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Impact of impaired fasting glucose and impaired glucose tolerance on arterial stiffness in an older Chinese population: the Guangzhou Biobank Cohort Study–CVD

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Abstract

The aim of the study was to compare the impact of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) on vascular function among older Chinese people. A random sample of 671 men and 603 women aged 50 to 85 years without known diabetes from the Guangzhou Biobank Study–CVD was examined in a cross-sectional study. Subjects with no previously confirmed or treated diabetes but with both fasting plasma glucose less than 5.6 mmol/L and 2-hour glucose from 7.8 to less than 11.0 mmol/L were classified as having isolated IGT, and those with no previously confirmed and treated diabetes but with both fasting plasma glucose from 5.6 to less than 7.0 mmol/L and 2-hour glucose less than 7.8 mmol/L were classified as having isolated IFG. A total of 11.0% of the men and 8.6% of the women had isolated IFG, and 17.7% of the men and 18.6% of the women had isolated IGT. The brachial-ankle pulse wave velocity and pulse pressure were increased in both the isolated IFG and isolated IGT subjects compared with the normoglycemia group (both Ps < .001). Compared with subjects with isolated IFG, those with isolated IGT appeared to have a higher age- and sex-adjusted brachial-ankle pulse wave velocity (1543 ± 22 vs 1566 ± 17, P = .07) and to be more insulin resistant (2-hour postload insulin: 54.2 ± 2.13 vs 26.8 ± 2.99 μU/mL, P < .001), had a worse lipid profile (apolipoprotein [apo] B: 1.07 ± 0.02 vs 0.97 ± 0.02g/L, P < .001; apo B/apo A-1 ratio: 0.80 ± 0.02 vs 0.69 ± 0.02, P < .001), but had lower glycosylated hemoglobin levels (6.03% ± 0.06% vs 5.86% ± 0.04%, P < .001) (values are mean ± SE). Subjects with isolated IGT had greater arterial stiffness, probably as a result of being more insulin resistant, with a worse lipid profile than those with isolated IFG. The sole use of fasting glucose level to identify prediabetic people would fail to identify a significant proportion of the at-risk population.

1. Introduction

China is one of the countries with the largest number of diabetic patients [1], and the number is estimated to increase from 20.8 million in 2000 to 42.3 million by 2030 [2]. The World Health Organization estimates that diabetes, heart disease, and stroke together will cost about $555.7 billion in lost income in China over the next 10 years. Both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are intermediate states of abnormal glucose regulation, which increase the risk of developing diabetes and associated vascular disease [3,4].

Although the 2 glucose-intolerant states have been associated with an increased risk for cardiovascular diseases, the differences between them remain unclear [5,6]. Previous studies conducted in Western countries have shown that cardiovascular risk factors may be more strongly related to IGT than IFG, and insulin resistance may partially account for this observation [5,7]. Increasing evidence has suggested that isolated IFG and isolated IGT have different etiologies [7,8]. Few studies in China have reported the different risk factor patterns between IFG and IGT. A small recent study

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from Shanghai, China, showed that the obese subjects with IGT had a similar pattern of insulin resistance to those with IFG, but those with IFG and combined IFG and IGT had a more prominent deficiency in insulin secretion than subjects with IGT [9]. The 2000 International Collaborative Study of Cardiovascular Disease in Asia reported that the prevalence of IFG was about 7.3% in 15 838 randomly selected Chinese aged 35 to 74 years [10]. The Hong Kong Cardiovascular Risk Factor Study reported that, among 2769 Hong Kong residents aged 25 to 74 years, 568 had nondiabetic hyperglycemia, of whom 49.5% had isolated IGT and 30.5% had isolated IFG; isolated IGT was more strongly related to obesity-related determinants; and isolated IFG appeared to particularly relate to early life development [11]. However, these studies did not assess the relative impact of the different hyperglycemic states on vascular function, which we now report from a Chinese community-based population.

2. Methods

2.1. Subjects

The Guangzhou Biobank Cohort Study (GBCS) is a 3-way collaboration among the Guangzhou No. 12 Hospital, China; the University of Hong Kong; and the University of Birmingham, United Kingdom. The study aims to examine environmental and occupational factors, and genetic and lifestyle determinants of common chronic diseases. We recruited about 30 000 older (>50 years) subjects from Guangzhou in southern China. Details of subject recruitment have been reported elsewhere [12]. A random sample of 1996 subjects were selected from 10 027 subjects from phase 3 of the GBCS during November 2006 to September 2007 for a more detailed substudy (GBCS-CVD) on cardiovascular and diabetes risk factors and outcomes, of which 1303 had an oral glucose tolerance test (OGTT) performed [13]. Sixty-three subjects with self-reported previously diagnosed type 1 or type 2 diabetes mellitus or on antihyperglycemic medication were excluded. Six hundred three women and 671 men who had data on fasting and 2-hour post–glucose-load glucose and insulin levels and glycosylated hemoglobin (HbA_{1c}) were selected into the present analysis. 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.

2.2. Measures

All subjects completed a detailed questionnaire for assessing their medical and family histories of cerebral and cardiovascular diseases, hypertension, and diabetes, and their lifestyle factors such as alcohol drinking, smoking history, and physical activity using the International Physical Activity Questionnaire (inactive/minimally active/active [vigorous activity at least 3 days a week, achieving at least 1500 MET minutes per week; activity on 7 days of the week achieving at least 3000 MET minutes per week]) [14]. Blood pressure was taken in triplicate in a seated position using an automated sphygmomanometer. Pulse pressure, as a crude measure of arterial stiffness, was calculated as the difference between systolic blood pressure and diastolic blood pressure. Fasting plasma glucose, insulin, and lipid profiles were measured in the Clinical Laboratory of the Guangzhou No. 12 Hospital using standardized procedures. Glycosylated hemoglobin was measured using enzyme-linked immunosorbent assay (DiaSTAT Hemoglobin A_{1c} Program; Bio-Rad Laboratories, Hercules, CA; normal values up to 6.5%). Two hours after drinking 75 g anhydrous dextrose dissolved in 250 to 300 mL of boiled water, plasma glucose (OGTT) and insulin were measured again.

Brachial-ankle pulse wave velocity (baPWV) was measured in the supine position after 5 minutes of bed rest using an automatic waveform analyzer (BP-203RPE; Colin Medical Technology, Komaki, Japan), an automated recording device that calculated the time delay between 2 pulse waves recorded simultaneously. This device stored data of the waveforms of both brachium and ankles for a sampling time. The time interval between the wave front of the brachial waveforms and the waveforms of the ankles was automatically measured, which was defined as ΔT. The distance of each segment (La − Lb) was automatically calculated based on the patient's height. Afterward, baPWV was calculated using the following equation: baPWV (in centimeters per second) = (La − Lb)/ΔT. The mean of the left and right baPWV (average baPWV) was obtained from all subjects and used in the analysis.

Based on the American Diabetes Association diagnostic criteria for diabetes mellitus, subjects were classified into 5 groups [15]: (1) subjects with no previously confirmed or treated diabetes but with fasting plasma glucose of 7.0 mmol/L or higher or with 2-hour glucose of 11.1 mmol/L or higher were classified as newly diagnosed or as having unknown diabetes (unknown DM); (2) subjects with no previously confirmed or treated diabetes but with both fasting plasma glucose less than 5.6 mmol/L and 2-hour glucose from 7.8 to less than 11.0 mmol/L were classified as having isolated IGT; (3) subjects with no previously confirmed and treated diabetes but with both fasting plasma glucose from 5.6 to less than 7.0 mmol/L and 2-hour glucose less than 7.8 mmol/L were classified as having isolated IFG; (4) subjects with both IFG and IGT were classified as IFG + IGT; and (5) the remainder with both fasting plasma glucose less than 5.6 mmol/L and 2-hour glucose less than 7.8 mmol/L were classified as normoglycemic (normal fasting glucose [NFG] + normal glucose tolerance [NGT]). All the unknown DM cases in the present study had type 2 diabetes mellitus. Glycosylated hemoglobin was used to assess long-term glycemic level. The homeostasis model assessment of insulin resistance

(HOMA-IR) was calculated as fasting insulin × fasting glucose/22.5; and HOMA-β cell function, as fasting insulin × 20/(fasting glucose − 3.5) [16].

All data analyses were conducted using Stata/SE 8.0 (Stata, College Station, TX). Statistical significance was set at a 2-tailed P value of < .05. Pearson χ^2 test was performed for analyzing categorical variables. Analysis of covariance was used for assessing continuous variables with adjustment of sex (male/female) and age (years). Regression models were performed to assess the trends from NFG/NGT to IFG to IGT to unknown DM for selected risk factors with adjustment of age and sex, and the results are presented with P for trend (Table 2).

3. Results

Table 1 shows that the prevalence of IFG, IGT, and unknown DM increased with age in both men and women. More subjects had IGT than IFG in both men and women for all age groups. The prevalence of DM increased with decreasing levels of physical activity. Otherwise, the demographic and lifestyle parameters were similar among the 5 groups. Compared with the NFG + NGT group, isolated IFG and isolated IGT both had higher levels of the traditional vascular risk factors, including body mass index (BMI), waist circumference, triglycerides, systolic and diastolic blood pressure, HbA_{1c}, and insulin resistance indices, and lower high-density lipoprotein (HDL) cholesterol level. The baPWV and pulse pressure were increased in both the isolated IFG and isolated IGT subjects compared with the normoglycemia group (both Ps < .001) (Table 2). Subjects with isolated IFG had a lower HOMA-β cell function index than the isolated IGT group (0.85 ± 0.04 vs 0.59 ± 0.08, P = .01), and subjects with isolated IGT had higher apolipoprotein (apo) B levels than those with isolated IFG (1.01 ± 0.01 vs 1.07 ± 0.02, P = .002). Compared with subjects with isolated IFG, subjects with isolated IGT had higher low-density lipoprotein (LDL) cholesterol, apo B, apo B/apo A-1 ratio, 2-hour postload insulin, HOMA-β cell function index, and baPWV, and had a lower level of apo A-1 and HbA_{1c} (Table 2).

Table 1
Distribution of unknown DM, IFG, and IGT (number, percentage) by demographic characteristics

	NFG + NGT	Isolated IFG	Isolated IGT	IFG + IGT	Unknown DM
Age (y)					
Men					
50-59	153 (51.9)	26 (8.8)	50 (16.9)	38 (12.9)	28 (9.5)
60-69	147 (50.2)	33 (11.3)	47 (16.0)	34 (11.6)	32 (10.9)
70+	32 (38.6)	15 (18.1)	22 (26.5)	6 (7.2)	8 (9.6)
Total	332 (49.5)	74 (11.0)	119 (17.7)	78 (11.6)	68 (10.1)
Women					
50-59	279 (59.1)	42 (8.9)	87 (18.4)	35 (7.4)	29 (6.1)
60-69	41 (38.0)	8 (7.4)	22 (20.4)	14 (12.9)	23 (21.3)
70+	10 (43.5)	2 (8.7)	3 (13.0)	3 (13.0)	5 (21.8)[a]
Total	330 (54.7)	52 (8.6)	112 (18.6)	52 (8.6)	57 (9.5)
Education					
Primary or below	164 (47.8)	32 (9.3)	67 (19.5)	39 (11.4)	41 (12.0)
Middle school	410 (53.6)	79 (10.3)	134 (17.5)	79 (10.3)	63 (8.2)
College or above	88 (53.0)	15 (9.0)	30 (18.1)	12 (7.2)	21 (12.6)
Smoking					
Never	438 (51.8)	75 (8.9)	164 (19.4)	81 (9.6)	88 (10.4)
Former	82 (47.7)	21 (12.2)	34 (19.8)	19 (11.0)	16 (9.3)
Current	141 (56.9)	29 (11.7)	31 (12.5)	28 (11.3)	19 (7.7)
Drinking					
No	266 (54.3)	39 (8.0)	90 (18.4)	43 (8.8)	52 (10.6)
Yes	395 (50.8)	86 (11.1)	139 (17.9)	85 (10.9)	72 (9.3)
Physical activity					
Active	417 (54.9)	75 (9.9)	133 (17.5)	73 (9.6)	62 (8.2)
Minimally active	175 (48.6)	34 (9.4)	68 (18.9)	44 (12.2)	39 (10.8)
Inactive	49 (44.5)	14 (12.7)	19 (17.3)	9 (8.2)	19 (17.3)[b]

[a] P for χ^2 test < .001.
[b] P for χ^2 test = .05.

4. Discussion

Prediabetic glucose-intolerant states (IFG or IGT) have been identified as important mediators in the development of diabetes [3,4]. However, there is a lack of data describing the prevalence of isolated IFG or IGT in older Chinese adults. Our results showed that IFG and IGT in older Chinese were common. Impaired glucose tolerance, which would be missed in most studies that focused on only fasting hyperglycemia as recommended by some major guidelines [17], was more common than IFG in both men and women. The proportion of isolated IGT reached the peak at 60 to 69 years in women (20.4%) and 70-plus years in men (26.5%). The measurement of postload glucose is essential for the detection of isolated IGT, which is more common by almost 100% than isolated IFG in our older subjects.

Significantly increasing trends were found for most of the conventional risk factors from NFG + NGT to unknown DM, supporting earlier observations that there is already increased vascular risk before the development of overt disease [18,19]. Our study, as with data in Chinese from Hong Kong, has shown that both isolated IFG and isolated IGT groups had similar levels of insulin resistance based on fasting levels, which were elevated compared with those of the normoglycemic group. We have previously shown that those with both forms of glucose intolerance have had poorer fetal development that may contribute to decreased lean muscle mass, the major site of glucose disposal, which may contribute to the relative insulin resistance observed in these groups [11].

When postload parameters were examined, those with isolated IGT were more insulin resistant, by almost 100% as indicated by directly measured 2-hour postload insulin level, than subjects with isolated IFG. The difference was only slightly attenuated after adjusting for demographic factors,

Table 2
Age- and sex-adjusted parameters by diabetes status (mean ± standard error)

	NFG + NGT[0] (n = 662)	Isolated IFG[1] (n = 126)	Isolated IGT[2] (n = 231)	IFG + IGT[3] (n = 130)	Unknown DM[a] (n = 125)	*P* values			
						0 vs 1	0 vs 2	1 vs 2	*P* for trend
BMI (kg/m^2)	22.7 ± 0.1	24.2 ± 0.3	23.8 ± 0.2	24.6 ± 0.3	25.1 ± 0.3‡	<.001	<.001	.22	<.001
Waist circumference (cm)	76.8 ± 0.32	80.9 ± 0.74	80.4 ± 0.55	82.1 ± 0.73	82.9 ± 0.74‡	<.001	<.001	.66	<.001
Total cholesterol (mmol/L)	5.67 ± 0.04	5.70 ± 0.09	5.75 ± 0.07	5.76 ± 0.09	5.91 ± 0.09	.43	.21	.71	.02
HDL cholesterol (mmol/L)	1.61 ± 0.01	1.56 ± 0.03	1.54 ± 0.02	1.43 ± 0.03	1.46 ± 0.03‡	<.001	<.001	.65	<.001
LDL cholesterol (mmol/L)	3.34 ± 0.03	3.26 ± 0.06	3.42 ± 0.04	3.36 ± 0.06	3.48 ± 0.06	.56	.18	.03	.04
Triglyceride (mmol/L)	1.55 ± 0.05	1.76 ± 0.12	2.01 ± 0.09	1.98 ± 0.12	2.70 ± 0.12‡	<.001	<.001	0.11	<.001
Apo A-1 (g/L)	1.43 ± 0.01	1.49 ± 0.03	1.39 ± 0.02	1.39 ± 0.02	1.46 ± 0.03*	.45	.09	.003	.81
Apo B (g/L)	1.01 ± 0.01	0.97 ± 0.02	1.07 ± 0.02	1.06 ± 0.02	1.05 ± 0.02†	.99	.002	<.001	.01
Apo B/apo A-1	0.75 ± 0.01	0.69 ± 0.02	0.80 ± 0.02	0.79 ± 0.02	0.75 ± 0.02	.68	.003	<.001	.09
Systolic blood pressure (mm Hg)	121 ± 1	128 ± 2	128 ± 1	132 ± 2	134 ± 2‡	<.001	<.001	.99	<.001
Diastolic blood pressure (mm Hg)	72.0 ± 0.4	74.8 ± 0.9	75.2 ± 0.7	76.8 ± 0.9	76.9 ± 0.9‡	<.001	<.001	.69	<.001
Pulse pressure (mm Hg)	49.0 ± 0.5	53.4 ± 1.1	53.1 ± 0.8	54.8 ± 1.1	56.8 ± 1.1‡	<.001	<.001	.81	<.001
Fasting plasma glucose (mmol/L)	5.01 ± 0.04	5.91 ± 0.08	5.12 ± 0.06	5.95 ± 0.08	7.24 ± 0.08‡	<.001	<.001	<.001	<.001
2-h OGTT (mmol/L)	6.17 ± 0.06	6.39 ± 0.15	8.78 ± 0.11	9.17 ± 0.15	14.47 ± 0.15‡	<.001	<.001	<.001	<.001
Fasting insulin (μU/mL)	6.05 ± 0.28	7.07 ± 0.65	7.38 ± 0.46	8.90 ± 0.62	9.54 ± 0.66‡	<.001	<.001	.55	<.001
Postload insulin (μU/mL)	23.8 ± 1.0	26.8 ± 3.0	54.2 ± 2.1	49.1 ± 2.9	59.5 ± 3.0‡	<.001	<.001	<.001	<.001
HOMA-IR	1.36 ± 0.07	1.86 ± 0.16	1.68 ± 0.11	2.36 ± 0.15	2.96 ± 0.16‡	<.001	<.001	.37	<.001
HOMA-β cell function	0.85 ± 0.04	0.59 ± 0.08	0.96 ± 0.06	0.74 ± 0.08	0.67 ± 0.08‡	.01	.12	<.001	.21
HbA_{1c} (%)	5.76 ± 0.02	6.03 ± 0.06	5.86 ± 0.04	6.17 ± 0.06	7.01 ± 0.06‡	<.001	.002	<.001	<.001
baPWV (cm/s)	1487 ± 10	1543 ± 22	1566 ± 17	1589 ± 22	1609 ± 23	<.001	<.001	.07	<.001

[a] Analysis of covariance for 5 groups adjusting for age and sex.
* $P < .05$ for 5 groups.
† $P < .01$ for 5 groups.
‡ $P < .001$ for 5 groups.

BMI, waist circumference, and lipids. Consistent with previous findings, our results showed that the β-cell function index was higher in those with IGT than in the IFG group, suggesting a defect in the first phase of glucose-induced insulin secretion in those with IFG [8,20]. In the isolated IGT group, β-cell function index showed no difference from those with normoglycemia. These findings have been used in other studies to indicate that IGT or postload hyperglycemia is the result of increased insulin resistance rather than impaired insulin secretion, whereas fasting hyperglycemia reflects β-cell dysfunction [8,20]. However, this conclusion does not consider the potential differences in insulin resistance at key sites. Studies have suggested that subjects with IFG have resistance to insulin in skeletal muscle, but most importantly in the liver, which prevents suppression of hepatic gluconeogenesis, whereas in the IGT group, skeletal insulin resistance is the predominant form [21]. Glycosylated hemoglobin reflects average plasma glucose over the previous 2 to 3 months and is the criterion standard for assessing glycemic control status in people with diabetes [22]. The elevated level of HbA_{1c} in the IFG subjects supports a greater relative exposure to hyperglycemia in that group relative to the IGT group, which has been observed in other studies [23]. Those with IFG are therefore more likely to be susceptible to glucose-related disorders, such as neuropathy, and microvascular complications including retinopathy.

There has been much debate regarding the relative contributions of insulin resistance and secretion in populations with IGT and IFG [7,20,24,25]. Studies using HOMA as a surrogate estimate of insulin resistance resulted in heterogeneous outcomes including that subjects with IFG have increased insulin resistance [7,24] or decreased insulin secretion [20]. The heterogeneity in these observations may result from the inability of the index to differentiate effectively insulin resistance in the fasting and postprandial state given that, by definition, HOMA is based on fasting glucose and fasting insulin, which do not reflect insulin response or secretion after an oral glucose load. This is despite the good correlation between HOMA and the euglycemic-hyperinsulinemic clamp, which measures whole-body glucose disposal, in population-based studies [26]. Using postload insulin resistance markers would therefore be expected to show that people with IGT are more resistant to the actions of insulin, which we observe here.

The IGT group had significantly worse levels of apo A-1, apo B, apo B/apo A-1 ratio ($P < .01$), and LDL cholesterol ($P = .03$) than the IFG group; but the difference in HDL, although consistent with apo A-1, was not statistically significant. One explanation was the insufficient sample size to detect the small difference in HDL. We reviewed the literature but could not find a biological explanation for the small difference in HDL as compared with other lipid markers. Further studies on large sample size are warranted. Nevertheless, those in the IGT group clearly had a worse lipid profile than the IFG group, including an elevated apo B/apo A-1 ratio, which has been associated with a direct measurement of insulin resistance and to the prevalence of the metabolic syndrome [27]. This

further supports the contention that the IGT group is relatively more insulin resistant. The worse lipid profile in the IGT group may lead to the increased vascular events reported in other studies relative to those with isolated IFG [28,29], although this remains to be confirmed [30]. Our results have also shown a higher level of baPWV, supporting the contention of a higher risk for cardiovascular disease in those with isolated IGT compared those with isolated IFG [31,32], although the difference did not quite reach significance (P = .07) probably because of the relatively small number of observations. Recent studies have indicated that increased arterial stiffness could be a feature of insulin resistance and may act as a possible mechanism for the link between insulin resistance and cardiovascular disease [33]. Increased arterial stiffness predicts the development of cardiovascular disease and mortality in the general population and in type 2 diabetes mellitus patients [34,35].

Although our study was relatively limited in size because of limitations in resources, the subjects were well characterized, enabling the examination of the effects of hyperglycemic status on vascular function, which had not been reported in Chinese previously. The subjects in the present sample were randomly selected from the 10 027 participants of phase 3 of GBCS, and the latter should be reasonably representative of the older and relatively healthy populations in Southern China. The small Cohen effect size comparing this sample and the 10 027 subjects (data not shown) suggests that the present sample should also be quite representative. The use of standardized questionnaires and laboratory methods with specially trained staff for data collection and quality control maintained the quality of the data. However, the limitations of our study should be addressed, particularly in regard to the one-off measurement of the fasting insulin and glucose in our randomly selected population. Because of the cross-sectional nature of our study design, the future impact of IFG and IGT to the vascular function cannot be established.

To conclude, we have shown that there are clear differences between those subjects with isolated IGT compared with those with isolated IFG, suggesting that the former are more insulin resistant with a worse lipid profile, which was associated with worse vascular function. These at-risk subjects would not be identified without performing an OGTT. The worse vascular disease risk factor profile in both glucose-intolerant groups than the normoglycemia group suggests that close monitoring and risk factor reduction are warranted.

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