

One-Hour Post-Load Plasma Glucose Levels are Associated with Early Arterial Stiffness in Subjects with Different Glucose Tolerance

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Objective: The purpose of this study was to explore the relationship between one-hour post-load plasma glucose levels and early arterial stiffness in subjects with different glucose tolerance.

Methods: This case-control study included 57 subjects with normal glucose tolerance, 38 subjects with pre-diabetes, and 30 subjects with type 2 diabetes. All subjects underwent an oral glucose tolerance test (OGTT) with 75 g of oral anhydrous glucose at 8:00 AM. The brachial-ankle pulse wave velocity (baPWV) was used as a surrogate marker of early arterial stiffness.

Results: baPWV was significantly higher in the diabetes group than in the normal glucose tolerance group (diabetes group: 1501.8 ± 270.4 cm/s, pre-diabetes group: 1428.6 ± 173.1 cm/s vs normal glucose tolerance group: 1368.0 ± 242.8 cm/s) ($p < 0.05$). baPWV was positively correlated with age ($r = 0.512$, $p < 0.001$), systolic blood pressure (SBP) ($r = 0.526$, $p < 0.001$), diastolic blood pressure (DBP) ($r = 0.298$, $p = 0.001$), fasting plasma glucose (FPG) ($r = 0.213$, $p = 0.017$), 1-h plasma glucose levels from the OGTT ($r = 0.407$, $p < 0.001$) and 2-h plasma glucose levels from the OGTT ($r = 0.202$, $p = 0.024$). When baPWV was considered as the dependent variable in a multiple regression analysis, the 1-h plasma glucose level from the OGTT maintained an independent association with baPWV ($\beta = 23.129$, 95% CI: 8.142–38.115, $p = 0.003$, $R^2 = 0.036$).

Conclusion: The present study demonstrated the presence of early arterial stiffness in diabetes. Elevated 1-hour post-load plasma glucose level is closely related to the change of arterial elasticity in diabetes.

Keywords: early arterial stiffness, brachial-ankle pulse wave velocity, post-load glucose

Introduction

Type 2 diabetes is correlated with an increased risk for atherosclerosis. Compared with non-diabetes patients, those with type 2 diabetes mellitus have higher frequency of lower extremity vascular diseases and carotid stenosis.¹ Acute hyperglycemia, in particular, postprandial hyperglycemia plays a more important role in the development of atherosclerotic disease than fasting state.² Hyperglycemia at 1-hour during oral glucose tolerance test (OGTT) is a useful tool to identify individuals at higher risk of developing type 2 diabetes and cardiovascular diseases.³ Several studies found that elevated one-hour post-load plasma glucose level correlates with early carotid atherosclerosis.^{4–6} Large-scale studies have proven that one-hour post-load plasma glucose was an important predictor of long-term cardiovascular events.⁷

Arterial elasticity value is an early parameter for evaluating atherosclerosis. Brachial-ankle pulse wave velocity (baPWV) is a unique measure of systemic arterial elasticity that is measured by brachial and tibial arterial wave analyses. Measurement of baPWV is easy and reproducible.⁸ baPWV is known to be a significant predictor of cardiovascular events.⁹ Incremental glucose peak and insulin resistance were associated with greater arterial stiffness.^{10–12} Studies have confirmed that one-hour post-load plasma glucose levels were associated with baPWV in subjects with normal glucose tolerance, essential hypertension or apparently healthy men.^{13–15} Choi et al reported that 30-minute post-load glucose

level was a weak but significant determinant for baPWV.¹⁶ However, very little information is available on the relationship between one-hour post-load plasma glucose levels and baPWV in subjects with different glucose tolerance.

In this study, the baPWV was used to evaluate arterial elasticity in subjects with different glucose tolerance to explore the relationship between one-hour post-load plasma glucose levels and baPWV, since baPWV is considered to be a well-recognized marker of early arterial stiffness.

Methods

Study Design

We performed a case-control study of adults aged ≥ 18 years with different glucose tolerance. All subjects were of the Han ethnicity, and underwent an oral glucose tolerance test (OGTT) with 75 g of oral anhydrous glucose at 8:00 AM. Peripheral venous blood samples were taken at 0, 60, and 120 minutes after glucose loading. The exclusion criteria were as follows: 1) subjects with previous medical history of coronary artery diseases, peripheral arterial disease or cerebral stroke; 2) subjects with clinical evidence of endocrinopathy, such as Cushing's syndrome, primary hyperaldosteronism, hyperthyroidism, hypothyroidism, etc; and 3) subjects with acute or chronic inflammation, such as flu, pneumonia, urinary infection, etc. This study was approved by the ethics committee of the First Hospital of Qinhuangdao. All subjects provided written informed consent before study initiation. The study complied with the principles of the Declaration of Helsinki.

Cases and Controls

Between January 2019 and July 2019, 57 subjects with normal glucose tolerance, 38 subjects with pre-diabetes, and 30 subjects with type 2 diabetes were enrolled in this study. The definition of glucose tolerance status was according to the criteria of the Diabetes Society of Chinese Medical Association.¹⁷ All subjects with type 2 diabetes were new-onset patients, with no prior diabetes treatment.

Anthropometric Measurements

Anthropometric measurements, including height, weight, waist circumference (WC) and blood pressure, were obtained while the subjects were wearing light clothing and no shoes. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Blood pressure was measured twice with a mercury sphygmomanometer after 10 min of rest while the subjects were seated, and the average of the two measurements was used for analysis.

Laboratory Examinations

Plasma glucose levels were measured using the glucose oxidase method. Serum lipid levels were measured using enzymatic assays with an autoanalyzer (Hitachi, Tokyo, Japan). Plasma concentrations of insulin were measured by chemiluminescent immunoassay (Roche 2010 Elecsys). The following equation was used to calculate the homeostasis model assessment (HOMA)-IR index: (fasting insulin level x fasting glucose level)/22.5.

Brachial-Ankle Pulse Wave Velocity (baPWV)

The baPWV measurement was performed using an oscillometry-based device (HBP-8000, Omron, Japan) by a trained technician according to a standard protocol. Each subject rested for at least 5 minutes and then lay in the supine position with four monitoring cuffs wrapped around both ankles and upper arms. The lower edge of the cuff was 2–3 cm above the cross grain of the cubital fossa, and 1–2 cm above the malleolus medialis. The instrument was set to repeat the measurement twice, and the data of the second measurement was taken as the result. The mean values of baPWV on the left and right sides were calculated.

Statistical Analyses

All analyses were performed using the SPSS 11.5 statistical software (SPSS 11.5 for Windows; SPSS, Inc., Chicago, IL). Numerical variables were reported as mean \pm standard deviation. The data with skewed distribution were ln-transformed

for analysis, and expressed as median with interquartile range. Comparisons were conducted between groups using the one-way analysis of variance (ANOVA). Categorical data were reported as abnormal subjects (%), and chi-square test was used. A Pearson's correlation coefficient was used to measure the strength of association between variables. Multiple linear regression analyses were performed to examine the relationships between glycemic variability and baPWV. A p -value <0.05 was considered as statistically significant.

Results

Age, anthropometric, biochemical and baPWV data, are presented in Table 1. There were no significant differences in gender between the three groups ($p>0.05$). The patients in the pre-diabetes group were significantly older compared to the diabetes group and the normal group ($p<0.05$). The levels of systolic blood pressure (SBP) were significantly higher in the diabetes group than in the normal group ($p<0.05$). The levels of fasting plasma glucose (FPG), and 1-h and 2-h plasma glucose levels from the OGTT were significantly higher in the pre-diabetes group and the diabetes group than in the normal group ($p<0.05$). The levels of FPG, and 1-h and 2-h plasma glucose levels from the OGTT were significantly higher in the diabetes group than in the pre-diabetes group ($p<0.05$). Two-h insulin levels from the OGTT were significantly higher in the pre-diabetes group than in the normal group ($p<0.05$). The levels of baPWV were significantly higher in the diabetes group than in the normal group ($p<0.05$). No significant differences were observed in any of the other variables between the three groups ($p>0.05$).

The correlation coefficients between baPWV and the other variables for all the subjects are shown in Table 2. The baPWV was positively correlated with age ($r=0.512$, $p<0.001$), SBP ($r=0.526$, $p<0.001$), diastolic blood pressure (DBP) ($r=0.298$, $p=0.001$), FPG ($r=0.213$, $p=0.017$), 1-h plasma glucose levels from the OGTT ($r=0.407$, $p<0.001$) and 2-h plasma glucose levels from the OGTT ($r=0.202$, $p=0.024$). When baPWV was considered as the dependent variable in a multiple regression analysis with age, gender (males=0, females=1), BMI, WC, SBP, DBP, TG, TC, HDL-C, LDL-C, FPG, 1-h and 2-h plasma glucose levels from the OGTT and HOMA-IR as independent variables, the 1-h plasma glucose

Table 1 Clinical and Laboratory Characteristics of the Subjects in Each Group

Variable	Normal Group (n=57)	Pre-Diabetes Group (n=38)	Diabetes Group (n=30)	F or χ^2	p
Age (y) mean (SD)	48.3(9.3)	52.6(8.3)*	56.0(10.8)*	6.933	0.001
Gender (Male/Female)	30/27	25/13	17/13	1.630	0.443
BMI (kg/m ²) mean (SD)	24.6(3.6)	25.3(2.7)	25.6(3.4)	0.951	0.389
WC (cm) mean (SD)	85.3(11.1)	86.9(9.0)	88.2(9.4)	0.822	0.442
SBP (mmHg) mean (SD)	122.2(16.8)	128.5(15.0)	130.9(17.7)*	3.271	0.041
DBP (mmHg) mean (SD)	79.9(12.2)	82.2(9.4)	82.4(14.1)	0.640	0.529
TG (mmol/L) mean (SD)	1.80(1.09)	1.74(0.96)	1.69(0.87)	0.131	0.877
TC (mmol/L) mean (SD)	5.35(1.09)	5.04(0.93)	5.25(0.99)	1.026	0.361
HDL-C (mmol/L) mean (SD)	1.47(0.35)	1.35(0.33)	1.45(0.32)	1.451	0.238
LDL-C (mmol/L) mean (SD)	2.84(0.86)	2.71(0.70)	2.73(0.77)	0.394	0.675
FPG (mmol/L) mean (SD)	5.07(0.57)	5.45(0.72)*	6.00(1.13)* [#]	13.822	<0.001
OGTT, 1-h Plasma Glucose (mmol/L) mean (SD)	8.93(1.42)	10.35(1.50)*	11.41(2.98)* [#]	17.460	<0.001
OGTT, 2-h Plasma Glucose (mmol/L) mean (SD)	6.32(1.18)	9.23(1.09)*	13.55(3.06)* [#]	159.971	<0.001
Fasting Insulin (uIU/mL) median (IQR)	8.8(6.2~14.4)	7.1(5.5~10.9)	6.5(5.3~11.1)	2.488	0.087
OGTT, 1-h Insulin (uIU/mL) median (IQR)	38.1(24.2~82.6)	41.8(20.5~60.3)	30.7(12.4~40.1)	2.971	0.055
OGTT, 2-h Insulin (uIU/mL) median (IQR)	28.6(16.7~48.5)	42.9(29.9~77.1)*	39.4(25.1~62.7)	4.233	0.017
HOMA-IR median (IQR)	2.06(1.36~3.30)	1.73(1.16~2.74)	1.86(1.28~2.90)	0.882	0.417
baPWV (mm) mean (SD)	1368.0(242.8)	1428.6(173.1)	1501.8(270.4)*	3.341	0.039

Note: Values are expressed as mean (SD), and when not normally distributed, they were ln-transformed for analysis and are expressed as median (IQR). *Compared with the Normal Group $p<0.05$, [#]compared with the Pre-diabetes Group $p<0.05$.

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment insulin resistance; baPWV, brachial-ankle pulse wave velocity.

Table 2 Simple Correlations Between the Brachial-Ankle Pulse Wave Velocity and Other Variables

Variable	r	p
Age (y)	0.512	<0.001
BMI (kg/m ²)	-0.130	0.148
WC (cm)	0.050	0.577
SBP (mmHg)	0.526	<0.001
DBP (mmHg)	0.298	0.001
TG (mmol/L)	0.067	0.461
TC (mmol/L)	0.139	0.122
HDL-C (mmol/L)	0.145	0.106
LDL-C (mmol/L)	0.082	0.361
FPG (mmol/L)	0.213	0.017
OGTT, 1-h Plasma Glucose (mmol/L)	0.407	<0.001
OGTT, 2-h Plasma Glucose (mmol/L)	0.202	0.024
Fasting Insulin (uIU/mL)	-0.042	0.639
OGTT, 1-h Insulin (uIU/mL)	-0.070	0.436
OGTT, 2-h Insulin (uIU/mL)	0.114	0.204
HOMA-IR	0.006	0.949

Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment insulin resistance.

level from the OGTT maintained an independent association with baPWV ($\beta=23.129$, 95% CI: 8.142–38.115, $p=0.003$, $R^2=0.036$) (Table 3).

Discussion

The results of the present study showed that baPWV was increased in subjects with type 2 diabetes. The baPWV is the pressure wave conduction velocity generated by each pulse ejection of the heart and propagated along the wall of the aorta. The faster the baPWV, the worse the dilation and elasticity of the artery. The baPWV can quickly and accurately evaluate the stiffness of the arterial system, and can be used for the early detection of arterial vascular lesions. It is a traditional and noninvasive comprehensive index for assessing the degree of atherosclerosis.¹⁸ The results of this study suggested that type 2 diabetes subjects without macroangiopathy already have early arteriosclerosis. The level of baPWV was also higher in the pre-diabetes group, but there was no statistical difference. This may be due to the small sample size of this study.

As expected, fasting and post-load plasma glucose levels were also higher in subjects with type 2 diabetes. Fasting and post-load plasma glucose levels were correlated with baPWV, but the association between 1-hour post-load plasma

Table 3 Multiple Linear Regression Analyses for Brachial-Ankle Pulse Wave Velocity (Stepwise Method)

Model	Unstandardized Coefficient B	Std. Error	Standardized Coefficient B	t	p	95% CI	R ²	VIF
(Constant)	278.943	177.047		1.576	0.118	-71.627 to 629.513		
SBP (mmHg)	6.598	1.004	0.469	6.574	<0.001	4.611 to 8.585	0.276	1.245
Age (y)	6.120	1.778	0.256	3.442	0.001	2.599 to 9.640	0.419	1.348
OGTT, 1-h Plasma Glucose (mmol/L)	23.129	7.569	0.213	3.056	0.003	8.142 to 38.115	0.455	1.186

Note: Dependent Variable: brachial-ankle pulse wave velocity.

Abbreviations: SBP, systolic blood pressure; OGTT, oral glucose tolerance test.

glucose level and baPWV was the strongest. These results are consistent with previous studies. Two studies had reported that fasting and 2-hour post-load plasma glucose levels were correlated with baPWV in univariate regression analyses, but was not in multivariate regression analyses.^{12,16}

Both blood pressure and age are important determinants of baPWV.^{19,20} SBP and age were positively correlated with baPWV. Subjects with type 2 diabetes had higher age and SBP. Multivariate regression models showed that 1-hour post-load plasma glucose level was independently associated with baPWV after adjusting for these confounding factors, and 3.6% of the total variance of baPWV was due to 1-hour post-load plasma glucose.

Intermittent hyperglycemia can induce oxidative stress²¹ and increased expression of adhesion molecules,²² which can promote the adhesion of monocytes to arterial endothelial cells and thicken the intima media of the artery, leading to atherosclerosis. Several studies have reported that elevated 1-hour post-load plasma glucose levels obtained during an OGTT in people with normal glucose tolerance are associated with baPWV.^{13,14} Similar to previous studies, this study also found that 1-hour post-load plasma glucose level is a predictor of arterial stiffness in subjects with different glucose tolerance.

This study had several limitations. First, the sample size was small, especially in the type 2 diabetes group. So we could not analyze the association between 1-hour post-load plasma glucose and baPWV stratified by different glucose tolerance status. Second, smoking status of participants was not determined in this study. Hence, we could not evaluate the impact of smoking on the arterial elasticity.

In summary, the present study demonstrated that early arterial stiffness is present in patients with type 2 diabetes. Moreover, elevated 1-hour post-load plasma glucose level is closely associated with the change of arterial elasticity in type 2 diabetes.

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Disclosure

The authors report no relevant conflicts of interest in this work.

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