Original Article

The Combination of IMT and Stiffness Parameter $\beta$ is Highly Associated with Concurrent Coronary Artery Disease in Type 2 Diabetes

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Aims: The clinical implications of stiffness of the carotid artery (CA) have not been fully clarified in the prediction of coronary artery disease (CAD), although intima-media thickness (IMT) has been established as a surrogate marker. We examined the associations of stiffness parameter $\beta$ (ST) and IMT with concurrent CAD.

Methods: IMT and ST were measured by ultrasound in 439 nondiabetic subjects as a control and 1528 type 2 diabetic subjects (T2DM) with or without CAD in a cross-sectional study.

Results: Both IMT and ST significantly increased with age and group category, in the order of control, T2DM without CAD, and T2DM with CAD ($p<0.001$). The area under the curve on ROC analysis of ST for concurrent CAD was comparable to that for IMT. On multivariate logistic regression analysis, High IMT ($\geq 1.30$ mm) and High stiffness ($\geq 20.0$) had significant odds ratios for concurrent CAD (2.205, $p<0.001$ and 1.548, $p<0.05$, respectively). The group with High IMT and High Stiffness exhibited a stronger multivariate odds ratio (3.115, $p=0.0001$).

Conclusions: ST and IMT are associated with CAD and exhibited significant odds ratios for CAD. Our findings suggest that the combination of IMT and ST is a useful marker of atherosclerosis.


Key words; Carotid atherosclerosis, Type 2 diabetes, Coronary artery disease, Ultrasound

Introduction

One of the most important clinical issues in the management of diabetes is to prevent the development of cardiovascular disease, the main cause of death of individuals with diabetes. For this clinical purpose, the assessment of superficial arteries, especially the carotid arteries, by ultrasound is quite useful in terms of its high precision, repeatability, low cost, and non-invasiveness, compared with other imaging techniques, in the routine clinical setting. In particular, ultrasound with a high-resolution echo-tracking system enables the assessment of two properties of local atherosclerosis at the same time, i.e. both morphological and functional changes of arterial walls$^{1-4}$. Intima-media thickness (IMT) is a well-recognized representative surrogate marker of morphological changes, and its clinical implications have been investigated in many studies$^{5-11}$. A recent review indicated the validity of IMT of the carotid artery in predicting the incidence of coronary artery disease (CAD)$^{10-12}$.

On the other hand, few studies have examined the elastic properties of the carotid artery by ultrasound, such as arterial distensibility, compliance, Peterson elastic modulus (Ep), and stiffness parameter $\beta$.$^{3, 4, 13, 14}$. These indices of elasticity are used for mechanistic analyses in pathophysiology, pharmacology, and therapeutics, rather than epidemiological

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studies. Stiffness parameter $\beta$ is unique among these indices since it features correction for the ratio of systolic and diastolic blood pressures and minimal effects of acute changes in blood pressure. Increased stiffness parameter $\beta$ of the carotid artery and/or aorta has been reported to be associated with chronic kidney disease, latent symptoms of peripheral artery disease, insulin resistance, and hypo-adiponectinemia. Furthermore, stiffness parameter $\beta$ in T2DM has been found to be, at least in part, reversibly improved by aerobic exercise and the insulin sensitizer pioglitazone. These findings suggest the possibility of a close association of stiffness parameter $\beta$ with CAD and that it may be useful as a predictive marker for concurrent CAD; however, to date, no studies have examined whether stiffness parameter $\beta$ is associated with and/or predicts the development of CAD.

The aim of the present study was to investigate the association of both stiffness parameter $\beta$ and IMT of the carotid artery (CA) with the concurrence of CAD in a large number of T2DM and control subjects in cross-sectional fashion. We present here the cut-off level for IMT and stiffness parameter $\beta$ of the carotid artery determined from the distribution in control subjects and odds ratios for concurrent CAD.

### Subjects and Methods

#### Subjects

A total of 1,967 subjects, 1,068 men and 899 women, ranging from 15 to 87 years, were consecutively selected from patients attending our diabetes center at Osaka City University Hospital from 1993 to 2007, and from participants in the health check program of Osaka Municipal Health Promotion Center (Table 1). They consisted of 1528 type 2 diabetic subjects (T2DM) and 439 nondiabetic subjects as a control group (Control). The known duration of diabetes of the T2DM subjects, obtained by attending diabetologists taking their medical history was 10.7 ± 8.8 (SD) years, and ranged from 1 to 42 years. The diagnosis of diabetes was based on the criteria of the American Diabetes Association, that of hypertension on WHO/ISH, and of hyperlipidemia on the Japan Atherosclerosis Society (JAS) Guidelines. Four hundred thirty-three subjects with T2DM were treated with dietary therapy alone, 367 with sulfonylureas, 44 with alpha-glucosidase inhibitors, 15 with biguanide, 23 with insulin secretagogues (nateglinide or metformin), and all with alpha-glucosidase inhibitors. A total of 439 subjects were without diabetes, with 221 with type 2 diabetes (T2DM), 150 with type 1 diabetes (T1DM), and 68 with gestational diabetes (GDM). The known duration of diabetes of the T1DM subjects, obtained by attending diabetologists taking their medical history was 8.8 ± 4.8 (SD) years, and ranged from 1 to 42 years. The diagnosis of diabetes was based on the criteria of the American Diabetes Association, that of hypertension on WHO/ISH, and of hyperlipidemia on the Japan Atherosclerosis Society (JAS) Guidelines. Four hundred thirty-three subjects with T2DM were treated with dietary therapy alone, 367 with sulfonylureas, 44 with alpha-glucosidase inhibitors, 15 with biguanide, 23 with insulin secretagogues (nateglinide or metformin), and all with alpha-glucosidase inhibitors. A total of 439 subjects were without diabetes, with 221 with type 2 diabetes (T2DM), 150 with type 1 diabetes (T1DM), and 68 with gestational diabetes (GDM).

### Table 1. Clinical characteristics of T2DM with and without CAD and the control group

<table>
<thead>
<tr>
<th></th>
<th>T2DM With CAD</th>
<th>T2DM Without CAD</th>
<th>All T2DM</th>
<th>Control Nondiabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66 ± 9</td>
<td>60 ± 11</td>
<td>61 ± 11</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 ± 3.8</td>
<td>24.3 ± 4.0</td>
<td>24.3 ± 4.0</td>
<td>23.4 ± 4.3</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>15.4 ± 10.4</td>
<td>10.3 ± 8.4</td>
<td>10.7 ± 8.8</td>
<td>124 ± 18</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134 ± 21</td>
<td>133 ± 21</td>
<td>133 ± 21</td>
<td>124 ± 18</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70 ± 10</td>
<td>75 ± 11</td>
<td>74 ± 11</td>
<td>73 ± 10</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>136 ± 39</td>
<td>142 ± 42</td>
<td>142 ± 42</td>
<td>95 ± 8</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.2 ± 1.5</td>
<td>8.1 ± 1.8</td>
<td>8.1 ± 1.8</td>
<td>5.2 ± 0.4</td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>115 ± 35</td>
<td>126 ± 36</td>
<td>125 ± 36</td>
<td>129 ± 38</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>46 ± 14</td>
<td>51 ± 14</td>
<td>53 ± 10</td>
<td>61 ± 17</td>
</tr>
<tr>
<td>sCreat (mg/dL)</td>
<td>1.19 ± 0.96</td>
<td>0.86 ± 0.66</td>
<td>0.89 ± 0.69</td>
<td>0.70 ± 0.28</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>41 (27.7)***</td>
<td>343 (24.9)***</td>
<td>384 (25.1)***</td>
<td>43 (9.8)</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>76 (51.4)***</td>
<td>390 (28.3)***</td>
<td>466 (30.5)***</td>
<td>89 (20.3)</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>148 (100)***</td>
<td>0 (0)***</td>
<td>148 (9.7)***</td>
<td>10 (2.3)</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>1.36 ± 0.75</td>
<td>1.06 ± 0.53</td>
<td>1.09 ± 0.56</td>
<td>0.79 ± 0.40</td>
</tr>
<tr>
<td>Stiffness parameter $\beta$</td>
<td>17.3 ± 7.3***</td>
<td>14.8 ± 6.2***</td>
<td>15.0 ± 6.4***</td>
<td>11.6 ± 5.4***</td>
</tr>
</tbody>
</table>

All values are the mean ± SD or the number with the percentage of subjects in parentheses. Abbreviations: BMI, body mass index; SBP and DBP, systolic and diastolic blood pressures; FPG, fasting plasma glucose; LDL- or HDL-c, low-density or high-density lipoprotein cholesterol; CAD, coronary artery disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; IMT, intima-media thickness. $^*$, $p<0.05$; $^{**}$, $p<0.01$; $^{***}$, $p<0.001$ compared with control, T2DM with, and T2DM without CAD groups by ANOVA (Scheffe test) or chi-square test.
glinide), 18 with thiazolidinediones (15 pioglitazone, 3 troglitazone), 372 with insulin and 256 with a combination of drugs among sulfonylureas, a-glucosidase inhibitors, buiguaniide, pioglitazone, and glinide. The nondiabetic subjects included 84 subjects with hypertension and 256 with hyperlipidemia. Fifty-three nondiabetic subjects and 466 T2DM had both hypertension and hyperlipidemia. Four hundred sixty-six subjects with T2DM and 89 control subjects were treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), and 384 diabetic subjects and 43 control subjects with angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEIs). Subjects who met the following criteria were excluded from this study: those with type 1 diabetes, other types of diabetes, and those with serum creatinine ≥7.0 mg/dL and/or undergoing chronic dialysis therapy. Written informed consent was obtained from all participants, and the study was approved by the local ethics committee.

CAD was diagnosed based on the following criteria: 1) past history of attack and/or treatment for myocardial infarction and/or angina pectoris, 2) abnormal ischemic findings of the electrocardiogram (ECG) and/or myocardial scintigraphy at rest and/or during exercise load, and 3) definitive findings of stenosis on coronary angiography (CAG) by cardiologists. The ischemic changes of ECG included abnormal Q waves, and/or specific ST-T changes with ST depression and/or negative T wave on ECG. Significant stenosis of the coronary artery by coronary angiography was defined as greater than 75% stenosis. In patients with 50–75% stenosis of the coronary artery, or no examinations of CAG, cardiologists made a diagnosis of CAD according to the total findings of myocardial scintigraphy, echocardiography, in addition to symptoms and ECG findings. The existence or inexistence of CAD was reviewed from the medical records of each patient by attending diabetologists and registered in the patient database. According to these criteria, 148 T2DM subjects and 10 nondiabetic controls diagnosed with concurrent CAD. Among these CAD subjects, 111 were finally verified by CAG (42 subjects with a past history of coronary artery bypass graft operation, 60 with percutaneous coronary intervention, and 8 with medication alone) and 47 subjects diagnosed by cardiologists according to the criteria stated above.

Measurement of IMT and Stiffness Parameter β by Ultrasound

The IMT and stiffness parameter β of the common carotid artery were measured by an ultrasonic phase-locked echo-tracking system, which was equipped with a high-resolution real-time 13 MHz linear scanner (ProSound SSD 6500, Aloka, Tokyo), as previously reported. In brief, the examination included approximately 4 cm of the common carotid artery. This region was scanned bilaterally in longitudinal and transverse projections. The image was focused on the far wall of the artery. IMT was measured in both carotid arteries at the site of the most advanced atherosclerotic lesion which exhibited the greatest distance between the lumen-intimal interface and the media-adventitia interface of the far wall. Stiffness parameter β, an index of arterial wall stiffness, was calculated as ln (Ps/Pd) × Dd/(Ds-Dd), where Ps and Pd are systolic and diastolic blood pressures and Ds and Dd are systolic and diastolic inner diameters of the artery, respectively. We used the greatest carotid IMT, including plaque and stiffness parameter β, as a marker of atherosclerotic change in the carotid arteries.

Physical and Laboratory Measurements

Blood pressure was determined by the conventional cuff method using a mercury sphygmomanometer after the subject had rested for at least 15 min. Blood was withdrawn after an overnight fast for analysis of serum concentrations of glucose, total cholesterol, triglyceride, HDL cholesterol, and HbA1c by standard laboratory methods.

Statistical Analysis

All values are the means ± SD unless otherwise indicated. Statistical analysis was performed using the StatView 5 system (SAS Institute, Cary, NC) and SPSS 15.0J system (SPSS Japan Inc., Tokyo). Student’s t-test, analysis of variance (ANOVA) with Scheffe’s test, chi-square test, and receiver operating characteristic curve (ROC) analysis were used as appropriate. Logistic regression models were also used to determine odds ratios with their 95% confidence intervals (95% CI) for IMT and stiffness parameter β for concurrent CAD. P values < 0.05 were considered significant.

Results

Clinical Characteristics of Subjects with T2DM and Controls

The clinical characteristics of subjects with T2DM and controls are shown in Table 1. Age, BMI, systolic and diastolic blood pressure, fasting plasma glucose, HbA1c, and serum creatinine were significantly higher in T2DM than in control subjects. Age, known duration of diabetes, and serum creatinine level in T2DM...
Both IMT and stiffness parameter \( \beta \) in the T2DM group with and without CAD were significantly higher than in the control group (IMT, \( 1.36 \pm 0.75, 1.06 \pm 0.53, 0.79 \pm 0.40, p < 0.001 \); ST, \( 17.3 \pm 7.3, 14.8 \pm 6.2, 11.6 \pm 5.4, p < 0.001 \), respectively). Both IMT and stiffness parameter \( \beta \) significantly increased with age and group category, in the order of control, T2DM without CAD, and T2DM with CAD \( (p < 0.0001 \text{ for age groups and } p < 0.001 \text{ for group category}) \) (Fig. 1).

In the control group, the 95th percentile of IMT was 1.30 mm, while that of stiffness parameter \( \beta \) was 20.0. For all subjects, the sensitivity and specificity of IMT and stiffness parameter \( \beta \) for the prediction of concurrent CAD were explored by ROC analysis, as shown in Fig. 2. The cut-off level for the greatest sensitivity and specificity for IMT was 1.18 mm (sensitivity 0.480, specificity 0.806) and for stiffness parameter \( \beta \) was 13.3 (sensitivity 0.658, specificity 0.538). The area under the curve (AUC) for IMT \( (0.672, 95\%CI \ 0.626-0.719) \) was comparable to that for stiffness parameter \( \beta \) \( (0.629, 95\%CI 0.583-0.675) \).

We next determined the odds ratios of IMT or stiffness parameter \( \beta \) with 95th percentile cut-offs to predict concurrent CAD in all subjects. Subjects with greater than 1.30 mm IMT or a stiffness parameter \( \beta \) of at least 20 were categorized into the High IMT or High Stiffness group, respectively. Subjects with both High IMT (\( \geq 1.30 \text{ mm} \)) and High Stiffness (\( \geq 20 \)) were categorized into the High IMT/ST group. Logistic regression analyses were performed with the presence of CAD as a dependent variable, and age, sex \( (\text{male}=1) \), systolic blood pressure, diabetes \( (=1) \), HbA1c, serum creatinine level, High IMT, and High Stiffness as independent variables (Table 2). Both High IMT and Stiffness groups had significant odds ratios for the presence of CAD (3.585, 95\%CI 2.538-
5.064, \( p < 0.0001 \) and 2.468, 1.701–3.582, \( p < 0.0001 \), respectively. After adjustment for age, sex, diabetes, and BP, the odds ratios for High IMT and Stiffness groups were still significant (2.205, 1.520–3.201, \( p < 0.001 \), and 1.548, 1.024–2.339, \( p = 0.038 \), respectively). Furthermore, the High IMT/ST group exhibited stronger univariate and multivariate odds ratios (6.195, 3.746–10.245, \( p < 0.0001 \), and 3.115, 1.751–5.540, \( p = 0.0001 \)) than High IMT and High Stiffness groups.

### Discussion

The present study revealed that both stiffness parameter \( \beta \) and IMT of CA were closely associated with the presence of diabetes and CAD in a population of 1967 subjects. High IMT and stiffness parameter \( \beta \) exhibited predictive multivariate odds ratios for concurrent CAD, which were further strengthened by the combination of high IMT and stiffness parameter \( \beta \); therefore, in addition to the specific characteristics of stiffness parameter \( \beta \), as recently reviewed \(^4\) and reported by us \(^{20-22, 24-26}\), our findings suggest that the combination of arterial stiffness and IMT determined by ultrasound is a unique tool for the evaluation of atherosclerosis in type 2 diabetes.

IMT of the carotid artery has been established as a surrogate marker or predictor of CAD by many cross-sectional \(^{5,7, 9, 29}\) and longitudinal studies \(^{8, 10, 11}\). Kablak-Zeimicka et al. \(^7\) found in a study of 558 CAD patients assessed by CAG that those with a mean IMT of greater 1.15 mm had a 94% probability of having CAD, with sensitivity of 65% and specificity of 80% in patients with a high risk of CAD. Another study showed that in 270 CAD patients, the ROC area was 0.64 to 0.76 for IMT of the carotid artery in predicting the presence of coronary lesions with >50% diameter stenosis in coronary arteries \(^{29}\). In a population of 297 patients with hypertension and CAD, IMT, as well as stenosis of the coronary arteries, was found to be a predictor of death, and patients with low IMT (equal to or less than 1.13 mm) exhibited better survival for 5 years than those with high IMT \(^{10}\). In the EDUCATE study, carotid atherosclerosis with IMT of greater than 1 mm had an odds ratio of 2.7 for the prediction of future cardiovascular events, with sensitivity and specificity for severe CAD of 72% and 49%, respectively \(^{11}\). Recent meta-analysis showed that patients with IMT higher than the cut-off level of 0.97–1.18 mm had significant year-incident rates of CAD of 1.21 to 1.64% \(^{12}\). The cut-off level and AUC determined by ROC analysis of IMT in our study were comparable to those in previous studies \(^7, 29\) of subjects verified to have CAD by coronary angiography. Furthermore, the odds ratio for the prediction of CAD with IMT was comparable to those in previous studies \(^{10, 11}\).

There have been fewer studies of the clinical implications of stiffness parameter \( \beta \) than of IMT. We and several other investigators have reported that stiffness parameter \( \beta \) is associated with left ventricular function \(^{30, 31}\), insulin resistance \(^{22, 23, 32, 33}\), peripheral artery disease \(^{21}\), decreased GFR \(^{20}\), and drug treatments \(^{15, 24-26, 34, 35}\). These findings suggest the possible use of stiffness parameter \( \beta \) as both a surrogate marker of atherosclerosis in treatment and a predictor of CAD. Hirai et al. first demonstrated that stiffness parameter \( \beta \) of CA and aorta increased with the number of stenoses of coronary arteries as determined by CAG \(^{17}\). Alan et al. found that IMT and stiffness parameter \( \beta \) in the CAD group were higher than those in the control group, and that the sensitivity, specificity, and positive predictive and negative predictive val-

### Table 2. Odds ratios of clinical factors for concurrent CAD determined by logistic regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Age, sex, BP, and DM-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95%CI</td>
</tr>
<tr>
<td>Age per 10 years</td>
<td>1.96***</td>
<td>1.62–2.38</td>
</tr>
<tr>
<td>Sex (male = 1, female = 0)</td>
<td>2.77***</td>
<td>1.90–4.02</td>
</tr>
<tr>
<td>SBP (per 10 mmHg)</td>
<td>1.07***</td>
<td>0.99–1.15</td>
</tr>
<tr>
<td>DM (yes = 1, no = 0)</td>
<td>4.66***</td>
<td>2.43–8.92</td>
</tr>
<tr>
<td>HbA1C (per %)</td>
<td>1.14***</td>
<td>1.06–1.23</td>
</tr>
<tr>
<td>sCrE (per mg/dL)</td>
<td>1.61***</td>
<td>1.36–1.89</td>
</tr>
<tr>
<td>High IMT (≥ 1.30 mm)</td>
<td>3.59***</td>
<td>2.54–5.06</td>
</tr>
<tr>
<td>High Stiffness (≥ 20.0)</td>
<td>2.47***</td>
<td>1.70–3.58</td>
</tr>
<tr>
<td>High IMT/ST</td>
<td>6.20***</td>
<td>3.75–10.25</td>
</tr>
</tbody>
</table>

Values are odds ratios with 95% confidence intervals. *, \( p < 0.05 \); **, \( p < 0.01 \); ***, \( p < 0.001 \)}
ues of IMT for angiographic CAD diagnosis were 70%, 75%, 77%, and 66%, respectively. In elderly men, stiffness parameter $\beta$ was also found to be a significant predictor of cardiovascular mortality (HR, 1.68) during 48-month follow-up.

In the present study, the odds ratio in the High Stiffness group was comparable to that in the High IMT group; however, the combination of IMT and stiffness parameter $\beta$ was found to yield a higher predictive value for concurrent CAD than either index alone. It is also reported that increased arterial stiffness may decrease diastolic pressure, and subsequently coronary artery blood flow, even in the absence of coronary artery stenosis. This impact of arterial stiffness on myocardial function independent of atherotic change may explain the high association of the combination of two indexes. Taken together, these advantages increase the usefulness of measuring stiffness parameter $\beta$ in addition to IMT of the carotid artery.

There are a few limitations to our study. First, since it was a cross-sectional study, we were unable to determine whether stiffness parameter $\beta$ truly predicts the future incidence of CAD from our findings. Second, all our subjects with CAD were not necessarily diagnosed with CAD by CAG. Third, our subjects were recruited from a university hospital or health check program of a Municipal Health Promotion Center; thus, there is a possibility of selection bias of subjects. Our findings suggest that not only IMT but also stiffness parameter $\beta$ are useful markers of atherosclerosis. Further prospective study is needed to clarify the predictive value of stiffness parameter $\beta$ as well as IMT of CA for CAD.

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