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Title: Arterial stiffness is strongly associated with insulin resistance in Chinese –A Population-based Study (Taichung Community Health Study, TCHS)

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Short running title: ***arterial stiffness & insulin resistance***

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Abstract

Aim: Studies are limited investigating the association between insulin resistance and arterial stiffness in Chinese. We aimed to investigate this relationship in a population-based study of middle-aged Chinese.

Methods: A total of 2,188 subjects aged 40 years and older were recruited in 2004 in Taiwan. The association between arterial stiffness(measured by brachial-ankle pulse wave velocity(baPWV)) and insulin resistance (represented by homeostasis model assessment(HOMA-IR) and fasting glucose levels) was studied by multiple logistic and linear regression analyses.

Results: The respective prevalence of diabetes and impaired fasting glucose (IFG) was 13.9% and 30.6% in males and 10.4% and 20.8% in females. Using multiple linear regression analyses, we found baPWV to be strongly associated with age, gender, body mass index (BMI), waist circumference (WC), systolic blood pressure (BP), diastolic BP, fasting glucose, and triglycerides. Compared to the lowest HOMA-IR tertile I and adjusting for age, BMI, WC, gender, triglycerides, systolic BP, diastolic BP, smoking, alcohol drinking, betel nut chewing, and physical activity, the odds ratios(95% confidence interval) of arterial stiffness for the higher HOMA-IR tertiles II and III were 1.15(0.77-1.71) and 1.60(1.05-2.46), respectively. Using a general linear model with adjustment for age, systolic BP, diastolic BP, BMI, WC, and triglycerides, baPWV was significantly lower in the diabetic group by 90.3 cm/sec in

males and 100.5 cm/sec in females compared to the IFG group. When comparing the IFG group to the normal glucose group, baPWV was 28.5 cm/sec lower in males and 14.4 cm/sec lower in females.

Conclusions: Arterial stiffness is independently associated with insulin resistance in Chinese middle-age adults. Subjects with diabetes or IFG have higher baPWV than normoglycemic subjects.

Key Words: arterial stiffness, pulse wave velocity, insulin resistance, diabetes,

Introduction

Insulin resistance is common characteristic of subjects with metabolic syndrome, diabetes, or hypertension, and is closely associated with cardiovascular morbidity and mortality[1-3]. The pathophysiological mechanisms underlying these relationships are not well understood. Increasing arterial stiffness may be one of the mechanisms linking insulin resistance and cardiovascular diseases. It is well known that increasing arterial stiffness is related to an increased risk of chronic kidney disease, cardiovascular morbidity and mortality[4-8]. Pulse wave velocity (PWV) reflects the stiffness of both central and peripheral muscular arteries and serves as an index of arterial stiffness and atherosclerosis[9, 10]. Brachial-ankle PWV (BaPWV) has been shown to be an index of central arterial stiffness with a good correlation with the aortic PWV obtained by invasive recording, which has been demonstrated to have a close relationship with carotid-femoral PWV [9, 11]. Previous studies have also shown that baPWV is strongly associated with cardiovascular diseases and metabolic syndrome [4, 12, 13]. In addition, insulin resistance has been found to be related to arterial stiffness in adolescents, in adults with metabolic syndrome, diabetes, or hypertension, and in healthy non-diabetic middle-aged women [5, 14-16]. To our knowledge, however, no population-based study of these relationships has been done in Chinese. Furthermore, most of these studies had a small sample size, focused on specific disease groups, or were not population-based studies. Thus, we conducted a population-based study in a metropolitan city in Taiwan to investigate the

associations between insulin resistance (represented by homeostasis model assessment of insulin resistance (HOMA-IR) with different fasting glucose levels) and arterial stiffness (measured by baPWV) in Chinese middle-aged adults.

Methods

Study subjects

The target population consisted of residents aged 40 and above in Taichung city, Taiwan in October, 2004. Details of sampling have been described previously[13, 17-19]. In brief, there were a total of 363,543 residents in this area at the time of the study, which represented about 4.09 % of the national population of the same age. A stratified, two-stage random sampling approach was used for the selection of the survey sample, and the sampling rate was proportional to size within each stage. A total of 4280 individuals were selected. During household visits, we identified 750 individuals that were not eligible for various reasons that might confound the primary study objectives, and we excluded them from study sample. The reasons for exclusion included death (n=18), hospitalization or imprisonment (n=14), living abroad (n=39), moving out (n=411), living in their children's house (n=7), mistakes of the sampling frame (n=59), and not being at home during 3 visits made by interviewers (n=202). Among 3530 individuals selected, 2359 agreed to participate. Thus, the overall response rate was 66.8%[13, 17, 20]. Subjects with an ankle-brachial index < 0.9 or incomplete data for baPWV examination were excluded. The final population was 2188 subjects (men=1063, mean age=58.6±12.2 years; women=1125, 55.4±10.4 years). There were no statistically significant differences between selected subjects (n=2188) and deleted subjects (n=179) with regard to age, height, weight, body mass index (BMI), and waist circumference (WC). Ethics approval

for patient recruitment and analyzing the data was obtained from the Institutional Review Board of the China Medical University Hospital. Informed consent was obtained from every subject. The reported investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Anthropometric indices

Trained staff measured height, weight (measured to nearest 0.1kg), WC (measured to nearest 0.1cm), and heart rate. WC was taken at the midway point between the inferior margin of the last rib and the crest of the ilium in a horizontal plane. BMI was calculated as weight (kg) divided by height squared (m^2).

Biomedical markers

Blood pressure (BP) was measured by the same trained staff on the right arm using an appropriately sized cuff and a standard mercury sphygmomanometer while subjects were seated quietly for at least 5 minutes in a chair, with feet on the floor, and arm supported at heart level[21)]. The physicians measured BP using the same methods in the same arm while they did a physical examination. If the differences of BP measured between trained staff and physicians exceed 5mmHg (either systolic BP or diastolic BP), then a third BP measurement was taken by the physicians. The average of these BP measurements was recorded. Blood was drawn in the morning after a 12-hour overnight fast and was sent for analysis within four hours of collection. Total cholesterol (TCHOL), high density lipoprotein cholesterol (HDL-C),

triglycerides, and fasting glucose level were analyzed by a biochemical autoanalyzer (Beckman Cou, Fullerton, CA, USA) at the Clinical Laboratory Department (China Medical University Hospital, Taichung, Taiwan). High sensitivity C-reactive protein (hsCRP) levels were measured by nephelometry, a latex particle-enhanced immunoassay (TBA-200FR, Tokyo, Japan). Insulin levels were measured by a radioimmunoassay kit (DPC Coat-A-Count Insulin, Los Angeles, CA, USA). HOMA-IR was used to estimate the degree of insulin resistance (HOMA-IR = fasting insulin x fasting serum glucose/22.5, where insulin inμU/mL and glucose in mmol/L). Among these 2188 subjects, only 1207 individuals who had checked serum insulin level were selected to estimate insulin resistance. There were not statistically significance between insulin and non-insulin check-up group with regards to height, weight, BMI, fasting glucose, and baPWV.

Sociodemographic factors and life style behaviors

Age, gender, past major medical history, medication history, and lifestyle (such as smoking, alcohol drinking, betel nut chewing, and physical activity) were collected by self-administered questionnaires. Smoking, alcohol drinking, and betel nut chewing history were divided into 3 classes as follows: never, former, and current. Physical activity status was divided into 2 classes: never/seldom and current.

Diabetes, impaired fasting glucose, and insulin resistance

Diabetes was defines as: (1) fasting plasma glucose concentration ≥ 7.0 mmol/L (126 mg/dL) and/or (2) diabetes history on oral hypoglycemic agents or insulin treatment. Impaired

fasting glucose was defined as fasting plasma glucose concentration ≥ 5.6 mmol/L (100mg/dL) and <7.0 mmol/L (126 mg/dL) and no diabetes history or on oral hypoglycemic agents or on insulin treatment. Normal fasting glucose was defined as fasting plasma glucose concentration < 5.6 mmol/L (100mg/dL) and no history of diabetes, taking oral hypoglycemic agents or treatment by insulin. For every subject, the average of left and right baPWV was calculated for subsequent analyses. Insulin resistance was defined according to HOMA-IR, which was divided into tertiles (I, II, III).

Arterial stiffness

BaPWV was measured in subjects with supine position using a volume-plethysmographic apparatus (VP-1000 automated PWV/ABI analyzer; Colin, Co., Ltd., Komaki, Japan) as previous report[9, 22]. In brief, this device records PWV, blood pressure, electrocardiogram, and heart sounds simultaneously. Electrocardiogram electrodes were placed on both wrists and a heartsound microphone placed on the left sternal edge. The cuffs wrapped on both the brachia and ankles were connected to a plethysmographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures blood pressure[9, 22]. Every subject was measured by trained staff. The degree of arterial stiffness was represented by baPWV measurements. We have previously demonstrated that baPWV is closely associated with metabolic syndrome and proposed an optimal cut-off baPWV value for detecting cardiovascular diseases which was 1540 cm/sec in men and 1480 cm/sec in women[13].

Therefore, increasing arterial stiffness was defined as baPWV values that exceeded these sex-specific thresholds.

Statistical Analysis

The data are presented as means and standard deviation (SD) for continuous variables unless otherwise indicated. Multiple logistic regression analyses of having arterial stiffness with adjustment for age and sex was used in Table 1. Multinominal logistic regression analyses for different glucose levels with adjustment for age and gender were used in table 2. Multiple linear regression analyses were used to assess the associations between baPWV and other variables, such as age, gender, BMI, WC, BP. Multiple logistic regression analyses were used to estimate the adjusted odds ratios (ORs) and their 95% confidence intervals for the presence of arterial stiffness in relation to insulin resistance. Three different models were derived by adjusting for different confounders (such as age, lifestyle behavior, and laboratory assays) to minimize residual confounding. General linear models were used to investigate the differences of baPWV among subjects with different degrees of insulin resistance. All statistical tests were 2-sided at the 0.05 significance level. These statistical analyses were performed using the PC version of SPSS statistical software (13th version, SPSS Inc., Chicago, IL, USA).

Results

The prevalence of diabetes was 13.9% and 10.4%, and impaired fasting glucose (IFG) was 30.6% and 20.8% in males and females, respectively.

Table 1 shows baseline characteristics between subjects with and without arterial stiffness. Subjects with arterial stiffness were older and had greater BMI, WC, systolic BP, diastolic BP, heart rate, fasting glucose, TCHOL, triglycerides, TCHOL/HDL-C, and insulin but lower HDL-C, after adjustment for age and sex, than subjects without arterial stiffness.

Table 2 shows the baseline characteristics across glucose levels. We found that age, BMI, WC, systolic BP, diastolic BP, heart rate, TCHOL, triglycerides, TCHOL/HDL-C, baPWV, and HOMA-IR were statistically increased by glucose level (normal fasting glucose, impaired fasting glucose, and diabetes), after adjustment for age and sex.

In **Table 3**, using multiple linear regression analyses, we found baPWV to be strongly associated with age, BMI, systolic BP, heart rate, and fasting glucose (models 1-4).

In **Table 4**, compared to the lowest HOMA-IR tertile (tertile I), adjustment for age, BMI, WC, gender, triglycerides, systolic BP, diastolic BP, smoking, alcohol drinking, betel nut chewing, and physical activity, the odds ratios (95% confidence interval) of having arterial stiffness within the HOMA-IR tertiles II and III were 1.15 (0.77-1.71) and 1.60 (1.05-2.46), respectively. Compared to subjects with normal glucose level, the adjusted odds ratios of having arterial stiffness among subjects with impaired fasting glucose and diabetes were 1.48

(1.11-1.97) and 2.33 (1.51-3.62), respectively.

In **Figure 1**, the baPWVs (mean±SD) among subjects with normal glucose, impaired fasting glucose, and diabetes were, respectively, 1590±379, 1686±382, and 1874±424 cm/sec in men, and 1480±381, 1624±436, and 1936±461 cm/sec in women. Using a general linear model with adjustment for age, systolic BP, diastolic BP, BMI, WC, and triglycerides, baPWV was significantly lower in the diabetic group by 90.3 cm/sec in males and 100.5 cm/sec in females compared to the IFG group. When comparing the IFG group, baPWV was 28.5 cm/sec lower in males and 14.4 cm/sec lower in females. The baPWVs (mean±SD) among subjects with HOMA-IR tertile I, II, and III are 1599±406, 1661±411, and 1699±405 cm/sec in men, and 1442±355, 1550±442, and 1628±421 cm/sec in women, respectively. BaPWV is significantly greater in the highest HOMA-IR tertile than the lowest HOMA-IR tertile in both sexes (figure not shown).

Discussion

We have demonstrated that increasing arterial stiffness is closely associated to insulin resistance independent of age, obesity, lipid, blood pressure, and lifestyles in a population-based middle-aged Chinese sample. This association was also found in the early stage of diabetes (i.e. impaired fasting glucose). Our study also found that, in a Chinese population, the degree of insulin resistance is positively proportioned to the degree of arterial stiffness. This finding has important implications because China will be one of the top three countries with the greatest increase in newly diagnosed diabetes[23]. Early lifestyle modification to improve insulin resistance in subjects with impaired fasting glucose may be important in the prevention of further atherosclerosis and cardiovascular diseases.

In 1995, the Atherosclerosis Risk in Communities (ARIC) study found that subjects with diabetes or borderline glucose intolerance have stiffer arteries than subjects with normal glucose tolerance[24]. Another study done in 2003 showed that baPWV value increased with increasing plasma glucose level in Japan[25]. Seo et al. found that insulin resistance is associated with arterial stiffness in non-diabetic hypertensive subjects[14]. Lee et al. also showed that insulin resistance is associated with baPWV in male adolescents[15]. Although these studies all revealed similar results, this is the first study with a community-dwelling design undertaken in a Chinese population. Our results are in agreement with above studies and extend them to population-based application within Chinese subjects. Another novel

aspect of this study is the finding that not only subjects with diabetes, but also those with impaired fasting glucose had increased arterial stiffness. These findings provide evidence that macrovascular disease associated with type 2 diabetes begins as early in the development of insulin resistance as the impaired fasting glucose state. Early intervention should target the pre-diabetes stage.

The mechanisms linking insulin resistance and arterial stiffness is still unclear. Many potential mechanisms had been mentioned. First, hyeprinsulinemia may increase sympathetic tone, promote sodium reabsorption, activate rennin-angiotensin-aldosterone system, and increase systemic and vascular inflammation [26, 27]. In this study, we also found that high sensitivity C-reactive protein (a marker of systemic inflammation) increased with the increasing fasting glucose levels (Table 2). Subjects with arterial stiffness also have greater high sensitivity C-reactive protein than subjects without arterial stiffness (Table 1). From this finding, systemic inflammation could be a possible mechanism linking arterial stiffness and insulin resistance. The major determinants of PWV are age and blood pressure. In this study, we adjusted for the effects of these two determinants and other cardiovascular disease related risk factors (such as obesity, lipids, etc.), but the close association between arterial stiffness and insulin resistance persisted.

Although our results demonstrate a clear relationship between arterial stiffness and insulin resistance, there are some limitations in this study. First, the study is of cross-sectional design.

The causality between insulin resistance and arterial stiffness cannot be assumed. Second, the degree of insulin resistance assessed by HOMA-IR and fasting glucose levels is not an exact determinant of insulin resistance. The gold standard method for directly measurement of insulin sensitivity is hyperinsulinemic-euglycemic clamp[28]. However, this measurement procedure is invasive, costly, and inconvenient for use in population-based studies. Thus, HOMA-IR has been developed and validated as a surrogate index which is highly associated with hyperinsulinemic-euglycemic clamp in humans and is simple enough to be used reliably in large-scale or epidemiological studies [29]. Furthermore, the fasting glucose level is positively proportional to insulin resistance and can be treated as a marker of insulin resistance. With these measures, our study still was able to demonstrate the strong associations between arterial stiffness and insulin resistance. One drawback to using HOMA-IR for subjects with diabetes is that it is strongly influenced by fasting plasma glucose levels. In consequence, HOMA-IR is very high in patients with overt diabetes mellitus, because patients with diabetes have higher fasting plasma glucose than those with normal or impaired fasting glucose levels. Thus, we analyzed the association between arterial stiffness and insulin resistance among subjects without diabetes. Compared to subjects in the first tertile of HOMA-IR values, the adjusted odds ratios of having arterial stiffness among subjects with HOMA-IR tertile II and III were 1.04(0.68-1.69) and 1.53(1.004-2.35), respectively. Therefore, the significant association between arterial stiffness and insulin

resistance existed not only among subjects with diabetes, but also among the pre-diseased general population. Finally, baPWV is depending on blood pressure during the measurement. Accordingly, clinical evaluation of baPWV including blood pressure was complicated, because it is difficult to evaluate whether the effect of blood pressure is due to chronic stress of hypertension on artery or merely due to stiffness modified with blood pressure at a measuring time. This should be alerted when we used baPWV to be a maker of arterial stiffness.

In summary, the strong association between insulin resistance and arterial stiffness in Chinese is evident as early as during the impaired fasting glucose stage. Early intervention either in diet or physical activity to improve insulin resistance as well as arterial stiffness seems to be important in the prevention of cardiovascular disease. Further prospective study is necessary to clarify these associations in the early stage of glucose impairment.

Disclosure

The authors declared no conflict of interest.

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Table 1. Baseline characteristics according to the status of arterial stiffness[a]

	Arterial stiffness (n=1091)	Non-arterial stiffness (n=1097)	*p* value
Age (years) †	63.4±11.0	50.5±7.7	<0.001
BMI (kg/m^2) †	24.6±3.4	24.0±3.2	<0.001
WC (cm) †	83.3±9.9	79.4±9.7	<0.001
Systolic BP (mmHg) †	147.6±20.7	122.7±14.3	<0.001
Diastolic BP (mmHg) †	84.3±11.8	73.4±10.3	<0.001
Heart rate (beats/min) †	69.6±10.4	66.0±9.0	<0.001
Fasting glucose (mmol/L) †	6.09±1.83	5.39±1.12	<0.001
TCHOL (mmol/L) †	5.31±0.99	5.17±0.95	0.001
Triglycerides(mmol/L) †	1.53±1.18	1.22±0.95	<0.001
HDL-C (mmol/L) †	1.16±0.32	1.22±0.33	<0.001
TCHOL/HDL-C †	4.81±1.23	4.49±1.22	<0.001
Insulin(μU/ml) †,*	9.24±7.44	7.79±5.89	0.002
HOMA-IR †,*	2.65±2.68	1.91±1.64	<0.001
hsCRP (mg/dL) †	0.28±0.61	0.21±0.38	0.061
Fasting glucose level†,‡			<0.001
Diabetes (n, %)	213 (19.5 %)	52 (4.7 %)	

Impaired fasting glucose (n, %)	233 (21.2 %)	326 (29.9 %)	
Normal fasting glucose (n, %)	812 (74.0 %)	552 (50.6 %)	
Smoking (n, %)†			0.634
Current	145 (13.3%)	189 (17.2%)	
Former	155 (14.2%)	103 (9.4%)	
Never	789 (72.5%)	804 (73.4%)	
Alcohol drinking†			0.816
Current	221 (20.3%)	290 (26.5%)	
Former	61 (5.6%)	47 (4.3%)	
Never	808 (74.1%)	759 (69.3%)	
Betel nut chewing†			0.171
Current	35 (3.2%)	44 (4.0%)	
Former	53 (4.9%)	68 (6.2%)	
Never	998 (91.9%)	984 (89.8%)	
Physical activity†			0.073
Current	789 (72.4%)	705 (64.3%)	
Never/seldom	301 (27.6%)	391 (35.7%)	

Abbreviations: BMI, body mass index; WC, waist circumference; BP, blood pressure; TCHO, total cholesterol; HDL-C, high-density-lipoprotein cholesterol; HOMA-IR: insulin resistance

index by homeostasis model assessment = fasting glucose(mmol/L) x Insulin(μU/ml)/22.5 ; baPWV: brachial-ankle pulse wave velocity;

[a]: Arterial stiffness was defined as baPWV ≥ 1540 cm/sec in men or ≥ 1480 cm/sec in women

[†]: Multiple logistic regression of having arterial stiffness with adjustment for age and gender was used (except age); data are means ± SD for continuous variable and percentage for categorical data;

[*]: N= 1207

[‡]: Diabetes was defined as: (1) fasting plasma glucose concentration ≥ 7.0 mmol/L (126 mg/dL) and/or (2) history of diabetes, or treatment with oral hypoglycemic agents or insulin. Impaired fasting glucose was defined as fasting plasma glucose concentration ≥ 5.6 mmol/L (100mg/dL) and <7.0 mmol/L (126 mg/dL) and (2) no history of diabetes or treatment by oral hypoglycemic agents or insulin. Normal fasting glucose was defined as fasting plasma glucose concentration < 5.6 mmol/L (100mg/dL) and (2) no history of diabetes or treatment by oral hypoglycemic agents or insulin.

Table 2. Demographic characteristics categorized by fasting glucose status (N=2188)

	Individuals with normal glucose (n=1364)*	Individuals with impaired fasting glucose (n=559)*	Individuals with diabetes (n=265)*	*p* value†
Male (%)	590 (43.3%)	325 (58.1%)	148 (55.8%)	<0.001
Age (years)	55.1±11.0	58.8±11.5	62.7±11.1	<0.001
BMI (kg/m^2)†	23.8±3.1	25.0±3.3	25.2±3.5	<0.001
WC (cm)†	79.4±9.5	84.1±9.7	85.7±10.3	<0.001
Systolic BP (mmHg)†	131.5±21.0	138.2±20.6	147.3±22.2	<0.001
Diastolic BP (mmHg)†	77.2±12.2	80.8±12.0	83.2±12.0	<0.001
Heart rate (beats/min)†	66.2±9.2	68.6±10.3	72.1±11.3	<0.001
TCHOL (mmol/L)†	5.20±0.97	5.32±0.93	5.32±1.04	0.002
Triglycerides (mmol/L)†	1.22±0.93	1.49±1.08	1.94±1.51	<0.001
HDL-C (mmol/L)†	1.23±0.34	1.15±0.31	1.08±0.27	<0.001
TCHOL/HDL-C†	4.14±1.33	4.74±1.48	5.22±1.57	<0.001
baPWV (cm/sec)†	1528±384	1660±406	1901±441	<0.001
hsCRP (mg/dL)†	0.22±0.47	0.25±0.45	0.35±0.77	0.136
HOMA-IR†	1.62±1.20	2.63±1.80	4.83±4.21	<0.001
Smoking (n, %)†				0.238

Current	202 (14.8%)	91 (16.3%)	41 (15.5%)	
Former	126 (9.3%)	85 (15.2%)	47 (17.7%)	
Never	1033 (75.9%)	383 (68.5%)	177 (66.8%)	
Alcohol drinking[†]				0.003
Current	287 (21.1%)	170 (30.4%)	54 (20.4%)	
Former	63 (4.6%)	24 (4.3%)	21 (7.9%)	
Never	1012 (74.3%)	365 (65.3%)	190 (71.7%)	
Betel nut chewing[†]				0.158
Current	41 (3.0%)	254 (4.5%)	13 (4.9%)	
Former	65 (4.8%)	42 (7.5%)	14 (5.3%)	
Never	1252 (92.2%)	492 (88.0%)	238 (89.8%)	
Physical activity[†]				0.087
Current	907 (66.6%)	406 (72.6%)	181 (68.3%)	
Never/seldom	455 (33.4%)	153 (27.4%)	84 (31.7%)	

Abbreviations: BMI, body mass index; WC, waist circumference; BP, blood pressure; TCHO, total cholesterol; HDL-C, high-density lipoprotein cholesterol; baPWV, brachial-ankle pulse wave velocity;

[*]: Diabetes was defined as: (1) fasting plasma glucose concentration ≥ 7.0 mmol/L (126 mg/dL) and/or (2) history of diabetes or treatment with oral hypoglycemic agents or insulin.

Impaired fasting glucose was defined as fasting plasma glucose concentration ≥ 5.6 mmol/L (100mg/dL) and <7.0 mmol/L (126 mg/dL) and (2) no history of diabetes or treatment with oral hypoglycemic agents or insulin. Normal fasting glucose was defined as fasting plasma glucose concentration < 5.6 mmol/L (100mg/dL) and (2) no history of diabetes or treatment with oral hypoglycemic agents or insulin.

†: Multinominal logistic regression analyses for different glucose levels with adjustment for age and sex was used (except age); data are means ± SD for continuous variable and percentage for categorical data;

‡: N=1207 (men:591, women:616).

Table 3. Multiple linear regression models showing regression coefficients (β±S.E) with arterial stiffness (assessed by baPWV) as dependent variable, and listed variables as independent variables.

Variables	Model 1 (R^2=0.463) β±S.E(Standardized coefficients)	Model 2 (R^2=0.653) β±S.E(Standardized coefficients)	Model 3 (R^2=0.665) β±S.E(Standardized coefficients)	Model 4 (R^2=0.669) β±S.E(Standardized coefficients)
Age	24.7±0.57‡(0.680)	17.5±0.55‡(0.483)	16.7±0.55‡(0.460)	16.6±0.55‡(0.459)
Sex	-	-4.91±11.4(-0.006)	3.56±13.8(0.004)	4.62±13.7(0.006)
Systolic BP(mmHg)	-	8.12±0.48‡(0.424)	8.69±0.48‡(0.454)	8.52±0.48‡(0.445)
Diastolic BP(mmHg)	-	0.30±0.81(0.009)	0.79±0.80(0.024)	0.81±0.80(0.024)
Heart rate (beats/min)	-	6.88±0.54‡(0.164)	6.64±0.54‡(12.37)	6.15±0.55‡(0.147)
BMI (kg/m^2)	-	-	-19.6±2.91‡(-0.156)	-19.6±2.90‡(-0.155)
WC (cm)	-	-	2.33±1.09*(0.056)	1.79±1.09(0.043)
Fasting glucose(mmol/I	-	-	-	14.1±3.54‡(0.053)
Triglycerides (mmol/L)	-	-	-	8.35±5.12(0.022)

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; WC, waist circumference; BMI, body mass index; Sex: male is baseline; S.E.:standard error;

*: $p < 0.05$, †: $p < 0.01$, ‡: $p < 0.001$.

Table 4. Odds ratios (95% confidence interval) of having arterial stiffness[a] in several different models derived from a multiple logistic regression analysis using insulin resistance[b] (assessed by HOMA-IR) and different glucose levels [c] as independent variables, adjusted for some potential confounders.

Variable (n)	Model 1	Model 2	Model 3
HOMA-IR I (n=402)[b]	1.00 (reference)	1.00 (reference)	1.00 (reference)
HOMA-IR II (n=403)[b]	1.53 (1.15,2.02)[†]	1.21 (0.86,1.71)	1.15 (0.77,1.71)
HOMA-IR III (n=402)[b]	2.34 (1.76,3.10)[‡]	2.17 (1.54,3.07)[‡]	1.60 (1.05,2.46)[*]
Normal glucose (n=1364)[c]	1.00 (reference)	1.00 (reference)	1.00 (reference)
Impaired fasting glucose (n=559)[c]	2.16 (1.75,2.67)[‡]	1.61 (1.25,2.07)[‡]	1.48 (1.11,1.97)[†]
Diabetes (n=265)[c]	6.86 (4.60,10.2)[‡]	4.01 (2.58,6.24)[‡]	2.33 (1.51,3.62)[‡]

[a]: Arterial stiffness was defined as baPWV ≥ 1540 cm/sec in men or ≥ 1480 cm/sec in women

[b]: HOMA-IR was used to estimate the degree of insulin resistance (HOMA-IR = fasting insulin x fasting serum glucose/22.5, where insulin inμU/mL and glucose in mmol/L). HOMA-IR was divided by tertiles.

[c]: Diabetes was defined as: (1) fasting plasma glucose concentration ≥ 7.0 mmol/L (126 mg/dL) and/or (2) history of diabetes or treatment with oral hypoglycemic agents or insulin. Impaired fasting glucose was defined as fasting plasma glucose concentration ≥ 5.6 mmol/L (100mg/dL) and <7.0 mmol/L (126 mg/dL) and (2) no history of diabetes or treatment with

oral hypoglycemic agents or insulin. Normal fasting glucose was defined as fasting plasma glucose concentration < 5.6 mmol/L (100mg/dL) and (2) no history of diabetes or treatment with oral hypoglycemic agents or insulin.

Model 1: unadjusted.

Model 2: adjusted for age, gender, smoking, alcohol drinking, betel nut chewing, and physical activity.

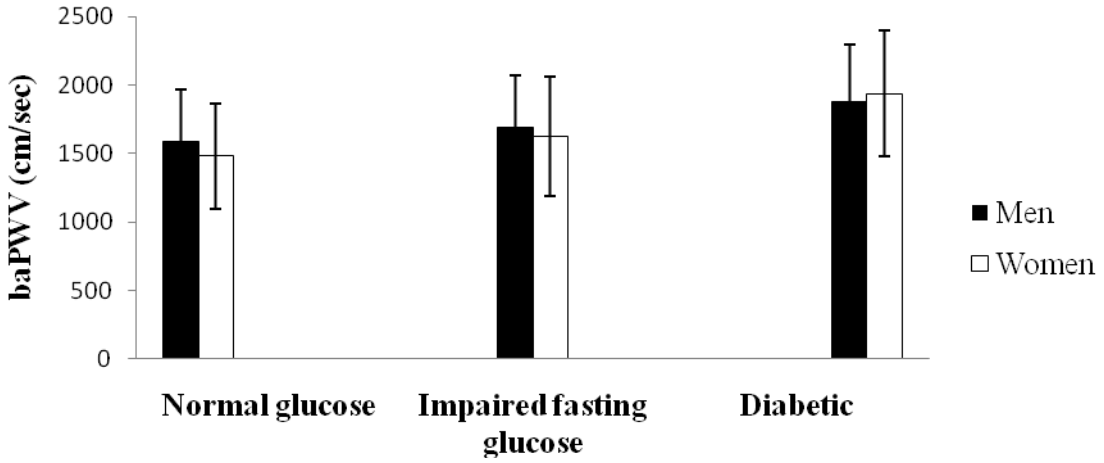
Model 3: adjusted for age, gender, BMI, waist circumference, triglycerides, systolic BP, diastolic BP, heart rate, smoking, alcohol drinking, betel nut chewing, and physical activity.

*: $p < 0.05$, †: $p < 0.01$, ‡: $p < 0.001$.

Legend to Figure

Figure 1. The mean arterial stiffness (measured by baPWV (cm/sec)) among different fasting glucose levels are shown in males and females. The baPWVs (mean±SD) among normal glucose, impaired fasting glucose, and diabetic subjects are 1590±379, 1686±382, and 1874±424 cm/sec in men, and1480±381, 1624±436, and 1936±461 cm/sec in women, respectively. Using a general linear model with adjustment for age, systolic BP, diastolic BP, BMI, WC, and triglycerides, baPWV was significantly lower in the diabetic group by 90.3 cm/sec in males and 100.5 cm/sec in females compared to the IFG group. In the IFG group, baPWV was 28.5 cm/sec lower in males and 14.4 cm/sec lower in females compared to subjects with normal glucose.

Figure 1.


2500
2000
1500
1000
500
0
baPWV (cm/sec)
Normal glucose
Impaired fasting glucose
Diabetic
Men
Women