Effects of Deranged Glucose Homeostasis on Peripheral Arterial Stiffness Index in Patients With Pre-Diabetes Mellitus

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SUMMARY

Premature arteriosclerosis may be one of the mechanisms linking pre-diabetes mellitus (pre-DM) and cardiovascular disease. We sought to characterize premature arteriosclerosis in pre-DM using different arterial stiffness indices and to find the independent contributors of this process. We recruited 33 patients without DM, 53 patients with pre-DM, and 34 subjects with DM. Both the compliance index (CI) and stiffness index (SI) were measured. Patients with pre-DM and DM had lower CI (3.8 ± 2.1 versus 5.2 ± 3.0 units; P < 0.05 and 3.6 ± 1.8 versus 5.2 ± 3.0 units; P < 0.05, respectively) and higher SI (8.0 ± 2.0 versus 6.7 ± 1.6 m/s; P < 0.01 and 9.4 ± 2.3 versus 6.7 ± 1.6 m/s; P < 0.001, respectively) than patients without DM. Using multivariate linear regression analysis, age, heart rate, and HOMA index were independent determinants for SI (whole model: $R^2 = 0.47$, $P < 0.001$), whereas male gender, hsCRP, and HOMA index were independent determinants for CI (whole model: $R^2 = 0.34$, $P < 0.01$). The HOMA index was an independent determinant for arterial stiffness. Increased insulin resistance may associate with increased arterial stiffness at peripheral arteries in pre-DM patients. (Int Heart J 2013; 54: 27-32)

Key words: Insulin resistance

It has been reported that early atherosclerosis is already evident in subjects with either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) as well as in those with diabetes mellitus (DM), and the risk of cardiovascular disease is greater in subjects with IFG/IGT than in patients with normal glucose homeostasis.1,2,12 Hemoglobin A1c (HbA1c) can be used to quantify average blood glucose levels over a 3-month period. Many studies have also reported that high levels of HbA1c are strongly associated with an increased risk of cardiovascular disease.2,13 However, the pathophysiological mechanisms underlying these relationships have largely not yet been well elucidated.

Our previous study showed that increased indices of aortic stiffness, including central systolic blood pressure and the pressure wave reflection index, were associated with development of new DM in essential hypertension.3 Central systolic blood pressure can be elevated as part of essential hypertension together with diastolic blood pressure (and thus increased mean arterial pressure) and thus reflect increased peripheral resistance in the muscular arteries with normal elasticity of the central elastic arteries. Premature arteriosclerosis and atherosclerosis may be one of the mechanisms linking abnormal glucose homeostasis and cardiovascular disease.4,5 Estimation of arterial stiffness has been reported to be a useful method for assessment of early preclinical atherosclerosis.9 Nonetheless, the relationships between different arterial stiffness indices and glucose homeostasis status were reported individually10,11 or as a cumulative effect of the metabolic syndrome.12,13 It is rare that studies have specifically addressed the effects of different stages of glucose homeostasis on peripheral arterial stiffness index.

As a potentially clinically useful means for evaluating peripheral arterial stiffness, we have developed a novel compliance index (CI) derived from a dual-channel photoplethysmography system, which measures the relationship between volume and pressure changes in the fingertip.14,15 The stiffness index (SI), calculated from the digital volume pulse (DVP) measured by photoplethysmography, is an index of wave reflections and also an acceptable marker for large arterial stiffness.16,17

According to the 2010 American Diabetes Association (ADA) guideline for diagnosis and classification of DM,18 pre-DM patients have a HbA1c level between 5.7% to 6.4%. The aim of this study was to compare the independent associations of variables of glucose homeostasis, namely fasting glucose and HbA1c, and insulin resistance (HOMA index = fasting insulin (μU/mL) × fasting serum glucose (mg/dL)/405) with SI and CI in patients with pre-DM. We sought to characterize premature arteriosclerosis in glucose homeostasis disorders outside the DM and compare the independent contributions of different glucose indices to this process with different arterial stiffness indices, especially CI.
METHODS

Study population: Apparent healthy subjects who visited a teaching regional hospital for a routine check-up for a health examination between September 2010 and February 2011 were eligible for this study. Patients with cardiovascular disease, cerebrovascular disease, peripheral vascular disease, and overt kidney or liver diseases were excluded. We defined our study subjects as: (1) no DM: fasting glucose < 100 mg/dL and HbA1c level < 5.7%; (2) DM: fasting glucose ≥ 126 mg/dL or HbA1c level ≥ 6.5% or being treated with antidiabetic medications; (3) pre-DM: fasting glucose ≥ 100 mg/dL and < 126 mg/dL, or HbA1c level between 5.7% and 6.4%. In summary, we recruited 120 subjects, consisting of 33 patients (15 men) without DM, 53 patients (34 men) with pre-DM, and 34 subjects with DM (21 men).

A review of each patient chart and a structured interview were conducted by trained medical staff to gather data on basic demographic data and medications. Traditional cardiovascular risk factors, including hypertension, hypercholesterolemia, and current smoking, were all carefully evaluated for each patient. Hypertension was diagnosed if blood pressure was > 140/90 mmHg on 3 occasions or if the subject was taking any antihypertensive medication. Hypercholesterolemia was defined as a total serum cholesterol concentration ≥ 200 mg/dL, or as use of lipid-lowering therapy. Smokers were defined as those who habitually smoked cigarettes at the start of this study. Antihypertensive and lipid lowering drugs were also carefully reviewed in hypertensive and hyperlipidemia patients. All patients gave written informed consent for this study, and the study protocol was approved by the Human Research Committee of National Cheng Kung University Hospital.

Clinical and laboratory evaluation: Anthropometric measurements were performed by trained medical staff. The weight and height of the patients were measured with a calibrated scale after the patients had removed their shoes and any heavy clothing. The body mass index (BMI) was calculated as weight (kg) divided by transition time (s) from the first systolic peak to the inflection point of the reflection waveform. A digital volume pulse (DVP) interface. The infrared sensor was placed on the right index finger. For each measurement, DVP was recorded every 5 seconds for a total of 1 minute. The area under the curve of each DVP was measured automatically using the system from the finger. CI was derived by dividing the average area under the curve of the finger DVP by the brachial pulse pressure. The average of measurements in 1 minute was used for analysis.

SI was measured in the right index finger by a commercially available photoplethysmograph (MicroMedical, Gillingham, UK). SI was formulated automatically by computer as body height (m) divided by transition time (s) from the first systolic peak to the inflection point of the reflection waveform of DVP.

Definitions of metabolic syndrome: Participants having 3 or more of the following criteria were defined as having metabolic syndrome according to the Taiwan Bureau of National Health Insurance: waist circumference greater than 90 cm in men and 80 cm in women; serum triglyceride level of at least 150 mg/dL; HDL-C less than 40 mg/dL in men and 50 mg/dL in women; blood pressure of at least 130/85 mmHg (including using antihypertensive medication); or a glucose level of at least 100 mg/dL (including the use of antidiabetic medication, insulin or oral agents).

Statistical analysis: Continuous variables are presented as the mean ± standard deviation (SD). Differences between groups were compared using Student’s t-test or the χ² test, as appropriate. Except for a priori confounders, such as age, gender, mean blood pressure, heart rate, and BMI, we selected other potential confounders, which were significantly different (Table 1). Multivariate linear regression analysis models controlling for important confounders were used for assessment of the independent determinants of SI and CI in patients both without DM and with pre-DM. A P value < 0.05 was considered statistically significant. All analyses were performed with SPSS version 11.5 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Clinical characteristics between each group: There were 33 patients without DM (15 men, 37 ± 10 years-old), 53 patients with pre-DM (34 men, 45 ± 11 years-old), and 34 subjects with DM (21 men, 48 ± 10 years-old). Both pre-DM and DM patients had significantly higher age, body weight, BMI, waist circumference, and both systolic and diastolic blood pressures than patients without DM. In the blood examination, we found
that both pre-DM and DM patients had higher glucose and HbA1c, higher HOMA index, lower HDL, higher hsCRP, and lower adiponectin levels than patients without DM (Table I). With regard to arterial stiffness indices, patients with pre-DM and DM had lower CI (3.8 ± 2.1 versus 5.2 ± 3.0 units; P < 0.05 and 3.6 ± 1.8 versus 5.2 ± 3.0 units; P < 0.05, respectively) and higher SI (8.0 ± 2.0 versus 6.7 ± 1.6 m/s; P < 0.01 and 9.4 ± 2.3 versus 6.7 ± 1.6 m/s; P < 0.001, respectively) than patients without DM. Between pre-DM and DM patients, BMI (26.8 ± 4.5 versus 30.0 ± 5.7 kg/m²; P < 0.01), waist circumference (90 ± 14 versus 99 ± 14 cm; P < 0.001), HOMA index (3.0 ± 2.4 versus 6.8 ± 8.2; P < 0.01), hsCRP (2.0 ± 2.2 versus 3.7 ± 2.7 μg/mL; P < 0.01), and adiponectin (2.5 ± 1.2 versus 1.9 ± 1.0 μg/mL; P = 0.05) were significantly different. There was no difference in medications between patients without DM and pre-DM (Table I).

Independent determinants of SI and CI with regard to different glucose homeostasis indices in non-DM and pre-DM patients: Using multivariate linear regression analysis adjusted for confounders (age, gender, mean blood pressure, heart rate, BMI, hsCRP, adiponectin, and HbA1c) in model 1 of Table II, we found that age (P < 0.001), heart rate (P < 0.01), hsCRP (P < 0.05) and HbA1c (P < 0.01) were independent determinants for SI (whole model R² = 0.50, P < 0.001). Using the same analysis adjusted for confounders (age, gender, mean blood pressure, heart rate, BMI, hsCRP, adiponectin, and HOMA index) in model 2 of Table II, age (P < 0.001), heart rate (P < 0.05), and HOMA index (P < 0.05) were independent determinants for SI (whole model: R² = 0.47, P < 0.001). Although fasting glucose was added in place of HbA1c or HOMA index in the same model, it was not an independent determinant for SI (whole model: R² = 0.49, P < 0.01; fasting glucose: P > 0.05).

Using multivariate linear regression analysis adjusted for confounders (age, gender, mean blood pressure, heart rate,
In model 1 of Table III, we found that male gender ($P < 0.01$) and hsCRP ($P < 0.05$) were independent determinants for CI (whole model $R^2 = 0.28$, $P < 0.05$). Using the same analysis adjusted for confounders (age, gender, mean blood pressure, heart rate, BMI, hsCRP, adiponectin, and HOMA index) in model 2 of Table III, male gender ($P < 0.01$), hsCRP ($P < 0.05$), and HOMA index ($P < 0.05$) were independent determinants for CI (whole model $R^2 = 0.34, P < 0.01$). Fasting glucose was also added in place of HbA1c or HOMA index in the same model, and it was not an independent determinant for CI (whole model $R^2 = 0.38, P < 0.05$; fasting glucose: $P > 0.05$).

We also found that pre-DM patients with metabolic syndrome had a higher SI but similar CI compared to subjects without metabolic syndrome (Figure). There were no statistically significant differences of SI with regard to each component of metabolic syndrome, including obesity, high blood pressure, high triglyceride level, and low high-density lipoprotein in pre-DM patients (data not shown).

**Discussion**

**Main findings:** The results of the current study add to the body of evidence that increasing arterial stiffness both in peripheral and large arteries exists in pre-DM patients. We also demonstrated a strong relationship between HbA1c or HOMA index and two arterial stiffening indices independent of other known risk factors for premature vascular disease. Both HbA1c and HOMA index are independent determinants for SI, a validated, noninvasive measure of large artery stiffness. Metabolic syndrome also contributes to the increasing SI in pre-DM patients. Regarding the new peripheral arterial stiffness index, CI, HOMA index is an independent factor. Although the structural integrity of the vascular wall is determined by a number of diverse and potentially modifiable pathogenic mechanisms, impaired glucose regulation, characterized in particular by insulin resistance, is a readily treatable example of an alternative path-
way promoting arterial stiffness.

Association between glucose homeostasis indices and different arterial stiffness indices in pre-DM: Different criteria for classification of subjects with impaired glucose metabolism and different measurements of arterial stiffness may result in entirely different conclusions and clinical implications. In middle-aged adults and elderly patients (45~85 years of age), the pre-DM state of IFG is associated with an increase in arterial stiffening that primarily impacts regions exclusive of the ascending thoracic aorta. Total arterial compliance, measured using magnetic resonance imaging techniques, is worse in subjects with IFG compared with those with normal fasting glucose; however, proximal thoracic aortic stiffness and left ventricular mass are similar in subjects with IFG and normal fasting glucose. The Hoorn Study revealed that subjects with impaired glucose tolerance and DM had arterial stiffening in both the central and peripheral arterial system using planimetry and tonometry and that the central arterial stiffness of those with impaired glucose tolerance was intermediate in severity between the group with normal glucose tolerance and DM.

In our current study, we also observed that pre-DM patients have statistically significantly higher SI and lower CI than those without DM. SI, derived from the DVP measured by photoplethysmography, is a valid index of wave reflections and also an acceptable marker for large artery stiffness. CI, derived from our photoplethysmography system, may be clinically useful for evaluating arterial stiffness of small to medium sized arteries. We showed that both large and small arterial stiffening occurs in pre-DM patients in the current study. In Table III of our study, we found that the HOMA index, rather than fasting glucose and HbA1c, was an independent determinant for CI after adjusting for important confounders. Insulin resistance may be a predictor for early peripheral arterial stiffening in pre-DM patients.

Possible mechanisms of increased arterial stiffness in pre-DM: There are several possible mechanisms by which increased SI and decreased CI occurred in individuals with pre-DM. Elevations in blood glucose result in the formation and deposition of advanced glycation end products, which promote the crosslinking of collagen that stiffens the structural components of the arterial wall. It is not surprising that those with pre-DM exhibit abnormal vascular stiffness of the entire vascular tree because pre-DM also adversely impacts endothelial function, atherosclerosis, and vasomotor tone. Many of these processes inhibit endothelial nitric oxide synthase, which consequently impairs peripheral endothelial function and adversely affects vascular stiffness. We also showed pre-DM subjects had a significantly higher HOMA index than non-DM patients and insulin resistance was an important factor in the stiffening of arteries. HOMA index may reflect pro-inflammatory signals and increase systemic inflammation induced by visceral fat that alter insulin function and possibly the structural integrity of the vascular wall. Hs-CRP, an acute-phase reactant, is also a reliable marker of current inflammatory status. Increased hs-CRP level was an independent predictor of abnormal flow mediated dilation, which indicated systemic endothelial function, after adjusting for age, systolic and diastolic blood pressure, and total cholesterol. Systemic endothelial cell dysfunction may contribute to arterial stiffness. In the pre-DM patients in the present study, an increased HOMA index and increased hs-CRP level may result in systemic endothelial cell dysfunction, subsequently affecting arterial stiffness indices.

Individuals with IFG often exhibit reduced exercise capacity. We have previously showed that CI was lower in patients with risk factors and was associated with poor exercise capacity. This index may be clinically useful for evaluating exercise capacity related to peripheral arterial stiffness. Abnormal peripheral arterial endothelial function may be more responsible for exercise intolerance in individuals with IFG.

In this cross-sectional analysis of our data, subjects with pre-DM demonstrated higher waist circumference, higher blood pressure, and lower HDL compared with those without DM. These are all clinical features of the metabolic syndrome, which may be strongly associated with or even lead to arterial stiffness. We further found that each component of metabolic syndrome could not affect SI independently in pre-DM subjects. In the pre-DM stage, clustering of more atherosclerotic risk factors might reveal their significant effects on arterial stiffness.

Limitations: Some limitations merit consideration in this study. Firstly, we did not perform the 75 gram OGTT test in each participant. Some subjects may have been misclassified into a study group. Secondly, our study had a cross-sectional design, which hampered the assessment of cause and effect. Thirdly, good and steady DVP is necessary for these measurements; however, it was difficult to make DVP measurements using photoplethysmography in patients with deformed fingers, arrhythmias, or peripheral occlusive artery diseases. In the present study, analyzable DVP measurements were obtainable for every patient included. Fourthly, the population size was relatively small, and thus, comparisons and multivariable models should be interpreted with appropriate caution.

Conclusions: In conclusion, this study demonstrates that pre-DM patients have a lower CI, a novel peripheral arterial stiffness index, than non-DM patients. Increased insulin resistance may be associated with increased arterial stiffness in pre-DM patients. Metabolic syndrome may affect arterial stiffness in pre-DM subjects.

REFERENCES


