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One-Hour Hyperglycaemia is Associated with Coronary Artery Disease in Chinese Subjects

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Abstract

Objective: To investigate the association between 1-h OGTT glucose ≥ 11.1 mmol/L and the severity of Coronary Artery Disease (CAD) in Chinese patients.

Methods: Coronary angiography and standard 75 g OGTT were performed on 120 patients with coronary artery disease. The severity of CAD was assessed by using Gensini score.

Results: After adjustments for age and gender, the Gensini scores of NGTN were lower than that of any other group (P<0.05). The levels of Lipoprotein-α (Lp-α), glycohemoglobin (HbA1C), C-Reactive Protein (CRP) and Uric Acid (UA) were lower in NGTN groups than those of NGT1H (P<0.05), while the Area Under the Curve of glucose (AUCg) of NGT1H was larger than those of NGTN (P<0.05). The Insulinogenic Index (IGI) of NGT1H and DM1H was found to be lower than that of NGTN and of DMN, respectively (P<0.05), however there was no significant difference between NGTN and NGT1H, IGRN and IGR1H respectively as far as Oral Glucose Insulin Sensitivity (OGIS) was concerned. In a linear stepwise regression analysis model, both 1 h glucose and 2 h glucose showed significant positive correlations with Gensini scores (P<0.05).

Conclusion: One-hour hyperglycaemia is associated with coronary artery disease and may be a risk factor for coronary artery disease in Chinese subjects.

Keywords: Type 2 Diabetes mellitus; Coronary artery disease; Coronary angiography; Atherosclerosis; 1-hour hyperglycemia

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Introduction

Decreased insulin sensitivity and beta cell dysfunction are the two main contributors to the progression of type 2 diabetes. Now it is generally believed that type 2 diabetes is risk equivalent to the coronary artery disease [1], and lower insulin sensitivity is closely associated with the cardiovascular disease [2], however, few studies investigate the role of beta cell function failure in the pathogenesis of atherosclerosis.

Unlike Pima Indians, Mexican Americans and Caucasians, impaired insulin secretion is being considered as more important factor in Asian subjects than insulin resistance in the pathogenesis of type 2 diabetes [3-5], and we also have found it is the same with Chinese subjects [6]. According to the study we performed before, Chinese subjects with 1-h plasma glucose ≥ 11.1 mmol/L have impaired early insulin release function instead of aggravated insulin resistance [7].

To clarify whether beta cell dysfunction is associated with the progression of atherosclerosis, we compared metabolic and angiographic profiles in a group of Chinese subjects.

Methods

Subjects

A population of 120 subjects of Han ethnicity in China, aged 61.47 ± 10.44 years was recruited between October 2008 and November 2009 from patients referred to the department of cardiology of Shanghai East Hospital Affiliated to Tongji University for emergent coronary angiography. The study was designed and performed in compliance with the ethics regulations of the Helsinki Declaration. All participants had not previously been diagnosed with coronary artery disease or diabetes or any type of Impaired Glucose Regulation (IGR) and were free of signs of hepatic, renal or malignant disease. Subjects were excluded for any of the following reasons: Prior gastrectomy, taking any medication known to affect glucose metabolism, or prior diagnosis of other endocrine

disease known to alter glucose metabolism (e.g., thyroid, adrenal, pituitary, gonadal, etc.). We measured participants' standing height (cm) and weight (kg) without shoes in light clothing. Blood pressure was measured in the right arm three times by auscultation using a mercury manometer, and the average of the last two measurements was used for analysis. We obtained institutional review board approval and informed consent from all participants before the study.

Oral glucose tolerance test and coronary angiography

An OGTT was performed in all 120 subjects according to the WHO standard [8]. After a 12 h overnight fasting, subjects ingested a solution containing 75 g of dextrose and venous blood samples were collected at 0, 30, 60, 120 and 180 min for the determination of plasma glucose and insulin.

Normal Glucose Tolerance (NGT) was defined as having a Fasting Plasma Glucose (FPG) of <5.6 mmol/L and a 2-h plasma glucose of <7.8 mmol/L. We stratified persons with NGT into two groups: NGT with 1-h OGTT glucose of <11.1 mmol/L, which defined the normal 1-h OGTT glucose (NGTN); NGT with 1-h OGTT glucose of ≥ 11.1 mmol/L (NGT1H). IGR was defined as having either FPG ≥ 5.6 and <7.0 mmol/L or 2-h plasma glucose >7.8 and <11.1 mmol/L. IGR was further stratified into two groups: IGR with 1-h OGTT glucose <11.1 mmol/L (IGRN) and IGR with 1-h OGTT glucose ≥ 11.1 mmol/L (IGR1H) [7]. DM was defined as having either FPG ≥ 7.0 mmol/L or 2-h plasma glucose ≥ 11.1 mmol/L [9]. DM was further stratified into two groups: DM with 1-h OGTT glucose <11.1 mmol/L (DMN) and IGR with 1-h OGTT glucose ≥ 11.1 mmol/L (DM1H).

Cardiac catheterization was performed according to the standard method. After intracoronary injections of isosorbide dinitrate, angiograms were obtained in 2 or more views. The severity of coronary atherosclerosis is defined by the Gensini score [10].

Biochemical assays

Blood samples for measurements of Uric Acid (UA), Total Cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), Lipoprotein-α (Lp-α), High-Density Lipoprotein Cholesterol (HDL-C), Triglyceride (TG), Glycosylated Hemoglobin (HbA1c) and C Reactive Protein (CRP) levels were collected after an overnight fast. Plasma glucose was assayed by an automated glucose oxidize method. All measurements were performed from one laboratory.

Calculations and statistical analysis

The Area Under the Curve of glucose (AUCg) during OGTT was calculated using the trapezoidal method [11]. An OGTT-based insulin sensitivity (Oral Glucose Insulin Sensitivity, OGIS) index was calculated by a model-derived equation as OGIS=f (G0, G 120, G180, I0, I120, D0), where G and I are glucose and insulin concentrations (subscripts represent time point or OGTT) and D0 is the oral glucose dose (g/m^2 body surface area). The function f is very complex, so OGIS was implemented on a spreadsheet according to Mari [12]. Insulin secretion was estimated by the Insulinogenic Index as IGI= (Ins30–Ins0)/ (Glu30–Glu0) [13]. The formulas for the HOMA model are as follows:

Insulin resistance (HOMA-IR) = (fasting insulin (FI) × FPG)/22.5, and β-cell function (HOMA-B) = (20 × fasting insulin (FI))/(FPG–3.5) [14].

Data were log transformed and expressed as mean ± SD. We used ANCOVA to compare differences between groups in means and the Bonferroni test to assess differences between selected groups. Adjustment for age and sex was made in all analyses. Correlation between Gensini score and cardio-metabolic variables were studied after adjusted for age and gender. In order to evaluate the contribution of variables to the severity of Coronary Artery Disease (CAD), stepwise multivariate linear regression analysis was performed. The statistical significance level was set at P<0.05.

Results

Comparison of clinical profiles of Chinese patients after adjustment for age and gender, by 1-h OGTT glucose

Table 1 showed that after adjustments for age and gender, the levels of Lipoprotein-α (Lp-α), glycohemoglobin (HbA1C), C-Reactive Protein (CRP) and Uric Acid (UA) were found lower in NGTN groups than those of NGT1H (P<0.05), while the Area Under the Curve of glucose (AUCg) of NGT1H was larger than that of NGTN (P<0.05). The Insulinogenic Index (IGI) of NGT1H and DM1H was found to be lower than those of NGTN and of DMN, respectively (P<0.05), however there was no significant difference between NGTN and NGT1H, IGRN and IGR1H respectively as far as Oral Glucose Insulin Sensitivity (OGIS) was concerned. Homeostasis model assessment for Insulin Resistance (Homa-IR) of NGTN was lowest in all groups, while that of DMN was highest (P<0.05). No differences in homeostasis model assessment for beta cell function (Homa-B) were found among all these groups. The Gensini scores of NGTN were lower than that of any other group (P<0.05).

Correlations between Gensini scores and cardio-metabolic factors

Table 2 showed that 1 h glucose, 2 h glucose, TC, LDL-C and CRP were positively correlated with Gensini scores after adjusted for age, gender and BMI, while the level of HDL-C was negatively correlated with Gensini scores.

The independent contribution of fasting, 1-h, 2-h postload plasma glucose and other atherosclerosis risk factors to Gensini score

To estimate the independent contribution of fasting, 1-h or 2-h postload plasma glucose to Gensini score, a stepwise multivariate regression analysis was performed in a model also enrolling age, gender, BMI, systolic and diastolic blood pressure, TG, HDL-C, IGI, OGIS and CRP levels. We found five factors remained significantly associated with Gensini scores. These variables respectively were age (P<0.01), BMI (P<0.01), 1-h glucose (P=0.04), 2-h glucose (P=0.02) and CRP (P=0.02).

Discussion

In this study we found that NGT subjects with 1 h hyperglycemia has much severer coronary atherosclerosis than NGT subjects with 1 h glucose <11.1 mmol/L, and the levels of atherosclerosis risk factors like Lp-α, UA and CRP were higher in the former than those in the latter respectively. We also found early insulin release function of NGT1H subjects was lower than that of NGTN, while there was no difference between these two groups in OGIS.

In fact, several studies have shown that a cutoff point of 155 mg/dL for the 1-h postload plasma glucose during the Oral Glucose Tolerance Test (OGTT) is able to identify subjects with NGT at high-risk for future type 2 diabetes [15,16]. Whether these subjects also have an increased risk for atherosclerotic cardiovascular disease is still unknown [17]. Several studies using coronary angiogram have shown an association between hyperinsulinemia and the severity of coronary

Table 1: Comparison of clinical profiles of Chinese patients after adjustment for age and gender, by 1-hour OGTT glucose.

	NGTN	NGT1H	IGRN	IGR1H	DMN	DMH
Age (years)	65 ± 3.37	62 ± 5.86	65.28 ± 2.12	66.58 ± 4.75	64.63 ± 3.64	65.21 ± 2.73
Male (female)	17 (9)	4 (2)	20 (9)	7 (5)	6 (2)	19 (15)
BMI (kg/m^2)	23.25 ± 0.45	25.97 ± 0.82a	24.42 ± 0.23	25.49 ± 0.92	26.48 ± 0.78	25.18 ± 0.41
CRP (mg/L)	3.99 ± 1.01	4.36 ± 1.54a	4.99 ± 1.27ab	8.02 ± 1.12abc	5.26 ± 1.49abc	5.97 ± 1.02abc
Uric Acid (umol/L)	327 ± 29.74	367 ± 36.91a	362.38 ± 31.66a	385.23 ± 37.95a	360.33 ± 40.32a	368.96 ± 33.06a
TC (mmol/L)	4.56 ± 0.21	4.52 ± 0.48	4.78 ± 0.19ab	4.82 ± 0.26ab	4.60 ± 0.23ab	4.94 ± 0.14abe
TG (mmol/L)	1.47 ± 0.13	1.58 ± 0.57	1.55 ± 0.33	2.18 ± 0.40abc	2.60 ± 0.84abc	2.16 ± 0.19abce
LDL-C(mmol/L)	1.14 ± 0.34	1.09 ± 0.21	1.15 ± 0.36	1.02 ± 0.19	1.02 ± 0.33	1.10 ± 0.17
Lp-α (nmol/L)	282.48 ± 32.96	436.67 ± 33.57a	387.29 ± 40.10ab	364.8 ± 40.34ab	355.87 ± 29.88abc	381.73 ± 26.97abe
HDL-C (mmol/L)	1.14 ± 0.54	1.09 ± 0.31	1.15 ± 0.42	1.02 ± 0.37	1.02 ± 0.48	1.10 ± 0.30
SBP (mmHg)	134.76 ± 1.91	131.33 ± 2.27	130.31 ± 1.74	141.33 ± 2.35abc	140.63 ± 2.43abc	140.71 ± 1.77abc
DBP (mmHg)	80.28 ± 1.46	81.67 ± 2.32	77.59 ± 2.45ab	82.17 ± 1.87c	79.5 ± 1.55abcd	82.77 ± 2.01ace
HbA1C (%)	5.73 ± 0.13	6.075 ± 0.23a	6.09 ± 0.46a	6.01 ± 0.22a	6.05 ± 0.34a	6.08 ± 0.10a
AUCg (mmol/L/180 min)	6.53 ± 0.34	7.60 ± 0.42a	8.17 ± 0.53ab	9.46 ± 0.50abc	10.18 ± 0.43abcd	11.56 ± 0.49abcde
Homa-IR	1.79 ± 0.21	1.85 ± 0.13	1.76 ± 0.09	2.42 ± 0.14abc	4.37 ± 0.36bcd	3.05 ± 0.22abcd
Homa-B	1.93 ± 0.03	2.03 ± 0.05	1.97 ± 0.32	1.94 ± 0.07	2.24 ± 0.05	1.95 ± 0.02
IGI (mU/mmol)	17.35 ± 2.32	14.96 ± 2.76a	12.24 ± 1.99ab	10.67 ± 2.30abc	12.39 ± 3.13abd	10.58 ± 1.87abe
OGIS (ml/min/m^2)	486.71 ± 38.67	488.39 ± 60.08	391.85 ± 46.80a	376.49 ± 312.05a	301.19 ± 27.43a	358.79 ± 42.15abcde
Gensini Score	19.86 ± 2.31	33 ± 2.89a	29.08 ± 3.56a	35.69 ± 2.42a	38.06 ± 3.01a	50.75 ± 3.49abcde

Data are means ± SD, a: P<0.05 *vs.* NGTN, b: P<0.05 *vs*. NGT1H, c: P<0.05 *vs.* IGRN, d: P<0.05 *vs.* IGR1H, e: P<0.05 *vs*. DMN. BMI: Body Mass Index; TG: Plasma Triglycerides; TC: Plasma Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density-Lipoprotein Cholesterol; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; AUCg: Area Under the Curve of Glucose; IGI: Insulinogenic Index; OGIS: Oral Glucose Insulin Sensitivity; NDA: Number of Diseased Arteries

Table 2: Correlations between Gensini scores and cardio-metabolic factors.

	Partial regression coefficient	*P*
Age (years)	0.42*	<0.001
BMI (kg/m^2)	0.29#	<0.001
SBP (mmHg)	0.21	0.33
DBP (mmHg)	0.14	0.21
FBG (mmol/L)	0.11	0.15
1 h glucose (mmol/L)	0.13	0.01
2 h glucose (mmol/L)	0.27	0.03
TC (mmol/L)	0.23	0.05
TG (mmol/L)	0.17	0.36
HDL-C(mmol/L)	-0.22	0.04
LDL-C (mmol/L)	0.25	0.03
UA (mmol/L)	0.14	0.56
CRP	0.16	0.001

All analyses of correlation have been performed after the adjustment of gender, age and BMI, except for age and BMI. BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TG: Plasma Triglycerides; TC: Plasma Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density-Lipoprotein Cholesterol; UA: Uric Acid; CRP: C Reactive Protein. *Adjusted for gender and BMI. # Adjusted for age and gender

artery disease, however almost all the studies included patients with IGT or DM [18,19]. Numerous studies suggest that an increase in postprandial plasma glucose levels in non-diabetic patients is a strong predictor of cardiovascular events [20,21].

The mechanism by which elevated 1-h postload plasma glucose levels are associated with increased risk for both type 2 diabetes and atherosclerosis is undefined. A greater degree of insulin resistance in these subjects is one possibility accounting for both the progression of diabetes and development of atherosclerosis [22]. Accordingly, we observed that NGT subjects with 1-h postload plasma glucose ≥ 11.1 mmol/L have worse beta cell function as compared with NGT individuals with 1-h postload plasma <155 mg/dL. In addition, chronic sub-clinical inflammation could be a unifying mechanistic factor because it is a precursor of cardiovascular disease, and precedes development of type 2 diabetes [23]. Among plasma markers of inflammation, the most reliable and accessible for clinical use is CRP. We found that NGT subjects with 1-h postload plasma glucose ≥ 11.1 mmol/L have increased CRP levels as compared with NGT individuals with 1-h postload plasma <11.1 mmol/L. An elevation in CRP may be an indicator of systemic inflammation but may be also directly involved in the pathogenesis of both atherosclerosis and type 2 diabetes. Moreover, acute hyperglycemia in response to oral glucose load suppresses endothelium-dependant vasodilatation, activates thrombosis, and increases oxidative stress, all of which are processes involved in atherogenesis.

The present findings showing a link between postload hyperglycemia and cardiovascular risk may have clinical implications [24]. It has been reported that, in subjects with type 2 diabetes, maximal incremental increase in blood glucose occurring within 1h after a meal showed a stronger correlation with carotid IMT than other markers of glycemic control such as HbA1c, fasting and 2-h post-meal blood glucose levels [25]. Taken together, these data suggest that the subjects with 1-h hyperglycemia may bear much severer cardiovascular disease.

Some limitations should be acknowledged in the interpretation of our results. OGTTs were performed once, thus intra-individual variation in plasma glucose levels cannot be taken into account. In

addition, the results are only based on Chinese subjects, and different findings might be obtained in other ethnic groups. Finally, the cross-sectional design of the study precludes the definition of casual relationships.

In conclusion, our data suggested that 1-h hyperglycemia may be a risk factor for CAD in Chinese subjects, which may be caused by the impairment of early insulin release function.

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