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Grading effect of abnormal glucose status on arterial stiffness and a new threshold of 2-h post-load glucose based on a Chinese community study

Zhi-Ke Liu[1], Ke-Ye Wu[1], Xiao-Tong Dai[1], Qian-Zi Che[1], Si Chen[1], Jia Jia[2], Jian-Ping Li[2], Yong Huo[2], Yan Zhang[2]*, Da-Fang Chen[1]*

[1]Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, and [2]Department of Cardiology, Peking University First Hospital, Beijing, China

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***Correspondence**
Da-Fang Chen
Tel.: +86-10-8280-2644
Fax: +86-10-8280-2644
E-mail address:
dafangchen@bjmu.edu.cn

Yan Zhang
Tel.: +86-10-8357-2283
Fax: +86-10-8357-2283
E-mail address:
drzhy1108@163.com

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ABSTRACT

Aims/Introduction: To investigate the relationship between various glucose metabolic status and arterial stiffness, and further explore the threshold of blood glucose indices for the risk of arterial stiffness.

Materials and Methods: The present cross-sectional study included 4,851 individuals from a Chinese community. Overnight fasting blood glucose and 2-h post-load glucose were sampled. Arterial stiffness was measured as brachial-ankle pulse wave velocity. The association was examined using generalized linear regression models. The threshold effect was explored using two piecewise linear regression models by the smoothing plot.

Results: After adjustment for covariates, isolated impaired fasting glucose, isolated impaired glucose tolerance, combined glucose intolerance and newly diagnosed diabetes mellitus were associated with a greater risk of arterial stiffness compared with normal glucose tolerance (B = 18.09, 95% confidence interval [CI] 0.42–35.76, $P = 0.045$; B = 28.51, 95% CI: 3.40–53.62, $P = 0.026$; B = 60.70, 95% CI: 38.37–83.04, $P < 0.001$; B = 95.06, 95% CI: 71.88–118.25, $P < 0.001$, respectively). Furthermore, there was a non-linear relationship between 2-h post-load glucose and arterial stiffness. A threshold for 2-h post-load glucose of 6.14 mmol/L was observed for the risk of arterial stiffness.

Conclusions: Impaired fasting glucose, impaired glucose tolerance, combined glucose intolerance and newly diagnosed diabetes mellitus were related to a greater risk of arterial stiffness compared with normal glucose levels. A threshold for 2-h post-load glucose of 6.14 mmol/L probably exists for the risk of arterial stiffness.

INTRODUCTION

Arterial stiffness, an age-related progressive process, is increasingly conceptualizing as a significantly integrated mechanism for the development of parenchymal organs damage, such as the heart, brain and kidney[1]. Pulse wave velocity (PWV) is a most common and robust marker of arterial stiffness, and is associated with an increased risk for vascular damage[2], atherosclerosis[3], and cardiovascular events in diabetes patients and the general population[4]. At present, brachial-ankle PWV (baPWV) is a simple, non-invasive marker of arterial stiffness, and it has been clinically validated[5].

Type 2 diabetes mellitus, as well as prediabetic status, are risk factors for cardiovascular disease and poor prognosis[6,7]. Arterial stiffness is associated with type 2 diabetes mellitus, and is causally involved in the progression of diabetes complications[8,9]. However, the relationship between impaired fasting glucose (IFG), impaired glucose intolerance (IGT) and arterial stiffness remains controversial. For IFG, several studies suggested that baPWV was not linked with IFG[10,11], but an increased risk of baPWV is observed even in high-normal fasting blood glucose (FBG)[12–14]. For IGT, a study reported no significant association

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between IGT and baPWV[15]. Other studies found that IGT increased the risk of baPWV, while either the covariates affecting arterial stiffness were not adjusted[11] or the impact of IGT was not separated from combined glucose intolerance (CGI)[10]. Up to 20–30% of individuals with IGT have IFG[16].

To further clarify the effect of abnormal glucose status *per se* on the risk of baPWV, and explore the glycemic target value for increasing the risk of arterial stiffness, we aimed to assess the relationship between various impaired glucose regulation states and baPWV, and attempted to examine the threshold of fasting blood glucose and 2-h post-load glucose.

METHODS

Study participants

The present cross-sectional study was carried out from December 2011 to April 2012 using the baseline data from a Chinese community-based atherosclerosis cohort. The 9,540 participants were recruited from Gucheng and Pingguaoyuan communities in Shijingshan district of Beijing, China. The study design and selection criteria have been detailed previously[17]. To avert the bias from the atherosclerosis disease, we excluded patients with a history of coronary heart disease, stroke/transient ischemic attack and peripheral arterial disease (ankle-brachial index <0.9; n = 1,410). We also excluded patients with a history of anemia, chronic kidney disease and renal artery stenosis (n = 233). Given the impact of medication on arterial stiffness or blood glucose levels, we did not include the individuals who received an antihypertensive drug, antidiabetic drug and lipid-lowering drug, or had a history of diabetes mellitus (n = 2,768). Furthermore, missing data were deleted: PWV (n = 221), FBG (n = 7), 2-h plasma glucose (2-h PG; n = 47) and ankle-brachial index (n = 3). Finally, 4,851 eligible participants were involved in our analyses. All of them offered written informed consent. The study protocol was approved by the ethics committee of Peking University First Hospital, and it conforms to the provisions of the Declaration of Helsinki.

Data collection

The data were collected by trained research staff according to a standard operation procedure. Participants were interviewed using a standardized questionnaire, such as demographic characteristics, health behavior, and histories of drugs and diseases. Current drinking habit was defined as drinking once per week for at least half of the year. Current smoking habit was defined as current active smokers with one cigarette per day for at least half of the year. Body mass index (BMI) was calculated as weight (kg) / height $(m)^2$. Seated blood pressure was obtained from the right arm with a calibrated sphygmomanometer HEM 7117 device (Omron Healthcare Co. Ltd., Dalian, China) after the participants had rested in the seated position for 5 min in a quiet room. The average was calculated using three consecutive measurements separated by ≥1-min interval. Mean arterial pressure (MAP) was calculated as (systolic blood pressure + 2 × diastolic blood pressure) / 3.

Blood glucose tests

Overnight fasting blood samples after at least 12 h were drawn from the antecubital vein using 4-mL coagulation-promoting vacuum tubes in the morning. Subsequently, the participants underwent a standard 75-g oral glucose tolerance test (or, diabetes mellitus patients consumed a bread equivalent) with 2-h PG sampled. A biochemistry index in plasma, including fasting blood glucose, 2-h post-load glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and total triglycerides (TG) was examined by the automatic biochemical analyzer (Roche-C8000; Roche Co. Ltd., Basel, Switzerland) according to a standard procedure. In line with the American Diabetes Association diagnostic criteria, participants were classified into five groups: (i) normal fasting glucose and normal glucose tolerance (NGT; FBG <5.6 mmol/L and 2-h PG <7.8 mmol/L); (ii) isolated impaired fasting glucose (I-IFG; FBG 5.6–6.9 mmol/L and 2-h PG <7.8 mmol/L); (iii) isolated impaired glucose tolerance (I-IGT; FBG <5.6 mmol/L and 2-h PG 7.8–11.0 mmol/L); (iv) combined glucose intolerance (CGI; FBG 5.6–6.9 mmol/L and 2-h PG 7.8–11.0 mmol/L); and (v) newly diagnosed diabetes mellitus (NDM; FBG ≥7.0 mmol/L or 2-h PG ≥11.1 mmol/L).

Brachial-ankle pulse wave velocity

After 5 min of seated rest in a quiet room, four pneumatic pressure cuffs were placed around the arms and ankles over the skin in the supine position. The baPWV measurement was generated using a non-invasive vascular screening device (BP-203RPE II device; Omron Healthcare, Kyoto, Japan) by a trained technician according to standard procedures. PWV in the bilateral brachial tibial arteries was recorded automatically. The average of the left and right sides was calculated due to the strong correlation between them (r = 0.96, P < 0.001).

Statistical analysis

All data are represented as mean ± standard deviation for continuous variables or proportion for categorical variables. Comparisons of characteristics were made using ANOVA for continuous variables, and the χ^2-test for categorical variables. Generalized linear regression models were applied to assess the association between various glucose metabolic states and baPWV in an unadjusted model, and in an age-, sex-, BMI-, MAP-adjusted model (model 2), and further adjusting for waist-to-hip ratio (WHR), current smoking, current drinking, physical exercise, TG, TC and HDL-C (model 3). P-values for trend among various glucose metabolic states were derived from the generalized linear regression models, assuming equally spaced levels for the five groups. We further applied a two piecewise linear regression model to examine the threshold effect of FBG and 2-h PG on the risk of baPWV by the smoothing plot. An inflection of FBG/2-h PG, at which the relationship between baPWV and FBG/2-h PG began to change and become eminent, was determined using a trial method. The latter was to move the trial inflection point along a

pre-defined interval, and detect the inflection point that gave the maximum model likelihood. The analyses were carried out using SAS 9.3 and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, Massachusetts, USA) and R (http://www.R-project.org). A two-sided *P*-value <0.05 was considered statistically significant.

RESULTS

Characteristics by various glucose metabolic states

Characteristics of the participants by various glucose metabolic states are summarized in Table 1. In the total of 4,851 participants, the mean age was 54.41 ± 8.17 years, and 65.2% were women. NGT, I-IFG, I-IGT, CGI and NDM accounted for 49.66, 20.16, 8.14, 11.32 and 10.72% respectively. Age, sex, BMI, WHR, current smoking, current drinking, SBP, DBP, MAP, TG, TC and HDL-C were statistically significant between the five groups ($P < 0.05$). There was no significant difference for physical exercise ($P > 0.05$).

Effect of various glucose metabolic states on an increased risk of baPWV

The effect of various glucose metabolic states on an increased risk of baPWV from generalized linear regression is presented in Table 2. In the unadjusted model, I-IFG, I-IGT, CGI and NDM were associated with a greater risk of baPWV compared with NGT ($P < 0.001$). In model 2, the regression coefficients attenuated on further adjustment for age, sex, BMI and MAP ($P < 0.05$). In model 3, similar trends were observed, and the association remained statistically significant after adjusting for other covariates (B = 18.09, 95% confidence interval [CI]: 0.42–35.76, $P = 0.045$; B = 28.51, 95% CI: 3.40–53.62, $P = 0.026$; B = 60.70, 95% CI: 38.37–83.04, $P < 0.001$; B = 95.06, 95% CI: 71.88–118.25, $P < 0.001$; respectively). Finally, the baPWV showed a significant and gradual increase from NGT to NDM ($P < 0.001$).

Non-linear relationship between FBG/2-h PG and baPWV

After adjusting for the aforementioned covariates, there was a non-linear relationship between FBG, 2-h PG and baPWV (Figures 1 and 2). The threshold effect of FBG and 2-h PG on the risk of baPWV from piecewise linear regression is presented in Table 3. As FBG was below the inflection point (6.66 mmol/L), the FBG was positively related to baPWV (B = 31.83, 95% CI: 19.08–44.58, $P < 0.001$), and then the regression coefficient attenuated in the participants with FBG ≥6.66 mmol/L (B = 17.22, 95% CI: 8.68–25.77, $P < 0.001$). The baPWV was higher in participants with FBG ≥6.66 mmol/L than the participants with FBG <6.66 mmol/L ($P < 0.001$). When 2-h PG was below the inflection point (6.14 mmol/L), there was no significant association between baPWV and 2-h PG ($P = 0.241$). Whereas in participants with 2-h PG ≥6.14 mmol/L, 2-h PG was associated with a greater risk of baPWV (B = 11.82, 95% CI: 9.33–14.31, $P < 0.001$). The baPWV was higher in participants with 2-h PG

Table 1 | Characteristics by different impaired glucose regulation state

Variable	Total *n* = 4,851	NGT *n* = 2,409	I-IFG *n* = 978	I-IGT *n* = 395	CGI *n* = 549	NDM *n* = 520	*P*
Age (years)	54.41 ± 8.17	53.17 ± 7.95	54.55 ± 7.33	55.72 ± 8.84	56.58 ± 8.48	56.64 ± 8.71	<0.001
Sex (female)	3,165 (65.24)	1,654 (68.66)	580 (59.30)	275 (69.62)	357 (65.03)	299 (57.50)	<0.001
BMI (kg/m^2)	25.51 ± 3.29	24.84 ± 3.09	25.85 ± 3.18	25.68 ± 3.62	26.50 ± 3.42	26.81 ± 3.25	<0.001
WHR (%)	0.89 ± 0.06	0.88 ± 0.06	0.89 ± 0.06	0.90 ± 0.06	0.91 ± 0.06	0.92 ± 0.06	<0.001
Current smoking	976 (20.12)	471 (19.55)	227 (23.21)	56 (14.18)	101 (18.40)	121 (23.27)	<0.001
Current drinking	1,171 (24.14)	524 (21.75)	277 (28.32)	96 (24.30)	133 (24.23)	141 (27.12)	<0.001
Physical exercise (≥3 times per week)	3,775 (77.82)	1,847 (76.67)	780 (79.75)	313 (79.24)	433 (78.87)	402 (77.31)	0.297
SBP (mmHg)	129.40 ± 15.57	126.16 ± 14.52	130.87 ± 15.02	129.20 ± 15.61	134.06 ± 15.67	136.87 ± 16.92	<0.001
DBP (mmHg)	74.43 ± 9.41	73.11 ± 9.17	75.57 ± 9.25	73.88 ± 8.71	75.88 ± 9.46	77.32 ± 10.11	<0.001
MAP (mmHg)	92.75 ± 10.40	90.79 ± 10.08	94.00 ± 10.11	92.32 ± 9.75	95.27 ± 10.23	97.17 ± 10.88	<0.001
TG (mmol/L)	1.54 ± 1.32	1.36 ± 1.26	1.57 ± 1.35	1.63 ± 1.18	1.77 ± 1.12	2.00 ± 1.65	<0.001
TC (mmol/L)	5.37 ± 0.98	5.25 ± 0.93	5.44 ± 0.95	5.39 ± 0.94	5.51 ± 1.02	5.61 ± 1.12	<0.001
HDL (mmol/L)	1.47 ± 0.39	1.53 ± 0.40	1.45 ± 0.38	1.46 ± 0.39	1.40 ± 0.35	1.35 ± 0.36	<0.001

BMI, body mass index; CGI, combined glucose intolerance; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; IFG, isolated impaired fasting glucose; IGT, isolated impaired glucose tolerance; I-IFG, isolated impaired fasting glucose; I-IGT, isolated impaired glucose tolerance; MAP, mean arterial pressure; NDM, newly diabetes mellitus; NGT, normal fasting glucose and normal glucose tolerance; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

Table 2 | Effect of impaired glucose regulation state on increased brachial-ankle pulse wave velocity risk

Variable	Model 1		Model 2		Model 3	
	B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*P*
NGT	Reference		Reference		Reference	
I-IFG	81.13 (58.60–103.66)	<0.001	20.69 (2.96–38.42)	0.022	18.09 (0.42–35.76)	0.045
I-IGT	95.20 (62.94–127.45)	<0.001	34.50 (9.32–59.69)	0.007	28.51 (3.40–53.62)	0.026
CGT	177.28 (149.17–205.38)	<0.001	68.67 (46.32–91.02)	<0.001	60.70 (38.37–83.04)	<0.001
NDM	239.93 (211.20–268.67)	<0.001	108.02 (84.95–131.09)	<0.001	95.06 (71.88–118.25)	<0.001
	$P_{for\ trend}$ <0.001		$P_{for\ trend}$ <0.001		$P_{for\ trend}$ <0.001	

Model 1 is the unadjusted model. Model 2 is adjusted for age, sex, body mass index and mean arterial pressure. Model 3 is adjusted for age, sex, body mass index, waist-to-hip ratio, physical exercise, current smoking, current drinking, mean arterial pressure, triglyceride, total cholesterol and high-density lipoprotein cholesterol. CI, confidence interval; CGI, combined glucose intolerance; IFG, isolated impaired fasting glucose; IGT, isolated impaired glucose tolerance; I-IFG, isolated impaired fasting glucose; I-IGT, isolated impaired glucose tolerance; NDM, newly diabetes mellitus; NGT, normal fasting glucose and normal glucose tolerance.

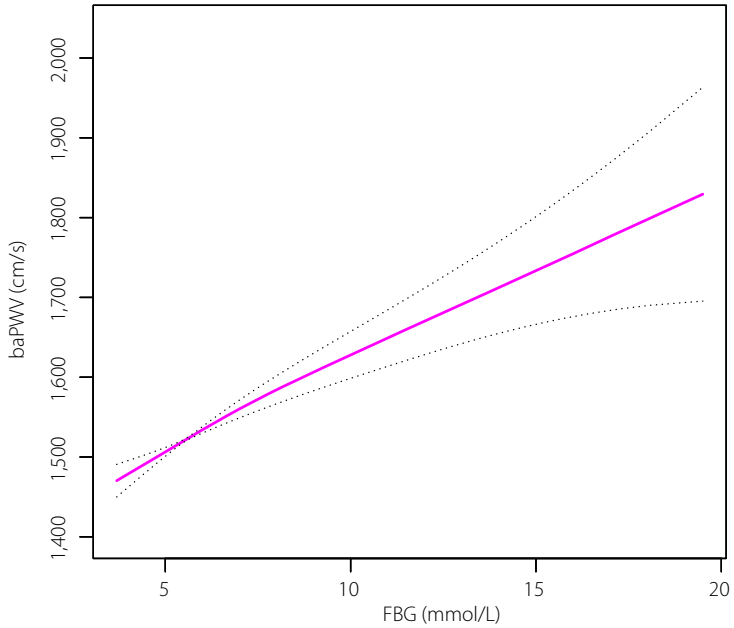

Figure 1 | The non-linear relationship between fasting blood glucose (FBG) and brachial-ankle pulse wave velocity (baPWV) was evaluated after adjusting for confounding factors. The inflection point for FBG of 6.66 existed for the risk of baPWV.

≥6.14 mmol/L than participants with 2-h PG <6.14 mmol/L ($P < 0.001$).

DISCUSSION

We showed that I-IFG, I-IGT, CGI and NDM are associated with a greater risk of baPWV compared with NGT, and a grading effect on baPWV was observed as glucose metabolism deteriorated, independently of age, sex, BMI, WHR, MAP, physical exercise, TG, TC and HDL-C. Furthermore, there was a non-linear relationship between FBG, 2-h PG and baPWV, and a threshold for 2-h PG of 6.14 mmol/L existed for the risk of baPWV.

Several studies have shown that baPWV was higher in individuals with IFG than normoglycemia[14,15,18,19]. However, IFG was accompanied with IGT in nearly half of the participants[16], and these studies did not distinguish the impact of IFG on baPWV from the coexistence of IGT. In contrast, no significant association between isolated IFG and baPWV was observed[10,11]. However, in the present study, isolated IFG increased the risk of baPWV after adjusting for all potential covariates. The discrepancy could be due to the relatively small sample size in the previous studies ($n = 38$, $n = 221$, respectively), and the statistical power was insufficient to estimate the association. The previous studies consistently suggested that IGT increased the risk

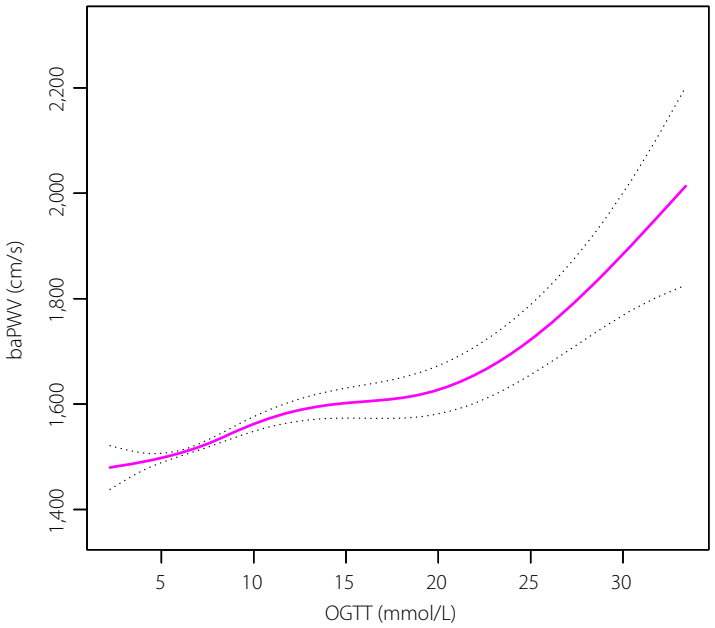

Figure 2 | The non-linear relationship between 2-h post-load glucose and brachial-ankle pulse wave velocity (baPWV) was evaluated after adjusting for confounding factors. A threshold for 2-h PG of 6.14 existed for the risk of baPWV. OGTT, oral glucose tolerance test.

Table 3 | Threshold effect of different blood glucose indices on the risk of brachial-ankle pulse wave velocity using piecewise linear regression

Inflection point of blood glucose indices (mmol/L)	*n*	Adjusted model		
		Mean ± SE	B (95% CI)	*P*
FBG				
<6.66	4,404	1,518.8 ± 3.5	31.83 (19.08–44.58)	<0.001
≥6.66	447	1,588.0 ± 11.4	17.22 (8.68–25.77)	<0.001
2-h PG				
<6.14	1,767	1,503.5 ± 5.8	6.51 (–4.38–17.40)	0.241
≥6.14	3,084	1,537.5 ± 4.3	11.82 (9.33–14.31)	<0.001

Adjusted for age, sex, body mass index, waist-to-hip ratio, physical exercise, current smoking, current drinking, mean arterial pressure, triglyceride, total cholesterol and high-density lipoprotein cholesterol. 2-h PG, 2-h plasma glucose; FBG, fasting plasma glucose; SE, standard error.

of baPWV, whereas Rahman *et al.*[15] only found a borderline significant association, and Li *et al.*[10] failed to separate IGT individuals from CGI. In the present study, we further showed that I-IGT and CGI are related to the risk of baPWV independently of the other covariates. The positive correlation between baPWV and NDM is in line with previous studies[10,11,19]. Finally, there is a grading effect of abnormal glucose state on baPWV from NGT to NDM. Except for baPWV, impaired glucose regulation and diabetes mellitus are also associated with a greater risk of carotid–femoral pulse wave velocity[20,21], and these results are consistent with the present study. The carotid–femoral pulse wave velocity is measured from the carotid and femoral arteries, and is a strong marker of aortic stiffness. The baPWV is measured from the brachial and ankle arteries, and is taken as representative of the central and peripheral arteries[5]. Both of them have a strong correlation with invasively measured aortic PWV, and are closely linked with cardiovascular risk factors and target organ damage[22].

The FBG even within the normal range can increase the risk of arterial stiffening measured as baPWV[14], carotid intima-media thickness and endothelial function[23]. Likewise, the high normoglycemic state without diabetes (FBG >85 mg/dL) had a 1.4-fold risk of cardiovascular death from a 22-year follow-up cohort[24]. In the present study, there was a non-linear relationship between FBG and baPWV. As it was below the inflection point (6.66 mmol/L), FBG was linearly associated with baPWV, and then the regression coefficient attenuated in the participants with FBG ≥6.66 mmol/L. Of the 447 participants with

FBG ≥6.66 mmol/L, 81.66% were diabetes patients and the others had IFG. This could be due to advanced arterial stiffening in the individuals with FBG ≥6.66 mmol/L and the potential biomechanism need to further study. In the present study, the minimum value of FBG was 3.69 mmol/L, and the relationship between hypoglycemia and baPWV should be further investigated. This is the first study to show that there was a threshold of 2-h PG for the risk of baPWV. A 2-h PG <6.14 mmol/L had no relationship to the risk of baPWV ($P = 0.241$), whereas for 2-h PG ≥6.14 mmol/L, there was a significant association between 2-h PG and baPWV. Therefore, it suggested that 2-h PG of 6.14 mmol/L might be a good cut-off point as a precaution for arterial stiffening.

Both advanced glycation end-products and endothelial nitric oxide dysregulation play a critical role in the pathogenesis of arterial stiffness[8]. Advanced glycation end-products are proteins or lipids that become glycated as a result of exposure to hyperglycemia. Advanced glycation end-products could accelerate age-related vascular changes, and lead to the development of cardiovascular events in both diabetic and non-diabetic populations[25–27]. Furthermore, the insulin-resistant state and hyperglycemia could reduce the bioavailability of nitric oxide synthase and increase the production of superoxide, and eventually, that will give rise to arterial stiffness and herald the onset of microvascular changes[28–30].

There were several strengths in the present study, such as the relatively large sample size, community-based population, comprehensive measurement of impaired glucose regulation status and threshold effect analyses. However, limitations are inevitable. First, the cross-sectional design did not allow us to conclude the causal inference about the relationship between impaired glucose regulation and arterial stiffness, and the threshold effects of blood glucose indices. In the future, a cohort study would be warranted. Second, we did not measure the parameters of insulin, and insulin resistance should be taken into consideration in further studies.

In conclusion, IFG, IGT, combined glucose intolerance and NDM are independently related to greater arterial stiffness risk. A threshold for 2-h PG of 6.14 mmol/L might exist for the risk of arterial stiffness.

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DISCLOSURE

The authors declare no conflict of interest.

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