



# Femoral artery wall thickness and stiffness in evaluation of peripheral vascular disease in type 2 diabetes mellitus

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## Abstract

Stiffening and thickening of arterial wall are two important components of atherosclerosis. The purpose of this study was to evaluate the effects of femoral artery wall stiffness on clinical manifestation of peripheral vascular disease (PVD) in type 2 diabetes mellitus. The subjects were 315 patients with type 2 diabetes. Presence of intermittent claudication and/or leg pain at rest and reduced ankle-brachial blood pressure index (ABI < 0.9) were used as a subjective and an objective index of PVD, respectively. Femoral artery intima-media thickness (FA-IMT) and stiffness parameter  $\beta$  (FA-stiffness  $\beta$ ) were measured by ultrasound methods. Symptomatic patients ( $N = 58$ ) showed greater values for both FA-IMT and FA-stiffness  $\beta$  than those without symptom ( $N = 257$ ). Similarly, patients with reduced ABI ( $N = 56$ ) had greater FA-IMT and FA-stiffness  $\beta$  than those without ( $N = 259$ ). However, correlation between FA-IMT and FA-stiffness  $\beta$  was not impressive, especially in the symptomatic patients. To evaluate the effect of FA-stiffness  $\beta$  on PVD symptoms, the subjects were divided into three subgroups according to FA-IMT, and then FA-stiffness  $\beta$  was compared between those with and without PVD symptoms in each subgroup. The symptomatic patients had greater FA-stiffness  $\beta$  values than the asymptomatic subjects in all the three subgroups. Multiple logistic regression analysis indicated that the presence of PVD symptoms was associated more closely with increased FA-stiffness  $\beta$  than with increased FA-IMT, whereas reduced ABI was associated more closely with FA-IMT than with FA-stiffness  $\beta$ . These data suggest that stiffening of arterial wall has a significant impact on PVD manifestations, particularly on the leg symptoms, in patients with type 2 diabetes. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Intima-media thickness; Stiffness  $\beta$ ; Arteriosclerosis obliterance; Peripheral vascular disease; Diabetes

## 1. Introduction

Peripheral vascular disease (PVD) is one of the major manifestations of atherosclerosis. The prevalence of PVD is higher in patients with diabetes mellitus than the general population [1–3]. PVD is a significant predictor for amputation [4] and mortality [5] in type 2 diabetes. Intermittent claudication and reduction of ankle-brachial blood pressure index (ABI) are both of diagnostic value for the presence and severity of PVD in lower extremity or arteriosclerosis obliterance (ASO) [6].

Atherosclerosis involves the combination of fatty degeneration (atherosis) and stiffening (sclerosis) of the arterial wall [7]. Atherosclerosis results in thickening of the arterial wall, narrowing of the lumen and blood flow impairment. Intima-media thickness (IMT) can be measured non-invasively by high-resolution B-mode ultrasonography and gives morphological information of the arterial wall thickening [8]. We [9,10] and others [11] have shown that IMT of carotid artery was greater in patients with diabetes mellitus than non-diabetic subjects. As compared with the morphological alterations, sclerotic changes of arteries have received less attention due to the greater difficulty entailed in their assessment. For example, standard evaluations by histopathology and serial angiography are both sensitive to atherosclerosis,

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but not to sclerotic changes [4]. Sclerotic changes of arterial wall are measured in terms of stiffness, distensibility, or compliance [12]. Pulse wave velocity is also measured in the assessment of sclerotic changes of arteries [12]. Several studies including ours have shown the advanced sclerotic changes of large arteries in patients with diabetes [10,13–16], hypertension [17] and chronic renal failure [18,19].

So far, it is not well demonstrated to what extent stiffness and thickness of the femoral artery correlate with each other. In addition, little is known whether the sclerotic change of femoral artery has any impacts on clinical manifestations of PVD independent of morphological changes of the artery. The aim of this study was to evaluate the possible impact of femoral artery wall stiffening on PVD in patients with type 2 diabetes mellitus.

## 2. Subjects and methods

### 2.1. Subjects

The subjects were 315 consecutive patients with type 2 diabetes mellitus who were hospitalized in the Osaka City University Hospital for the treatment of diabetes or for attending an educational course on diabetes. The diagnosis of diabetes was based on a previous history of diabetes or criteria according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [20]. Of the patients, 77 (24%) was treated with insulin injection, 157 (50%) received oral anti-diabetic agents, and 81 (26%) were treated only with life style modification. In addition, 211 (67%) and

153 (49%) received medications for dyslipidemia and hypertension, respectively.

History was carefully taken for the leg symptoms attributable to PVD. Intermittent claudication was taken as a PVD symptom when the exercise-pain-rest cycle was constant. Leg pain that occurred at rest was also diagnosed as PVD when the patient had experienced typical intermittent claudication. Complaints such as numbness, tingling and weakness of the lower limb were not included in the PVD symptoms in the present study, because it was difficult to distinguish them from symptoms of peripheral neuropathy. Orthopedic diseases in the lumbar spine were also excluded. Of the 315 patients, 49 had intermittent claudication and 9 had leg pain at rest attributable to PVD. These 58 patients were pooled and called the symptomatic group, and the remaining 257 patients were called the asymptomatic group in the present study. The clinical characteristics of these two groups are given in Table 1. The two groups were different in age, duration of diabetes, hemoglobin A1c (HbA1c), serum creatinine, total cholesterol, triglycerides and systolic blood pressure.

### 2.2. Blood pressure and ABI

Blood pressure was measured with a standard mercury sphygmomanometer and cuffs adapted to arm circumference, after the subject had rested in the supine position for at least 5 min. The systolic and diastolic blood pressure levels were taken as the points of appearance and disappearance of Korotokof sounds, respectively. The average of three measurements was used for analysis.

Table 1  
Clinical characteristics of the subjects (median (range))<sup>a</sup>

	Asymptomatic	Symptomatic	Significance
Number of subjects	257	58	–
Gender (male/female)	150/107	36/22	NS <sup>b</sup>
Age (yr)	60 (16–83)	64 (43–82)	$P = 0.008$
Body mass index (kg/m <sup>2</sup> )	22.7 (14.3–33.8)	23.2 (17.3–33.6)	NS
DM therapy (LSM/OHA/INS)	14/29/18	67/128/59	NS <sup>b</sup>
Duration of DM (yr)	9 (0.1–35)	15 (0.1–37)	$P < 0.0001$
FPG (mmol/l)	9.2 (2.9–19.8)	8.2 (4.2–19.2)	$P = 0.061$
HbA1c (%)	9.0 (4.6–17.6)	8.4 (4.5–15.6)	$P = 0.024$
Serum creatinine (μmol/l)	62 (26–1158)	71 (18–919)	$P < 0.0001$
Total cholesterol (mmol/l)	5.15 (2.09–10.71)	5.59 (3.34–12.49)	$P = 0.011$
Triglycerides (mmol/l)	1.24 (0.46–5.49)	1.58 (0.76–5.82)	$P = 0.0001$
HDL-cholesterol (mmol/l)	1.14 (0.52–3.03)	1.09 (0.52–2.09)	NS
Systolic BP (mmHg)	134 (83–213)	152 (97–242)	$P < 0.0001$
Diastolic BP (mmHg)	73 (40–109)	75 (48–114)	NS
Smoking index (cigarette-year)	220 (0–2580)	600 (0–3000)	$P = 0.067$

<sup>a</sup> The patients with type 2 diabetes mellitus were divided into two categories, the asymptomatic and symptomatic groups according to the criteria described in the text. Difference between the two groups was assessed by Mann-Whitney's U-test and <sup>b</sup> $\chi^2$  test. Median (range) for continuous variables. Abbreviations: LSM, life style modification; OHA, oral hyperglycemic agent; INS, insulin injection; FBP, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; BP, blood pressure.

ABI was determined by measuring the systolic blood pressure at the posterior tibial artery with an 8-MHz continuous-wave Doppler probe (Fukuda Denshi Co. Ltd., Tokyo, Japan) in the supine position. The ratio of the systolic blood pressure values at the ankle and the brachial arteries was calculated for each leg, and the lower ABI was used in this study. The cut-off level was set at 0.9 for ABI according to the studies by Fowkes et al. [21] and by Schroll and Munck [22]. Fifty-six patients out of the 315 subjects were categorized in the low ABI group having ABI less than 0.9, whereas the remaining 259 patients had normal ABI of 0.9 or greater. In the low ABI group, 26 patients had PVD symptoms whereas 30 did not.

### 2.3. Measurements of thickness and stiffness of femoral artery by ultrasound

Femoral artery intima-media thickness (FA-IMT) was measured by a high-resolution B-mode ultrasonography using a real-time ultrasonograph with a 10-MHz in-line Sectascanner (SSD 650 CL, Aloka Co. Ltd., Tokyo, Japan) as described elsewhere [9,23,24]. In this study, the femoral artery of the leg showing a lower ABI was scanned distal to inguinal ligament at the site where the artery divides into the superficial and the profound femoral arteries, including ~4 cm proximal and 1 cm distal to the flow divider. The greatest thickness of intima-media complex at longitudinal projections was used for analysis in this study. The intra-observer coefficient of variation for FA-IMT was 3.2% when 20 subjects were examined at two different occasions.

Femoral artery stiffness parameter  $\beta$  was measured by monitoring vessel diameter and pulsatile changes in diameter by echo-tracking sonography [25], using a recently developed ultrasound echo-tracking system [15]. The system consists of an electronic echo-tracking instrument interfaced with a real-time ultrasound scanner and fitted with a 7.5 MHz linear array transducer (Aloka SSD610, Aloka Co. Ltd.). In short, two electronic markers automatically lock to the luminal interface of echoes from the anterior and posterior sides of vessel wall and follow the pulsatile movement of the vessel wall. The markers are displayed on the real-time monitor to indicate the level at which the registration is performed. In this system, the smallest detectable movement is 10  $\mu\text{m}$  [26]. The stiffness parameter  $\beta$  of the arterial wall was calculated as following:

Stiffness parameter  $\beta = (\ln(P_s/P_d)) \times D_d/(D_s - D_d)$ ,

where  $P_s$  and  $P_d$  are the systolic and end-diastolic blood pressure levels in mmHg, respectively.  $D_s$  and  $D_d$  are the corresponding vessel diameters in mm. Each subject was examined three times at each location and the average was used for analysis. The coefficient of

variation for FA-stiffness  $\beta$  was 3.6% for the patients with type 2 diabetes mellitus.

### 2.4. Blood sampling and assays

Fasting blood samples were obtained in the morning of the day of the ultrasound examinations. Plasma glucose and HbA1c were measured by a glucose oxidase method and high performance liquid chromatography, respectively. Total cholesterol and triglycerides were measured by enzymatical methods [27]. High-density lipoprotein (HDL) cholesterol was determined in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with dextran sulfate and  $\text{Mg}^{2+}$  [28]. Other measurements were done by routine laboratory methods.

### 2.5. Statistical analysis

Data were summarized as median (range) for continuous variables. Difference between two groups was assessed by Mann-Whitney's U-test. Difference in prevalence was evaluated by  $\chi^2$  test. Correlation was assessed by Spearman's rank correlation analysis. Multiple logistic regression analysis was employed to determine factors, which were independently associated with categories of a dependent variable.

## 3. Results

### 3.1. FA-IMT and FA-stiffness $\beta$ in relation to PVD symptoms

Thickness of femoral artery was compared between the diabetic patients with and without lower limb PVD symptoms. The symptomatic patients had greater FA-IMT than the asymptomatic patients. Also, the patients with symptoms had greater FA-stiffness  $\beta$  values than those without (Fig. 1).

### 3.2. FA-IMT and FA-stiffness $\beta$ in relation to ABI

Similar comparison was made using ABI, instead of the symptoms, as an objective index of lower limb PVD. The patients with reduced ABI ( $<0.9$ ) showed a significant increase in either FA-IMT or FA-stiffness  $\beta$  as compared with those with ABI of 0.9 or greater (Fig. 2).

### 3.3. Correlation between FA-IMT and FA-stiffness $\beta$

Correlation was examined between FA-IMT and FA-stiffness  $\beta$  (Fig. 3). The correlation between these parameters of femoral atherosclerosis was statistically significant but not very impressive in the asymptomatic

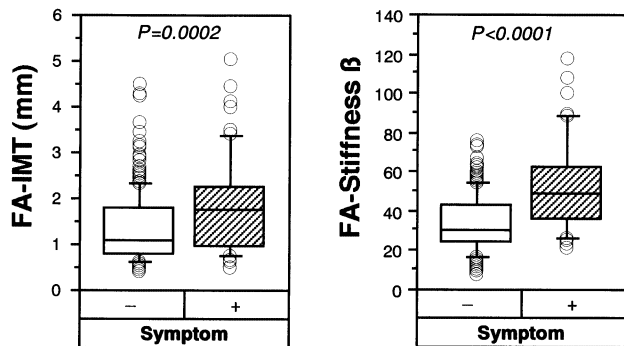


Fig. 1. Comparison of thickness and stiffness of femoral arteries between diabetic patients with and without PVD symptoms. Horizontal lines indicate 10th, 25th, 50th, 75th and 90th percentile levels.  $P$ -values by Mann-Whitney's U-test. FA-IMT, femoral artery intima-media thickness.

group ( $r_s = 0.338$ ,  $P < 0.0001$ ). In the symptomatic group, such correlation was no longer significant ( $r_s = 0.221$ ,  $P = 0.10$ ).

#### 3.4. IMT-matched comparison of stiffness $\beta$ between groups with and without symptoms

Since both FA-IMT and FA-stiffness  $\beta$  were associated with lower limb PVD symptoms, IMT-matched comparisons were made to examine the effect of FA-stiffness  $\beta$  on the symptoms independent of FA-IMT (Fig. 4). The subjects were stratified into three subgroups according to their FA-IMT ( $< 1$  mm, 1–2 mm,  $> 2$  mm), and then FA-stiffness  $\beta$  was compared between the symptomatic and asymptomatic patients in the same subgroup. In either subgroup, the patients with symptoms showed a greater FA-stiffness  $\beta$  than those without.

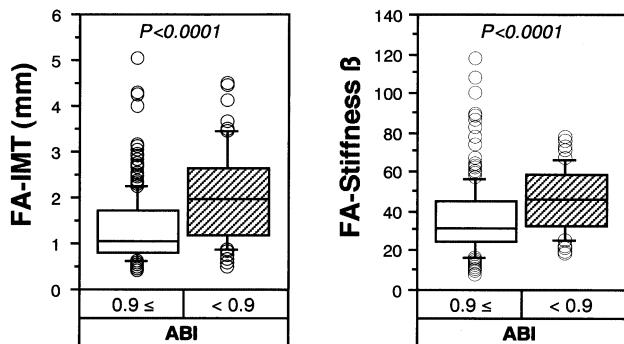


Fig. 2. Comparison of thickness and stiffness of femoral arteries between diabetic patients with and without reduced ABI. Horizontal lines indicate 10th, 25th, 50th, 75th and 90th percentile levels.  $P$ -values by Mann-Whitney's U-test. ABI, ankle-brachial blood pressure index; FA-IMT, femoral artery intima-media thickness.

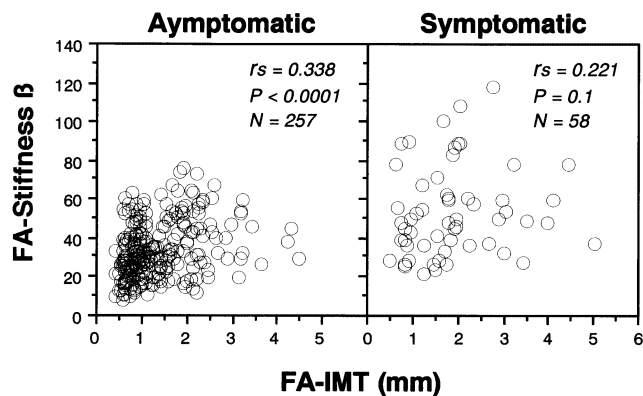


Fig. 3. Correlation between thickness and stiffness of femoral arteries in diabetic patients (A) with and (B) without PVD symptoms. Pearson's correlation coefficient ( $r_s$ ) was 0.221 ( $P = 0.10$ ) and 0.338 ( $P < 0.0001$ ) in the (A) symptomatic and (B) asymptomatic patients, respectively. FA-IMT, femoral artery intima-media thickness.

#### 3.5. IMT-matched comparison of stiffness $\beta$ between groups with and without reduced ABI

Similar IMT-stratified comparisons were done using ABI instead of the symptoms (Fig. 5). In these comparisons, however, the difference in FA-stiffness  $\beta$  was not significant between the patients with and without reduced ABI whose FA-IMT was less than 1 mm or greater than 2 mm. It was only significant in those with FA-IMT of 1–2 mm.

#### 3.6. Multiple logistic regression analysis of factors affecting PVD symptoms

Multiple logistic regression analysis was performed to further examine whether the association between FA-stiffness  $\beta$  and the PVD symptoms was independent of FA-IMT and other confounding variables (Table 2).

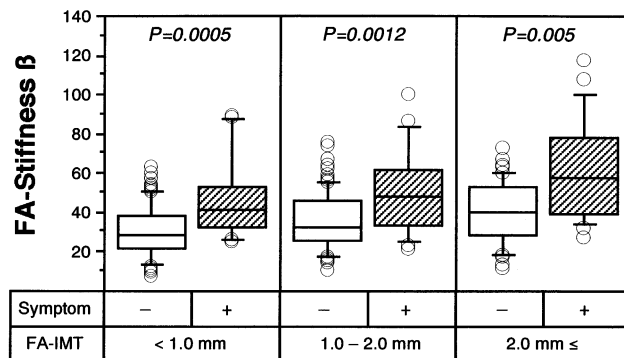


Fig. 4. FA-IMT-stratified comparison of femoral artery stiffness between diabetic patients with and without PVD symptoms. The subjects were divided into three subgroups according to FA-IMT, and then FA-stiffness parameter  $\beta$  was compared between those with and without PVD symptoms. Horizontal lines indicate 10th, 25th, 50th, 75th and 90th percentile levels.  $P$ -values by Mann-Whitney's U-test. FA-IMT, femoral artery intima-media thickness.

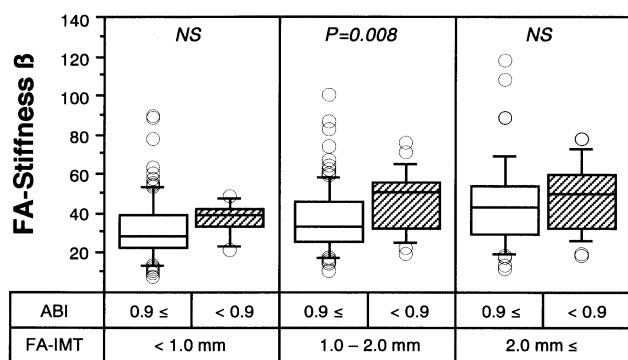


Fig. 5. FA-IMT-stratified comparison of femoral artery stiffness between diabetic patients with and without reduced ABI. The subjects were divided into three subgroups according to FA-IMT, and then FA-stiffness parameter  $\beta$  was compared between those with and without PVD symptoms. Horizontal lines indicate 10th, 25th, 50th, 75th and 90th percentile levels. *P*-values by Mann-Whitney's U-test. FA-IMT, femoral artery intima-media thickness; ABI, ankle-brachial blood pressure index.

Model 1 included age, gender, smoking, HbA1c, duration of diabetes, total cholesterol, triglycerides, HDL-cholesterol, serum creatinine, and blood pressure as independent variables explaining the presence of symptoms. Among these, duration of diabetes, triglycerides and systolic blood pressure were associated with an increased risk for the presence of the PVD symptoms, whereas a higher HbA1c was associated with a reduced risk for the symptoms. Next, FA-IMT was added to the model (model 2), but FA-IMT showed no significant association with the symptoms independent of the other confounders. When FA-stiffness  $\beta$  was entered in place of FA-IMT in

model 3, FA-stiffness  $\beta$  showed a highly significant association with the lower limb symptoms, and the result indicated that 1-unit increase in FA-stiffness increased the risk by 5.3%. In the final model (model 4) which included both FA-IMT and FA-stiffness  $\beta$  simultaneously, FA-stiffness  $\beta$  again showed a significant association with the presence of lower limb symptoms.

### 3.7. Multiple logistic regression analysis of factors affecting ABI

Multiple logistic regression analysis was also performed to examine the factors independently affecting ABI (Table 3). The independent variables used in this analysis were the same as those in Table 2. Model 1 indicated that age, smoking, duration of diabetes and systolic blood pressure were significantly and independently associated with an increased risk for ABI reduction less than 0.9. When FA-IMT was added to the model (model 2), FA-IMT was the most important factor for ABI reduction. The model indicated that 1-mm increase in FA-IMT almost doubled the risk for having a lowered ABP. In that model, the associations of age, smoking, duration of diabetes and systolic blood pressure with ABI became less significant, suggesting close interactions between FA-IMT and these variables. When FA-stiffness  $\beta$  was entered in place of FA-IMT (model 3), FA-stiffness  $\beta$  showed no significant impact on ABI. In the final model (model 4), a reduced ABI was closely associated with FA-IMT but not with FA-stiffness  $\beta$ .

Table 2  
Multiple logistic regression analysis of factors affecting symptoms of lower limb PVD in 315 patients with type 2 diabetes mellitus<sup>a</sup>

Independent variables	Model 1	Model 2	Model 3	Model 4
Age	1.039 (0.999–1.081)	1.033 (0.992–1.076)	1.035 (0.992–1.080)	1.032 (0.998–1.078)
Male gender	1.041 (0.431–2.514)	0.987 (0.406–2.398)	1.332 (0.512–3.443)	1.299 (0.501–3.370)
Smoking index	1.001 (1.000–1.001)	1.000 (1.000–1.001)	1.000 (0.999–1.001)	1.000 (0.999–1.001)
Duration of diabetes	1.060 (1.022–1.100)**	1.058 (1.019–1.099)**	1.056 (1.015–1.099)**	1.055 (1.014–1.098)**
HbA1c	0.852 (0.736–0.986)*	0.860 (0.742–0.995)*	0.862 (0.708–0.977)*	0.836 (0.711–0.983)*
Total cholesterol	1.225 (0.934–1.607)	1.234 (0.939–1.621)	1.103 (0.820–1.484)	1.112 (0.826–1.498)
Triglycerides	1.903 (1.161–3.119)*	1.874 (1.139–3.082)*	2.076 (1.157–3.724)*	2.047 (1.139–3.679)*
HDL-cholesterol	0.958 (0.341–2.694)	0.960 (0.340–2.714)	0.797 (0.256–2.478)	0.796 (0.255–2.480)
Serum creatinine	1.000 (0.997–1.002)	0.999 (0.997–1.002)	1.000 (0.997–1.002)	1.000 (0.997–1.002)
Systolic blood pressure	1.017 (1.000–1.034)*	1.015 (0.998–1.032)	1.001 (0.982–1.021)	1.000 (0.981–1.020)
Diastolic blood pressure	0.997 (0.965–1.031)	0.998 (0.965–1.031)	1.014 (0.978–1.051)	1.014 (0.978–1.051)
FA-IMT	–	1.290 (0.874–1.905)	–	1.133 (0.742–1.731)
FA-stiffness $\beta$	–	–	1.053 (1.03–1.077)***	1.052 (1.029–1.077)***
R <sup>2</sup>	0.201***	0.206***	0.282***	0.283***

<sup>a</sup> Odd ratios for the symptomatic group relative to the asymptomatic group.

\* *P* < 0.05; \*\* *P* < 0.01; \*\*\* *P* < 0.001.

Table 3  
Multiple logistic regression analysis of factors affecting ABI in 315 patients with type 2 diabetes mellitus<sup>a</sup>

Independent variables	Model 1	Model 2	Model 3	Model 4
Age	1.052 (1.011–1.094)*	1.037 (0.995–1.082) <sup>#</sup>	1.052 (1.011–1.095)*	1.037 (0.995–1.082) <sup>#</sup>
Male gender	0.541 (0.223–1.311)	0.441 (0.175–1.113)	0.552 (0.227–1.342)	0.445 (0.176–1.127)
Smoking index	1.001 (1.000–1.001)*	1.001 (1.000–1.001) <sup>#</sup>	1.001 (1.000–1.001)*	1.001 (1.000–1.001) <sup>#</sup>
Duration of diabetes	1.038 (1.002–1.076)*	1.034 (0.996–1.073) <sup>#</sup>	1.036 (1.000–1.074)*	1.033 (0.995–1.073) <sup>#</sup>
HbA1c	1.018 (0.891–1.163)	1.047 (0.913–1.202)	1.020 (0.893–1.166)	1.048 (0.913–1.203)
Total cholesterol	1.131 (0.869–1.471)	1.145 (0.875–1.498)	1.116 (0.855–1.459)	1.141 (0.870–1.497)
Triglycerides	1.149 (0.732–1.806)	1.129 (0.715–1.781)	1.134 (0.720–1.787)	1.124 (0.710–1.778)
HDL-cholesterol	0.946 (0.363–2.463)	0.954 (0.354–2.570)	0.911 (0.347–2.393)	0.944 (0.348–2.561)
Serum creatinine	1.001 (0.998–1.003)	1.000 (0.818–1.287)	1.001 (0.998–1.003)	1.000 (0.998–1.003)
Systolic blood pressure	1.019 (1.003–1.035)*	1.013 (0.998–1.003)	1.016 (0.999–1.034) <sup>#</sup>	1.012 (0.994–1.031)
Diastolic blood pressure	0.998 (0.965–1.031)	1.000 (0.967–1.035)	1.000 (0.967–1.034)	1.001 (0.967–1.037)
FA-IMT	–	2.019 (1.377–2.959)**	–	2.008 (1.364–2.954)**
FA-stiffness $\beta$	–	–	1.007 (0.988–1.026)	1.002 (0.983–1.022)
R <sup>2</sup>	0.141**	0.186**	0.143**	0.186**

<sup>a</sup> The table gives odd ratios (95% confidence intervals) for the low ABI (less than 0.9) group relative to the normal ABI (0.9 or greater) group.

<sup>#</sup>  $P = 0.05$ – $0.08$ ; \* $P < 0.05$ ; \*\* $P < 0.001$ .

### 3.8. Power of ABI, FA-IMT and FA-stiffness $\beta$ in predicting symptomatic PVD

Since ABI is more usually used in the screening and monitoring of PVD than ultrasonographic measurement of FA-IMT and/or FA-stiffness  $\beta$ , we determined whether these measurements could provide further information over ABI in predicting symptomatic PVD. As shown in Table 4, ABI was a significant predictor of symptomatic PVD (model 1). When FA-IMT was combined with ABI, FA-IMT did not increase the predictive power of ABI (model 2). In contrast, FA-stiffness  $\beta$  was a significant predictor independent of ABI (model 3) and FA-IMT (model 4). The predictive power was significantly improved when ABI and FA-stiffness  $\beta$  were measured simultaneously.

## 4. Discussion

Although stiffening of arterial wall is one of the important changes resulting from atherosclerosis, little has been demonstrated whether the stiffening of artery per se has any impacts on clinical manifestations of atherosclerosis. Thickening of large arteries including carotid and femoral arteries was demonstrated in type 1 [29,30] and type 2 diabetes [9–11], hypertension [31], hyperlipidemia [32], and chronic renal failure [23]. Sclerotic changes of the aorta and carotid artery were also demonstrated in these diseases [10,16,18,19,29]. To the best of our knowledge, this is the first study that measured both thickness and stiffness of the same segment of femoral artery to examine the differential roles of these changes in relation to the subjective and objective indices of PVD. The results indicate that stiffening of the femoral artery is closely associated

with the symptoms of PVD independent of wall thickening in the type 2 diabetes patients.

We first expected a close correlation between FA-stiffness  $\beta$  and FA-IMT. However, the correlation between these measurements was not very impressive. It is important to emphasize that the correlation was no longer significant in patients with the PVD symptoms, suggesting thickening and stiffening of the femoral arteries do not necessarily occur in parallel. In the present study, ABI was closely related to FA-IMT in both univariate and multivariate analyses. On the other hand, the association between ABI and FA-stiffness  $\beta$  was significant in univariate comparisons but not in multiple logistic regression analysis. In contrast, we demonstrated that PVD symptom was closely related to FA-stiffness  $\beta$  in both univariate and multivariate analyses, whereas the association between the symptoms and FA-IMT was significant in the univariate comparison but not in multiple logistic regression analysis. These results suggest preferential associations between FA-IMT and ABI and between FA-stiffness  $\beta$  and the symptoms.

Of clinical interest is the underlying mechanism for such a preferential association of the PVD symptoms with arterial wall stiffness over thickness. One possible explanation would be that sclerotic changes of arteries might impair the blood flow during the diastole. It is well known that elastic arteries work as “the second heart” and exert so-called “Windkessel function” [33]. That is, large arteries receive the pulsatile output from the heart in the systole by passively expanding their diameters. Then the arterial diameter returns to the initial level and the released extra energy maintains a continuous blood flow to downstream during the diastole. Therefore, stiffening or loss of the cushioning function of large arteries could result in impaired blood

Table 4  
Power of ABI, FA-IMT and FA-stiffness  $\beta$  in predicting symptomatic PVD<sup>a</sup>

	Model 1	Model 2	Model 3	Model 4
ABI < 0.9 (vs. 0.9 or greater)	2.524* (1.197–5.320)	2.354* (1.086–5.106)	2.510* (1.134–5.554)	2.512* (1.103–5.720)
FA-IMT (per 1 mm increase)		1.149 (0.763–1.731)		0.998 (0.636–1.567)
FA-stiffness $\beta$ (per 1 unit increase)			1.053** (1.029–1.076)	1.053** (1.029–1.077)
R <sup>2</sup>	0.220**	0.221**	0.299**	0.299**

<sup>a</sup> The table gives odds ratios (95% confidence intervals) for the symptomatic group ( $N = 58$ ) relative to the asymptomatic group ( $N = 257$ ) in multiple logistic regression models adjusted for age, gender, smoking index, duration of diabetes, HbA1c, total cholesterol, triglycerides, HDL-cholesterol, serum creatinine, systolic blood pressure and diastolic blood pressure.

\*  $P < 0.05$ ; \*\*  $P < 0.001$ .

supply during the diastole. Importantly, since ABI is the ratio of systolic blood pressure at the ankle and the arm, the index gives information on the systolic phase only.

Increased serum triglyceride level was a significant risk factor for the presence of PVD symptom whereas total cholesterol was not in the present study. Recent studies reappraise the higher atherogenicity of triglyceride-rich lipoproteins including very low density lipoprotein (VLDL) remnants and intermediate density lipoprotein (IDL) as compared with that of low density lipoprotein [34,35]. Reports of atherosclerosis in patients with primary type III hyperlipoproteinemia [36] emphasized the increased frequency of PVD in this lipid disorder. As reviewed by Brewer et al. [37], approximately 33% of patients with the type III phenotype had PVD and 20% had both PVD and coronary artery disease at the time of diagnosis. Senti et al. [38] showed the importance of IDL in PVD. According to Kasama et al. [39], IDL level correlated well with serum triglycerides, and that IDL level was elevated even in normolipidemic patients with type 2 diabetes [39]. Although we did not measure IDL in this study, the independent association between serum triglycerides and PVD symptoms may indicate the adverse impacts of IDL and other remnant lipoproteins on PVD.

A higher HbA1c level was associated with a lower risk for the presence of PVD symptoms including intermittent claudication and leg pain at rest in this study. This does not imply that hyperglycemia has a favorable effect on femoral atherosclerosis, since HbA1c level did not correlate with FA-IMT or FA-stiffness  $\beta$  (data not shown). It rather suggests impaired nerve function due to hyperglycemia [40,41]. It is well known that diabetic peripheral neuropathy often masks the pain due to myocardial ischemia [42].

We determined whether measurement of FA-IMT and/or FA-stiffness  $\beta$  could provide further information over ABI in predicting symptomatic PVD, since ABI is more usually used in the screening and monitoring of PVD. The results clearly indicated that combination of FA-stiffness  $\beta$ , but not FA-IMT, increased the predictive power of ABI, suggesting that the simulta-

neous assessment of arterial stiffness could improve the diagnostic precision based on ABI.

In conclusion, the present study revealed that FA-stiffness  $\beta$  was associated with PVD symptoms independent of FA-IMT in patients with type 2 diabetes. The results may implicate the importance of assessing sclerotic changes in addition to morphological evaluation of arteries.

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