in comparison with non-diabetic subjects [1,2]. Therefore, hyperglycemia is supposed to exert a harmful effect on the arterial wall and has recently been a focus of keen research. Although the relevance of glycemic exposure is indisputable, fasting plasma glucose (FPG) and HbA1c, the most commonly measured glycemic parameters, do not completely explain the risk. And then studies suggest that postchallenge plasma glucose is more strongly associated with atherosclerosis than fasting glucose and HbA1c. Although there is increasing evidence that postprandial hyperglycemia, which is not inevitably reflected by HbA1c, is a strong risk factor for the development of macrovascular complications in diabetes [3–6], and even in

Abbreviations: PGS, postchallenge glucose spikes; T2DM, type 2 diabetes mellitus; IGR, impaired glucose regulation; NGT, normal glucose tolerance; TG, triglyceride; VLDL, very low density lipoprotein; IMT, intima-media thickness; FPG, fasting plasma glucose; CHD, coronary heart disease; CVD, cerebrovascular disease; OGTT, oral glucose tolerance test; CCA, common carotid artery.

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impaired glucose tolerance (IGT) [7,8], it also do not completely explain the risk [9]. And now some authors suggest that postprandial glucose excursion may play a role in the development of macrovascular complications in diabetes [10]. It has also been suggested that glycemic control may be more appropriately expressed in terms of glucose variability in conjunction with HbA1c, FPG and postchallenge plasma glucose, rather than by HbA1c, FPG and postchallenge plasma glucose alone.

So far, few investigators have examined the importance of postchallenge glucose excursion for macrovascular risk factor profile and the development of macrovascular complications in diabetes. Non-invasive measurement of the carotid intima-media thickness (IMT) by ultrasound is accepted as a surrogate continuous variable for macroangiopathy. The use of such a surrogate quantitative variable better qualifies the early steps of the disease itself and provides increased statistical power over case control studies which are exposed to selection bias [11]. Moreover, the echographic measurement of carotid IMT has been closely related to coronary heart disease (CHD), cerebrovascular disease (CVD) in both transversal and prospective studies [12–15]. It is therefore of interest to evaluate the association between postchallenge glucose spikes (PGS), carotid IMT, and known risk factors for atherosclerosis.

We hypothesized that PGS would be positively associated with prevalent cardiovascular disease, cerebrovascular disease and carotid IMT even after adjustment for other risk factors in individuals with type 2 diabetes. We also hypothesized that PGS would be correlated with risk factors for atherosclerosis including plasma lipids, blood pressure (BP) and waist-to-hip ratio (WHR).

2. Subjects and methods

2.1. Subjects

We received 948 unrelated Chinese patients with type 2 DM (mean age = 58.1 [SD 9.7] yr, sex ratio M/F = 426/522) who fulfilled the World Health Organization criteria for DM [16] from Renji Hospital of Shanghai Jiaotong University. The patients were Han nationality and free of rheumatic disease. According to the IMT which was measured by B-mode ultrasonography, 474 individuals with type 2 diabetes who were within the highest or lowest IMT distribution quartile were included and these patients of type 2 DM could be divided into two subgroups: one is the highest quartile of IMT (IMT ≥ 0.88 mm), another is the lowest quartile of IMT (IMT ≤ 0.63 mm).

An additional control group of nondiabetic healthy subjects with a normal glucose tolerance test (n = 896, mean age = 61.4 (S.D. 11.3) year, sex ratio M/F = 468/428) was selected during routine health examination. They were Han nationality and unrelated to the diabetic patients.

Written, informed consent was obtained from patients who agreed to participate in the study and the study had the approval of our local ethics committee.

2.2. Laboratory measurements

Venous blood samples were drawn after an overnight fast of at least 10 h. OGTT was performed with 75 g glucose, and blood was collected for the measurement of plasma glucose every 30 min or 1 h for 3 h. The PGS were defined as the difference between the maximal PG level during OGTT, irrespective of the time after glucose challenge, and the level of FPG [10,17].

Serum cholesterol, HDL-cholesterol and triglyceride (TG) were measured by automated enzymatic methods; LDL-cholesterol was calculated according to Friedewalds formula. HbA1c was measured by high-performance liquid chromatography.

Table 1
Clinical and biological characteristics between type 2 DM and control group.

Items	Type 2 DM group (n = 948)	Control group (n = 896)
Age (year)	61.7 ± 12.6	61.4 ± 11.3
Sex (M/F)	494/454	468/428
BMI (kg/m^2)	25.0 ± 7.6*	23.5 ± 3.5
WHR	0.92 ± 0.09*	0.84 ± 0.04
SBP (mmHg)	136 ± 29.6*	124 ± 13.7
DBP (mmHg)	80.5 ± 10.8	80.1 ± 11.6
TC (mmol/L)	4.97 ± 2.42*	4.57 ± 1.08
TG (mmol/L)	1.86 ± 0.99*	1.23 ± 0.38
HDL-C (mmol/L)	1.29 ± 0.76*	1.39 ± 0.41
LDL-C (mmol/L)	3.02 ± 1.03*	2.50 ± 0.87
FPG (mmol/L)	7.98 ± 2.71*	5.01 ± 0.90
PG120 (mmol/L)	16.6 ± 5.98*	6.81 ± 1.31
HbA1c (mmol/L)	9.68 ± 3.65*	5.11 ± 0.29
IMT	0.79 ± 0.25*	0.61 ± 0.19

Note: compared with control group, * $P < 0.05$.

2.3. IMT measurement

IMT of common carotid artery (CCA) was measured with high-resolution B-mode ultrasonography (LOGIQ 500, USA) equipped with a 11 MHZ transducer. For each subject, the measurements of IMT on both sides were performed by the same physician blinded to clinical data. IMT values were averaged on three determinations for right and left CCAs, one of the three determinations is the site of greatest thickness within 10 mm segment proximal to the carotid bifureation of the CCA, and the other two determinations are the 10 mm point proximal and distal to the site of greatest thickness respectively.

2.4. Statistical analysis

Data are presented as mean ± SEM. Categorical variables were compared by chi-square analysis. Differences between continuous variables were evaluated by Student's t-test. The relationships between IMT and variables likely to have an influence were assessed by logistic linear regression analysis to evaluate the independent association of each with IMT. The correlation of PGS to atherosclerosis risk factors was assessed using Pearson correlation coefficients. $P < 0.05$ was considered significant. Data were evaluated using SPSS version 10.0 (SPSS, Chicago, IL).

3. Results

3.1. Clinical and biological characteristics between type 2 DM and control group (Table 1)

The clinical and biological characteristics of type 2 diabetic patients and healthy control group are reported in Table 1. Compared with subjects of healthy control group, the subjects with type 2 diabetes had significantly higher levels of BMI, WHR, SBP, TG, TC, LDL-C, FPG, PG120, HbA1c and IMT ($P \leq 0.05$) and relatively lower levels of HDL-C ($P \leq 0.05$); but no significant differences were noted with regard to age, sex, and DBP level ($P > 0.05$).

3.2. Clinical and biological characteristics between IMT ≤ P_{25} and IMT ≥ P_{75} subgroup in type 2 diabetes (Table 2)

According to the IMT which was measured by B-mode ultrasonography, 474 individuals with type 2 diabetes who were within the highest or lowest IMT distribution quartile were included and these patients of type 2 DM could be divided into two subgroups: