Prevalence and Major Risk Factors of Reduced Flow Volume in Lower Extremities With Normal Ankle-Brachial Index in Japanese Patients With Type 2 Diabetes

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OBJECTIVE — To clarify the prevalence and major risk factors of reduced flow volume in lower extremities with normal ankle-brachial index (ABI) in Japanese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We recruited 208 consecutive type 2 diabetic patients and 33 age-matched nondiabetic subjects (control group) admitted to our hospital. Thirty-two of the patients had low ABI (<0.90) and intermittent claudication (peripheral arterial disease [PAD] group), and 176 patients had normal ABI (>0.9) (non-PAD group). We evaluated flow volume and resistive index, as an index of arterial resistance to blood flow, at the popliteal artery using gated two-dimensional cine-mode phase-contrast magnetic resonance imaging.

RESULTS — Simple linear regression analysis showed a negative correlation between resistive index and total flow volume in the non-PAD group ($r = -0.714$, $P < 0.001$). We defined the means ± 2 SD of these parameters in the control group as the normal range; abnormal resistive index was >1.017, and abnormal flow volume was <50.8 ml/min. The non-PAD group was divided according to the levels of these parameters: 80 patients had both normal resistive index and normal flow volume (normal group); of 96 patients with higher resistive index, 63 had normal flow volume (borderline group) and 33 had reduced flow volume (reduced group). Multiple regression analysis demonstrated that the major risk factors for reduced flow volume were age, hypertension, and diabetic nephropathy ($r^2 = 0.303$, $P < 0.001$).

CONCLUSIONS — The prevalence of patients without PAD with reduced flow volume in the lower extremities was 16% ($n = 33$) and comparable with that of patients with PAD with intermittent claudication ($n = 32$), suggesting that increase in arterial resistance to blood flow may be one of the major causes of lower extremity arterial disease in Japan.

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Abbreviations: 2D-cine-PC MRI, two-dimensional cine-mode phase-contrast magnetic resonance imaging; ABI, ankle-brachial index; CV_{R-R}, coefficient of variation of the R-R interval; dBP, diastolic blood pressure; FPG, fasting plasma glucose; PAD, peripheral arterial disease; sBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Peripheral arterial disease (PAD), which is usually caused by atherosclerotic occlusive lesions of the lower leg arteries, reduces flow volume to the lower limb during exercise or at rest (1). To aid in identifying patients at high risk of PAD, the ankle-brachial index (ABI) is generally used (2). However, patients with diabetes (3) or renal failure (4) have rigid or calcified lower leg arteries, rendering the arteries incompressible and causing a falsely elevated ABI. Although a negative ABI does not exclude PAD, an abnormal ABI is extremely useful in predicting an increase in cardiovascular mortality in epidemiological studies. Low ABI is closely associated with increased risk of death from myocardial infarction (5–7). In contrast, we previously reported that increased arterial resistance to blood flow because of increased arterial wall stiffness limits flow volume in the lower-extremity arteries in diabetic patients, although they have a normal ABI (non-PAD) (8). Some patients without PAD had critically reduced flow volume in the lower extremities and were considered at high risk for foot lesions. Although the existence of this condition is recognized in clinical settings, its prevalence and major risk factors are still unclear.

To evaluate the clinical significance in diabetic patients of non-PAD with reduced flow volume in the lower extremities, we examined the usefulness of waveform analysis at the popliteal artery using gated two-dimensional cine-mode phase-contrast magnetic resonance imaging (2D-cine-PC MRI) (9). This newly developed noninvasive technique can provide physiological flow data such as direction, velocity, and volume through the cardiac cycle. Its accuracy and reproducibility have been confirmed in healthy subjects (10).

The present study was designed to clarify the prevalence and major risk fac-

tors in Japanese diabetic patients of non-PAD with reduced flow volume in the lower extremities using gated 2D-cine-PC MRI.

RESEARCH DESIGN AND METHODS

Diabetic patients and control subjects

We enrolled 208 type 2 diabetic patients ranging in age from 50 to 69 years and 33 age-matched nondiabetic subjects (control group) admitted consecutively to our hospital between July 1997 and February 2002. All 208 diabetic patients were admitted for strict glycemic control or assessment of diabetic complications. Thirty-two of the patients had an ABI <0.90 in at least one leg (PAD group) (2), and the presence of occlusive lesions and developing collateral arterial branches from the aortic bifurcation to the femoral artery was confirmed by contrast angiography. These patients had intermittent claudication but no resting pain in the distal foot or ischemic foot ulcer. Intermittent claudication was defined as tightness or cramping discomfort in the calf, clearly provoked by walking, with rapidly increasing pain when walking quickly or uphill and being relieved within a few minutes of rest. The remaining 176 patients had normal ABI (>0.9) (non-PAD group) and sensation of coldness, which was considered as Fontaine grade 1, at the time of the study (11). The nondiabetic subjects were identified according to World Health Organization criteria (12) and had no history of either hypertension (>140/90 mmHg) (13) or dyslipidemia (total cholesterol [TC] >6.21 mmol/l) (14) at the time of the study. Patients who had apparent soft tissue necrosis or inflammatory signs on laboratory testing, foot edema caused by apparent heart failure, liver cirrhosis or severe nephropathy (serum creatinine >133 μmol/l), alcohol abuse, or acute illness were excluded from the study. The ethics committee of our institution approved the study, and informed consent was obtained from all patients before the examinations, which were performed during their hospital stay.

Clinical evaluations

The ABI was examined using a hand-held ultrasound Doppler (ES-1000SP; Nihon Kohden, Tokyo, Japan) to assess occlusive arterial disease in the lower extremities. Autonomic function was evaluated by the measurement of the coefficient of variation of the R-R interval (CV_{R-R}) during deep breathing monitored on an electrocardiogram (Cardimax FX-3301; Fukuda Denshi, Kyoto, Japan). A trained ophthalmologist carried out fundus ophthalmoscopies and classified diabetic patients as having no retinopathy, simple retinopathy corresponding to levels 21–53 of the modified Airlie House System, or proliferative retinopathy corresponding to levels 60–80 (15). Furthermore, diabetic patients with normoalbuminuria, microalbuminuria, or overt proteinuria were grouped as having a urinary albumin excretion rate <15, 15–200, or >200 μg/min, respectively, by 24-h urine collection in our university hospital. These patients were also classed as either current smokers or nonsmokers.

Magnetic resonance equipment

An MRI scanner at 1.5 Tesla (Signa Horizon-LX; GE Medical Systems, Milwaukee, WI) was used for the following experimental protocols. After a rest of at least 15 min, all patients were evaluated in the supine position in a temperature-controlled room at 25°C.

Flow analysis at the popliteal artery

To set up the individual flow analysis, the popliteal artery was depicted by two-dimensional time-of-flight magnetic resonance angiography. A single slice with 5 mm thickness was oriented perpendicular to the flow direction, and flow data were obtained using 2D-cine-PC MRI with 80 cm/s velocity encoding triggered by peripheral gating (8–10). Flow data were analyzed with the flow analysis version 5.8 software package (GE Medical Systems) to determine direction and velocity through the cardiac cycle. The instantaneous flow volume at 16 equally spaced time points through the cardiac cycle was calculated from the individual velocity images by integrating the velocity across the area of the vessel. The resultant 16 flow volumes allowed assessment of flow variations in pulsatility and hemodynamics during the cardiac cycle. The control group had a typically triphasic waveform at the popliteal artery that could clearly be separated into systolic, early diastolic, and late diastolic phases (9). Flow volumes in these cardiac phases were calculated from the integration of the waveform. A resistive index, which allows quantitative analysis of the waveform and is associated with arterial resistance to blood flow, has already been defined as (A − B)/A, in which A is the systolic peak velocity and B is the end-diastolic velocity (9).

Statistical analysis

Statistical evaluation was performed using StatView-J 5.0 software (SAS Institute, Cary, NC) on a Macintosh computer. Comparison between the diabetic patients and their respective control subjects was performed using the unpaired Student's *t* test. A multiple comparison of significant differences among the three groups was carried out by one-way ANOVA followed by Scheffe's *F* test. The χ^2 test for two by two or Bonferroni's test for two by three contingency tables was used to compare the frequencies between two or among three groups. Stepwise multiple regression analysis was performed to evaluate the association among late diastolic flow volume at the popliteal artery and various clinical characteristics of the subjects. Diabetic retinopathy and nephropathy were classified into three grades based on the severity. The *F* value was set at 4.0 at each step. Values were expressed as the means ± SD. We considered *P* values <0.05 to be statistically significant.

RESULTS

Clinical characteristics in all subjects

The 208 diabetic patients comprised 176 patients with normal ABI (>0.9) (non-PAD group) and 32 patients with abnormal ABI (<0.9) (PAD group) identified by conventional criteria. The clinical characteristics in these groups are shown in Table 1. The control, non-PAD, and PAD groups were comparable with respect to age, BMI, TC, triglycerides (TGs), and brachial diastolic blood pressure (dBP). Compared with the PAD group, the non-PAD group showed a higher HbA_{1c} level ($P < 0.05$) and lower brachial systolic blood pressure (sBP) ($P < 0.05$) and prevalence of male sex ($P < 0.05$) and smoking habit ($P < 0.01$). However, the duration of diabetes, fasting plasma glucose (FPG), HDL cholesterol, CV_{R-R}, fre-

Table 1—*Background data for diabetic patients with normal (non-PAD group) or abnormal (PAD group) ABI and age-matched nondiabetic subjects (control group)*

	Control group	Non-PAD group	PAD group
ABI	1.13 ± 0.09	1.15 ± 0.11	0.70 ± 0.13
n	33	176	32
Sex (male/female)	17/16	103/73*	27/5†
Age (years)	60.1 ± 6.5	60.9 ± 6.4	63.6 ± 6.0
BMI (kg/m^2)	22.6 ± 2.0	23.9 ± 3.4	22.7 ± 3.9
Duration of diabetes (years)	—	14.2 ± 8.5	17.5 ± 10.2
Treatment (D/OHD/I)	—	9/67/100	2/12/18
FPG (mmol/l)	5.30 ± 0.40	8.12 ± 2.26‡	8.17 ± 2.37‡
HbA_{1c} (%)	4.7 ± 0.4	8.8 ± 1.7*‡	8.1 ± 1.4‡
TC (mmol/l)	4.89 ± 0.62	5.00 ± 0.90	4.83 ± 0.80
HDL cholesterol (mmol/l)	1.38 ± 0.42	1.22 ± 0.37	1.12 ± 0.30†
TGs (mmol/l)	1.14 ± 0.33	1.46 ± 0.78	1.38 ± 0.47
sBP (mmHg)	122 ± 7	132 ± 12*‡	138 ± 14‡
dBP (mmHg)	76 ± 8	71 ± 10	72 ± 13
Smokers (%)	14 (42)	69 (39)§	29 (91)†
$CV_{R\text{-}R}$ (%)	3.2 ± 1.0	2.1 ± 1.1‡	2.1 ± 0.9‡
Retinopathy (%)	—	106 (60)	21 (66)
Nephropathy (%)	—	83 (47)	18 (56)

Data are means ± SD or *n* (%). D, diet; OHD, oral hypoglycemic drugs; I, insulin. †$P < 0.05$, ‡$P < 0.001$ vs. the control group; *$P < 0.05$, §$P < 0.01$ vs. the PAD group.

quency of retinopathy, and nephropathy were similar in the two groups. Heart rate (72 ± 8, 71 ± 12, and 73 ± 12 bpm) and total flow volume at the popliteal artery (90.6 ± 19.9, 78.4 ± 26.2, and 76.3 ± 31.5 ml/min) were similar in the control, non-PAD, and PAD groups. Compared with the control group, the non-PAD group showed lower late diastolic forward flow (16.7 ± 6.9 vs. 7.6 ± 8.5 ml/min, $P < 0.001$), although systolic flow volume (84.1 ± 15.8 vs. 83.3 ± 20.8 ml/min) and early diastolic flow reversal (−10.1 ± 7.6 vs. −12.4 ± 8.7 ml/min) were similar in the two groups. The resistive index was higher in the non-PAD group (1.013 ± 0.040, $P < 0.01$) and lower in the PAD group (0.844 ± 0.169, $P < 0.001$) than that in the control group (0.965 ± 0.026). In the PAD group, no significant association was found between total flow volume and resistive index.

Analysis of flow data for non-PAD patients

The distribution of the resistive index and total flow volume at the popliteal artery in the 176 patients in the non-PAD group is shown in Fig. 1. Simple linear regression analysis of these parameters revealed a significant negative correlation ($n = 176$, $r = -0.714$, $P < 0.001$). We defined the mean ±2 SD of the resistive index (ranging from 0.913 to 1.017) and total flow volume (ranging from 50.8 to 130.4 ml/min) in the control group as the normal range. Thus, abnormal resistive index was defined as >1.017 and abnormal total flow volume as <50.8 ml/min (Fig. 1). The non-PAD group was divided into three subgroups based on these levels: 80 patients had both normal resistive index and normal flow volume (normal group), the remaining 96 patients with abnormal resistive index comprised 63 patients with normal flow volume (borderline group), and 33 patients with reduced flow volume (reduced group).

The clinical characteristics of the normal, borderline, and reduced groups are shown in Table 2. The three groups showed similar values for prevalence of male sex, age, BMI, duration of diabetes, FPG, HbA_{1c}, TC, HDL cholesterol, TGs, dBP, ABI, prevalence of smoking habit, $CV_{R\text{-}R}$, and frequency of retinopathy or nephropathy. However, the sBP in the borderline ($P < 0.01$) and reduced ($P < 0.001$) groups was higher than that in the normal group.

The waveforms at the popliteal artery in these subgroups are shown in Fig. 2. Instantaneous flow volume at 16 equally spaced time points through the cardiac cycle was reconstructed. The normal group had a typically triphasic waveform at the popliteal artery that could clearly be separated into systolic, early diastolic, and late diastolic phases (Fig. 2*A*). Heart rates (73 ± 11, 69 ± 11, and 69 ± 14 bpm) were similar in the normal, borderline, and reduced groups. Compared with the normal group, the borderline group had lower forward flow during both the systolic (93.3 ± 16.9 vs. 85.2 ± 15.8 ml/min, $P < 0.01$) and late diastolic (14.3 ± 6.7 vs. 3.6 ± 5.2 ml/min, $P < 0.001$)

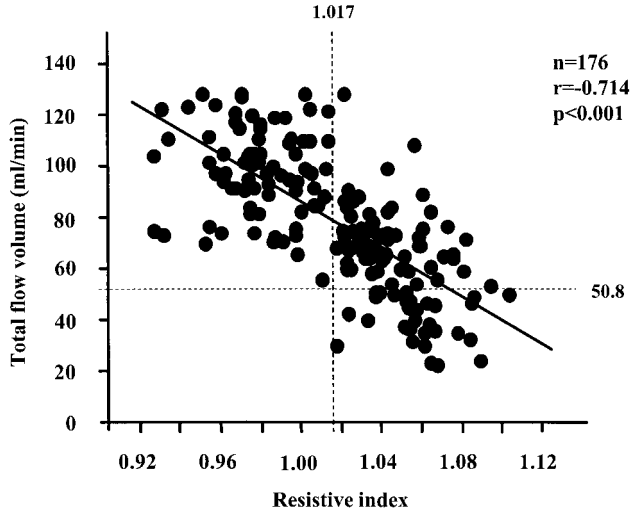

Figure 1—*Distribution of resistive index and total flow volume at the popliteal artery in 176 diabetic patients with normal ABI (non-PAD group). The means ± 2 SD for these parameters in the 33 nondiabetic subjects were defined as the normal range. Abnormal resistive index was thus defined as >1.017 and abnormal total flow volume as <50.8 ml/min. The non-PAD group was classified into normal, borderline, and reduced flow subgroups based on these levels.*

Table 2—*Background data for the 176 diabetic patients with normal ABI classified into three subgroups based on resistive index and total flow volume at the popliteal artery*

	Normal group	Borderline group	Reduced group
Resistive index	0.975 ± 0.022	1.038 ± 0.018	1.055 ± 0.020
total flow volume (ml/min)	98.8 ± 17.6	72.5 ± 13.1	40.4 ± 8.6
n	80	63	33
Sex (male/female)	47/33	33/30	23/10
Age (years)	60.3 ± 6.4	61.1 ± 6.5	61.7 ± 6.2
BMI (kg/m^2)	23.9 ± 3.4	24.3 ± 3.8	22.7 ± 2.4
Duration of diabetes (years)	13.9 ± 7.7	14.0 ± 9.4	15.4 ± 8.8
Treatment (D/OHD/I)	2/35/43	7/20/36	0/12/21
FPG (mmol/l)	7.96 ± 1.92	7.88 ± 2.11	8.99 ± 3.03
HbA_{1c} (%)	8.9 ± 1.6	8.7 ± 1.7	8.9 ± 1.9
TC (mmol/l)	4.97 ± 0.88	5.11 ± 0.91	4.87 ± 0.96
HDL cholesterol (mmol/l)	1.16 ± 0.36	1.27 ± 0.37	1.25 ± 0.41
TGs (mmol/l)	1.54 ± 0.85	1.47 ± 0.78	1.24 ± 0.50
sBP (mmHg)	127 ± 10	134 ± 14*	138 ± 10†
dBP (mmHg)	70 ± 8	73 ± 10	71 ± 11
ABI	1.16 ± 0.12	1.16 ± 0.09	1.12 ± 0.05
Smokers (%)	35 (44)	23 (37)	11 (33)
CV_{R-R} (%)	2.2 ± 1.2	2.0 ± 1.1	2.2 ± 1.2
Retinopathy (%)	41 (51)	41 (65)	24 (73)
Nephropathy (%)	31 (39)	30 (48)	22 (67)

Data are means ± SD or *n* (%). D, diet; OHD, oral hypoglycemic drugs; I, insulin. The 80 patients with both normal resistive index and normal flow volume and the 33 patients in whom both these parameters were abnormal are the normal and reduced groups, respectively. The remaining 63 patients comprise the borderline group. *$P < 0.01$, †$P < 0.001$ vs. the normal group.

phases and greater flow reversal during the early diastolic phase (−8.8 ± 7.0 vs. −16.3 ± 9.8 ml/min, $P < 0.001$) (Fig. 2*B*). Furthermore, compared with the borderline group, the reduced group had lower forward flow during both the systolic (85.2 ± 15.8 vs. 55.2 ± 10.7 ml/min, $P < 0.001$) and late diastolic (3.6 ± 5.2 vs. −1.2 ± 3.7 ml/min, $P < 0.001$) phases, although the early diastolic flow reversals (−16.3 ± 9.8 vs. −13.6 ± 6.6 ml/min) were similar (Fig. 2*C*).

Prevalence and major risk factors in patients without PAD with reduced flow volume

The prevalence of non-PAD with reduced flow volume was 16% ($n = 33$) and similar to that of PAD with intermittent claudication ($n = 32$). In our previous study, waveform analysis at the popliteal artery demonstrated that diabetic patients with stiffer arteries had a lower late diastolic flow volume (8). In the present study, late diastolic flow volume was more consistently associated with resistive index ($r = 0.774$, $P < 0.001$) than total flow volume ($r = 0.714$, $P < 0.001$). Therefore, late diastolic flow volume could be considered the better parameter to assess increased arterial resistance to blood flow. To characterize clinical variables determining arterial resistance to blood flow in the non-PAD group, we performed stepwise multiple regression analysis of the relation between late diastolic flow volume and 10 possible risk factors for atherosclerosis (age, duration of diabetes, FPG, HbA_{1c}, TC, HDL cholesterol, TGs, sBP, dBP, and percentage smokers), and three factors associated with diabetic microangiopathy (CV_{R-R}, retinopathy, and nephropathy). The age (β value = −0.242; *F* value = 14.1), sBP (β value = −0.315; *F* value = 21.7), and diabetic nephropathy (β value = −0.249; *F* value = 13.6) were identified as significant independent variables determining this flow parameter ($r^2 = 0.303$, $P < 0.001$).

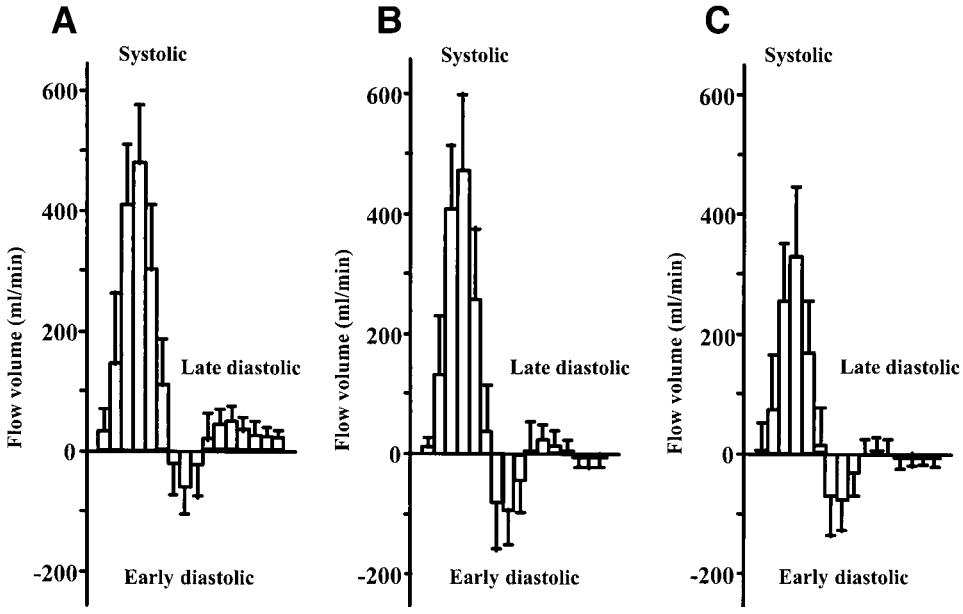

Figure 2—*Waveform analysis at the popliteal artery in 176 diabetic patients with normal ABI (non-PAD). The non-PAD group was divided into normal* (A), *borderline* (B), *and reduced* (C) *flow subgroups based on the resistive index and total flow volume at the popliteal artery. Instantaneous flow volumes at 16 equally spaced time points through the cardiac cycle were reconstructed. Values are expressed as means ± SD.*

CONCLUSIONS — Chronic insufficient arterial blood flow to the lower extremities can lead to intermittent claudication defined as calf pain on walking or exercise. The major cause of peripheral artery disease was suggested to be atherosclerotic occlusion of the lower leg arteries distal to the aortic bifurcation (PAD), resulting in a low ABI. Furthermore, as we previously reported, increased arterial wall stiffness increases arterial resistance to blood flow and limits total flow volume in the lower extremities in diabetic patients even when they show a normal ABI (non-PAD) (8). In the present study, we evaluated the diagnostic criteria, prevalence, and major risk factors in diabetic patients of non-PAD with reduced flow volume in the lower extremities.

Diagnostic criteria and clinical findings of non-PAD with reduced flow volume in the lower extremities

In the present study, we defined the means ± 2 SD of total flow volume at the popliteal artery in the nondiabetic subjects (ranging from 50.8 to 130.4 ml/min) as the normal range. Thus, abnormal total flow volume was defined as <50.8 ml/min. The phosphocreatine to inorganic phosphate ratio has been measured as an index of energy metabolism in the plantar muscle using ^{31}P-magnetic resonance spectroscopy as previously reported (9). Diabetic patients with low energy metabolism in the plantar muscle have been considered to be at high risk for foot lesions. When 60 diabetic patients were assigned to tertiles based on their levels of total flow volume at the popliteal artery, the lowest group (40.9 ± 14.1 ml/min) showed a significantly lower energy metabolism in the plantar muscle compared with the highest group (101.6 ± 15.0 ml/min). Simple linear regression analysis of these parameters showed a significant positive correlation ($n = 60$, $r = 0.400$, $P < 0.01$). Although we did not measure the phosphocreatine to inorganic phosphate ratio in the plantar muscle in the present study, we suggest that total flow volume at the popliteal artery <50.8 ml/min (mean = 40.4 ± 8.6 ml/min, $n = 33$) can be considered as a marker for patients at high risk of foot lesions.

Prevalence of non-PAD with reduced flow volume in the lower extremities

The ABI is widely used as a noninvasive measure of PAD in epidemiological studies. PAD is considered present when the ABI is <0.90 in at least one leg (2). The prevalence of low ABI in the general population was 19.1% in the Rotterdam study (16), of whom 6.3% suffered from intermittent claudication. Many studies have demonstrated an association between diabetes and the development of PAD. In the Hoorn study (17), the prevalence of low ABI in the diabetic patients was threefold that in the nondiabetic subjects (20.9 vs. 7.0%). Many population-based studies have revealed that the prevalence of low ABI is highly dependent on the geographic location of the subjects. The prevalence of low ABI was 16.7% in second-generation Japanese-American men with diabetes (18). In Japan, the prevalence of intermittent claudication was reported to be much lower than that in western countries (19). However, recent advances in the treatment of diabetes have increased the number of elderly patients with diabetes of longer duration, and adoption of a westernized lifestyle may have contributed to the gradual increase of this disease among Japanese patients with diabetes. In a recent study of such patients, the prevalence of low ABI was estimated to range from 9 to 12% and that of intermittent claudication from 0.2 to 10.9% (20). In the present study of 208 consecutive type 2 diabetic patients admitted to our hospital, the prevalence of non-PAD with reduced flow volume in the lower extremities was 16% ($n = 33$) and comparable with that of PAD with intermittent claudication ($n = 32$), suggesting that increase in arterial resistance to blood flow may be one of the major causes of lower-extremity arterial disease in Japan.

Major risk factors

Our statistical analysis of the major risk factors for non-PAD with reduced flow volume in the lower extremities demonstrated that age, sBP, and diabetic nephropathy were independent risk factors for this condition. Smoking habit was not correlated with this condition, indicating that the pathogenesis may be different from that of PAD (21). On the other hand, aging (4), renal function (4,22,23), and hypertension (24,25) are associated with decreased elasticity of the large arteries. Diabetic patients with chronic hyperglycemia have stiffer arteries (26). The nonenzymatic glycation of matrix proteins caused by chronic hyperglycemia (27), increased intima-media thickness (28), or medial arterial calcification may be responsible for the pathogenesis of vascular rigidity.

In conclusion, we clarified the prevalence among Japanese diabetic patients of non-PAD with reduced flow volume in the lower extremities. The major risk factors for this condition were identified as age, hypertension, and diabetic nephropathy.

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References

1. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, Strandness DE, Taylor LM: Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 94:3026–3049, 1996
2. Orchard TJ, Strandness DE: Assessment of peripheral vascular disease in diabetes: report and recommendations of an international workshop sponsored by the American Heart Association and the American Diabetes Association 18–20 September 1992, New Orleans, Louisiana. *Diabetes Care* 16:1199–1209, 1993
3. Young MJ, Adams JE, Anderson GF, Boulton AJM, Cavanagh PR: Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia* 36:615–621, 1993
4. Blacher J, London GM, Safar ME, Mourad JJ: Influence of age and end-stage renal disease on the stiffness of carotid wall material in hypertension. *J Hypertens* 17: 237–244, 1999
5. McKenna M, Wolfson S, Kuller L: The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 87:119–128, 1991
6. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D: Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 326:381–386, 1992
7. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D: Ankle-arm index as a predictor of cardiovascular disease and mortality in the cardiovascular health study. *Arterioscler Thromb Vasc Biol* 19: 538–545, 1999
8. Suzuki E, Kashiwagi A, Nishio Y, Egawa K, Shimizu S, Maegawa H, Haneda M, Yasuda H, Morikawa S, Inubushi T, Kikkawa R: Increased arterial wall stiff-

ness limits flow volume in the lower extremities in type 2 diabetic patients. *Diabetes Care* 24:2107–2114, 2001
9. Suzuki E, Kashiwagi A, Nishio Y, Kojima H, Maegawa H, Haneda M, Yasuda H, Morikawa S, Inubushi T, Kikkawa R: Usefulness of waveform analysis of popliteal artery in type II diabetic patients using gated magnetic resonance 2D-cine-PC imaging and ^{31}P spectroscopy. *Diabetologia* 43:1031–1038, 2000
10. Caputo GR, Masui T, Gooding GAW, Chang JM, Higgins CB: Popliteal and tibioperoneal arteries: feasibility of two-dimensional time-of-flight MR angiography and phase velocity mapping. *Radiology* 182:387–392, 1992
11. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN: Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 26:517–538, 1997
12. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
13. 1999 World Health Organization: International society of hypertension guidelines for the management of hypertension. *J Hypertens* 17:151–183, 1999
14. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
15. Diabetic Retinopathy Study Research Group: Report VII: a modification of the Airlie House classification of diabetic retinopathy. *Invest Ophthalmol Vis Sci* 21:210–226, 1981
16. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE: Peripheral arterial disease in the elderly: the Rotterdam study. *Arterioscler Thromb Vasc Biol* 18:185–192, 1998
17. Beks PJ, Mackaay AJC, De Neeling JND, De Vries H, Bouter LM, Heine RJ: Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn study. *Diabetologia* 38:86–96, 1995
18. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW: Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. *Diabetes* 36:730–739, 1987
19. Diabetes Drafting Group: The World Health Organization Multinational Study of Vascular Disease in Diabetics: prevalence of small vessel and large vessel disease in diabetic patients from 14 centers. *Diabetologia* 28:615–640, 1985
20. Matsuda A: Gangrene and ulcer of the lower extremities in diabetic patients. *Diabetes Res Clin Pract* 24:S209–S213, 1994
21. Kannel WB, McGee DL: Update on some epidemiologic features of intermittent claudication: the Framingham study. *J Am Geriatr Soc* 33:13–18, 1985
22. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 103:987–992, 2001
23. Lambert J, Smulders RA, Aarsen M, Donker AJM, Stehouwer CDA: Carotid artery stiffness is increased in microalbuminuric IDDM patients. *Diabetes Care* 21: 99–103, 1998
24. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M, Heiss G: Arterial stiffness and the development of hypertension: the ARIC study. *Hypertension* 34: 201–206, 1999
25. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, Thomas F, Pannier B, Asmar R, Zureik M, Safar M, Guize L: Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation* 105:1202–1207, 2002
26. Oxlund H, Rasmussen LM, Andreassen TT, Heickendorff L: Increased aortic stiffness in patients with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 32:748–752, 1989
27. Airaksinen KEJ, Salmela PI, Linnaluoto MK, Ikäheimo MJ, Ahola K, Ryhänen LJ: Diminished arterial elasticity in diabetes: association with fluorescent advanced glycosylation end products in collagen. *Cardiovasc Res* 27:942–945, 1993
28. Yamasaki Y, Kawamori R, Matsushima H, Nishizawa H, Kodama M, Kubota M, Kajimoto Y, Kamada T: Asymptomatic hyperglycaemia is associated with increased intimal plus medial thickness of the carotid artery. *Diabetologia* 38:585–591, 1995