Insulin Resistance Correlates with the Arterial Stiffness before Glucose Intolerance

Fu-Sheng Fang, Min-Yan Liu, Xiao-Ling Cheng, Wen-Wen Zhong, Xin-Yu Miao, Jian Li, Chun-Lin Li and Hui Tian

Abstract

**Objective**  The elevated plasma glucose level and/or insulin resistance in diabetes or impaired glucose tolerance play important roles in the pathogenesis of arterial stiffness. The present study investigated whether insulin resistance correlated with arterial stiffness before the development of glucose intolerance.

**Methods**  We conducted a cross-sectional analysis in 872 young to middle-age individuals with normal glucose tolerance (aged 36.2±8.5 years, BMI 24.6±3.1 kg/m² [mean±SD]). The homeostasis model assessment (HOMA) index was used as a quantitative assessment of the fasting insulin resistance (FIR), and the plasma insulin level after glucose loading was adopted as an index of the post-challenge insulin resistance (PIR). The Matsuda index [ISI (composite)] was used as a measurement of the insulin sensitivity. The arterial stiffness assessed by the brachial-ankle pulse wave velocity (baPWV) was adopted to quantify its independent associations with insulin resistance.

**Results**  The univariate linear regression analysis indicated that the fasting plasma glucose level (FPG, \( \beta = 68.2; 95\% CI 40.9, 95.6; p<0.001 \)), post-challenge plasma glucose level (PPG, \( \beta = 25.3; 95\% CI 15.6, 35.0; p<0.001 \)), FIR \( (\beta = 24.5; 95\% CI 14.1, 35.0; p<0.001) \), PIR \( (\beta = 1.30; 95\% CI 0.87, 1.73; p<0.001) \) and ISI (composite) \( (\beta = -3.55; 95\% CI -5.02, -2.07; p<0.001) \) were all significantly correlated with the baPWV. After adjustment for sex, age, BMI, heart rate, smoking, systolic blood pressure, total cholesterol, LDL-cholesterol and family history of diabetes, the multivariate linear regression analysis demonstrated that the PIR (model 1, \( \beta = 0.39, p=0.038 \); model 2, \( \beta = 0.39, p=0.035 \); model 3, \( \beta = 0.39, p=0.035 \)) was an independent contributor to the baPWV, while the FIR, FPG, PPG and ISI (composite) failed to show any significant contribution.

**Conclusion**  The insulin resistance correlated with the arterial stiffness before glucose intolerance.

Key words: insulin resistance, arterial stiffness, glucose intolerance

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Introduction

The elevated plasma glucose level in diabetes or an impaired glucose tolerance is a risk factor for cardiovascular events and mortality (1-3). Insulin resistance is recognized as an independent contributor to atherosclerosis (4), a strong predictor of cardiovascular disease (5) and is associated with an increased risk of death (6). The brachial-ankle pulse wave velocity (baPWV) has been demonstrated to be a potential marker of early atherosclerotic vascular impairment and cardiovascular risk (7, 8). A previous study has indicated that post-challenge hyperglycemia and insulin resistance in diabetes or impaired glucose regulation was related to significant vascular stiffness (9). However, no studies have evaluated how the plasma glucose level and insulin resistance affected the arterial stiffness before glucose intolerance. The aim of the present study was to investigate whether the fasting or post-challenge insulin resistance influences the arterial stiffness, as assessed by the baPWV before glucose intolerance.

Department of Geriatric Endocrinology, Chinese PLA General Hospital, China
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Correspondence to Dr. Hui Tian, Tianh5302@163.com
Materials and Methods

Study participants

This cross-sectional investigation was conducted among participants with normal glucose tolerance (NGT), and volunteers were recruited from a university-based annual routine health survey. A total of 1,221 employees underwent a health check-up in May 2008. The criteria for inclusion in our study were a diagnosis of NGT according to the 1999 World Health Organization (WHO) criteria, and willingness to undergo a baPWV measurement (n=932). The exclusion criteria were as follows: age ≥60 years, because the baPWV is significantly elevated with age (n=57) and an ankle-brachial index (ABI) <0.9, indicating a possible diagnosis of arterial stiffness (n=7). Consequently, 872 young to middle-age subjects (673 men and 199 women, aged 36.2±8.5 years, BMI 24.6±3.1 kg/m² [mean±SD]) were included in the final analysis of the study. The study protocol was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki.

Data collection and laboratory measurements

A standardized health questionnaire was administered by trained staff to obtain information on the sociodemographic characteristics, including the sex, age, education, dietary habits, personal medical history and family medical history. The participants underwent a routine examination, including height, body weight, waist circumference, heart rate, systolic blood pressure and diastolic blood pressure. Participants were instructed to maintain their usual physical activity and diet for at least three days before the oral glucose tolerance test (OGTT). After at least a 10-hour overnight fast, the participants without a history of diabetes were given a standard diet for at least three days before the oral glucose tolerance test (OGTT). After at least a 10-hour overnight fast, the participants without a history of diabetes were given a standard 75 g glucose solution, and the fasting plasma glucose (FPG) and 2 hours post-challenge plasma glucose (PPG) levels, as well as the serum insulin concentrations (fasting insulin; post-challenge insulin) were determined. The plasma glucose level was measured with a glucose oxidase method.

The total serum cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol levels were determined with enzymatic methods. The serum insulin concentration was measured using a radioimmunoassay kit from American Diagnostic Products Corporation. The inter-assay coefficient of variability of insulin was 5.9-8.0%, and the intra-assay coefficient of variability was 5.2-6.4%. NGT was diagnosed as a fasting plasma glucose <6.1 mmol/L and an OGTT 2-hour plasma glucose <7.8 mmol/L, and in patients not taking any anti-diabetic treatment. The homeostasis model assessment (HOMA) index was used as a quantitative assessment of the fasting insulin resistance (FIR) in the investigated population (10). HOMA-IR=(fasting glucose×fasting insulin)/22.5. The 2 hours plasma insulin level after glucose loading was adopted to evaluate post-challenge insulin resistance (PIR). The Matsuda index was used as a measurement of the insulin sensitivity (11). The insulin sensitivity index [ISI (composite)]=10,000/sqrt (fasting glucose×post-challenge glucose×fasting insulin×post-challenge insulin).

baPWV measurements

Measurements were performed by the same specialized technician, and operators were blinded to this process and participants were specifically asked not to reveal the results of the screening prior to the completion of the vascular tests. All participants underwent brachial-ankle pulse wave velocity (baPWV) measurements using a volumeplethysmographic apparatus (model BP-203RPE, Omron-Colin Co., Ltd., Japan), in accordance with a previously described methodology (12). Briefly, occlusion and monitoring cuffs were snugly placed around all four limbs with the subject in the supine position, and ECG electrodes were placed on both wrists. The pressure wave-forms of the brachial and tibial arteries were recorded with an automatic waveform analyzer after 5 minutes of bed rest. The mean of the bilateral baPWV (cm/s) measurements was used for the analysis, and the patients were then divided into four groups by quartiles.

Statistical analysis

The data are presented as the means±SD for normally distributed continuous variables and medians (5th and 95th percentiles) for non-normal continuous variables. An analysis of variance (ANOVA) was used to compare the normally distributed continuous variables across baPWV quartiles. Otherwise, a nonparametric analysis was applied. Categorical data were analyzed using the χ² test to determine univariate differences between the cohorts. A univariate linear regression analysis was performed to investigate the associations between the clinical variables and baPWV. Multivariate linear regression models were constructed to assess the influence of the FPG, PPG, FIR, PIR and ISI (composite) as independent contributors to the baPWV; p values <0.05 were considered to be statistically significant.

Results

The clinical characteristics of study subjects are shown in Table 1. When the patients were divided into quartiles based on the baPWV, the age, BMI, waist circumference, heart rate, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides and LDL-cholesterol were significantly increased with increasing baPWV quartiles (p<0.001), while the HDL-cholesterol decreased gradually with the quartile (p<0.001). The glucose metabolic index, including the FPG, PPG, fasting insulin, FIR, PIR and ISI (composite) gradually increased across the baPWV quartiles (p<0.001).

The correlations between the baPWV and the FPG, PPG, FIR, PIR, ISI (composite) or a range of other variables were determined using the univariate linear regression analyses (Table 2). The FPG (β=68.2; 95%CI 40.9, 95.6; p<0.001), PPG (β=25.3; 95%CI 15.6, 35.0; p<0.001), FIR (β=24.5;
95% CI 14.1, 35.0; p<0.001), PIR (β=1.30; 95% CI 0.87, 1.73; p<0.001) and ISI (composite) (β=-3.55; 95% CI -5.02, -2.07; p<0.001) were all significantly correlated with the baPWV in individuals with NGT. The univariate analysis also demonstrated significant correlations between the baPWV and selected variables such as sex, age, BMI, waist circumference, heart rate, smoking, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol (p<0.01).

To control the number of covariates entered and to limit the effects of collinearity, multivariate models were constructed to assess the correlations between the baPWV and the FPG, PPG, FIR, PIR or ISI (composite) after adjustment for selected variables (Table 3). Model 1 included the FPG, PPG, FIR, PIR or ISI (composite) index, sex, age, BMI, heart rate, smoking and systolic blood pressure. Model 2 further adjusted for the total cholesterol and LDL-cholesterol based on model 1, and model 3 further adjusted for a family history of diabetes as an independent variable based on model 2. All models demonstrated a relationship between the baPWV and PIR (model 1, β=0.39, p=0.038; model 2, β=0.39, p=0.035; model 3, β=0.39, p=0.035), but

### Table 1. The Clinical Characteristics of the Participants Categorized by baPWV Quartile

<table>
<thead>
<tr>
<th>Variables</th>
<th>baPWV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 1,146 cm/s</td>
<td>1,146-1,238 cm/s</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>118 (54.1)</td>
<td>174 (79.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.5±6.2</td>
<td>34.5±7.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3±3.1</td>
<td>24.5±2.7</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>77±2.9</td>
<td>81.9±8.6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69.2±9.6</td>
<td>69.3±8.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122±11.4</td>
<td>118±10.6</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71.5±8.4</td>
<td>74.6±8.4</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.41±0.75</td>
<td>4.60±0.81</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.33±1.66</td>
<td>1.33±0.71</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.15±0.55</td>
<td>2.32±0.60</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.47±0.36</td>
<td>1.41±0.33</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>4.72±0.39</td>
<td>4.87±0.39</td>
</tr>
<tr>
<td>PPG (mmol/L)</td>
<td>4.83±1.01</td>
<td>4.98±1.08</td>
</tr>
<tr>
<td>Fasting insulin (mU/L)</td>
<td>5.7 (2.0, 13.9)</td>
<td>5.8 (2.0, 16.3)</td>
</tr>
<tr>
<td>FHR (heart rate)</td>
<td>1.19 (0.40, 28.1)</td>
<td>1.24 (0.44, 3.81)</td>
</tr>
<tr>
<td>PIR (mU/L)</td>
<td>26.7 (10.1, 71.1)</td>
<td>26.3 (9.9, 79.7)</td>
</tr>
<tr>
<td>ISI (composite)</td>
<td>9.46 (3.78, 24.1)</td>
<td>8.67 (3.31, 25.1)</td>
</tr>
<tr>
<td>Smoking (yes)</td>
<td>5.0 (22.9)</td>
<td>6.0 (27.5)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>19 (8.7)</td>
<td>31 (14.2)</td>
</tr>
<tr>
<td>Hypertension history</td>
<td>0</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Dyslipidemia history</td>
<td>8 (3.7)</td>
<td>15 (6.9)</td>
</tr>
<tr>
<td>Cardiovascular disease history</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are the means ± SD, or medians (5th and 95th percentiles) or n (%).

### Table 2. The Results of the Univariate Linear Regression Analysis Demonstrating Standardized Parameter Associations in a Univariate Model, with baPWV as a Dependent Variable

<table>
<thead>
<tr>
<th>Variables</th>
<th>β (95%CI)</th>
<th>Standardized β</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>108.9 (83.8, 134.0)</td>
<td>0.28</td>
<td>&lt;0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>Age</td>
<td>9.20 (8.06, 10.3)</td>
<td>0.47</td>
<td>&lt;0.001</td>
<td>0.23</td>
</tr>
<tr>
<td>BMI</td>
<td>15.8 (12.4, 19.1)</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>0.09</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>5.76 (4.74, 6.79)</td>
<td>0.35</td>
<td>&lt;0.001</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart rate</td>
<td>4.51 (3.47, 5.55)</td>
<td>0.28</td>
<td>&lt;0.001</td>
<td>0.08</td>
</tr>
<tr>
<td>Smoking</td>
<td>41.9 (18.3, 65.5)</td>
<td>0.12</td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>5.93 (5.27, 6.60)</td>
<td>0.51</td>
<td>&lt;0.001</td>
<td>0.26</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>7.24 (6.26, 8.22)</td>
<td>0.44</td>
<td>&lt;0.001</td>
<td>0.20</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>37.0 (25.1, 49.0)</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>0.04</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>15.0 (7.60, 22.3)</td>
<td>0.13</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>55.4 (38.8, 72.0)</td>
<td>0.22</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>-88.1 (-120.5, -55.7)</td>
<td>-0.18</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>FPG</td>
<td>68.2 (40.9, 95.6)</td>
<td>0.16</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>PPG</td>
<td>25.3 (15.6, 35.0)</td>
<td>0.17</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>FIR</td>
<td>24.5 (14.1, 35.0)</td>
<td>0.16</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>PIR</td>
<td>1.30 (0.87, 1.73)</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>0.04</td>
</tr>
<tr>
<td>ISI (composite)</td>
<td>-3.55 (-5.02, -2.07)</td>
<td>-0.16</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
</tbody>
</table>
postload hyperinsulinemia in patients with a normal plasma adipokines (17). It was also already established that the signaling, reactive oxygen species (ROS), inflammation and thermore, insulin resistance reduces the endothelial progeni-
tance was associated with vascular dysfunction (16). Fur-
the findings of a previous study showing that insulin resis-
tance causes reduced production of NO by impairing the
Akt insulin-signaling pathway (14). In contrast, insulin resis-
tceptors through the phosphatidyl-inositol 3-kinase (PI3k)/
by the NO production that is accelerated by the insulin re-
lar endothelial function (13), and vasodilatation is induced
known to affect the vascular stiffness. It is generally consid-
ever, the oxidative stress induced by insulin resistance is
stiffness induced by insulin resistance remains unclear. How-
ment of glucose intolerance.
impairment of vascular stiffness even before the develop-
dence that insulin resistance has an important effect of the
impaired insulin resistance was significantly correlated with
PGT was a risk factor for arterial stiffness in subjects with
suggested that a higher 1 hour plasma glucose level after
insulin metabolism, including those with diabetes and impaired
bic alteration noted, and this variation existed earlier than elevated fasting insulin resistance, which may be the most
plausible cause of the elevated postprandial glucose in type
2 diabetes. Therefore, the significant correlation between
PIR and baPWV may be attributable to the PIR, which is present earlier than FIR before the development of glucose
intolerance.
In the previous studies, the plasma glucose level was re-
related to the arterial stiffness in subjects with abnormal glu-
cose metabolism, including those with diabetes and impaired
ance that the plasma glucose level, both at fasting and 2 hours af-
plasma glucose levels were not correlated with the baPWV .
Niijima et al. (24) demonstrated that, isolated impaired glucose tolerance had greater arterial stiff-
ess than those with isolated impaired fasting glucose,
which implied that the postprandial plasma glucose level
higher insulin resistance, which may be the most
thetic alteration noted, and this variation existed earlier than
the arterial stiffness in subjects with abnormal glu-
the arterial stiffness in subjects with no evidence
of glucose intolerance. This is important, because insulin re-
sistence is present in approximately 25% of nonobese indi-
viduals with NGT (25). Yanase et al. (26) demonstrated that
not with the FPG, PPG, FIR or ISI (composite).

**Discussion**

The present investigation demonstrated that 1) post-
challenge insulin resistance was significantly correlated with arterial stiffness before the development of glucose intolerance and 2) neither the FPG nor PPG were associated with the arterial stiffness. The current data provide important evidence that insulin resistance has an important effect of the impairment of vascular stiffness even before the development of glucose intolerance.

The mechanism underlying the impairment of vascular stiffness induced by insulin resistance remains unclear. However, the oxidative stress induced by insulin resistance is known to affect the vascular stiffness. It is generally considered that plasma insulin has a beneficial effect on the vascular endothelial function (13), and vasodilatation is induced by the NO production that is accelerated by the insulin receptors through the phosphatidyl-inositol 3-kinase (PI3k)/Akt insulin-signaling pathway (14). In contrast, insulin resistance causes reduced production of NO by impairing the PI3K/Akt signaling pathway (15), which is consistent with the findings of a previous study showing that insulin resistance was associated with vascular dysfunction (16). Furthermore, insulin resistance reduces the endothelial progenitor cells and vascular repair induced by disturbed PI3K/Akt signaling, reactive oxygen species (ROS), inflammation and adipokines (17). It was also already established that the postload hyperinsulinemia in patients with a normal plasma glucose level induced oxidative stress. This was demonstrated using a euglycemic-hyperglycemic insulin clamp model in healthy individuals (18). In addition, hyperinsulinemia induces an elevation of the blood pressure, reduction of lipid metabolism and abnormalities in the adipokcytokines in subjects with NGT (19), and the adverse effect of the metabolic alterations induced by insulin resistance are related to the impairment of vascular stiffness.

In comparison with FIR, PIR was observed to exert a more potent effect on the arterial stiffness before the development of glucose intolerance. Usually, the level of fasting insulin resistance is used to evaluate the insulin resistance, and it has been described to be associated with cardiovascular disease. Oterdoom et al. (5) demonstrated that the fasting insulin level was a strong cardiovascular risk factor, especially in women. However, Lautt (20) indicated that postprandial insulin resistance was an earlier predictor of cardiovascular risk. Before the onset of type 2 diabetes, elevated postprandial insulin resistance was the earliest metabolic alteration noted, and this variation existed earlier than elevated fasting insulin resistance, which may be the most plausible cause of the elevated postprandial glucose in type 2 diabetes. Therefore, the significant correlation between PIR and baPWV may be attributable to the PIR, which is present earlier than FIR before the development of glucose intolerance.

In the previous studies, the plasma glucose level was related to the arterial stiffness in subjects with abnormal glucose metabolism, including those with diabetes and impaired glucose tolerance. Li et al. (21) confirmed that, compared with NGT, subjects with impaired glucose tolerance and newly diagnosed diabetes exhibited a greater arterial stiffness. Evidence showed that, in nondiabetic healthy subjects (FPG <7.0 mmol/L), the fasting plasma glucose level was associated with arterial stiffness evaluated by the baPWV (22). In the study by Xu et al. (23), subjects with isolated impaired glucose tolerance had greater arterial stiffness than those with isolated impaired fasting glucose, which implied that the postprandial plasma glucose level may have a significant effect on the arterial stiffness.

However, few studies have evaluated whether the fasting or postprandial glucose affected the arterial stiffness before the development of glucose intolerance. Niijima et al. (24) suggested that a higher 1 hour plasma glucose level after OGTT was a risk factor for arterial stiffness in subjects with normal glucose tolerance, while the FPG and 2 hours plasma glucose levels were not correlated with the baPWV. In accordance with this study, our study also demonstrated that the plasma glucose level, both at fasting and 2 hours after the OGTT, was not associated with the baPWV before the development of glucose intolerance.

Our observations could have potentially important clinical implications, especially in the population with no evidence of glucose intolerance. This is important, because insulin resistance is present in approximately 25% of nonobese individuals with NGT (25). Yanase et al. (26) demonstrated that

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**Table 3. The Results of the Multivariate Linear Regression Analysis with Adjustments to Assess the Relationship between Insulin Resistance and the baPWV**

<table>
<thead>
<tr>
<th>Variables</th>
<th>β (95%CI) p</th>
<th>R²</th>
<th>β (95%CI) p</th>
<th>R²</th>
<th>β (95%CI) p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>1.44 (-20.2, 23.0) 0.896 0.46</td>
<td>1.59 (-20.0, 23.2) 0.885 0.46</td>
<td>1.14 (-20.5, 22.8) 0.918 0.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPG</td>
<td>3.35 (-43.2, 11.0) 0.392 0.47</td>
<td>3.35 (-43.4, 11.0) 0.393 0.47</td>
<td>3.29 (-44.0, 11.0) 0.401 0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIR</td>
<td>2.65 (-28.2, 11.6) 0.560 0.46</td>
<td>3.04 (-5.9, 12.0) 0.507 0.46</td>
<td>2.87 (-6.13, 11.9) 0.532 0.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIR</td>
<td>0.39 (0.02, 0.75) 0.038 0.47</td>
<td>0.39 (0.03, 0.76) 0.035 0.47</td>
<td>0.39 (0.03, 0.76) 0.035 0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI (composite)</td>
<td>-0.49 (-1.68, 0.71) 0.427 0.47</td>
<td>-0.46 (-1.67, 0.74) 0.452 0.47</td>
<td>-0.46 (-1.66, 0.74) 0.454 0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for sex, age, BMI, heart rate, smoking and systolic blood pressure
Model 2: adjusted for sex, age, BMI, heart rate, smoking, systolic blood pressure, total cholesterol and LDL-cholesterol
Model 3: adjusted for sex, age, BMI, heart rate, smoking, systolic blood pressure, total cholesterol, LDL-cholesterol and family history of diabetes
fasting hyperinsulinemia increased the risk of incident cardiovascular events in patients with NGT. In the study by Ausk et al. (27), insulin resistance, as evaluated by the HOMA-IR, was associated with all-cause mortality in the nondiabetic U.S. population with a normal BMI. Furthermore, the coexisting conditions with insulin resistance, such as hypertension, dyslipidemia and cardiovascular diseases, were suggested to be more closely related to the elevation of the baPWV than was the insulin resistance. Therefore, it is important to identify individuals with insulin resistance before the development of glucose intolerance in an effort to prevent vascular impairment.

The present data indicated a consistent outcome with several previous studies. The pulse wave velocity was found to be associated with an increased risk for cardiovascular events in the community-based Framingham Heart Study (28). Park et al. (29) found that insulin resistance, assessed by the HOMA-IR, was independently associated with the PWV in normoglycemic normotensive postmenopausal women. Patarrao et al. (30) suggested that postprandial, but not fasting, insulin resistance is an early identifier of dysmetabolism in overweight subjects. However, in the study by Urbina et al. (31), traditional cardiovascular risk factors were the major determinants of arterial stiffness, while the insulin resistance (evaluated based on the HOMA-IR) was not an independent determinant, which may be related to the findings using the HOMA-IR to evaluate the fasting insulin resistance in the study, without adopting the index of postprandial insulin resistance. The present study confirmed that insulin resistance was a significant determinant of the arterial stiffness before glucose intolerance, even after adjustment for traditional metabolic factors.

Our study is subject to a number of limitations. First, the principal limitation of our study was its cross-sectional design. Second, several therapeutic strategies, such as antihypertensive therapy or lipid-lowering therapy, can contribute to reducing the baPWV, but we had limited data regarding the medications used by the study subjects. Finally, the postprandial insulin peak usually appears within 1 hour after loading in normal glucose individuals. The areas under the curves (AUC) of plasma insulin after glucose loading was therefore an appropriate variable for evaluating the effect of PIR on baPWV. However, the 1 hours plasma insulin level was not measured in the study because our healthy check-up program does not include a 1 hours plasma glucose and insulin evaluation. Therefore, the 2 hours plasma insulin level after glucose loading was adopted to evaluate the PIR in the present study, which may have influenced the accuracy of the PIR assessment, and should be further studied in the future.

In summary, insulin resistance was correlated with the arterial stiffness before glucose intolerance. In contrast, the plasma glucose levels, both fasting and post-challenge, were not associated with the arterial stiffness before the development of glucose intolerance.

The authors state that they have no Conflict of Interest (COI).

The first two authors, Fu-Sheng Fang and Min-Yan Liu, contributed equally to this article.

References


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