UKPDS 59: Hyperglycemia and Other Potentially Modifiable Risk Factors for Peripheral Vascular Disease in Type 2 Diabetes

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OBJECTIVE — To determine the role of hyperglycemia in prospective analyses of peripheral vascular disease (PVD) in type 2 diabetes, taking into account other potential risk factors.

RESEARCH DESIGN AND METHODS — Potential risk factors for the development of PVD were examined in 3,834 of 5,102 individuals enrolled in the U.K. Prospective Diabetes Study (UKPDS) without PVD at diagnosis of diabetes, followed for 6 years, and for whom relevant data were available. PVD was defined as two of the following: ankle-arm blood pressure index <0.8, absence of both dorsalis pedis and posterior tibial pulses to palpation in one or both legs, and intermittent claudication. Logistic regression was used to estimate the association between potential risk factors measured 3–4 months after diagnosis of diabetes and incident PVD. The prevalence of PVD at 3-year intervals to 18 years was determined.

RESULTS — Hyperglycemia, assessed as HbA_{1c}, was associated with an increased risk for incident PVD, independent of other risk factors including age, increased systolic blood pressure, reduced HDL cholesterol, smoking, prior cardiovascular disease, peripheral sensory neuropathy, and retinopathy. Each 1% increase in HbA_{1c} was associated with a 28% increased risk of PVD (95% CI 12–46), and each 10-mmHg increase in systolic blood pressure with a 25% increase in risk (95% CI 10–43).

CONCLUSIONS — Hyperglycemia, as well as smoking, dyslipidemia, and blood pressure are potentially modifiable risk factors for the development of PVD.

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Peripheral vascular disease (PVD), defined as lower extremity arterial atherosclerosis, is a significant complication of type 2 diabetes. PVD, as with other manifestations of cardiovascular disease, is more common in individuals with type 2 diabetes than in the general population (1,2). Diabetes increases the risk of PVD progression (3), and PVD in patients with diabetes increases the risk of death (4,5) and lower extremity amputation (6). Of patients with PVD, those with diabetes have longer hospital stays and consume a greater percentage of resources (7).

Because PVD is more common in diabetes, and hyperglycemia is the defining characteristic of diabetes, it is logical that hyperglycemia may play a role in the development of PVD in diabetes. However, no prospective study has identified hyperglycemia as an independent risk factor for PVD in type 2 diabetes. A cross-sectional association between HbA_{1c} and peripheral artery disease has been shown (8,9). Blood glucose, but not HbA_{1c}, was significant in a small prospective study in univariate analyses only (10). This study sought to define the role of hyperglycemia in the development of incident PVD, taking into account other potential risk factors that might confound an association. Identification of hyperglycemia and other risk factors for PVD would permit detection of individuals at high risk and guide strategies for prevention, as few therapeutic options exist for PVD. We have used data from the U.K. Prospective Diabetes Study (UKPDS) to identify risk factors measured shortly after diagnosis of type 2 diabetes for the development of PVD at 6 years after diabetes. We have also estimated the prevalence of PVD up to 18 years after the diagnosis of diabetes.

RESEARCH DESIGN AND METHODS

Subjects

The UKPDS recruited 5,102 individuals with newly diagnosed type 2 diabetes, aged 25–65 years, from 23 centers in the U.K. between 1977 and 1991. The methods and main results of the study, which was designed primarily to evaluate the effect of improved glycemic control on diabetic complications, have been published (11). Of the 5,063 white, South Asian, and Afro-Caribbean subjects, 4,987 had data for the measurement of PVD available at diagnosis of diabetes. A total of 3,834 individuals who did not have PVD initially were reexamined at 6 years. Patients not followed to 6 years were slightly older (52.6 vs. 51.9 years), had

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Abbreviations: AAI, ankle-arm index; DBP, diastolic blood pressure; DP, dorsalis pedis; ESR, erythrocyte sedimentation rate; PT, posterior tibial; PVD, peripheral vascular disease; SBP, systolic blood pressure; UKPDS, U.K. Prospective Diabetes Study.

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

higher systolic blood pressure (138 vs. 134 mmHg), were more likely to be white (86 vs. 81%), and were more likely to smoke (35 vs. 30%) but were not different with respect to HbA_{1c} or sex. Of these 3,834 patients, 2,398 patients had data on all risk factors present in the final model. These 2,398 patients were not different with respect to age, sex, and ethnicity compared to patients examined for PVD at 6 years but for whom complete data were not available.

Definition of PVD

The diagnostic criteria for PVD were defined as the presence at examination of any two of the following: *1*) ankle-arm index (AAI) <0.8, *2*) absence of both dorsalis pedis (DP) and posterior tibial (PT) pulses to palpation in at least one leg, and *3*) intermittent claudication, defined as posterior calf pain on walking relieved by rest. The AAI was calculated for each leg from the mean of three Doppler readings of systolic blood pressure (SBP) measured in the PT arteries divided by the SBP from the right brachial artery based on three readings with a coefficient of variation <15%. The value for the worse leg was used. Subjects were assessed at diagnosis and every 3 years up to 18 years after diagnosis of diabetes. Incident PVD was defined as PVD present at 6 years in individuals without PVD at diagnosis of diabetes. Prevalence was defined as the proportion of individuals with PVD among individuals examined for all criteria.

Potential risk factors

Potential risk factors were chosen from risk factors for PVD in the general population and from those deemed biologically plausible in individuals with diabetes. They included age, sex, ethnic group, glycemia (HbA_{1c}), fasting plasma insulin, height, BMI, SBP, and diastolic blood pressure (DBP). Also included were smoking, alcohol use, aspirin use, albuminuria, retinopathy, cardiovascular disease, erectile dysfunction, erythrocyte sedimentation rate (ESR), white blood cell count, hemoglobin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fitness, and age at diagnosis of diabetes.

Peripheral sensory neuropathy was assessed by vibration perception threshold. Albuminuria was defined as a value >50 mg/l on spot urine collections (11). Alcohol consumption (any/none/former), fitness (sedentary to fit based on usual activity), erectile dysfunction (absence of erections), history of cardiovascular disease (previous myocardial infarction, stroke, or angina), and aspirin use (>1 dose per month) were self-reported during patient interviews. Diabetic retinopathy was defined by the presence of one or more microaneurysms in either eye on four field fundus photographs. Potential risk factors were measured at baseline (defined as the time of diagnosis of diabetes) for all variables, with the exception of BMI, HbA_{1c}, fasting insulin, and lipids, which were measured after a 3-month dietary run-in period (11). Univariate comparisons between individuals with and without PVD at diagnosis of diabetes used values from diagnosis of diabetes.

Analytical methods

Prevalence and 95% CIs were calculated at 3-year intervals. Logistic regression was used to evaluate the association between potential risk factors and PVD and for interactions with HbA_{1c}. Logistic regression was chosen over proportional hazards regression because the data were collected only every 3 years. Risk factors were considered eligible for inclusion in the backward stepwise multivariate model if a univariate screen (12) resulted in a level of statistical significance of $P \leq 0.2$. Estimated odds ratios are reported with 95% CIs. Fasting insulin and triglycerides were log-transformed. Vibration perception threshold, lipids, height, blood pressure, BMI, and HbA_{1c} were included as continuous variables. In further analyses, to examine the relationship of PVD to glycemia and blood pressure, HbA_{1c} was categorized as <6%, 6 to <7%, 7 to <8%, 8 to <9%, 9 to <10%, and ≥10% and SBP was categorized as <130, 130–139, 140–149, 150–159, and ≥ 160 mmHg. ESR values, measured by local laboratories, were classified as abnormal if they were higher than the 75th percentile by center.

RESULTS — At diagnosis of diabetes, 58 of 4,987 subjects (1.2%, 95% CI 0.9–1.5) had PVD, which increased to 12.5% (3.8–21.2) by 18 years. The prevalence of PVD at diagnosis and every 3 to 18 years is shown in Fig. 1. The mean follow-up was 8.9 years.

Comparison between the subjects with PVD present ($n = 58$) or absent ($n = 4,929$) at diagnosis of diabetes for characteristics measured at diagnosis of diabetes showed that subjects with PVD were older (60.4 vs. 52.0 years), slimmer (BMI 27.0 vs. 28.9 kgm^2), and had higher values for SBP (155 vs. 144 mmHg), biothesiometry readings (18.5 vs. 12.5 volts), cholesterol (6.1 vs. 5.6 mmol/l), triglyerceride geometric mean (2.2 vs. 1.8 mmol/l), hemoglobin (15.6 vs. 15.0 g/dl), and white blood cell count (8.6 vs. 6.9 1,000 cells/mm^3). They were also more likely to be current smokers (55 vs. 31%) and have erectile dysfunction (16 vs. 7%). They were not different ($P > 0.05$) with respect to sex, ethnicity, height, DBP, fasting plasma insulin, LDL, HDL, ESR, albuminuria, presence of retinopathy, or alcohol or aspirin use.

At 6 years, 105 of 3,834 patients (2.7%, 95% CI 2.2–3.2) had PVD that was not present at diagnosis of diabetes. A total of 2,398 patients had data on all variables, 61 of whom (2.5%) had PVD that was not present at diagnosis of diabetes. The characteristics of the patients and the univariate associations between potential risk factors and incident PVD are shown in Table 1. Of the 2,398 patients, 10.6% had at least one abnormal measure for PVD, as shown in Fig. 2. The average AAI in all patients examined at 6 years was 1.1 (SD 0.18).

Factors entered into the model, having been found to be significant ($P \leq 0.2$; Table 1) in the univariate screen for incident PVD, were older age, lower BMI, elevated SBP (but not DBP), HbA_{1c}, retinopathy, history of cardiovascular disease, smoking, increased total and LDL cholesterol, triglyceride, albuminuria, vibration perception threshold, ESR, and decreased HDL.

The results of the multivariate model for incident PVD at 6 years (Table 2) show increased age, increased HbA_{1c}, increased SBP, lower HDL cholesterol, previous cardiovascular disease, and smoking to be independent risk factors. Retinopathy and peripheral sensory neuropathy ($P = 0.07$ and 0.18, respectively) were included in the model because their absence altered the magnitude of the odds ratio for the association between previous cardiovascular disease and incident PVD. Each 1% increase in HbA_{1c} was associated with a 28% increase in risk of incident PVD. Current, but not former, smoking and history of cardiovascular disease were each associated with a more than doubling of risk. The association between

Table 1—*Characteristics measured at baseline in individuals with or without incident PVD at 6 years after diagnosis of diabetes*

Potential risk factor	PVD present at 6 years but not at diagnosis of diabetes: Yes	PVD present at 6 years but not at diagnosis of diabetes: No	*P* value*
n	61	2,337	
Age (years)	57.6	60.0	<0.001
Sex (% men/women)	57	60	0.67
Race (% White/South Asian/Afro-Caribbean)	84/11/5	82/11/7	0.79† 0.48‡
Height (cm)	166.6 (9)	167.8 (10)	0.35
BMI (kg/m^2)	26.7 (4.20)	27.6 (5.06)	0.17
SBP (mmHg)	145 (22)	134 (19)	<0.001
DBP (mmHg)	83 (10)	82 (10)	0.39
HbA_{1c} (%)	7.9 (1.8)	7.2 (1.8)	<0.001
Fasting plasma insulin (mU/l)	13.0 (7.0–23.6)	11.9 (6.7–21.2)	0.22
Total cholesterol (mmol/l)	5.5 (1.0)	5.3 (1.1)	0.12
LDL cholesterol (mmol/l)	3.7 (1.0)	3.5 (1.0)	0.013
HDL cholesterol (mmol/l)	1.0 (0.2)	1.1 (0.2)	0.011
Triglyceride (mmol/l)	1.7 (1.0–2.8)	1.5 (0.9–2.5)	0.057
Hemoglobin (g/dl)	14.9 (1.4)	15.0 (1.4)	0.58
White blood cell count (1,000 cells/mm^3)	7.2 (1.8)	6.9 (1.9)	0.24
ESR (upper quartile)	40%	25%	0.008
Albuminuria	16.2%	6.6%	0.003
Biothesiometer reading (volts)	15.7 (9.4–26.3)	12.2 (7.4–20.2)	<0.001
Retinopathy	49%	35%	0.021
Former cardiovascular disease	13%	4%	<0.001
Erectile dysfunction	9%	6%	0.57
Alcohol	72%	76%	0.49
Aspirin use (current)	18%	19%	0.83
Exercise (% sedentary/moderate/active/fit)	28/33/36/3	21/34/41/4	0.58
Smoking (% current/former smokers/never)	53/26/21	29/36/35	<0.001

Data are mean (SD), geometric mean (1-SD range), or %. *For univariate analyses, logistic regression was used. Reference is for South Asians† or Afro-Caribbean‡ relative to whites.

PVD and HbA_{1c} or SBP, when coded as categorical variables and adjusted for all other risk factors identified above, is shown in Fig. 3. Sex and year of diagnosis did not confound the association between any risk factor and PVD and were not associated with PVD. There was an interaction of borderline significance ($P = 0.053$) between glycemia and retinopathy. No other interaction between glycemia and other variables in the model was significant ($P < 0.05$).

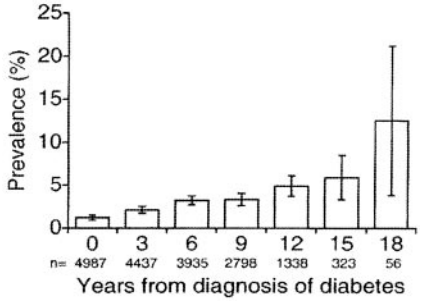

Figure 1—*Prevalence of PVD (95% CIs) defined as any two of the following: AAI <0.8, absence of both DP and PT pulses to palpation in at least one leg, intermittent claudication at diagnosis of diabetes, and at 3-year intervals to 18 years.*

CONCLUSIONS — In this large prospective study, we identified hyperglycemia, elevated SBP, low HDL, smoking, and presence of cardiovascular disease to be independent risk factors for PVD in type 2 diabetes. These results may be generalizable to other populations of patients with type 2 diabetes because the cohort in this study was population-based, multiethnic, and received care that is now considered to be standard.

A cutoff of 0.8 for AAI was used in another epidemiological study of diabetes (13) and has been shown to be highly specific (99%) for PVD in the general population (14), as are claudication and absence of peripheral pulses, with a specificity of 95% in a diabetic population (15). Because claudication and absent or diminished peripheral pulses individually have been shown to be present in only one-half and two-thirds of diabetic patients with PVD (15), our use of both criteria may be associated with increased sensitivity. Abnormal readings on multiple measures for PVD, including claudication and abnormal pulses, have been associated with a higher probability of having PVD (15). High AAI values have been associated with arterial calcification (15,16), with the possibility that these patients would be misclassified as not having PVD. However, evidence suggests that extensive calcification does not necessarily accompany poor tissue blood flow (17). In this study, this misclassification seems minimal, because only 2 of 56 individuals with AAI ≥1.5 had absent pulses and claudication. Patients with painful peripheral sensory neuropathy are unlikely to be diagnosed instead with claudication, because the pain experienced by those with

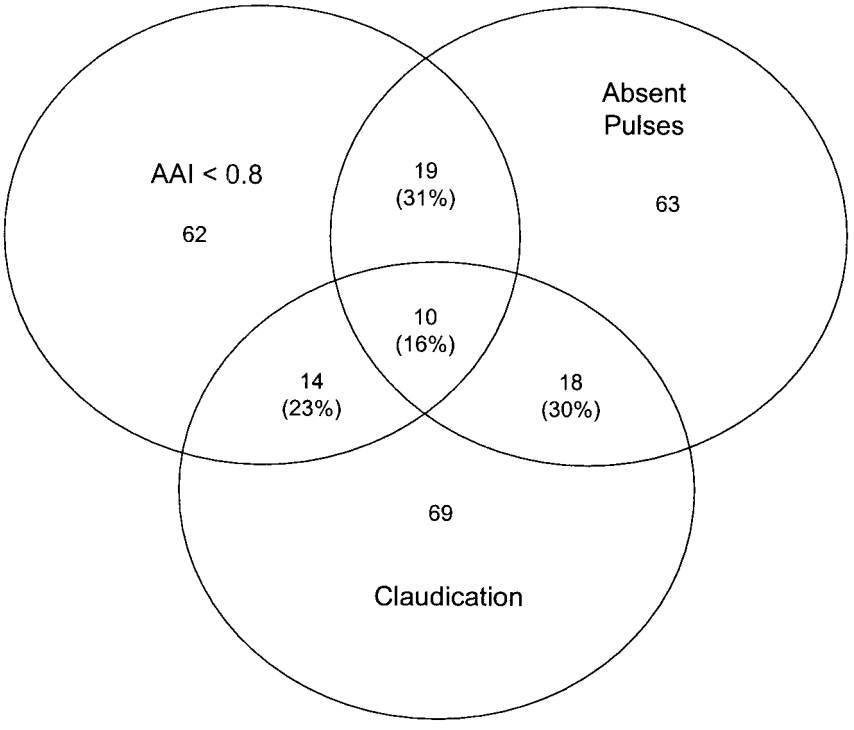

Figure 2—*Results of individual measures for PVD in 2,398 individuals included in the multivariate model. Percentages reflect measures in 61 individuals with incident PVD.*

neuropathy alone differs temporally and in character from claudication, being of a diffuse burning nature with onset at rest and nocturnal exacerbation. Lastly, multiple criteria for the diagnosis of PVD allow identification of patients when a single test might fail.

The prevalence data show the increasing burden of PVD with increasing duration of diabetes. Because of the long period of recruitment to the UKPDS, few patients were followed to 18 years, and as such, the precision of the prevalence estimates decreases.

This prospective report shows that hyperglycemia precedes the development of PVD in type 2 diabetes. Hyperglycemia has been documented to precede lower extremity amputation (18), for which PVD increases risk. In prospective studies, fasting blood glucose was not associated with claudication (19), and chronic hyperglycemia was not associated with peripheral arterial disease (20). In the University Group Diabetes Program, hyperglycemia following oral glucose was not associated with claudication or an absent DP pulse (21). The true association between hyperglycemia and PVD is possibly stronger than that observed in this study, given that this report is based on a measure of HbA_{1c} shortly after diagnosis of diabetes, because hyperglycemia is a risk factor for death, and because this study did not take into account glucose-lowering treatments. This study found no difference in HbA_{1c} values in univariate analysis between those with and without PVD at diagnosis of diabetes, an observation that may reflect decreased activity in patients with PVD. The association between hyperglycemia and incident PVD means that it may be possible that interventions to reduce glycemia would reduce the occurrence of PVD. This possibility is consistent with the nonsignificant trend to protection seen in the UKPDS for the combined end point of fatal PVD and amputation (11).

Hyperglycemia seems to be more strongly associated with PVD than coronary artery disease. The 28% estimated increase in risk for each 1% increment in HbA_{1c} is equivalent to a 22% decrease in risk for each 1% decrement in HbA_{1c}. This is greater than that estimated for myocardial infarction in the UKPDS (22). In type 1 diabetes, HbA_{1c} levels were elevated in lower extremity arterial disease but not coronary heart disease (23). In a cross-sectional study of elderly Dutch subjects, a 1% HbA_{1c} increment was associated with a 35–42% increased risk for AAI <0.9 (8) or obstructed crural arteries (24); this exceeded the magnitude of risk associated with coronary artery disease (25). Diabetic patients with PVD, compared with those without PVD, have similarly stenosed coronary arteries (5), indicating that the effects of hyperglycemia in PVD may be influenced by local factors. Glycemia may promote relatively stable atherosclerotic plaques, a feature more characteristic of PVD than myocardial infarction (23). If effective, one would expect a greater risk reduction from glycemic control in PVD than in coronary heart disease, although the number

Table 2—*Multivariate model of incident PVD at 6 years, based on 61 of 2,398 patients*

	Comparison	Odds ratio	95% CI
Age	Each year older at diagnosis of diabetes	1.10	1.05–1.15
HbA_{1c}	Each 1% increase	1.28	1.12–1.46
SBP	Each 10-mmHg increase	1.25	1.10–1.43
HDL	Each 0.1-mmol/l decrease	1.22	1.07–1.39
Former smoking	Never smoked	0.80	0.37–1.72
Current smoking	Never smoked	2.90	1.46–5.73
Cardiovascular disease	None	3.00	1.30–6.70
Retinopathy	Presence of retinopathy	1.64	0.97–2.78
Peripheral sensory neuropathy	Doubling of voltage threshold	1.31	0.89–1.93

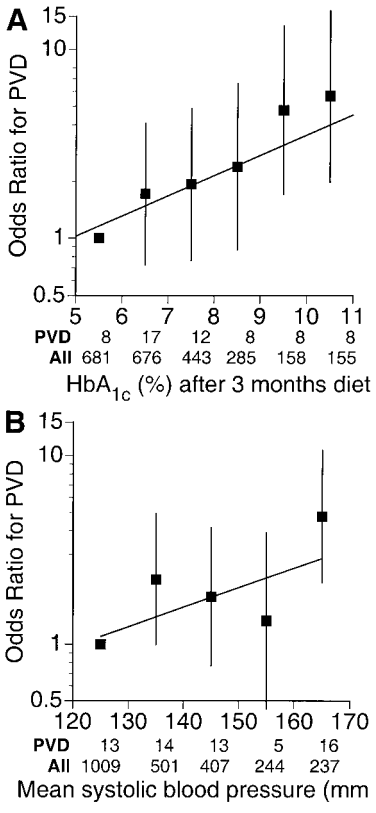

Figure 3—*Odds ratio for HbA_{1c} (*A*) and SBP (*B*) by category adjusted for age, HDL cholesterol, previous cardiovascular disease, smoking, retinopathy, and peripheral sensory neuropathy in 61 patients with incident PVD at 6 years of a total 2,398 patients.* A*: Adjusted also for SBP.* B*: Adjusted also for HbA_{1c}. Reference groups are HbA_{1c} <6% and SBP <130 mmHg.*

of people at risk and able to benefit remains higher for coronary disease.

There is ample evidence for mechanisms by which hyperglycemia might lead to arteriopathy. Accumulation of advanced glycosylation end products have been implicated as a means by which glycemia increases atherosclerosis (26) via glycation and preferential oxidation of LDL and subsequent uptake by macrophages to form foam cells (27). Hyperglycemia increases protein kinase C activity, which may increase the risk of diabetic complications (28). Whereas the results of this observational study cannot prove a causal role for hyperglycemia, the results of this study in the setting of a plausible pathologic mechanism lends credence to a causal role.

Both lipids and elevated blood pressure have been shown to be risk factors for PVD in type 2 diabetes (10,19). This study showed that only low HDL was associated independently with the risk for PVD. Smoking was associated in these analyses with a nearly threefold increased risk for PVD, and it is believed to be the most important risk factor in lower-limb arteriopathy (29). Based on this study, a patient would have to achieve a >2% reduction in HbA_{1c} and a >20 mmHg reduction in SBP to achieve the theoretical risk reduction associated with not smoking. The results suggest that hyperglycemia increases the risk of PVD in nonsmokers as well as smokers. It is noteworthy that former smokers were no more likely than those who never smoked to develop PVD.

This study supports the possibility of a shared pathogenesis of PVD with retinopathy. The possible interaction between HbA_{1c} and retinopathy may represent a chance finding or may indicate that hyperglycemia exerts a stronger risk of PVD in patients with retinopathy, which may be a marker for vascular dysfunction or duration of diabetes before diagnosis. PVD may have a microvascular component, as suggested in a histologic study of lower extremity small vessels of diabetic individuals with PVD: 80% were proliferative and 5% atheromatous (30). PVD and retinopathy are associated, to a similar degree, to hyperglycemia (11). Microvascular disease may increase peripheral resistance and intensify arterial atherosclerosis. It is hypothesized that microvascular disturbances of the foot result from altered arterial flow; our findings support the possibility that microvascular disease precedes arteriopathy.

The sex of an individual was not associated with the risk of PVD in this study or in many others (19,31,32). It is possible that diabetes increases the risk of PVD more in women than in men to the extent that the rates of PVD in men and women become equal. Other factors may be associated with PVD but were not evaluated in this study, including elevated plasma fibrinogen, which has been associated with an increased risk of cardiovascular disease in diabetes (33). Despite a correlation between ESR and fibrinogen (34), this study found no association between ESR and PVD. Plasminogen activation inhibitor-1, elevated in glucose-intolerant individuals (35), may increase cardiovascular risk. Vascular adhesion molecules, more common in the plasma and vitreous of diabetic individuals with complications, may play a causal role in angiopathy (36). Serum lipoprotein (a) has been associated with lower toe SBP index (37).

Potential limitations of this study include the infrequency with which PVD was assessed, making it difficult to define a time of onset and incidence rate, and its relatively low frequency, which may have precluded identification of more risk factors. The diagnostic criteria used for PVD, requiring two of three abnormalities, minimized the chance of false-positive diagnoses. It is possible that these noninvasive criteria, although widely used and appropriate in primary care, may have underestimated the prevalence of PVD. It is also possible that patients not followed to 6 years, being at higher risk, developed PVD.

In summary, this prospective study has shown that hyperglycemia, dyslipidemia, smoking, and higher blood pressure are associated with the subsequent development of PVD. Minimizing these risk factors may, in the future, prove to reduce the occurrence not only of PVD but also of cardiovascular disease, amputation, and death. Knowledge of risk factors makes it possible to identify the patients most likely to benefit from preventive measures if interventions prove effective, although the trials required to evaluate such interventions would likely need to be of a formidable size.

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