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PERIPHERAL ARTERIAL DISEASE AND DIABETES MELLITUS

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SUMMARY

The aim of this study was to establish clinical characteristics and consequences of peripheral arterial disease in diabetic patients. The study included 350 inpatients, 54.6% men and 45.4% women. Women were statistically significantly older than men (67.2±9.1 vs. 61.7±9.8 years; p<0.0001). There were no statistically significant differences in diabetes duration (15.1±9.4 and 16.0±8.2 years in men and women, respectively; χ^2-test=3.2; df=2; NS). Among study patients, 87.2% had lower leg peripheral arterial disease, 27.3% had an isolated form, and 59.9% had changes in proximal arteries. Asymptomatic stage of the disease was found in 12.6%, intermittent claudication in 38.9%, chronic critical ischemia in 25.7%, and foot ulcer or gangrene in 22.8% of patients. A total of 36 bypasses, 20 percutaneous transluminal angioplasties and 10 lumbar sympathectomies were performed in 15.7% of patients. A hundred and seven amputations, 70.1% minor and 29.9% major, were performed in 22.8% of patients. Early detection and regular ultrasound check-ups can increase the number of surgical or endovascular interventions, thus reducing the rate of amputations.

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INTRODUCTION

Peripheral arterial disease (PAD) has an important place in health care due to its high incidence and prevalence, as well as its consequences. A large number of epidemiological and clinical studies have pointed to the association of cumulative PAD incidence with patient age and diabetes duration (1-9) (Table 1). Differences in data on PAD incidence and prevalence obtained in various studies are due to non-standardized diagnostic procedures (subjective difficulties, physical examination, hemodynamic measurements, etc.) (10).

A diagnosis based on subjective difficulties only (intermittent claudication) or on the absence of foot artery palpation may be questionable, as sensory loss resulting from distal diabetic neuropathy may alleviate symptoms of intermittent claudication, whereas arterial calcification (Mönckeberg's sclerosis) may be the reason for good palpability of arterial pulsation even in severe ischemia of the extremities (11-13).

Table 1. **Epidemiological studies on the incidence and prevalence of peripheral arterial disease in diabetes mellitus according to different diagnostic procedures**

Study	Incidence	Prevalence
Framingham (n=4317) (1,2)	Claudication: ♂ 12.6/1000/yr ♀ 8.4/1000/yr	18.8% (diabetes duration 16 yrs)
UGDP (n=619) (3)		Palpation: ♂ 34.5%, ♀ 37.6% (diabetes duration 13 yrs) Claudication: ♂ 37.7%, ♀ 24.3% (diabetes duration 13 yrs)
Rochester (n=1073) (4)	Pulse deficit: ♂ 21.3/1000/yr ♀ 17.6/1000/yr	15.0% (diabetes duration 10 yrs) 45.0% (diabetes duration 20 yrs)
Kristianstad (n=374) (5)		Pulse deficit: 16.4% (diabetes duration 1.5 yrs) 38.7% (diabetes duration 20 yrs)
München (n=623) (6)		Ultrasound: ♂ 18.0% ♀ 14.4%
Oxford (n=186), type 2 DM (7)	Claudication: 16/1000/yr	
Pittsburg (n=657), type 1 DM8		♂ 11.0%, ♀ >30% (diabetes duration >30 yrs)
Zagreb (n=200), type 2 DM (9)		Plethysmography: 15.0% (diabetes duration 5 yrs) 18.5% (diabetes duration 10 yrs) 21.0% (diabetes duration >10 yrs)

PAD in patients with diabetes, although being the same pathologic process in terms of histology, differs significantly from that in non-diabetic patients. The differences are epidemiological (increased incidence and prevalence), clinical (multi-segmental localization with predominant changes in lower leg arteries, involvement of both lower extremities, rapid progression of the atherosclerotic process, frequent chronic critical ischemia, foot ulcer and gangrene, and lower extremity amputation), and therapeutic (more limitations in surgical reconstruction and endovascular recanalization) (14).

Arterial calcification is significantly more frequent in diabetic patients and in those with peripheral arterial disease in particular as compared to the non-diabetic population. In addition to causing diagnostic difficulties in the assessment of the degree of arterial flow hemodynamic disturbance, it is a factor that may adversely affect the results of endovascular recanalization (percutaneous transluminal angioplasty, PTA) requiring stent implantation to support dilatation (5,11-15).

Croatian literature lacks studies on PAD in patients with diabetes (9,16-20). In view of the medical, economic and social importance of PAD, the aim of this retrospective study was to establish epidemiological characteristics and clinical consequences of PAD in persons with diabetes mellitus.

PATIENTS AND METHODS

The study included 350 persons with diabetes and PAD (54.6% of men and 45.4% of women) hospitalized at the Vuk Vrhovac University Clinic from January 1, 1996 to December 31, 1999. Out of the total number of 350 patients, 5.1% had type 1 and 94.9% type 2 diabetes mellitus.

Patients with PAD diagnosed prior to the diagnosis of diabetes (n=7) and those in whom the time of diabetes or PAD diagnosis could not be determined from their medical records were not included in the study (n=19).

The diagnosis of PAD made during the patients' stay at the Vuk Vrhovac University Clinic (n=226) was based on subjective difficulties (intermittent claudication, ischemic pain at rest), clinical signs (absent or decreased artery pulsation, vascular murmur above the ilium and femur, prolonged reactive hyperemia), measurements of segmental systolic pressure (ankle, lower leg, thigh) and ankle brachial index, and analyses of doppler ultrasonograms of the common femoral artery, popliteal artery, posterior

tibial artery and dorsal foot artery using continuous wave Doppler (CW Doppler) (12-14). FLO-LINK 500 T (RIMED, Israel) was used.

Systolic pressure gradient of up to 20 mm Hg at any measurement site was considered as normal. Gradient of 20 to 30 mm Hg was defined as "borderline", and differences in systolic pressure greater than 30 mm Hg indicated stenosis or artery occlusion (21).

A normal artery waveform is triphasic. The first component of the waveform marks systolic forward blood flow, the second short component marks a reverse flow in diastole and indicates a degree of arterial resistance, and the third one indicates a late diastolic flow indicating arterial wall compliance. A change of triphasic form into a bi- or monophasic form indicates a degree of stenosis or artery occlusion.

The severity of the PAD clinical picture has been standardized according to the ankle brachial index (ABI) values into four stages: asymptomatic stage (ABI 0.80 to 0.95), intermittent claudication (ABI 0.5 to 0.8), chronic critical ischemia (ABI 0.3 to 0.5), and foot necrosis/gangrene (ABI ≤0.2) (21,22).

The criteria for chronic critical ischemia of lower extremities were based on the European consensus on critical limb ischemia (23,24). The criterion of continuous rest pain and values of systolic pressure measured above dorsal foot artery and/or anterior tibial artery of 50 mm Hg or lower were used in this study.

A disproportion between CW doppler sonogram and systolic pressure value, a systolic pressure greater than 250 mm Hg at either lower extremity, ankle systolic pressure by 70 mm Hg greater than that measured in the arm, and ABI of 1.30 or greater were the criteria for calcification with incompressible arteries. The criterion for calcification with compressible arteries was the difference between inflation and deflation pressures of the hydraulic cuff at any level of the extremity greater than 30 mm Hg (12,25).

Amputations (n=47) performed prior to the diagnosis of PAD were not taken into account in the assessment of interdependence of PAD and extremity amputation.

All data used in this study were obtained from medical records of patients hospitalized at the Vuk Vrhovac University Clinic.

T-test was used on statistical analysis of between-group differences in continuous variables, whereas χ^2-test was used to analyze associations between categorical variables. Values of $p<0.05$ were considered as significant.

RESULTS

Patient demographic characteristics are shown in Table 2. The mean age of female patients was 67.2±9.1 years. They were statistically significantly ($p<0.0001$) older than men whose mean age was 61.7±9.8 years. There was no statistically significant difference in diabetes duration between men (15.1±9.4) and women (16.0±8.2). Although women were statistically significantly older than men, the incidence of PAD was statistically significantly higher in men aged up to 60 than in women ($\chi^2=19.89$; df=1; $p<0.0001$) (Table 3). There was no statistically significant difference in diabetes duration between men and women as related to the prevalence of PAD (χ^2-test =3.2; df=2; NS). The

Table 2. **Demographic characteristics of persons with diabetes and peripheral arterial disease**

	♂	♀
Subjects	**191**	**159**
Age (yrs)*	61.7±9.8 (32-84)	67.2±9.1 (30-96)
Diabetes duration (yrs)*	15.1±9.4 (1 mo-40 yrs)	16.0±8.2 (1 mo-42 yrs)
Diabetes treatment (%)		
- diet	10.0	5.7
- oral hypoglycemic agents	15.1	9.7
- insulin	24.9	22.9
- insulin + oral hypoglycemics	4.6	7.1

*Mean±SD (range)

Table 3. **Prevalence of peripheral arterial disease in diabetic patients according to sex and age**

	Age group (yrs)			
Subjects	≤ 60		> 60	
Male (n=191)	81	42.4%	110	57.6%
Female (n=159)	31	19.5%	128	80.5%

analysis included patients with diabetes duration of up to 30 years (Table 4). Below-knee localization of PAD was present in 87.2% of patients, with above-knee and/or pelvic arteries involved by the stenotic obliterative process in 59.9% (Table 5). Asymptomatic PAD was found in 12.6%, intermittent claudication in 38.9%, chronic critical ischemia in 25.7%, and foot ulcers or gangrene in 22.8% of 350 patients (Table 6). Ultrasound or x-ray revealed arterial calcification in 16% of 319 patients.

Table 4. **Prevalence of peripheral arterial disease according to sex and diabetes duration**

	Diabetes duration (yrs)			
Subjects	up to 10	11-20	21-30	31+
Male (n=191)	70 (36.6%)	67 (35.2%)	40 (20.9%)	14 (7.3%)
Female (n=159)	47 (29.6%)	71 (44.6%)	34 (21.4%)	7 (4.4%)

Table 5. **Distribution of peripheral arterial disease according to the site of arterial narrowing or obstruction**

		n	%
Pelvis		2/319	0.6
Above knee		31/319	9.7
Pelvis/above knee		8/319	2.5
Below knee	**Total:**	278/319	87.2
a) isolated		87/319	27.3
b) with proximal changes		191/319	59.9

Table 6. **Clinical picture of peripheral arterial disease in diabetic patients**

	Number	%
Patients	350	100
Clinical picture		
Asymptomatic stage	44	12.6
Intermittent claudication	136	38.9
Critical ischemia	90	25.7
Ulcer/gangrene	80	22.8

Table 7. **Surgical interventions aimed at circulation improvement, and amputations in diabetic patients with peripheral arterial disease**

	Number	%
Patients	55	-
Revascularizations	56	100
bypasses	36	64.3
angioplasties	20	35.7
Lumbar sympathectomy	10	100

In order to improve arterial blood flow of lower extremities, 15.7% (55/350) of patients underwent 36 bypasses, 20 percutaneous transluminal angioplasties and 10 lumbar sympathectomies (Table 7).

Out of the total number of bypasses, there were 58.3% (21/36) of aortofemoral, 27.8% (10/36) of femoropopliteal and 13.9% (5/36) of femorocrural bypasses (Fig. 1). Out of the 20 percutaneous transluminal angioplasties performed, 17 (85%) were dilatations and 3 (15%) recanalizations of the arteries. The majority of interventions, i.e. 55% of them (11/20), were carried out on superficial femoral artery, 30% (6/20) on common iliac artery, 10% (2/20) on popliteal artery, and 5% (1/20) on external iliac artery (Table 8, Fig. 1).

A total of 107 amputations were performed in 22.8% out of 350 patients, among them 70.1% minor (toes or foot) and 29.9% major ones (below- or above-knee). The amputation rate was 30.5%, 14.9% of these major amputations. The greatest number of amputations (83.1%) were carried out in persons older than 60.

DISCUSSION

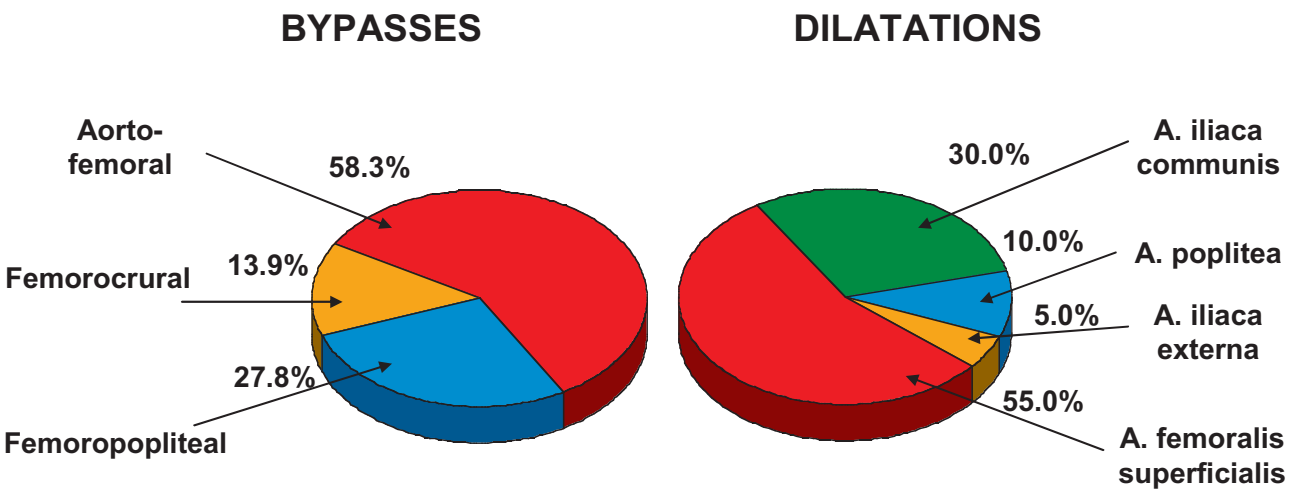
Based on clinical and epidemiological studies, it has been hypothesized that 10% to 20% of persons with type 2 diabetes mellitus have PAD (26). The complexity of the atherosclerotic process and the rapid development of the disease result in the high prevalence of chronic critical limb ischemia in persons with diabetes. McDaniell and Cronenwet have shown that persons with diabetes and claudication difficulties are at a 35% risk of developing critical extremity ischemia (27). Early identification of PAD can prevent its severe consequences such as limb amputation. In one third of persons with diabetes, limb ischemia is responsible for foot ulcers (28). The resulting infection of these ulcers rapidly leads to gangrene and consequential amputation.

Many authors have pointed to the fact that in diabetic patients, the diagnosis of PAD is made too late, especially at the primary health care level (29-31). The failure to recognize PAD symptoms and the absence of claudication-related difficulties are associated with sensory deficit caused by peripheral sensory

Table 8. **Prevalence of amputations in persons with peripheral arterial disease according to age groups and amputation level**

	Amputation level (%)			
Age group (yrs)	**Toe**	**Foot**	**Upper leg**	**Lower leg**
40-60 (n=15)	10.3	1.9	1.9	2.8
61+ (n=65)	52.3	5.6	14.0	11.2
Total (N=80)	62.6	7.5	15.9	14.0
	(n=67)	(n=8)	(n=17)	(n=15)

Figure 1. **Bypasses (n=36) and angioplasties (n=20) in diabetic patients with peripheral arterial disease.**



polyneuropathy. In addition, many patients do not walk much due to the concurrent neurospinal and/or neuromuscular diseases, thus avoiding possible claudication difficulties.

Ankle brachial index measurement (ankle systolic pressure/upper arm systolic pressure) is a gold diagnostic standard in the early detection of PAD. According to Orchard and Strandness, it should be determined in every diabetic patient with decreased posterior tibial artery pulsations, vascular murmur above the iliofemoral area and foot ulcer, and in those with muscle pain of unknown cause. Persons with ankle brachial index of 0.50 to 0.90 should be tested once in 3 months, and those with values above 0.90 every one or two years. These authors further recommend that ankle brachial index be determined once a year in type 2 diabetic patients older than 35 and diabetes duration of more than 20 years, as well as in type 2 diabetic patients older than 40 (12).

Although ankle brachial index measurement is a gold standard in the early diagnosis of PAD and assessment of the severity of hemodynamic impairment of arterial blood flow in lower extremities, its diagnostic value is lower in the presence of arterial calcification (11,13). Arterial calcification is present in 5% to 10% of diabetic population. Its incidence depends on age and diabetes duration and regulation (5,12,15,32). The Pittsburg study found a 29%-47% prevalence of arterial calcification. The range expressed in percentage depended on calcification of individual arteries (12). The severity of limb ischemia in the presence of arterial calcification was determined by toe pressure index (systolic toe pressure/systolic upper arm pressure). Normal values were 0.60±17% (12).

The present study showed PAD to have been diagnosed in 64.6% of patients only after their hospitalization at the Vuk Vrhovac University Clinic. The majority of patients had an advanced clinical stage of the disease; that is why angiography was indicated

and performed in only 28.6% of patients. Among patients undergoing angiography, 56% were subjected to surgical revascularization and endovascular recanalization. Late diagnosis of PAD was one of the reasons for extremity amputation in 80 out of 350 (22.8%) patients, including 32 major amputations.

Timely diagnosis, assessment and treatment of PAD can attenuate or diminish its serious sequels, improve the patient quality of life and reduce hospitalizations. Health care of persons with diabetes must therefore be comprehensive at all levels. Strict control of diabetic patients according to the principles of the Croatian Model could significantly reduce the incidence of PAD and its sequels.

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