Role of Systolic Blood Pressure and Plasma Triglycerides in Diabetic Peripheral Arterial Disease

The Edinburgh Artery Study

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OBJECTIVE — To determine the risk factors for peripheral arterial disease (PAD) in a diabetic population and to examine whether different levels of these risk factors might explain why diabetic subjects have an increased risk of PAD compared with normal glucose tolerance subjects.

RESEARCH DESIGN AND METHODS — There were 1,592 men and women aged 55–74 years selected at random from the age-sex registers of 11 general practices in Edinburgh, Scotland. Subjects underwent a comprehensive medical examination, including assessment for PAD (intermittent claudication on World Health Organization questionnaire or major asymptomatic disease on noninvasive testing) and a glucose tolerance test.

RESULTS — Of the subjects, 288 (18.7%) were found to have diabetes or impaired glucose tolerance (IGT). The prevalence of PAD was greater in those with diabetes/IGT (20.6%) compared with those with normal glucose tolerance (12.5%) (odds ratio [OR] 1.64, 95% CI 1.17–2.31). Among the diabetes/IGT group, mean levels of smoking, systolic blood pressure, and triglycerides were higher in subjects with PAD than in those without PAD ($P \leq 0.05$). Mean levels of systolic blood pressure and plasma triglycerides were also higher in diabetic subjects than in nondiabetic subjects with PAD ($P \leq 0.05$). In multivariate analysis, those with diabetes/IGT no longer had a significantly higher risk of PAD after adjusting separately for systolic blood pressure (OR 1.22, 95% CI 0.85–1.73) and plasma triglycerides (OR 1.26, 95% CI 0.89–1.79). Simultaneous adjustment for both systolic blood pressure and triglycerides reduced the risk of PAD among diabetic subjects to 1.11 (95% CI 0.78–1.58).

CONCLUSIONS — Increased mean levels of triglycerides and systolic blood pressure may help to explain the higher prevalence of PAD in diabetic subjects compared with that in normal glucose tolerance subjects.

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The prevalence of cardiovascular disease has been shown to be higher in the diabetic (both type 1 and 2) population than in the nondiabetic population (1–3). Most research, however, has focused on coronary heart disease in diabetic subjects (4–7), and there are relatively few general population studies that have examined the prevalence of atherosclerotic peripheral arterial disease (PAD) according to diabetic status. Studies looking at intermittent claudication and a range of surrogate measures of PAD, including lower-limb amputations, pulse deficits, and medial calcification, have led to the general acceptance that PAD is more common in diabetic than in nondiabetic subjects (8–15).

The cause of this higher prevalence of PAD in diabetic subjects is unknown, but at least some of the effect may be related to differing levels of intermediate cardiovascular risk factors. For example, diabetic subjects have been found to have higher levels of hypertension (5,16–18), cigarette smoking (11,19,20), triglycerides (5,11,20,21), cholesterol (11,20,22), and other blood lipids (5,11,23) compared with nondiabetic subjects. Epidemiological studies have implicated many of these factors in the development of PAD in diabetes, but such studies have often relied on clinic-based samples of diabetic subjects and/or questionable measures of PAD (such as lower-limb amputations or pulse deficits). Information on the relationship between putative risk factors and PAD in diabetic subjects from the general population is, therefore, scarce (8).

In the present report, we examined data from the Edinburgh Artery Study, a prospective survey of 1,592 men and women selected from the general population. The aims of the study were to determine the risk factors for PAD in a diabetic population and to investigate whether raised levels of such risk factors in diabetic subjects might help to explain their increased risk of PAD.

RESEARCH DESIGN AND METHODS

Baseline study

The Edinburgh Artery Study began in 1988 as a cross-sectional survey of 809 men and 783 women aged 55–74 years. This population was selected at random, in 5-year age bands, from 11 general practices serving a range of socioeconomic and geographic areas throughout the city. The response rate was 65% (resulting in the final study pop-

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Abbreviations: ABPI, ankle-brachial pressure index; IGT, impaired glucose tolerance; OR, odds ratio; PAD, peripheral arterial disease; WHO, World Health Organization.

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

ulation of 1,592), and follow-up of a sample of nonresponders showed no substantial bias. Subjects attended a university clinic to complete a questionnaire and have a comprehensive medical examination. Details of the study recruitment and examination process have been described (24). Ethics committee approval was given for this study, and informed consent was obtained from each subject.

Study measurements. Each subject completed a questionnaire that included the World Health Organization (WHO) intermittent claudication questionnaire (25) and a detailed section on smoking habit. After a 10-min rest in the supine position, systolic and diastolic (phase V) blood pressures were taken in the right arm using a Hawksley random zero sphygmomanometer. A single reading was taken unless the researcher experienced difficulty, in which case the reading was repeated until he or she felt confident with the reading. Ankle systolic blood pressures were taken in both legs using the random zero sphygmomanometer and a Sonicaid Doppler probe. Blood flow was detected where possible in the posterior tibial artery. The ankle-brachial pressure index (ABPI) was calculated as ankle divided by brachial systolic pressure, and the lesser ABPI from the two legs was used, since disease often occurs unilaterally. In the reactive hyperemia test that followed, ankle systolic pressure was measured 15 s after the release of a cuff occluding arterial flow just above the knee for 4 min at ~50 mmHg above systolic pressure. The timing was standardized using an electronic timer. This test was conducted to detect those subjects with peripheral arterial disease in whom the presence of medial arterial calcification (as may occur in diabetes) may have rendered measurement of the ABPI an unreliable marker of disease. Measuring the blood pressure 15–30 s after the cuff has been released has been shown to be the optimum time to distinguish between subjects with angiogram-positive disease and control subjects; in this situation, the test is >95% sensitive in detecting disease (26,27).

During the clinical examination, 20 ml of fasting blood was taken, after which subjects consumed 75 g glucose in the form of 335 ml of Solripe Gluctoza Health Drink (Strathmore Mineral Water, Forfar, Scotland, U.K.). A second blood specimen was taken 2 h after the oral glucose load. Standing height (without shoes) was measured to the nearest 5 mm using a free standing metal ruler on a heavy base. Weight without shoes and outer clothing was measured to the nearest 100 g on digital scales (Soehnle, Murrhardt, Germany). BMI as a measure of obesity was calculated as weight (in kilograms) divided by height (in meters) squared. In the laboratory, tests for serum total cholesterol, HDL cholesterol, triglycerides, thiocyanate, and plasma glucose were performed on a Cobas Bio analyzer (Roche, Welwyn Carden City, U.K.) using standard kits. LDL cholesterol was calculated using the formula: LDL cholesterol = total cholesterol − HDL cholesterol − triglycerides/5 (28). Quality control was measured by means of blind duplicate samples taken intermittently throughout the study.

Classification of PAD

For the purposes of this study, subjects were classified into two groups: *1*) the disease group, members of which had symptomatic PAD (determined by positive WHO intermittent claudication questionnaire) or major asymptomatic disease (ABPI ≤0.9 and drop in ankle systolic blood pressure during reactive hyperemia test of >20% or ABPI ≤0.7 or hyperemic drop of >35%), and *2*) the normal group, whose members met none of the above conditions and had ABPI >0.9 and hyperemic pressure reduction of <20%. This categorization has not been used in other studies, but results comparing the ABPI and reactive hyperemia test separately with angiography would suggest that it had adequate face validity; an ABPI of <0.9 has been shown to be up to 95% sensitive in detecting angiogram-positive disease (26). Also, we carried out duplex scanning on a subsample of cases confirming the presence of significant atherosclerotic disease. In the present study, 10% of subjects were classified as having PAD on the basis of an abnormal reactive hyperemia test alone (the remainder had intermittent claudication and/or an ABPI <0.9).

Diagnosis of diabetes/impaired glucose tolerance

Results of the oral glucose tolerance test were categorized according to WHO criteria (29). Subjects were classified as suffering from diabetes if *1*) they had been told by a doctor that they suffered from diabetes and were receiving treatment (insulin or oral therapy), *2*) the glucose concentration in the 2-h blood sample was ≥11.1 mmol/l, or *3*) because of a doctor diagnosis of diabetes, they did not undergo the oral glucose tolerance test (these subjects were classified as diabetic irrespective of whether or not they were on insulin or oral therapy). Impaired glucose tolerance (IGT) was diagnosed if the glucose concentration was between 7.8 and 11.1 mmol/l in the 2-h blood sample.

Data analysis

Data were analyzed on the Edinburgh University UNIX system using the SAS software package (version 6.11). Distributions of the fasted and 2-h glucose samples and triglycerides were positively skewed, thus logarithmic transformations were used in all analyses. The smoking history was sufficiently valid because reported consumption correlated well with mean thiocyanate level. Smoking status, defined as current, ex-, or never smokers, was used as a categorical variable. Tests for differences in the age-adjusted mean levels of the risk factors between those with and without PAD were conducted using *t* tests for both the diabetic/IGT group and the normal glucose tolerance group. Logistic regression using the statistical package Proc GENMOD (30) was used to calculate the odds ratio (OR) for having PAD in a person who had diabetes/IGT compared with the risk of PAD for a person in the normal glucose tolerance group. Age and sex adjustments were made, and then each of the other potential related factors was individually included in a multivariate model.

RESULTS — There were 288 subjects (18.7%) who had diabetes (n = 91) or IGT (n = 197), compared with 1,253 subjects with normal glucose tolerance (51 subjects could not be classified because of missing data). Of the subjects with diabetes, 9% were insulin treated, 20% were on oral treatments, and 19% did not admit to taking any treatment other than diet modification; the remainder were previously undiagnosed diabetic patients who were detected using the oral glucose tolerance test. Figure 1 shows that PAD was more common in those with diabetes (22.4%, $P \leq 0.05$) and IGT (19.9%, $P \leq 0.05$), compared with those with normal glucose tolerance (12.5%). The prevalence of PAD was not significantly different (P = 0.7) in the diabetes and IGT groups, and these groups were combined to increase the power of the study. The OR for PAD among the diabetes/IGT group compared with the normal glucose tolerance group was 1.64 (95% CI 1.17–2.31, $P \leq 0.01$).

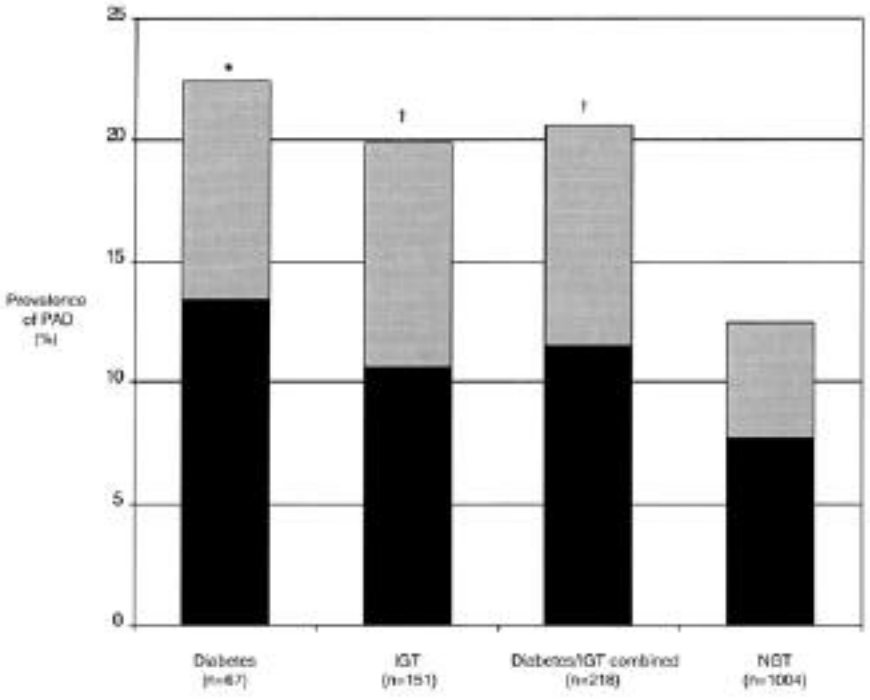

Figure 1—*Prevalence of PAD, categorized according to major asymptomatic disease (■) and intermittent claudication (■) in subjects with diabetes, IGT, and normal glucose tolerance (NGT). Difference in prevalence from NGT group* †$P \leq 0.05$, ‡$P \leq 0.01$.

The mean levels of risk factors in subjects with diabetes/IGT with and without PAD are summarized in Table 1. Subjects with PAD were older than those without PAD ($P \leq 0.001$), so all risk factor levels were adjusted for age. Diabetic/IGT subjects with PAD had significantly higher mean levels of systolic blood pressure ($P \leq 0.01$) and plasma triglycerides ($P \leq 0.01$) compared with those without PAD. In addition, 74.1% of the diabetic group with PAD were current or ex-smokers, compared with only 48.1% of the diabetic subjects without PAD ($P \leq 0.05$). The mean levels of total and LDL cholesterol tended to be higher, and HDL cholesterol levels lower, in those with PAD compared with those without PAD, but these differences were not statistically significant ($P > 0.05$).

Table 2 shows that in subjects with normal glucose tolerance, those with PAD had significantly higher mean levels of systolic blood pressure, triglycerides, and total and LDL cholesterol ($P \leq 0.001$), and significantly lower levels of HDL cholesterol ($P \leq 0.05$), compared with those without PAD. Some 83.5% of the normal glucose tolerance group who had PAD were current or ex-smokers, compared with 61.6% of the normal glucose tolerance subjects without PAD ($P \leq 0.01$). There were no statistically significant differences in sex, BMI, or diastolic blood pressure.

Risk factor levels among the diabetes/IGT group with PAD and the normal glucose tolerance subjects with PAD were then compared (Tables 1 and 2, *column 1*). Patients in the diabetes/IGT group with PAD were older ($P \leq 0.05$), with higher mean levels of systolic blood pressure ($P \leq 0.01$) and plasma triglycerides ($P \leq 0.05$), than those with normal glucose tolerance and PAD. Differences in mean levels of the other risk factors between the two groups did not reach statistical significance, although the diabetes/IGT subjects with PAD had a more adverse risk factor profile in general than the normal glucose tolerance subjects with PAD.

The unadjusted OR for diabetes/IGT as a risk factor for PAD was 1.64 (95% CI 1.17–2.31, $P \leq 0.01$). Table 3 shows the ORs for diabetes/IGT as a risk factor for PAD compared with normal glucose tolerance, after adjusting for each of the common risk factors in turn. After adjusting for age and sex, diabetic subjects still had a higher risk of PAD (OR 1.45, 95% CI 1.03–2.04, $P \leq 0.05$). In multivariate analysis, those with diabetes/IGT no longer had a significantly higher risk of PAD after adjusting separately for systolic blood pressure (OR 1.22, 95% CI 0.85–1.73) and plasma triglycerides (OR 1.26, 95% CI 0.89–1.79). However, it should be noted that every risk factor, with the exception of smoking status, individually reduced the odds of diabetes as a risk factor for PAD. For example, after adjusting for age, sex, and HDL cholesterol, diabetic subjects still had higher levels of PAD, but it was of borderline significance (OR 1.37, 95% CI 0.97–1.94, $P = 0.08$). Simultaneous adjustment for both systolic blood pressure and triglycerides reduced the risk of PAD among diabetic patients to 1.11 (95% CI 0.78–1.58, $P > 0.05$).

CONCLUSIONS — In this population-based study, we have confirmed that the prevalence of PAD in subjects with diabetes or IGT is considerably greater than that in those with normal glucose tolerance.

Table 1—*Age-adjusted levels of risk factors in subjects with diabetes/IGT with and without PAD*

Risk factor	Diabetes/IGT		
	PAD	No PAD	*P* value
n	45	173	—
Age (years)	68.8 ± 0.8	65.1 ± 0.4	≤0.001
Sex (% M)	43.1	58.4	NS
Smoking status (% current or former)	74.1	48.1	≤0.05
Systolic blood pressure (mmHg)	161.8 ± 3.7	150.4 ± 1.8	≤0.01
Diastolic blood pressure (mmHg)	80.5 ± 1.9	78.9 ± 0.9	NS
BMI (kg/m^2)	27.0 ± 0.7	26.8 ± 0.3	NS
Total cholesterol (mmol/l)	7.35 ± 0.22	6.99 ± 0.11	NS
LDL cholesterol (mmol/l)	5.61 ± 0.20	5.25 ± 0.10	NS
HDL cholesterol (mmol/l)	1.29 ± 0.06	1.38 ± 0.03	NS
Triglyceride (ln mmol/l)	0.69 ± 0.08	0.46 ± 0.04	≤0.01

Data are means ± SEM.

Table 2—*Age-adjusted levels of risk factors in normal glucose tolerant subjects with and without PAD*

Risk factor	Normal glucose tolerance		
	PAD	No PAD	*P* value
n	126	878	—
Age (years)	66.9 ± 0.5*	63.9 ± 0.2	≤0.001
Sex (% M)	50.4	52.7	NS
Smoking status (% current or former)	83.5	61.6	≤0.01
Systolic blood pressure (mmHg)	147.8 ± 1.9†	138.7 ± 0.7	≤0.001
Diastolic blood pressure (mmHg)	77.5 ± 1.1	76.1 ± 0.4	NS
BMI (kg/m^2)	25.2 ± 0.3	25.0 ± 0.1	NS
Total cholesterol (mmol/l)	7.32 ± 0.12	6.89 ± 0.04	≤0.001
LDL cholesterol (mmol/l)	5.62 ± 0.11	5.14 ± 0.04	≤0.001
HDL cholesterol (mmol/l)	1.38 ± 0.04	1.47 ± 0.01	≤0.05
Triglyceride (ln mmol/l)	0.46 ± 0.04*	0.27 ± 0.02	≤0.001

Data are means ± SEM. Mean levels higher in diabetic/PAD than normal glucose tolerance/PAD group: *$P \leq 0.05$, †$P \leq 0.01$.

In our sample of Scottish men and women aged 55–74 years, 20.6% of those with diabetes/IGT had PAD, compared with 12.5% of those with normal glucose tolerance, supporting the commonly held view that diabetic patients are at increased risk of developing PAD (8). The present study included those with intermittent claudication and major asymptomatic PAD diagnosed using the WHO questionnaire, the ABPI, and the reactive hyperemia test. Because the WHO questionnaire has limited sensitivity (30) and use of the ABPI as a single measure of PAD can also be criticized (22,31), it is a major strength of this study that three measures of PAD were used. In addition, research has shown that subjects with asymptomatic PAD have an increased risk of cardiovascular complications, as well as claudicants (24,27), and asymptomatic PAD is more common in diabetic subjects (22,31).

The prevalence of PAD in diabetic subjects in previous studies varies widely as a result of different definitions of PAD and glucose tolerance, as well as different characteristics of populations surveyed (including age and race). In general, the prevalence of PAD among diabetic (22.4%) and IGT (19.9%) subjects reported in this study is higher than has been reported previously (11,15,18,22,32,33), probably because of the inclusion of subjects with major asymptomatic PAD. For example, Uusitupa et al. (11), using the WHO questionnaire, reported prevalences of intermittent claudication among newly diagnosed type 2 diabetic patents (45–64 years of age) of 9% in men and 3% in women. In a recent population-based study in England, the prevalence of PAD, defined by history, peripheral pulse deficits, and an ABPI of <0.9, was 8.7% in insulin-dependent subjects (mean age 39.3 years) and 23.5% in subjects with type 2 diabetes (mean age 67.7 years) (22). The authors concluded that peripheral vascular disease was significantly more common in the diabetic than in the nondiabetic subjects only when asymptomatic cases of PAD were added to both groups. The prevalence of PAD in the present study was almost identical to that found in a population-based study of 50- to 75-year-old Dutch Caucasians, which examined crural artery obstructions in diabetic and nondiabetic subjects using Doppler waveform analysis in addition to the ABPI (31).

Our findings of a worse cardiovascular risk factor profile in normal glucose tolerance subjects with PAD compared with those without PAD are consistent with previous studies (34). This included higher levels of cigarette smoking, systolic blood pressure, triglycerides, total and LDL cholesterol, and lower levels of HDL cholesterol. We also found that among the diabetes/IGT group a similarly adverse risk factor profile was present in those with PAD compared with those without PAD. This suggests that the same risk factors that are important in the development of PAD in normal glucose tolerance subjects are also important in diabetic subjects. However, in diabetic subjects, differences in several of the risk factors studied did not reach statistical significance, possibly because of the relatively small numbers of subjects affected.

The greatest difference in risk factor levels between diabetic subjects with and without PAD was found for systolic blood pressure, triglycerides, and cigarette smoking, suggesting that these risk factors may be particularly important in the development of PAD in diabetic populations. Hypertension and hypertriglyceridemia have previously been found to be risk factors in the development of PAD in diabetic subjects (5,11,16–18,21). Two studies found a relationship between hypertension and a low ABPI in diabetic subjects (16,17), while in the University Group Diabetes program, baseline serum triglyceride was significantly related to risk of intermittent claudication in men only (21). In Finland, a study using the WHO questionnaire as a single measure of PAD (11) found a relationship between triglycerides and PAD on univariate analysis. An association between both hypertension and hypertriglyceridemia and risk of intermit-

Table 3—*Odds of PAD according to diabetic status (diabetes/IGT vs. normal glucose tolerance) before and after adjustment for each risk factor*

Risk factors adjusted for	OR	95% CI	*P* value
Age and sex	1.45	1.03–2.04	≤0.05
Smoking status	1.65	1.16–2.34	≤0.01
Systolic blood pressure (mmHg)	1.22	0.85–1.73	0.3
Diastolic blood pressure (mmHg)	1.42	1.01–2.01	≤0.05
BMI (kg/m^2)	1.42	1.00–2.01	≤0.05
Total cholesterol (mmol/l)	1.42	1.01–2.01	≤0.05
LDL cholesterol (mmol/l)	1.43	1.01–2.02	≤0.05
HDL cholesterol (mmol/l)	1.37	0.97–1.94	0.08
Triglyceride (ln mmol/l)	1.26	0.89–1.79	0.2
Systolic blood pressure and triglyceride*	1.11	0.78–1.58	0.6

Smoking status (current, ex, never) was used as a categorical variable. *This risk factor involves simultaneous adjustment for systolic blood pressure and triglycerides (log).

tent claudication was reported by the Framingham Study, which used its own questionnaire to ascertain claudication (5). In contrast, some other studies have failed to show a statistically significant relationship between mean levels of triglycerides and/or blood pressure and PAD in diabetic populations (19,21,22,33). The relationship between cigarette smoking and PAD in diabetic subjects has also been shown previously. A population-based study found an independent association between smoking and PAD upon multivariate analysis when both diabetic and nondiabetic subjects were pooled together (11). In a clinic-based study, logistic regression revealed a relationship between PAD and smoking in a sample of type 2 diabetic subjects (19).

Other studies have shown associations between cholesterol (total, HDL, and LDL) (5,11,22,23) and obesity (5,21) and manifestations of PAD among diabetic subjects. In our study, differences in total, LDL, and HDL cholesterol in diabetic/IGT subjects with PAD compared with those without PAD did not reach statistical significance, again possibly because of relatively small subject numbers.

Mean levels of several of the identified PAD risk factors were, in general, present at a more detrimental level in diabetic subjects than in nondiabetic subjects. For example, in subjects with PAD, systolic blood pressure and plasma triglycerides were both significantly higher in the diabetic subjects. These risk factors have previously been implicated in the development of PAD in diabetic subjects (5,11,16–18,21). A larger percentage of the nondiabetic PAD group, however, were current or ex-smokers (84.8%) compared with the diabetic PAD group (74.5%). The Framingham Study also found increased levels of cigarette smoking in male nondiabetic subjects compared with those in the male diabetic group, although women with diabetes tended to smoke more than women without diabetes (5).

It is possible that some of these differences in intermediary risk factors may contribute to the increased prevalence of PAD found in diabetic populations. To investigate this further, we calculated the risk of diabetes and then adjusted this for the other risk factors.

Adjustment for each risk factor examined in the present study reduced the impact of diabetic status on the likelihood of having PAD apart from cigarette smoking. This was due to the high percentage of never smokers in the diabetic subjects with PAD (25.9%) compared with the nondiabetic subjects with PAD (16.5%). Diabetic status was no longer a significant risk factor for PAD when adjustment was made for systolic blood pressure and triglycerides, suggesting that these two factors might be particularly important in helping to explain the increased prevalence of PAD in subjects with diabetes/IGT. The Framingham Study examined the influence of diabetes on manifestations of cardiovascular disease and did show a substantial reduction in the relative risk of PAD after adjusting for risk factors including cholesterol, smoking, and systolic blood pressure on multivariate analysis, compared with the age-adjusted figures. However, in this latter study the influence of diabetes on PAD remained significant after multivariate adjustment (5).

In conclusion, the results from this population-based study confirm that subjects with diabetes and IGT have a higher prevalence of PAD than those with normal glucose tolerance. Higher mean levels of triglycerides and systolic blood pressure in diabetic subjects may help to explain this higher prevalence. If the association between raised triglycerides and systolic blood pressure and the development of peripheral arterial disease in diabetic patients is found to be causal in future prospective studies, better control of these risk factors in diabetic patients should lead to a reduced incidence of PAD. Alternatively, it may be that some underlying phenomenon, such as insulin resistance syndrome (35), is responsible for both the elevation in systolic blood pressure and triglycerides and the higher prevalence of peripheral vascular disease. Indeed, we have shown previously that hyperinsulinemia is a risk factor for PAD, independent of blood pressure and serum lipids (36). Further longitudinal studies, including measurement of blood pressure, triglycerides, and insulin resistance, will be required to resolve these questions.

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