Peripheral Vascular Disease in Diabetes Mellitus and Its Relation to Cardiovascular Risk Factors: Screening with the Doppler Ultrasonic Technique

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Data of 623 nonselected diabetic outpatients are presented who were screened for peripheral vascular disease (PVD) and for cardiovascular risk factors. PVD was diagnosed in 15.9% of the diabetic patients (14.4% women and 18.0% men). Nine percent of the patients had signs of marked mediasclerosis at the ankle level. Multivariate statistical analysis revealed that PVD was closely associated with systolic hypertension and also with the duration of diabetes, a relationship that was highly significant ($P < 0.001$) for the peripheral type (below the knee) of PVD. Diabetic patients with arterial disease at the pelvic or femoral site exhibited a higher number of cardiovascular risk factors. In contrast, in patients with the peripheral type, significantly higher blood glucose values were found. Therefore, the quality of metabolic control may play an important part in the development of this form of diabetic macroangiopathy.

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A higher prevalence of atherosclerosis in diabetic patients has long been recognized.[1,2] In fact, atherosclerotic vascular disease among diabetic patients accounts today for most of their deaths.[3] This increased risk could not be explained adequately by the well-known cardiovascular risk factors.[4] Furthermore, there are still controversial opinions about duration of overt diabetes and control of blood glucose as risk factors for atherosclerosis.[5–12] Atherosclerosis is usually a generalized disease. The relative accessibility of the peripheral vessels for diagnostic studies can allow the early identification of persons with asymptomatic atherosclerotic disease.[13] It has been shown repeatedly that the macroangiopathy in diabetic persons has a predilection for the arteries of the lower leg.[14–17] Despite this typical pattern, an analysis of the site of obliteration and its relationship to cardiovascular risk factors has not been performed. The present study was designed as a careful survey and analysis of peripheral vascular (arterial) disease (PVD) in nonselected diabetic outpatients using noninvasive techniques. Doppler ultrasonic blood flow measurement was used as a screening method that offers a sensitive and noninvasive way to assess PVD, even in patients without intermittent claudication.[18–22] Furthermore, with this method signs of marked medial calcification of the arteries (mediasclerosis) can be obtained.[23] All data were correlated with cardiovascular risk factors, duration of diabetes, and control of blood glucose by a multivariate statistical analysis.

PATIENTS AND METHODS

This study is based on 623 nonselected outpatients treated at the Schwabing City Hospital in Munich, West Germany. All patients were overtly diabetic, i.e., had fasting hyperglycemia (≥ 140 mg/dl blood glucose). All available diabetic patients were included in the study who were seen in the outpatient department for metabolic control between November 1976 and March 1977. Patients who were referred for specific complications, e.g., "feet problems," were excluded from this study. Forty-five percent of all studied patients were treated by insulin, 40% by oral antidiabetic drugs, and 15% by diet alone. Age and sex distribution is indicated in Table 1. A complete history with particular reference to intermittent claudication and smoking habits was taken in all patients. Examination and blood sampling were performed in the morning after breakfast. After 5 min of relaxation blood pressure was recorded three times in the supine position. All measurements were done with 13-cm cuffs. The lowest value was used for the classification. Thereafter systolic blood pressure was measured on all four extremities with the Doppler ultrasonic method.[24] A reduction of the systolic blood pressure at the ankle by 30 mm Hg or

TABLE 1
Prevalence of peripheral vascular disease (PVD) in diabetic women and men in various age groups

All diabetic subjects	Age groups (yr)					All PVD
	10–49	50–59	60–69	70–79	80+	
Women	1.9%	1.9%	15.2%	31.0%	46.7%	14.4%
(N = 368)	(N = 2)	(N = 1)	(N = 17)	(N = 26)	(N = 7)	(N = 53)
Men	4.4%	21.1%	22.8%	38.5%	71.4%	18.0%
(N = 255)	(N = 5)	(N = 8)	(N = 13)	(N = 15)	(N = 5)	(N = 46)
	3.2%	10.0%	17.8%	33.3%	54.5%	Σ15.9%
Σ(N = 623)	(N = 7)	(N = 9)	(n = 30)	(N = 41)	(N = 12)	(N = 99)

more compared with the blood pressure taken on the arm or in one extremity in comparison to the contralateral was considered as a sign of significant stenosis or obliteration.[25] In nonedematous legs, nonsuppressible Doppler sounds or a pressure reading of more than 50 mm Hg higher compared with the arm were interpreted as signs of marked mediasclerosis.[23]

Patients with a pathologic result were submitted to a thorough angiologic examination to determine the site of obliteration or stenosis. It included a repetition of the Doppler ultrasonic method, palpation and ausculation of the large arteries, and an electronic oscillometry with exercise. Oscillometric amplitudes were judged abnormal if they were markedly diminished 1 min after exercise (30 stands on tiptoe in 30 sec) and did not reach the resting values after 2 min.[26] These tests were considered to provide sufficient clinical evidence for PVD. According to the site of obliteration or stenosis, PVD was classified as pelvic, femoropopliteal, and peripheral (below the knee) in the leg and as shoulder-arm and forearm in the arm. Peripheral PVD was assumed if a stenosis or obliteration were present in the lower leg in the presence of an easily palpable popliteal pulse and normal oscillometric readings just below the knee. If a bruit over the iliac or femoral arteries was heard, this type was called "peripheral with proximal stenosis." Pelvic and femoropopliteal PVD were classified similarly. Height and weight were registered in all patients. Ideal weight was defined as the Broca index minus 10% in men and minus 15% in women.[27] An increase of more than 20% of the ideal weight was considered as overweight. Hypertension was classified according to the WHO criteria (≥ 160/95 mm Hg). Blood pressure readings of 200/110 mm Hg and more were classified as hypertension II. Serum cholesterol and triglycerides values could be analyzed in the majority of patients. The serum levels were determined enzymatically by standard methods.[28,29] Patients who had either smoked cigarettes for more than a year in the past or who still did smoke were denoted as "smoker." The very few pipe and cigar smokers were not considered. The median of all available blood glucose values was used as criterion for glycemic control. This value was only used if at least 12 determinations were recorded.

Statistical calculations were performed by an univariate and multivariate analysis of variance and covariance with an one-way two-group or three-group design (SPSS-MANOVA program[30,31]) in order to better define the influence of the variable risk factors on the results. Thereby seven criteria (age, duration of diabetes, systolic and diastolic blood pressure, serum cholesterol, serum triglycerides, median of blood glucose values) were used as dependent continuous variables. Only patients without missing values were included in the analysis (N = 498). In addition, to eliminate the impact of age on the results, this variable was treated as a covariate, i.e., its influence was subtracted from the other variables by a linear regression. As a test of significance Hotelling's trace criterion was used.[32] The robustness of this test for the distributions in this analysis has been shown recently.[33] The standardized discrimination function coefficients were used to determine those variables (risk factors) that could best distinguish among the tested groups. Furthermore, the Roy-Bargman stepdown F-test was performed, although (except for age) a natural order of the variables was not given. Chi-square analysis from contingency tables was performed for the nonvariable risk factors (smoking, therapy, sex, hypertension). As a measure for dependency, the corrected Pearson's contingency coefficient ($CC_{corr.}$) was used.[34] To exclude the factor age in this test, a comparison of diabetic persons with and without PVD was made in the same age group. The statistics were performed at the Mathematical Institute of the University of Munich.

RESULTS

Prevalence of PVD. According to the chosen criteria PVD was diagnosed in 99 (15.9%) of 623 nonselected diabetic outpatients. The age distribution of patients with PVD is outlined in Table 1. Of the women 14.4% were affected and of the men 18.0%. There was a clear increase of PVD with age. Classification into clinical stages is as follows: 35% complained of intermittent claudication; 8% exhibited an ischemic foot lesion or had been operated on; in 57% PVD was diagnosed without any symptoms.

Site of PVD. PVD was predominantly found on the lower extremities (Table 2). Only 0.6% of all examined patients and 4% of the patients with PVD exhibited impaired circulation on the upper extremities. The most common type of

TABLE 2
PVD in diabetic patients: distribution according to location of obliteration or stenosis (N = 99)

Pelvic		6.1%
Femoropopliteal		26.3%
Peripheral		Total: 63.6%
Isolated	38.4%	
With proximal stenosis	25.3%	
Shoulder-arm		4.0%

obliteration or stenosis of the legs was the peripheral one (below the knee). In decreasing frequency the more proximal types followed: femoropopliteal and pelvic.

Mediasclerosis. A clue for marked mediasclerosis at the ankle level was obtained in 56 (9%) of the examined diabetic patients. In 51% of the patients with mediasclerosis impaired circulation also was recognized. An accumulation of cardiovascular risk factors in the patients was not observed. These patients exhibited long-term diabetes as the single significant characteristic feature.

Cardiovascular risk factors. In Figure 1 the distribution of cardiovascular risk factors in the whole study group is outlined. Except for cigarette smoking, there was an increase of all risk factors with age. Except in the very young patients in whom smoking was common, hypertension was the most frequent risk factor in all age groups, reaching 70% in the 60–69-yr group. The overall prevalence of hypertension (sys-

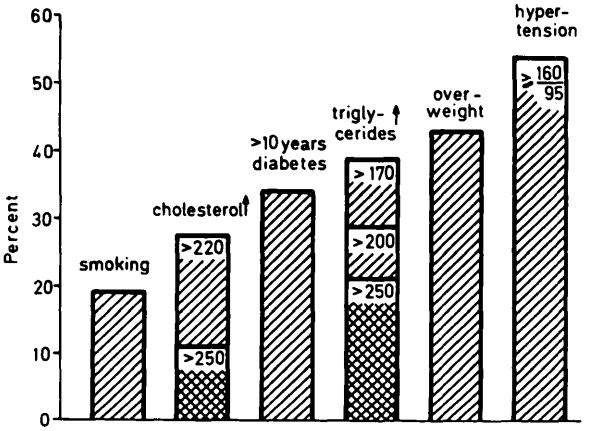

FIG. 1. Prevalence of cardiovascular risk factors in nonselected diabetic subjects (N = 623).

TABLE 3
Univariate and multivariate analysis of variance and covariance of the relationship of seven continuous variables to PVD (SSPS-MANOVA-program) (no vascular disease, N = 409; PVD, N = 89)

	Univariate analysis		Multivariate analysis		
			Standard discrimination function coefficient	Roy-Bargman stepdown F-test	
Variables	F-test	Significance of F	(absolute values)	F-test	Significance of F
Age	65.39	P < 0.00001	0.359	65.39	P < 0.0009
Duration of diabetes	41.62	P < 0.00001	0.464	22.55	P < 0.0001
Systolic blood pressure	63.53	P < 0.00001	0.623	16.23	P < 0.0006
Diastolic blood pressure	4.71	P < 0.03	0.196	1.69	P < 0.19
Cholesterol	7.35	P < 0.007	0.123	0.97	P < 0.32
Triglycerides	4.34	P < 0.038	0.049	0.49	P < 0.56
Blood glucose values (median)	2.11	P < 0.24	0.140	0.93	P < 0.33

Hotelling's trace criterion: trace = 0.229, F = 18.77, significance = P < 0.00001

Age adjustment (age as covariate)

	Univariate analysis		Multivariate analysis		
			Standard discrimination function coefficient	Roy-Bargman stepdown F-test	
Variables	F-test	Significance of F	(absolute values)	F-test	Significance of F
Duration of diabetes	22.55	P < 0.00001	0.700	22.55	P < 0.00001
Systolic blood pressure	18.55	P < 0.00005	0.812	16.23	P < 0.00006
Diastolic blood pressure	1.11	P < 0.29	0.298	1.69	P < 0.19
Cholesterol	1.58	P < 0.21	0.186	0.97	P < 0.32
Triglycerides	0.42	P < 0.52	0.075	0.49	P < 0.56
Blood glucose values (median)	1.31	P < 0.28	0.179	0.93	P < 0.33

Hotelling's trace criterion: trace = 0.086, F = 8.46, significance = P < 0.00001

tolic, diastolic or both) was 50.4%; women were affected 1 1/2 times more often than men. Results in detail were published previously.[35] In 20% of the hypertensive diabetic patients there was a fall of 15 mm Hg and more in systolic blood pressure and 10 mm Hg and more diastolic by changing from a supine to a sitting position.

Correlation of PVD with duration of diabetes, glycemic control, and other cardiovascular risk factors. In comparing cardiovascular risk factors in diabetic patients with and without PVD, age must be taken into account. In older age groups, increased rates of hypertension, obesity, and hyperlipidemias are generally observed along with the more frequent prevalence of PVD. As shown in univariate and multivariate analysis of variance (Table 3), age was a powerful risk factor for PVD. There were close associations of systolic blood pressure values and duration of diabetes with PVD, even after adjustment for age by a linear regression.

Classification of PVD into peripheral and proximal types revealed clear differences (Tables 4 and 5): Patients with proximal PVD were more frequently hypertensives and smokers and exhibited higher cholesterol values and a higher degree of multiple cardiovascular risk factors compared with diabetic persons without large vessel disease. An influence of the duration of diabetes was not seen. These patients were treated predominantly with oral antidiabetic agents or diet alone (expressed by the negative contingency coefficient). In contrast, patients with peripheral PVD did not exhibit more frequent cardiovascular risk factors except a higher prevalence of hypertension II (20%) and slightly higher systolic blood pressure values, although 20% remained normotensive. The proportion of patients with diabetes of long duration and patients under insulin therapy was significantly higher in this group. The relation of PVD with the duration of diabetes is outlined in Figure 2, an association that was

TABLE 4

Univariate and multivariate analysis of variance for six risk factors: age-adjusted PVD versus no PVD. (Age was treated as covariate, i.e., its influence was subtracted by a linear regression.) (No vascular disease, N = 409; peripheral type, N = 61; proximal type, N = 28)

Peripheral type			
	Univariate analysis		Multivariate analysis Standard discriminant function coefficient (absolute values)
Variables	F-test	Significance of F	
Duration of diabetes	44.34	$P < 0.00001$	0.821
Systolic blood pressure	4.92	$P < 0.013$	0.472
Diastolic blood pressure	0.38	$P < 0.53$	0.270
Cholesterol	0.043	$P < 0.84$	0.016
Triglycerides	0.0009	$P < 0.98$	0.120
Blood glucose values (median)	3.45	$P < 0.038$	0.431
Hotelling's trace criterion: trace = 0.134, F = 12.38, significance = $P < 0.00001$			

Proximal type			
	Univariate analysis		Multivariate analysis Standard discriminant function coefficient (absolute values)
Variables	F-test	Significance of F	
Duration of diabetes	0.34	$P < 0.56$	0.247
Systolic blood pressure	7.82	$P < 0.005$	1.118
Diastolic blood pressure	6.30	$P < 0.58$	0.661
Cholesterol	3.86	$P < 0.041$	0.479
Triglycerides	1.41	$P < 0.24$	0.072
Blood glucose values (median)	0.23	$P < 0.63$	0.202
Hotelling's trace criterion: trace = 0.034, F = 2.87, significance = $P < 0.015$			

TABLE 5

Correlation of peripheral and proximal PVD with insulin therapy, smoking, hypertension, sex, overweight, and a higher number of cardiovascular risk factors in the age group 60–79 yr (N = 291)

	Peripheral type		Proximal type*	
	Significance	$CC_{corr.}$	Significance	$CC_{corr.}$
Insulin therapy	$P < 0.001$	0.37	$P < 0.05$	−0.18
Smoking	NS		$P < 0.025$	0.20
Hypertension (≥160/95 mm Hg)	NS		$P < 0.05$	0.18
Hypertension II	$P < 0.001$	0.36	NS	
≥Two cardiovascular risk factors†	NS		$P < 0.025$	0.25
Male sex	NS		NS	
Overweight	NS		NS	

χ^2 test of contingency tables. $CC_{corr.}$ = corrected Pearson's contingency coefficient.

* Proximal type = pelvic and femoropopliteal type.

† Cardiovascular risk factors = excluding diabetes mellitus and overweight.

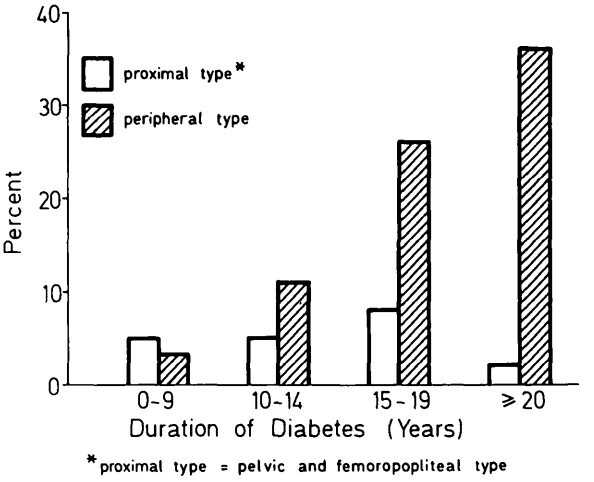

FIG. 2. Duration of diabetes and prevalence of different types of peripheral vascular disease (N = 95).

highly significant for peripheral PVD. Furthermore, there was a correlation of peripheral PVD with the degree of control of blood glucose: Patients with peripheral PVD exhibited significantly higher values (Table 4).

DISCUSSION

Information regarding the prevalence and clinical characteristics of PVD in diabetic patients has been obtained primarily from selected groups of patients, e.g., from autopsy studies,[14] from hospitalized diabetic patients,[7,36–40] and patients with claudication.[10,13,41–42] Of the few studies concerning nonselected diabetic persons, very different data regarding prevalence of impaired circulation of the extremities were observed. Dry and Hines[43] reported signs and symptoms of PVD in only 3% of patients; however, Semple[44] found PVD in 41% of examined patients with diabetes. Our study in nonselected diabetic outpatients proved the often made clinical impression that PVD is frequently associated with diabetes. Every sixth overt diabetic patient exhibited signs of considerable impairment of circulation. In contrast to reports in nondiabetic patients with PVD,[45] women were nearly as frequently affected as men. The study group was composed of diabetic subjects of all ages with a preponderance of older patients (over 60 yr) and of women, a distribution repeatedly found in large diabetic surveys.[10,46,47] The number of subjects was greater and the evaluation of vascular disease was more precise than in many previous reports, making possible a multivariate analysis of subgroups that sometimes could not have been performed.

In 57% of all patients with PVD, impaired circulation without symptoms was diagnosed. This observation demonstrates the value of the Doppler ultrasonic method used.[18–22] Screening with palpation and auscultation is not sufficiently specific and sensitive.[48] Widmer et al.[48] in a study on Swiss men found pathologic findings by palpation alone in only 35% of the patients with proven PVD. An improvement in noninvasive diagnostic means of PVD was made with the Doppler ultrasonic technique developed by Satomura,[24] which has been recognized as an excellent method for assessing the degree of arterial obliteration.[18–22] This simple and quick method makes it an ideal tool especially for epidemiologic studies. In addition to the assessment of PVD, signs of marked mediasclerosis can be obtained with this method.[23] Possibly, however, a small group of patients with asymptomatic PVD and a minor degree of mediasclerosis may show falsely normal values and may be overlooked.

In this study mediasclerosis at the ankle level was recognized in 9% of the examined diabetic patients. About half the patients with mediasclerosis had signs of PVD, and mediasclerosis was predominantly seen in peripheral PVD. These findings are in accord with the observations of Ferrier,[49] who demonstrated an additional intimal thickening with peripheral mediasclerosis and thereby an impairment of circulation. The predilection for the peripheral location (below the knee) in diabetic macroangiopathy has been reported repeatedly.[14–17] It was therefore speculated that the PVD of overt diabetes may be a distinct form of arteriosclerosis.[50] It has been generally accepted that the arteriosclerotic process involving the large arteries does not differ, at least qualitatively, from that of the nondiabetic person,[40] although some investigators described specific abnormalities in the small unnamed arteries and arterioles in diabetic patients.[51,52] However, there has been no explanation for the higher incidence of arterial occlusion below the knee. Also, a correlation of different types of PVD with cardiovascular risk factors has not yet been done in a nonselected group of diabetic patients.

In this study peripheral PVD, either isolated or combined with proximal stenosis, was also the most frequent. Furthermore, it was confirmed that diabetic patients exhibit cardiovascular risk factors in a high percentage (Figure 1), especially hypertension, overweight, and hypertriglyceridemia.[53] Hypercholesterolemia (≥ 250 mg/dl) was found only in 11%, which is no more frequent than that observed in a nondiabetic population.[53] The positive effect of diabetes on arteriosclerosis can therefore not be explained as a result of increased total cholesterol levels alone, as was previously suggested.[51] The predominant cardiovascular risk factor was hypertension. The very high percentage of patients with elevated blood pressure in this study may be partially explained by the position of the patient during measurement. About 20% of all hypertensive patients exhibited a significant fall of blood pressure by changing from a supine to a sitting position. Diabetic autonomic neuropathy might contribute to this phenomenon. Since in most of the other studies regarding hypertension in diabetic persons blood pressure was measured in a sitting position, a certain number of hypertensive patients may have been overlooked.

There was a close association of hypertension with PVD. Clear differences with regard to cardiovascular risk factors could be demonstrated when patients with proximal or peripheral PVD were examined separately (Tables 4 and 5). Diabetic patients with a pelvic or femoropopliteal type of obliteration were more often hypertensives and smokers and showed higher cholesterol values and an accumulation of cardiovascular risk factors compared with patients without impaired circulation. In this proximal type of PVD no influence of duration of diabetes was noted. The overall prevalence of the isolated proximal type was calculated to be 5.8%, a figure that is found in a general population.[48] From this it may be concluded that proximal PVD may represent an arteriosclerotic process with coexisting diabetes, but not a "diabetic macroangiopathy."

In contrast, there was no accumulation of cardiovascular risk factors other than diabetes—except slightly higher systolic blood pressure values—in patients with peripheral PVD. These diabetic patients were generally insulin dependent. A highly significant correlation was noted with the duration of the overt diabetes (Figure 2). These results suggest that the diabetes, if it exists a long time, may represent a risk for the occurrence of peripheral PVD. The influence of duration of diabetes on the occurrence of diabetic macroangiopathy has been controversial.[6,7,9,11,53,54] However, the loca-

tion of obliteration was not taken into consideration in any study. In our opinion the duration of diabetes is etiologically related to peripheral but not proximal PVD.

It was noted, however, that juvenile diabetic patients of long duration exhibited fewer signs of PVD than older patients with advanced diabetes. Possibly, in the elderly diabetic patients, the high incidence of hypertension might be an additional pathogenetic factor. In this study, the patients with peripheral PVD did not have a higher incidence of hypertension (≥ 160/95 mm Hg) than age-matched diabetic subjects without PVD. They exhibited, however, an increased frequency of the severe form of hypertension (hypertension II). Very likely, the duration of hypertension might be important.

Similarly, different opinions exist in the literature concerning the influence of glycemic control as a pathogenetic factor in diabetic macroangiopathy. Since different criteria for the evaluation of metabolic control were used, and no pertinent follow-up parameters were available, the correlation with the macroangiopathy was often dependent on the interpretation of the investigators. In this study, however, significant differences were found using median postprandial blood glucose values as criteria of metabolic control. Compared with diabetic persons without vascular disease, higher values were found in patients with peripheral PVD. To a large degree, these patients were insulin dependent. So it seems likely that metabolic control plays an important part in the development of diabetic macroangiopathy. People with diabetes may benefit from tight control of blood glucose not only as a prophylactic measurement of diabetic microangiopathy,[55] but also of the macroangiopathy below the knee.

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