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Association of vascular risk factors with increasing glycemia even in normoglycemic subjects in an older Chinese population: the Guangzhou Biobank Cohort Study

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Abstract

Hyperglycemia increases cardiovascular disease risk, but the association between increasing glycemia and cardiovascular risk factors, angina, and coronary heart disease in normoglycemic subjects is less clear, particularly in Chinese. We report on possible associations in a large group of Mainland Chinese subjects. A total of 10 400 older subjects (≥ 50 years) were recruited, and vascular risk factors were measured, including anthropometry, blood pressure, and fasting plasma biochemical factors including glucose, lipid profile, and C-reactive protein (CRP). Subjects were categorized by glycemic status, and the relationship between glycemia and cardiovascular risk factors was investigated using analysis of variance and multiple linear regression analyses. Tertiles of fasting glucose levels showed a clear positive relationship with cardiovascular risk factors including age, obesity, blood pressure, lipid levels, and CRP ($P < .001$ for all). The overall prevalence of self-reported vascular disease was low, but significantly associated with increasing glycemia. Multiple regression showed that waist circumference (standardized regression coefficient $\beta = .10$, $P < .001$), triglycerides ($\beta = 0.16$, $P < .001$), CRP ($\beta = 0.06$, $P < .001$), female sex ($\beta = .03$, $P = .007$), high-density lipoprotein cholesterol ($\beta = -.02$, $P = .016$), and mean arterial pressure ($\beta = .06$, $P < .001$) were independently associated with fasting glucose levels. Among the normoglycemic subjects (n = 5190), increasing glycemia was still associated with increasing obesity indices, systolic blood pressure, triglyceride, and CRP levels (all $P < .05$). Increasing glycemia, even in the reference range, is associated with increasing prevalence of vascular risk factors. Control of these risk factors, particularly obesity, the most important avoidable independent determinant of glycemia in normoglycemic subjects, is critical to reduce the risk of the associated vascular disease.

1. Introduction

Type 2 diabetes mellitus is closely associated with micro- and macrovascular diseases, the major causes of morbidity and mortality in these patients [1-3]. Patients with type 2 diabetes mellitus have a 2- to 3-fold increased risk from cardiovascular disease than those without diabetes [1,3]. It has been reported that diabetic patients may have a similar risk for a first myocardial infarction as nondiabetic patients with a history of myocardial infarction experiencing a secondary event [4]. There is increasing evidence that patients with impaired fasting glucose (IFG) also experience increased risk of cardiovascular disease complications [5-7]. Studies have reported a similar prevalence of vascular risk factors in subjects with IFG as with postload impaired glucose tolerance [5], but others have suggested that impaired glucose tolerance may be more strongly related to vascular disease [8]. However, the strongest evidence comes from the Asia Pacific Cohort Collaboration, the data from which would suggest that there is an increase in mortality from at least a fasting glucose level of 4.9 mmol/L [6], well within accepted levels of normoglycemia. The Expert Committee on the Diagnosis and Classification of

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Diabetes Mellitus of the American Diabetes Association recently reduced the lower limit for IFG from 6.1 to 5.6 mmol/L [9]. Overall though, there are limited data to suggest that the risk from glycemia, which is a continuous variable, may begin below the current diagnostic levels for IFG or diabetes. We have previously shown an independent contribution of increasing glycemia within the reference range to worsening brachial arterial endothelial function and carotid intima-media thickening [7]. However, that study group included Chinese subjects from several countries and may thus have limited external validity. Furthermore, not all studies have identified the increase in carotid intima-media thickening with glucose in the reference range [10]. In the current study, we examine the relationship between increasing levels of fasting glycemia on cardiovascular disease and its risk factors in a group of older Mainland Chinese subjects in a rapidly developing city in Southern China.

2. Methods

The Guangzhou Biobank Cohort Study is a 3-way collaboration between the Guangzhou People's 12th Hospital, Guangzhou, China, and the universities of Hong Kong, Hong Kong, and Birmingham, UK. The hospital specializes in occupational health, and they have all the facilities of a general medium-sized hospital and an infrastructure for occupational health surveillance for workers of many factories and employees of some service industries.

In developed countries, physician registrations are often used as the sampling frame for studies similar to the present one. In developing countries the infrastructure to facilitate such studies is much less readily available, so the community social and welfare association "The Guangzhou Health and Happiness Association for the Respectable Elders" aligned with the provincial government was chosen as a sampling frame because it is a large association with branches throughout Guangzhou, and its membership is open to anyone for a nominal, discretionary fee of 48 Yuan (US$6) per month. It has a citywide network with around 100 000 members, approximately 9% of the Guangzhou older population. All the willing male and female subjects were randomly recruited from the association's membership list of eligible subjects. About 5% of eligible subjects refused to participate, with less than 1% of females and about 10% of males refusing. The male volunteers were less willing to participate because of a cultural unwillingness to give blood because of an associated loss of *shung qi* ("life energy") or as a result of job commitments. There were also more women than men in the older population because of the longer life expectancy. Generally, however, most of the subjects were keen to participate as they could receive free health examinations. However, we only included those who were capable of consenting to the study, ambulatory, and not receiving treatment modalities, which if omitted may result in immediate life-threatening risk, such as chemotherapy or radiotherapy for cancer or dialysis for renal failure. Those with less immediate risk, such as those with a history of vascular disease or associated risk factors including diabetes and hypertension, were not excluded from the study. The study has received ethical approval from the Guangzhou Medical Ethics Committee of the Chinese Medical Association, Guangzhou, China. All subjects gave written informed consent before participating in the study. The 10 400 subjects included in this study form the baseline data of the first recruitment phase of the Guangzhou Cohort Study, which plans to examine environmental and genetic determinants of a number of chronic diseases in an older southern Chinese population from Guangzhou, the major city in southern China with a population of 6.7 million people.

It is a prospective study that will recruit approximately 30 000 older subjects (aged $\geq$50 years). During 2003 to 2004, the subjects received a full medical checkup including measurement of blood pressure, obesity indices, ECG, lung function, and chest x-ray. Each subject was screened for a range of fasting biochemical parameters, including cardiovascular risk factors (lipids: total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, apolipoprotein [apo] A-I, apoB); glucose; C-reactive protein (CRP); renal, liver, and cardiac function; and a detailed blood cell count. A detailed questionnaire was applied to assess exposure to air pollutants, occupational exposures, family and personal disease histories, cognitive function, and lifestyle including dietary and physical activity habits (International Physical Activity Questionnaire [11]). Self-reported smoking (smoker: consumed at least 1 cigarette per day or 7 cigarettes per week for at least 6 months) and alcohol (drank regularly more than 1 time per month) consumption (never/ever) histories were also collected. Validation of the questionnaire was performed 6 months into recruitment by recalling 200 randomly selected subjects for reinterview. The κ values were as follows: 0.66 for self-reported vascular disease, 0.96 and 0.88 for the 2 questions on smoking status, 0.60 for drinking, 0.90 for education, and 0.80 for occupation. Plasma and live leukocytes are stored under liquid nitrogen for long-term preservation, with additional plasma samples stored at -80°C. The leukocytes will subsequently be immortalized to produce a long-term source of genetic material and cells for further investigations.

Subjects were considered hypertensive if their systolic and/or diastolic blood pressures were 140/90 mm Hg or higher, or if they reported they were receiving blood pressure–lowering drugs [12]. Subjects were classified as having a normal glycemic profile if their fasting plasma glucose was less than 5.6 mmol/L. Diabetes was classified as a fasting glucose of 7.0 or higher, or if they reported that they were receiving hypoglycemic medication, whereas IFG in the nondiabetic patients was classified as fasting glucose between $\geq$5.6 and $<$7.0 mmol/L [9,13]. Dyslipidemia was classified as either fasting plasma triglycerides of

≥2.3 mmol/L and/or total cholesterol of ≥6.2 mmol/L or between 5.2 and 6.2 mmol/L with a total cholesterol–HDL-C ratio of higher than 5.0, or if they reported they were receiving treatment to lower lipid concentrations [14,15]. General obesity was classified as a body mass index of 25.0 kg/m^2 or higher, and central obesity as a waist circumference of 80 cm or more in females or 90 cm or more in males [16]. The National Cholesterol Education Program Adult Treatment Panel III guidelines [15] classify individuals as having the metabolic syndrome if they possess 3 or more of the following criteria: (*a*) high blood pressure: if their systolic and/or diastolic blood pressures were 130/85 mm Hg or higher, or were receiving blood pressure–lowering drugs; (*b*) hyperglycemia: fasting plasma glucose was 6.1 mmol/L or higher (110 mg/dL), or were receiving glucose-lowering drugs; (*c*) hypertriglyceridemia: fasting plasma triglycerides of 1.69 mmol/L or higher (150 mg/dL); (*d*) low HDL-C: fasting HDL-C of less than 1.04 or 1.29 mmol (40 or 50 mg/dL) in males and females, respectively; (*e*) central obesity: waist circumference of more than 88 or 102 cm in females and males, respectively. However, we also present the prevalence using the World Health Organization Western Pacific Region Asian criteria for central obesity as described above [16].

There were 5190 subjects without IFG or diabetes who were categorized by tertiles of their fasting glucose concentrations. As glucose concentration was recorded to only 1 decimal place and had a relatively narrow range, significant numbers of subjects were recorded as having the same glucose concentrations and were categorized within the same tertile, and, as such, the numbers within the tertiles varied. Data from normally distributed parameters were presented as mean ± SD, whereas skewed data were logarithmically transformed and expressed as geometric mean with 95% confidence intervals. Analysis of variance was used to determine differences in continuous variables between the tertile groups. The χ^2 test was used to determine differences in the prevalence rates of the categorical variables between the tertile groups.

Sex was coded 0 and 1 for male and female, respectively. The variables included in the analyses were linearly related to the dependent variables. For the multiple regression, age, sex, mean arterial blood pressure, waist circumference, weight and waist change since 18 years of age, HDL-C, LDL-C/apoB ratio, triglycerides, CRP, exercise activity (International Physical Activity Questionnaire), family history of vascular disease, job history, education, and smoking and alcohol histories were included in the analyses

Table 1
Biochemical and anthropometric parameters, prevalence of morbidity, and treatment in 10400 Chinese subjects with normoglycemia, IFG, and diabetes

Parameters	Normoglycemia	IFG	Diabetes	*P*
N = 10400	1 (n = 5190)	2 (n = 3645)	3 (n = 1565)	
Age (y)	63.9 (63.7-64.0)	63.7 (63.5-63.9)	64.6 (64.3-64.9)	<.001
Sex (% female)	70.1	69.6	74.5	.008
Fasting glucose (mmol/L)	5.16 (5.15-5.18)	6.07 (6.05-6.10)	8.30 (8.24-8.36)	<.001
Body mass index (kg/m^2)	23.3 (23.2-23.4)	24.2 (24.1-24.3)	24.7 (24.5-24.9)	<.001
Waist circumference (cm)	79.2 (79.0-79.4)	81.7 (81.5-82.0)	83.9 (83.5-84.3)	<.001
Systolic blood pressure (mm Hg)	131.5 (130.9-132.1)	136.3 (135.6-137.0)	141.5 (139.4-142.6)	<.001
Diastolic blood pressure (mm Hg)	74.2 (73.9-74.5)	76.2 (75.8-76.6)	76.4 (75.8-76.9)	<.001
Mean arterial pressure (mm Hg)	93.3 (92.9-93.7)	96.2 (95.7-96.6)	97.8 (97.1-98.4)	<.001
Total cholesterol (mmol/L)	5.78 (5.75-5.81)	5.88 (5.85-5.92)	5.86 (5.79-5.90)	<.001
HDL-C (mmol/L)	1.69 (1.68-1.70)	1.68 (1.69-1.70)	1.66 (1.64-1.67)	.001
ApoA-I (mmol/L)	1.57 (1.56-1.58)	1.54 (1.53-1.55)	1.50 (1.48-1.52)	<.001
LDL-cholesterol (mmol/L)	2.98 (2.96-2.99)	3.03 (3.01-3.05)	3.04 (3.01-3.07)	<.001
ApoB (mmol/L)	1.07 (1.06-1.08)	1.10 (1.09-1.11)	1.12 (1.11-1.13)	<.001
LDL-C/apoB ratio	2.82 (2.81-2.83)	2.80 (2.78-2.81)	2.75 (2.72-2.77)	<.001
Triglyceride (mmol/L)	1.29 (1.27-1.31)	1.48 (1.46-1.51)	1.73 (1.69-1.77)	<.001
CRP (mg/L)	2.64 (2.57-2.70)	2.77 (2.69-2.86)	3.11 (2.97-3.26)	<.001
Obesity (body mass index, %)	27.9 (26.6-29.2)	39.0 (37.5-40.6)	44.1 (41.7-46.4)	<.001
Weight gained since 18 y old (%)	71.3 (70.1-72.6)	77.1 (75.6-78.5)	80.4 (78.2-82.6)	<.001
Obesity (waist circumference) (%)	35.3 (34.0-36.5)	47.1 (45.6-48.6)	56.8 (24.5-59.2)	<.001
Waist increased since 18 y old (%)	51.8 (50.2-53.5)	63.2 (61.3-65.2)	68.2 (65.2-71.2)	<.001
Hypertension (%)	43.0 (41.6-44.3)	52.3 (50.7-53.9)	64.3 (61.9-66.7)	<.001
Hypertension treatment (%)	25.8 (24.6-27.0)	31.4 (29.9-32.9)	48.0 (45.7-50.2)	<.001
Dyslipidemia (%)	41.2 (40.3-43.0)	49.0 (47.5-50.6)	73.6 (70.9-76.4)	<.001
Dyslipidemia treatment (%)	5.0 (4.4-5.7)	5.9 (5.1-6.7)	14.9 (13.6-16.1)	<.001
NCEP metabolic syndrome (%)	4.7 (3.8-5.7)	19.3 (18.2-20.4)	50.4 (48.7-52.0)	<.001
NCEP metabolic syndrome, Asian waists (%)	11.1 (10.0-12.2)	31.1 (29.8-32.4)	66.5 (64.5-68.5)	<.001
Self-reported myocardial infarction (%)	0.25 (0.09-0.41)	0.35 (0.16-0.55)	0.72 (0.42-1.02)	.024
Self-reported vascular disease (%)	5.7 (5.1-6.4)	6.5 (5.7-7.3)	7.8 (6.6-9.0)	.010

Data are expressed as age- and sex-adjusted mean (95% confidence intervals), or age- and sex-adjusted mean prevalence, or percentage (95% confidence intervals), except for age and sex. Normoglycemia and IFG were defined as fasting plasma glucose of <5.6 or between ≥5.6 and <7.0 mmol/L, respectively, and diabetes as ≥7.0 mmol/L or receiving hypoglycemic medication. NCEP indicates National Cholesterol Education Program.

to determine independent determinants of fasting glucose concentrations. The appropriateness of the regression model was judged from the Durbin-Watson statistic (testing for serial correlation of adjacent error terms) and partial plots of the residuals. The tolerance and variance inflation factors were taken as measures of colinearity, with low tolerance and high variance inflation factors being signs of colinearity, indicating that a variable should not be included in the model. There was no evidence to suggest that sex confounded the relationships between vascular risk factors and glucose levels; therefore, only combined sex analyses, adjusted for age and sex, are presented. The Statistical Package for the Social Sciences (SPSS for Windows, version 11.0.1, 2001, SPSS, Chicago, IL) was used for all the analyses.

3. Results

Of the 10400 Chinese subjects recruited into the study, 1565 (15.1%) subjects were found to have diabetes based on the fasting glucose concentrations, with an additional 3645 (35.0%) having IFG levels. There was a small (0.7 years) clinically insignificant, but statistically significant nonlinear increase in age between the normoglycemic and the diabetic subjects (Table 1). Similarly, there was a 4.4% increase in the proportion of females. All of the conventional (blood pressure, lipids, obesity indices) and newer risk factors (LDL-C/apoB ratio, C-reactive protein) significantly increased with increasing glycemia. In addition, the treatment and prevalence of hypertension and dyslipidemia, and central and general obesity increased with glucose concentration. A total of 74.8% of the subjects had had at least a 5-kg weight increase since the age of 18 years, and 58.3% had had a significant increase in waist circumference. Subjects with diabetes had the highest prevalence of having gained weight or girth (Table 1). The overall prevalence of self-reported vascular disease was low at only 6.3%. Increasing levels of glycemia from normal levels, IFG, to those defined as diabetes were associated with an increase in the self-reported prevalence of all vascular disease (Table 1).

There were 5190 subjects who had normal glucose levels (<5.6 mmol/L) based on the new American Diabetes Association guidelines [9]. When they were categorized into tertiles based on fasting glucose levels, several vascular risk factors continued to be associated with increasing glycemia even within the reference range. Systolic blood pressure significantly increased, as did the indices of general and central obesity, and the prevalence of the metabolic syndrome (Table 2). Triglyceride levels also increased, but not the other lipid parameters.

Table 2
Biochemical and anthropometric parameters, prevalence of morbidity, and treatment in 5190 non-IFG or nondiabetic Chinese subjects grouped by tertiles of increasing fasting glucose levels

Parameters (%)	Tertiles of increasing fasting glucose levels			*P*
N = 5190	1 (n = 1593)	2 (n = 1728)	3 (n = 1869)	
Fasting glucose (mmol/L), range	4.78 (4.77-4.78), 2.5-5.0	5.21 (5.20-5.22), 5.1-5.3	5.50 (5.49-5.51), 5.4-5.6	<.001
Age (y)	64.0 (63.7-64.3)	63.9 (63.6-64.2)	63.8 (63.5-64.0)	NS
Sex (% female)	69.7	70.4	70.1	NS
Body mass index (kg/m^2)	22.9 (22.7-23.0)	23.4 (23.2-23.5)	23.5 (23.4-23.7)	<.001
Waist circumference (cm)	78.3 (77.9-78.7)	79.5 (79.1-79.9)	79.8 (79.4-80.2)	<.001
Systolic blood pressure (mm Hg)	130.3 (129.2-131.3)	131.8 (130.8-132.8)	132.3 (131.3-133.3)	.015
Diastolic blood pressure (mm Hg)	73.9 (73.3-74.4)	74.3 (73.8-74.8)	74.5 (73.9-75.0)	NS
Mean arterial pressure (mm Hg)	92.7 (92.0-93.4)	93.5 (92.8-94.1)	93.7 (93.1-94.3)	.081
Total cholesterol (mmol/L)	5.75 (5.70-5.80)	5.77 (5.72-5.82)	5.81 (5.76-5.86)	NS
HDL-C (mmol/L)	1.70 (1.69-1.72)	1.69 (1.67-1.71)	1.68 (1.67-1.70)	NS
ApoA-I (mmol/L)	1.55 (1.53-1.57)	1.58 (1.56-1.60)	1.57 (1.55-1.59)	NS
LDL-C (mmol/L)	2.97 (2.94-3.00)	2.98 (2.95-3.01)	2.98 (2.95-3.01)	NS
ApoB (mmol/L)	1.07 (1.06-1.08)	1.06 (1.05-1.07)	1.07 (1.06-1.08)	NS
LDL-C/apoB ratio	2.81 (2.78-2.83)	2.84 (2.81-2.86)	2.82 (2.79-2.84)	NS
Triglyceride (mmol/L)	1.25 (1.22-1.28)	1.29 (1.26-1.32)	1.33 (1.30-1.36)	.001
CRP (mg/L)	2.77 (2.65-2.90)	2.56 (2.45-2.67)	2.58 (2.48-2.69)	.021
Obesity (body mass index, %)	24.5 (22.3-26.7)	29.1 (27.0-31.3)	29.6 (27.6-31.5)	.002
Weight gained since 18 y old	67.0 (64.7-69.3)	73.5 (71.3-75.7)	73.0 (70.9-75.2)	<.001
Obesity (waist circumference, %)	32.0 (29.7-34.3)	36.2 (34.0-38.4)	36.7 (34.6-38.8)	.006
Waist increased since 18 y old	45.9 (42.9-48.9)	54.1 (51.2-57.1)	54.9 (52.1-57.7)	<.001
Hypertension	40.1 (37.7-42.5)	42.7 (40.4-45.0)	45.5 (43.3-47.7)	.005
Hypertension treatment	23.9 (21.8-26.1)	25.2 (23.1-27.2)	27.8 (25.9-29.8)	.024
Dyslipidemia	39.3 (4.2)	41.4 (3.4)	41.7 (3.7)	NS
Dyslipidemia treatment	5.2 (4.2-6.3)	4.7 (3.7-5.7)	5.2 (4.2-6.2)	NS
NCEP metabolic syndrome	3.7 (2.6-4.7)	4.7 (3.7-5.7)	5.6 (4.6-6.5)	.035
NCEP metabolic syndrome, Asian waists (%)	9.1 (7.5-10.6)	10.5 (9.0-12.0)	13.2 (11.8-14.6)	<.001
Self-reported vascular disease	5.8 (4.7-7.0)	5.5 (4.4-6.6)	5.9 (4.8-6.9)	NS

Data are expressed as age- and sex-adjusted mean (95% confidence intervals), or age- and sex-adjusted mean prevalence, or percentage (95% confidence intervals), except for age and sex. NS indicates nonsignificant.

C-reactive protein levels were highest in the lowest glucose tertile group and appear to demonstrate a "J-shaped" relationship with glucose concentrations. The proportion of those whose weight or girth had significantly increased since 18 years of age also increased (Table 2).

Multiple regression analyses identified the following independent determinants of fasting glucose concentrations: waist circumference (standardized regression coefficient β = .11, $P < .001$), triglycerides (β = .17, $P < .001$), CRP (β = .06, $P < .001$), female sex (β = .04, $P < .001$), HDL-C (β = −.02, P = .020), and mean arterial pressure (β = .06, $P < .001$) in the total group (R^2 = 0.07, F = 88.5, $P < .001$). In the normoglycemic subjects alone, multiple regression analyses identified the following independent determinants of fasting glucose concentrations: waist circumference (β = .05, P = .025), triglycerides (β = .04, P = .033), ever smoker (β = −.04, P = .015), waist change since 18 years of age (β = .06, P = .004), and CRP (β = −.05, P = .008) (R^2 = 0.01, F = 4.2, $P < .001$).

4. Discussion

Increasing fasting glucose concentrations after categorization of the subjects into normoglycemia, IFG, and diabetes groups were associated with a concomitant increase in all of the vascular disease risk factors in this study including obesity indices, blood pressure, adverse lipid profile, and the metabolic syndrome. In addition, although the overall prevalence was low, there was also a significant increase in the prevalence of self-reported vascular disease with increasing glycemia. The strong relationship between glucose concentrations in the diabetic range and vascular disease has been well described in Western, and increasingly in Chinese, populations [2,4,17,18].

Glycemia can have direct detrimental effects on the cardiovasculature. Even modest levels of glucose can lead to the accumulative formation of advanced glycation end products, which alter the structure and function of macromolecules [19]. These end products are responsible for a range of effects, including quenching nitric oxide, and contributing to oxidative stress and inflammatory processes [19,20]. Glycation end products, which undergo receptor-mediated endocytosis into vascular endothelial and smooth muscle cells, have been associated with atherogenesis, even in normoglycemic subjects [20]. The mechanism whereby increasing glucose acts as a determinant of vascular disease may be mediated through the formation of these products, which may then disrupt homeostasis of endothelial and smooth muscle cells promoting vascular disease.

Even after exclusion of those subjects with diabetes or glucose intolerance by the fasting glucose the linear increment in a number of concomitant vascular risk factors, blood pressure, triglyceride concentrations, the prevalence of the metabolic syndrome, and all the anthropometric parameters consistently increased with increasing glycemia within the reference range. Our data show clearly that, as with other biologic parameters, the risk associated with glucose levels is a continuum. Although on an individual level the increase in risk is limited, on a population basis, the associated increase, for instance in central obesity, metabolic syndrome, and hypertension of approximately 4% to 5%, may have a significant detrimental impact on population health, particularly in older groups such as those included in this study [21]. Prevention or treatment of risk factors, such as obesity or hypertension, to reduce the associated vascular risk is therefore of great importance.

Central adiposity, as measured by waist circumference, incorporates both visceral and subcutaneous abdominal fat, and is closely associated with a range of cardiovascular risk factors and the development of insulin resistance [22,23]. It has been proposed that centrally deposited fat is metabolically more active than that in the periphery and is more sensitive to catecholamine-induced lipolysis, but less sensitive to the antilipolytic actions of insulin [24,25]. Increased free fatty acid production with the subsequent rise in triglyceride concentrations is associated with a reduction in insulin clearance, increased gluconeogenesis, and insulin resistance, the latter by reducing skeletal muscle glucose uptake [24-26]. Central obesity appears to be an important underlying factor predisposing to the development of metabolic syndrome components in Chinese populations [27,28]. Waist circumference and triglycerides were significantly and independently associated with increasing glycemia. Obesity, and the associated insulin resistance, is therefore a major predisposing factors to the development of hyperglycemia, as well as other cardiovascular risk factors, such as hypertension, elevated triglycerides, and reduced HDL-C concentrations, which constitute the constellation of risk factors termed the *metabolic syndrome* [16,28,29], all of which were independently associated with glycemia. Elevated triglycerides and reduced HDL-C are important predictors of coronary heart disease, particularly in patients with the metabolic syndrome [30]. Previously, we also observed an increase in small dense LDL-C particles as indicated by the decrease in LDL-C/apoB ratio [26]. These particles are highly atherogenic after glycation or oxidation, with uptake leading to foam cell formation [26,31]. The dyslipidemia associated with glycemia and central obesity can therefore contribute to the increased vascular disease reported in the present study.

Systemic inflammation, as described by CRP, has been reported to be an integral component of the atherogenic process [26,32]. C-reactive protein increased significantly in the glucose intolerant groups compared with the normoglycemic subjects, but overall appeared to exhibit a J-shaped relationship with glucose concentrations. C-reactive protein also appears to be a proinflammatory cytokine that directly contributes to atherogenesis [26]. Hepatic CRP is closely related to central obesity, and particularly visceral fat depots, mediated through adipocyte production of interleukin 6 [33], further supporting the interactive nature of the

metabolic syndrome components and their contribution to vascular disease [26].

The determinants incorporated in the regression models only identified a small proportion of the variance in glucose levels. In part, this is a consequence of the complexity and in-built redundancies of the control mechanisms that maintain glucose balance, whereby the actions of certain determinants may be offset by compensatory changes, such as initially as obesity and insulin resistance increases, potential hyperglycemia is offset by augmented insulin secretion. Other studies have shown that measurements taken at multiple time points, for instance, glycosylated hemoglobin, improve prediction of vascular disease [34], highlighting the chronic fluctuating nature of regulatory homeostatic mechanisms.

We recognize that our subjects are unlikely to be completely representative of the older population of Guangzhou, and in common with any older study population in a developing country, they are strongly selected survivors. Thus, it could be inappropriate to infer population prevalences from this study. However, investigation of relationships within the study will only be biased if the probability of inclusion within the study varies according to the outcome of interest within levels of a determinant [35], that is, if the data are not missing at random, which is unlikely. With regard to survivorship, from an imaginary birth cohort in Guangzhou in the 1930s and 1940s we are missing those who died of childhood infections, of widespread famine in the late 1950s, those who died in adulthood, and those who migrated to Hong Kong. Thus, the reasons for survival into this cohort are heterogeneous, and there is no reason to think that any of these groups would have been more or less susceptible to the effects of glycemia on other vascular risk factors. Moreover, if survivorship were an issue, we might expect different relationships in the older than the younger subjects, which was not apparent. We also did not have the resources to measure insulin levels, which limits our interpretation of the contribution of insulin resistance to the interrelationship between increasing glycemia and vascular risk.

In summary, there was a close relationship between a number of vascular risk factors, particularly waist circumference and triglycerides, and glycemia even in normoglycemic subjects. These data support a close interrelationship between these risk factors associated with the metabolic syndrome with a potential underlying role for central obesity. Weight control is therefore important if the development of glucose intolerance is to be delayed or prevented.

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