Original Article

Increased Arterial Stiffness in Subjects with Pre-diabetes among Middle Aged Population in Beijing, China*

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Abstract

Objective To investigate the relationship between arterial stiffness and pre-diabetes when assessed by the new glycosylated hemoglobin A_{1c} (HbA_{1c}) 5.7%-6.4% criterion or by impaired fasting glucose in middle aged Chinese.

Methods 1122 adults aged 55 years or younger in the health examination centers for physical check-ups were enrolled in the two large-sized Tertiary Comprehensive Hospitals in Beijing from June 2011 to June 2012 after excluding those who previously had been diagnosed or treated as diabetes or cardiovascular disease. Subjects with a diagnosis of pre-diabetes according to impaired fasting glucose (IFG) (fasting plasma glucose (FPG) levels at 5.6-6.9 mmol/L), HbA_{1c} levels at 5.7%-6.4%, or both, were classified into four groups for observation: (1) Normoglycaemia (HbA_{1c}<5.7% and FPG <5.6 mmol/L); (2) IFG alone (FPG levels at 5.6-6.9 mmol/L and HbA_{1c}<5.7%); (3) HbA_{1c} 5.7%-6.4% alone (HbA_{1c} levels at 5.7%-6.4% and FPG <5.6 mmol/L); and (4) both HbA_{1c} 5.7%-6.4% and IFG (HbA_{1c} levels at 5.7%-6.4% and FPG levels at 5.6-6.9 mmol/L). All subjects were measured for weight, height, waist circumference, blood pressure, fasting plasma glucose, HbA_{1c}, lipid profile and brachial-ankle pulse wave velocity (baPWV).

Results The mean values of baPWV were 1282±8, 1311±10, 1398±30, and 1418±27 cm/s (Mean±SE) in *Normoglycaemia*, HbA_{1c} 5.7%-6.4% alone, IFG alone and the both HbA_{1c} 5.7%-6.4% and IFG groups, respectively. After adjusting for age, gender, blood pressure, BMI and triglyceride, baPWV was significantly higher in subjects with both HbA_{1c} 5.7%-6.4% and IFG compared among the subjects with *Normoglycaemia* (1350±14 *vs.* 1301±6 cm/s, *P*=0.002) and HbA_{1c} 5.7%-6.4% alone (1350±14 *vs.* 1309±8 cm/s, *P*=0.013).

Conclusion Subjects with pre-diabetes exhibited a greater arterial stiffness.

Key words: Pre-diabetes; Vascular stiffness; Arterial stiffness

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INTRODUCTION

Diabetes causes long-term complications affecting eyes, kidneys, and nervous system that could lead to the development of atherosclerosis. High blood glucose in adults with diabetes increases the risk for heart attack, stroke, angina, and coronary artery disease[1-2]. Pre-diabetes, which is thought to place individuals at high risk for developing diabetes according to the

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American Diabetes Association (ADA), is defined as someone's blood glucose levels higher than normal but not high enough to be diagnosed as diabetes[3]. Data from the 2007-2008 China National Diabetes and Metabolic Disorders Study showed that the overall age-standardized prevalence rates of diabetes and pre-diabetes were 9.7% and 15.5%, respectively, suggesting that 92.4 million adults with diabetes and 148.2 million adults with pre-diabetes existed in China[4]. Since the prevalence rates of both diabetes and pre-diabetes were high in China as reported in the said literature, early detection and intervention on diabetic patients as well as pre-diabetes subjects were considered as important public health issue in the public health arena.

Clinical practice guidelines have defined pre-diabetes as either having impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) according to fasting glucose test or 2-h oral glucose tolerance test (2h-OGTT). Glycosylated hemoglobin A_{1C} (HbA_{1C}) is an indirect index which measuring the mean blood glucose over the previous 2-3 months, but not under fasting and considered to be more reliable than fasting glucose[5-7]. Due to the recent advancement of HbA_{1C} measurement, the ADA has updated its screening recommendation for pre-diabetes to include HbA_{1C} as another diagnostic testing option, proposing HbA_{1C} levels from 5.7% to 6.4% to be adopted as one of the diagnostic criteria for pre-diabetes[3,8].

Arterial stiffness refers to the thickening and loss of elasticity of the arterial walls. Measurement of arterial stiffness has been considered as a useful surrogate marker for early-stage atherosclerosis, because it has been associated with various cardiovascular diseases as well as many atherosclerotic risk factors[9]. Among the several noninvasive methods available to assess arterial stiffness, pulse wave velocity (PWV), defined as the speed with which the pulse wave travels along a length of artery, is considered as a reliable and valid index[10-13]. Although the gold standard is measuring the central arterial stiffness via carotid-femoral PWV (cfPWV)[14], it is inconvenient since this technique requires subjects to expose part of their groin region in order for the femoral artery to be accessed[15]. A simple device has recently been developed which allows the measurement of brachial-ankle PWV (baPWV) conveniently using pressure cuffs wrapped around the brachium and ankle. Studies of baPWV are now plentiful and have been conducted in healthy volunteers as well as in patients with diabetes or hypertension[16-18]. BaPWV has been demonstrated to have a close relationship with cfPWV[19-20] and considered as a powerful predictor of cardiovascular disease mortality and all-cause mortality[21-23].

Recently, studies regarding the association between blood glucose and atherosclerosis have focused on the relationship between pre-diabetes and arterial stiffness, but results are less consistent. Shin et al. (2011) and Paik et al. (2012) found the association between IFG and increased baPWV[24-25]. However, Ando et al. (2010) noticed that although subjects with IFG showing a marginal increased baPWV values compared with subjects with normal glucose tolerance, the difference was not significant[26]. Yokoyama et al. (2007) showed that increasing HbA_{1c} was associated with increased baPWV among Japanese type 2 diabetic patients[27], however, Choi et al. (2011) reported the significant association between HbA_{1c} and baPWV was not observed in Korean type 2 diabetic patients[28]. Additionally, studies on the relationship between arterial stiffness and pre-diabetes which used updated criteria including HbA_{1c} for definition were relatively lacking[29].

As prevention of cardiovascular disease remains a major challenge for subjects with impaired glucose regulation or diabetes, it is important to study the association of pre-diabetes with arterial stiffness in order to guide approaches to prevent or delay the development of atherosclerosis in these two populations. In this study, our aim is to investigate the relationship between baPWV (a marker of arterial stiffness) and pre-diabetes when assessed by the existence of either HbA_{1c} levels at 5.7%-6.4% or impaired fasting glucose in a middle aged Chinese population without known cases of diabetes or cardiovascular disease.

METHODS

Study Population

We consecutively recruited 1194 adult subjects aged 55 years or younger who participated in medical check-ups at the health examination centers in two large-sized Tertiary Comprehensive Hospitals in Beijing from June 2011 to June 2012. All subjects participated in the medical check-ups voluntarily. A standardized questionnaire was performed by trained physicians to collect information such as age, gender, self-reported medical history of hypertension,

diabetes, coronary heart disease and stroke. Subjects with previously diagnosed or treated diabetes, stroke or coronary heart disease and who either showed fasting plasma glucose as ≥7.0 mmol/L or HbA1c ≥6.4% were excluded in the analyses[3]. Finally, 1122 subjects involving 800 men and 322 women, between 24 and 55 years of age, with a mean age of 45.3±5.6 years were included in the final analyses. Written informed consent was obtained from each subject for the study, which received ethical approval from Biomedical Ethics Committee of Peking University, Beijing, China.

Clinical Parameter Assessment

Body weight and height were measured with participants wearing light indoor clothing but no shoes in standing position. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured as following: the upper borders of iliac crests were located, and the tape was wrapped around above this point, parallel to the floor, ensuing that it was adjusted without compressing the skin with reading of waist circumference taken at the end of a normal breath. Blood pressure was measured in duplicate in a seated position using an automated sphygmomanometer after resting for more than five minutes. If the readings differed by ≥4 mmHg, a third reading was taken. Mean arterial pressure was calculated as 1/3×(diastolic blood pressure) + 2/3×(diastolic blood pressure).

Venous blood sample was drawn from all subjects after an overnight fast. Plasma glucose was measured using the hexokinase glucose-6-phosphate dehydrogenase method (Type 7600; Hitachi Ltd., Tokyo, Japan). The levels of total-cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides were determined enzymatically using an auto-analyzer (Type 7600; Hitachi Ltd., Tokyo, Japan). HbA_{1c} was measured using High Performance Liquid Chromatography (HPLC) (Bio-Rad Variant II, USA) under standardized procedures. The intraassay coefficient of variation was less than 1% and the interassay coefficient of variation was less than 2%.

Diagnosis of pre-diabetes was based on the new ADA criterion[3] of impaired fasting glucose (IFG) (fasting plasma glucose (FPG) levels at 5.6-6.9 mmol/L) or HbA_{1c} levels at 5.7%-6.4%, or both. Participants were divided into four groups on the basis of diagnosis of pre-diabetes: (1) Normoglycaemia (HbA_{1c} <5.7% and FPG <5.6 mmol/L); (2) IFG alone (FPG levels at 5.6-6.9 mmol/L and HbA_{1c} <5.7%); (3) HbA_{1c} 5.7%-6.4% alone (HbA_{1c} levels at 5.7%-6.4% and FPG <5.6 mmol/L); and (4) both HbA_{1c} 5.7%-6.4% and IFG (HbA_{1c} levels at 5.7%-6.4% and FPG levels at 5.6-6.9 mmol/L).

Vascular Assessment

Brachial-ankle pulse wave velocity (baPWV) was measured by the VP-1000 automatic noninvasive arteriosclerosis measurement system (model BP-203 RPE-II, Colin Co, Ltd, Komaki, Japan) with four pneumatic pressure cuffs that simultaneously measured blood pressure and pulse waves in bilateral brachial and tibial arteries. The validity and reproducibility have been reported previously[39]. The correlation coefficients of interobserver and intraobserver reproducibility were 0.98 and 0.87, respectively. The corresponding coefficients of variation were 8.4% and 10.0%, respectively. Measurements were taken after the subject had a 15 min rest in the supine position in a room with ambient temperature of 22 to 24 °C. Participants were advised to avoid consuming coffee/tobacco for at least 8 h prior to the measurement or vigorous exercise 2 h before the examination. Mean baPWV was used for final analysis because of the significant positive correlation between left and right baPWV (r=0.945, P<0.001).

Statistical Methods

Data analysis was carried out using SPSS 18.0 statistical analysis software (from the original software sharing platform of Peking University). Data from normally distributed parameters were presented as mean±S.D. or mean (95% confidence interval), whereas skewed data were logarithmically transformed and expressed as geometric means with 95% confidences intervals. Categorical variables were presented as frequencies (percentages). Chi-square test and analysis of variance (ANOVA) were used to assess the categorical variables and continuous variables respectively. Continuous variables for which across-group differences were detected underwent *post hoc* pair wise tests (least squares difference test), and analysis of covariance (ANOVA) was used for continuous variables with adjustment of covariates. P value for trend analysis was calculated by using the linear regression models. Multivariate linear regression model was used to identify the independent determinants of baPWV. A two-tailed P value less than 0.05 was considered as statistically significant.

RESULTS

Table 1 shows the demographic and clinical characteristics of the 1122 subjects with normal fasting plasma glucose (NFG) and impaired fasting plasma glucose (IFG) groups. Among them, 946 subjects with NFG were categorized into three groups based on their fasting plasma glucose (FPG) tertiles, the range of FPG for the three groups were 3.60-4.62 mmol/L, 4.63-5.00 mmol/L, and 5.01-5.59 mmol/L, respectively. HbA_{1c}, age, percentage of male, BMI, waist circumference, systolic and diastolic blood pressure, mean artery pressure, total cholesterol, triglyceride, and LDL-C all tended to increase from first to third tertile of the NFG group to IFG group (all *P* values for trend for 4 groups <0.001). Additionally, significantly increasing trends were also found for baPWV, as shown in Table 1, with the mean baPWV values as 1255±181 cm/s, 1297±198 cm/s, 1324±197 cm/s, and 1410±268 cm/s in the four groups, respectively (*P* value for trend for 4 groups <0.001).

As illustrated in Table 2, compared with the *Normoglycaemia* group, after adjusted for gender and age, the pre-diabetes groups all showed having higher levels of traditional cardiovascular risk factors, including BMI, waist circumference, total cholesterol, triglycerides, LDL-cholesterol (*P* values from 0.022 to <0.001). Both HbA_{1c} 5.7%-6.4% alone and the IFG alone group had lower HDL-cholesterol when compared to the *Normoglycaemia* group (*P* values were 0.015 and 0.011 respectively).

Parameters of blood pressure including systolic and diastolic blood pressure as well as mean artery pressure and right side, left side and mean baPWV were significantly lower in *Normoglycaemia* subjects when compared to the IFG alone and both HbA_{1c} 5.7%-6.4% and IFG groups (all *P* values <0.001).

Subjects with IFG alone had increased baPWV and blood pressure, compared with HbA_{1c} 5.7%-6.4% alone group (e.g. $baPWV_{mean}$ 1391 cm/s *vs*. 1299 cm/s, Mean artery pressure 98 mmHg *vs*. 92 mmHg respectively, with both *P* values <0.001).

Subjects with the both HbA_{1c} 5.7%-6.4% and IFG had higher BMI, waist circumference, triglyceride and blood pressure as well as baPWV than the HbA_{1c} 5.7%-6.4% alone group (*P* values from 0.002 to <0.001) (Table 2).

Table 1. Demographic and Clinical Characteristics of 1122 Subjects According to the Fasting Plasma Glucose

	Tertiles of Normal Fasting Plasma Glucose			Impaired Fasting Plasma Glucose	*P*[a]	*P* for Trend
	1st (*n*=316)	2nd (*n*=314)	3rd (*n*=316)	(*n*=176)		
Fasting plasma glucose (mmol/L)	4.38±0.21	4.84±0.11	5.27±0.16	5.99±0.35	<0.001	<0.001
HbA_{1c} (%)	5.41±0.35	5.49±0.35	5.58±0.38	5.71±0.39	<0.001	<0.001
Age (years)	44.3±6.3	45.4±5.5	45.8±5.1	46.2±5.0	<0.001	<0.001
Gender (male %)	63.0	68.8	76.6	81.3	<0.001	<0.001
BMI (kg/m^2)	24.0±3.4	24.6±3.1	25.3±3.3	26.2±3.4	<0.001	<0.001
Waist circumference (cm)	84.4±9.8	85.9±9.6	88.7±9.7	91.4±9.8	<0.001	<0.001
Systolic blood pressure (mmHg)	120±14	121±15	123±15	129±17	<0.001	<0.001
Diastolic blood pressure (mmHg)	75±11	77±10	79±11	83±12	<0.001	<0.001
Mean artery pressure (mmHg)	90±11	92±11	94±12	98±13	<0.001	<0.001
Total cholesterol (mmol/L)	4.85±0.85	5.01±0.96	5.29±1.06	5.38±1.08	<0.001	<0.001
Triglyceride (mmol/L)[§]	1.20 (1.13,1.28)	1.29 (1.21,1.37)	1.50 (1.41,1.60)	1.78 (1.62,1.97)	<0.001	<0.001
HDL-C (mmol/L)	1.34±0.36	1.35±0.36	1.35±0.33	1.28±0.36	0.183	0.177
LDL-C (mmol/L)	3.01±0.71	3.15±0.83	3.40±0.86	3.46±0.85	<0.001	<0.001
$baPWV_{right}$ (cm/s)	1245±187	1293±206	1323±201	1406±264	<0.001	<0.001
$baPWV_{left}$ (cm/s)	1266±182	1300±195	1326±199	1414±278	<0.001	<0.001
$baPWV_{mean}$ (cm/s)	1255±181	1297±198	1324±197	1410±268	<0.001	<0.001

Note. Tertiles of Normal Fasting Plasma glucose, 1st=(3.60-4.62 mmol/L), 2nd=(4.63-5.00 mmol/L), 3rd=(5.01-5.59 mmol/L); Values were shown as mean±standard deviation and percentage (%); [§]values were expressed as geometric means (95% CI); p^a value were calculated using ANOVA.

Table 2. Age and Gender Adjusted Comparison of Clinical Characteristics (Means and 95% CI or Percentage) among Normoglycaemia and Pre-diabetes Groups

	Normoglycaemia[0]	Pre-diabetes			P^*	$P<0.05^{**}$
	(*n*=609)	HbA_{1c} 5.7%-6.4% alone[1] (*n*=337)	IFG alone[2] (*n*=68)	Both HbA_{1c} 5.7%-6.4%[3] and IFG (*n*=108)		
Age (years)	44.4 (43.9, 44.9)	46.5 (45.9, 47.1)	44.9 (43.7, 46.2)	46.9 (46.0, 47.9)	<0.001	a,c,d,f
Gender (% male)	68.0	72.1	80.9	81.5	0.001	----
HbA_{1c} (%)	5.29 (5.27, 5.31)	5.87 (5.84, 5.89)	5.33 (5.27, 5.38)	5.95 (5.90, 5.99)	<0.001	a,c,d,e,f
Fasting plasma glucose (mmol/L)	4.77 (4.74, 4.80)	4.94 (4.90, 4.98)	5.95 (5.86, 6.04)	6.00 (5.92, 6.07)	<0.001	a,b,c,d,e
BMI (kg/m^2)	24.4 (24.1, 24.6)	25.2 (24.8, 25.5)	25.4 (24.6, 26.1)	26.3 (25.7, 26.9)	<0.001	a,b,c,e
Waist circumference (cm)	86.1 (85.3, 86.8)	87.5 (86.5, 88.5)	89.6 (87.5, 91.7)	90.9 (89.1, 92.6)	<0.001	a,b,c,e
Total cholesterol (mmol/L)	4.98 (4.90, 5.06)	5.20 (5.09, 5.30)	5.39 (5.15, 5.62)	5.32 (5.13, 5.51)	<0.001	a,b,c
Triglyceride (mmol/L)[§]	1.29 (1.23, 1.35)	1.42 (1.34, 1.51)	1.63 (1.42, 1.86)	1.74 (1.57, 1.94)	<0.001	a,b,c,e
HDL-C (mmol/L)	1.36 (1.34, 1.39)	1.31 (1.27, 1.34)	1.36 (1.28, 1.44)	1.27 (1.21, 1.34)	0.016	a,c
LDL-C (mmol/L)	3.10 (3.03, 3.16)	3.37 (3.28, 3.45)	3.44 (3.24, 3.63)	3.41 (3.26, 3.57)	<0.001	a,b,c
Systolic blood pressure (mmHg)	122 (120, 123)	122 (120, 123)	129 (125, 132)	128 (125, 130)	<0.001	b,c,d,e
Diastolic blood pressure (mmHg)	77 (76, 78)	77 (76, 78)	82 (80, 85)	82 (80, 84)	<0.001	b,c,d,e
Mean artery pressure (mmHg)	92 (91, 93)	92 (91, 93)	98 (95, 100)	97 (95, 99)	<0.001	b,c,d,e
$baPWV_{right}$ (cm/s)	1288 (1272, 1304)	1294 (1273, 1315)	1389 (1342, 1436)	1386 (1348, 1423)	<0.001	b,c,d,e
$baPWV_{left}$ (cm/s)	1299 (1283, 1315)	1303 (1282, 1324)	1393 (1346, 1440)	1399 (1361, 1436)	<0.001	b,c,d,e
$baPWV_{mean}$ (cm/s)	1294 (1278, 1309)	1299 (1278, 1320)	1391 (1345, 1437)	1392 (1355, 1429)	<0.001	b,c,d,e

Note. All values above were adjusted for age and gender (expect for age and gender); [§]values were expressed as geometric means (95% CI) ; Group [0]: Normoglycaemia; Group [1]: HbA_{1c} 5.7%-6.4% alone; Group [2]: IFG alone; Group [3]: Both HbA_{1c} 5.7%-6.4% and IFG. P^*: *p* for difference among 4 groups by ANOVA; P^{**}: Analysis of covariance and *post hoc* tests: a, 0 versus 1; b, 0 versus 2; c, 0 versus 3; d, 1 versus 2; e, 1 versus 3; f, 2 versus 3.

When multiple linear regression analysis was used to assess factors associated with baPWV, we checked and excluded factors which could have showed multi-collinearity. In Table 3 (Model A) baPWV appeared independently and positively associated with age, systolic blood pressure, fasting plasma glucose, triglyceride, and males. BaPWV was independently and negatively associated with BMI, but was not associated with HDL-C and LDL-C. When BMI was replaced by waist circumference, a negative coefficient was also observed (Table 3 Model B). When total cholesterol, triglyceride, HDL-C and LDL-C entered into model C simultaneously, after mutual adjustment, triglyceride rather than total cholesterol or HDL-C or LDL-C was independently and positively associated with baPWV (Table 3 Model C).

Figure 1 summarizes the mean values of baPWV of *Normoglycaemia* and pre-diabetes subjects before and after the mutual adjustment.

Before mutual adjustment (Panel B), as compared with individuals with *Normoglycaemia*, those with HbA_{1c} 5.7%-6.4% alone, with IFG alone, and with both HbA_{1c} 5.7%-6.4% and IFG showed higher baPWV of 29 cm/s (1311±10 *vs*. 1282±8 cm/s, *P*=0.039), 116 cm/s (1398±30 *vs*. 1282±8 cm/s, *P*<0.001), and 136 cm/s (1418±27 *vs*. 1282±8 cm/s, *P*<0.001) (values were expressed as mean±SE).

After the adjustment for age and gender (Panel C), individuals with *IFG* alone had higher baPWV than the *Normoglycaemia* group (1391±24 cm/s *vs.* 1294±8 cm/s , *P*<0.001), and individuals with the both HbA_{1c} 5.7%-6.4% and IFG had higher baPWV than *Normoglycaemia* (1392±19 cm/s *vs.* 1294±8 cm/s, *P*<0.001) as well**.**

Further adjustment for other covariates including systolic blood pressure, BMI and triglyceride (Panel D), which were found to be independently associated with baPWV in the multiple linear regression analysis, baPWV was significantly higher in subjects with the both HbA_{1c} 5.7%-6.4% and IFG, when compared with those subjects having *Normoglycaemia* (1350±14 cm/s *vs*.

Table 3. Multiple Regression Analysis of the Relationship between baPWV and Associated Variables

Explanatory Variable	Model A Adjusted R^2=0.526 (*F*=155.099)		Model B Adjusted R^2=0.543 (*F*=154.042)		Model C Adjusted R^2=0.526 (*F*=137.839)	
	Beta	*P* value	Beta	*P* value	Beta	*P* value
Age (year)	0.157	<0.001	0.156	<0.001	0.158	<0.001
Gender (female=0, male=1)	0.139	<0.001	0.158	<0.001	0.139	<0.001
BMI	-0.088	<0.001	—	—	-0.088	<0.001
Waist circumference (cm)	—	—	-0.087	<0.001	—	—
Systolic blood pressure (mmHg)	0.637	<0.001	0.641	<0.001	0.636	<0.001
Fasting plasma glucose (mmol/L)	0.091	<0.001	0.104	<0.001	0.090	<0.001
Total cholesterol (mmol/L)	—	—	—	—	-0.040	NS
Triglyceride (mmol/L)	0.059	0.015	0.059	0.015	0.072	0.022
HDL-C (mmol/L)	0.009	NS	0.012	NS	0.023	NS
LDL-C (mmol/L)	0.025	NS	0.022	NS	0.058	NS

***Note*.** Waist circumference and total cholesterol are excluded from Model A; BMI and total cholesterol are excluded from Model B; Waist circumference is excluded from Model C; NS=not significant.

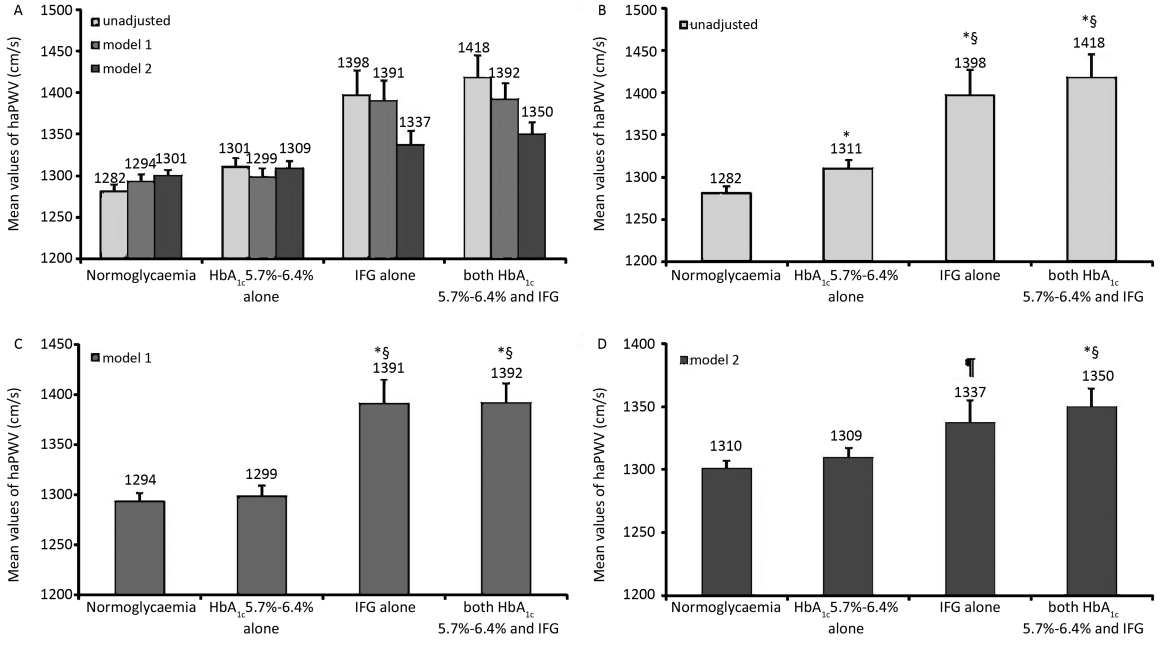

Figure 1. Mean values of baPWV according to fasting plasma glucose and HbA_{1c} level among 1122 subjects, Panel A summarizes the mean values of baPWV in the *normoglycaemia*, HbA_{1c} 5.7%-6.4% alone, IFG alone and the both HbA_{1c} 5.7%-6.4% and *IFG* group, before and after mutual adjustment. Model 1 is adjusted for age and gender, and model 2 is adjusted for age, gender, systolic blood pressure, BMI, and triglyceride. Panel B, C, and D illustrate the across-group differences among four groups with no adjustment (panel B), as well as with the use of model 1 (panel C) and model 2 (panel D) after adjustment, respectively. *denotes *P* value less than 0.05 comparing to *Normoglycaemia*; §denotes *P* value less than 0.05 comparing to HbA_{1c} 5.7%-6.4% alone; ¶denotes *P* value equals to 0.057 comparing to *Normoglycaemia*; I bar indicates standard Error.

1301±6 cm/s, *P*=0.002) and HbA_{1c} 5.7%-6.4% alone (1350±14 cm/s *vs.* 1309±8 cm/s , *P*=0.013). Although the mean values of baPWV between the *IFG* alone and *Normoglycaemia* groups were similar, there tended to be higher baPWV presented in the *IFG* alone than the *Normoglycaemia* (1337±18 cm/s *vs.* 1301±6 cm/s, *P*=0.057)**.**

DISCUSSION

In the present study, significantly increasing trends were noticed for baPWV across subgroups of subjects with increased degree of normal fasting plasma and impaired fasting plasma glucose. Compared with the *Normoglycaemia* group, pre-diabetes groups had higher levels of baPWV and traditional cardiovascular risk factors. After adjusting for age, gender, blood pressure, BMI as well as triglyceride, the baPWV appeared significantly higher in subjects with both HbA_{1c} 5.7%-6.4% and IFG, when compared with subjects in the *Normoglycaemia* and HbA_{1c} 5.7%-6.4% alone groups. These findings suggested that early atherosclerotic changes and risk of cardiovascular diseases increased in subjects with pre-diabetes, when compared to the *Normoglycaemia* ones in middle aged non-diabetic Chinese.

Our findings showed consistency with some of the previous studies. Shin et al. (2011) reported that subjects with increasing fasting plasma glucose, even within the normal range were associated with increased baPWV[24]. Paik et al. (2012) claimed that baPWV was higher in the IFG group than in subjects with normal fasting glucose even after adjustment for confounding variables[25]. One recent study (2010) on 1274 residents of 50 years or older from Guangzhou Biobank Cohort Study found that an increase of baPWV exist in both IFG and IGT subjects, when compared to the normal blood glucose subjects[30]. In addition, the association between high HbA_{1c} (5.7%-6.4%) and increased arterial stiffness (measured by carotid-femoral PWV [cfPWV]) was recently observed in a Chinese adult population of 18-93 year-olds. Liang et al. (2012) reported that after adjusting for age, gender and BMI, those with high HbA_{1c} (5.7%-6.4%) had a higher cfPWV[29] when compared to the individuals with fasting glucose <5.6 mmol/L and HbA_{1c}<5.7%. In the present study on middle aged adults, we observed an increased baPWV among subjects of HbA_{1c} levels at 5.7%-6.4% alone when compared with *Normoglycaemia* (1311±10 cm/s *vs.* 1282±8 cm/s, *P*=0.039), but after adjusting for age and gender, the degree of increase was attenuated to be not significant, statistically. Result from a Japanese study on 525 relatively healthy subjects showed a borderline statistically insignificant association (*P*=0.053) between baPWV and HbA_{1c} after adjusting for age and gender[31]. Zieman et al. (2012) reported that, contrary to the fasting glucose levels, HbA_{1c} was not associated with arterial stiffness, among 5888 community-dwelling elderly in the U.S.[32].

We found that triglyceride rather than total cholesterol or HDL-C or LDL-C, after mutual adjustment was independently and positively associated with baPWV. Our findings were also consistent with the previous reports which showed that triglyceride was independently associated with arterial stiffness but not HDL- or LDL- or total cholesterol in either the general or the impaired glucose regulation population[33-34].

Obesity and weight gain were associated with an increased risk of developing diabetes as reported by Hartemink N et al.[35], and weight control was important in the management of diabetes and could prevent the development of diabetes in the pre-diabetic individuals[36]. We found that BMI and waist circumference were both positively associated with baPWV prior to the mutual adjustment, however, in the multiple linear regression model, after adjusted for potential confounders, BMI and waist circumference became negatively associated with baPWV. Our findings were consistent with the previous reports by Xu et al. and Li et al.[15,34]. In lieu of the effect of obesity on baPWV that might be mediated by the intermediate parameters of cardiovascular risk factors, such as high blood pressure, this complicated relations might lead to collinearity when highly associated variables were included. This could also explain the negative association of BMI or waist circumference with baPWV in the study[15,34]. The effect of obesity on arterial stiffness should be further studied through prospective studies.

The limitations of our study should be addressed. Because of the cross-sectional nature of the study design, the causal relationship between pre-diabetes and baPWV could not be confirmed in the present study. Additionally, we did not measure the impaired glucose tolerance using the OGTT. Although the criteria of ADA which reduced the lower limit of IFG from 6.1 to 5.6 mmol/L, was used to expand the proportion of subjects diagnosed with IFG to the levels similar to those diagnosed with IGT under

OGTT. This criteria were not able to identify the same subjects[37-38] as indicated by results from other studies, implying that some people in the IFG group might actually have had diabetes mellitus. And using fasting glucose levels to identify pre-diabetes was not sufficient to recognize subjects with isolated postprandial hyper-glycemia. Besides, we did not evaluate some atherogenic factors, such as physical activity, smoking rate and the menopausal status of females. Moreover, it has been argued that the measurement of fasting plasma glucose or HbA1c levels might be influenced by various medical conditions, such as liver failure, kidney failure, and use of medicine. Although we have carefully excluded subjects with chronic diseases from the analysis, it is still possible that some conditions not assessed in our study might influence the associations. Finally, the subjects were recruited from a middle-aged population who voluntarily underwent medical check-ups, rather than being drawn from the general population using a random, multistage, stratified sampling method, thus our findings should be generalized to other populations with an appropriate degree of caution.

In conclusion, subjects with pre-diabetes showed greater arterial stiffness than the *Normoglycaemia*, and our results presented additional evidence to support the hypothesis that early development of adverse vascular changes already existed prior to the development of overt diabetes, suggesting that strict glycaemic control in pre-diabetes subjects might achieve a positive long-term protection against atherosclerosis.

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