PERIPHERAL ARTERIAL DISEASE AND DIABETES

Bosevski M

University Cardiology Clinic, Medical Faculty, Skopje, R. Macedonia

Abstract: There are two points of view for the interplay of peripheral arterial disease (PAD) with diabetes: the higher prevalence of PAD that is presented in diabetes than in the general population, and secondly that peripheral atherosclerosis is a marker of polyvascular disease in these pts. The main aim of this review is to describe risk factors, diagnostic approaches and treatment modalities of this condition.

Key words: peripheral arterial disease, diabetes mellitus.

Introduction

Diabetes together with smoking, age and fibrinogen are significant risk factors for the development and prognosis of peripheral arterial disease (PAD), also known as diabetic angiopathy [1]. The relative risk of the development of PAD in those with diabetes mellitus is three to four times higher compared to non-diabetic populations (Hoorn study) [2]. The increased risk of PAD in the presence of diabetes is independent of other risk factors.

In diabetic patients, the prevalence of PAD is 10% when defined as intermittent claudication, and up to 40% when defined as pathological ankle brachial indexes (ABI), assessed by Doppler sonography [3]. The prevalence of PAD in diabetic patients varies between 10–40%, depending on the method of detection and depending on the study population (main studies addressing the prevalence are Rochester, Framingham, UGDP, Kristanstand) [4–6]. In people with known coronary artery disease (CAD) there is a higher probability of PAD [7].
There is a lack of data on the influence of major risk factors for the development of PAD in patients with DM. The main risk factors suggested in the literature will be summarized below.

The Limburg study evaluated risk factors associated with PAD and showed that age, smoking and hypertension together with DM type 2 are significantly related to asymptomatic PAD. Male gender, hypertension and smoking have an independent relationship with symptomatic PAD, compared to those with asymptomatic PAD. Age together with fibrinogen values, smoking and DM type 2 are independent predictors for the development of PAD [8]. Critical limb ischaemia and amputations in diabetic patients depend on microangiopathy, age, diabetes duration and smoking [9–11].

Diabetes duration is a significant predictor for PAD development, including symptomatic PAD, according to unpublished data (Figure 1). Conflicting results are demonstrated in studies that have examined the influence of diabetes duration on the development of PAD. Al-Delaimy showed that diabetes duration has a relative risk of 1.4 over a period of 1–5 years, 3.6 over a period of 6–10 years, and 2.5 over a period of 11 to 25 years [12]. Other studies show that a diabetic subpopulation with a longer duration of the pre-diabetic phase did have an increased prevalence of PAD and coronary artery disease [13].

There is a great probability of the occurrence of PAD in people with diabetes and a duration of diabetes of more than 10 years. A limitation of most studies reporting on diabetes duration as the major risk factor for the occurrence of PAD is that there are no cut-offs presented for the time of its occurrence [14]: Kalio has indeed demonstrated a cut-off point at 10 years diabetes dura-
tion for the development of PAD [15]. Some vascular laboratories use the cut-off time of 10 years for screening programmes of diabetic patients.

The presence of neuropathy increases the risk of asymptomatic PAD threefold, which is due to both neuropathy and PAD presenting at the same time. They both have mutual underlying pathological mechanisms. The presence of PAD additionally worsens neuropathy due to decreased circulation. That is the reason why McDermott advises screening for PAD in patients with neuropathy [16].

Blood glucose levels increase the risk of development of the symptomatic PAD stage by 50%, according to our results. Despite the results of the UKPDS study on the association of cardiovascular risk in DM type 2 patients with fasting glycaemia, this association with PAD is still defined as weak. The values of glycaemic control assessed by HbA1C > 7.1% and the presence of insulin resistance have been shown to be associated with the presence of PAD [17, 18].

Our study results find as major risk factors for the presence of PAD in DM type 2: duration of diabetes, neuropathy and glycaemia levels. Multivariate regression analysis did not demonstrate smoking and patients’ age as risk factors for PAD in DM type 2 patients. These two major risk factors for PAD, referred from the Trans-Atlantic Inter-Society on Peripheral Arterial Disease consensus, do not show an incremental independent value, based on multivariable analysis in diabetic people [13].

Our findings suggest that risk factors are comparable in asymptomatic and symptomatic diabetic patients with PAD [19]. In this context, prevention (primary and secondary) should be applied for the control of risk factors in both subgroups of patients with PAD and DM type 2.

**Diagnostic approach for Peripheral Arterial Disease**

The presence of DM in the general population is in accordance with the measured pathological ABI values (< 0.9 or > 1.3). The ABI index is the most accurate diagnostic marker of PAD in epidemiological studies in general and diabetic populations. *(Edinburgh, San Luis Valley Diabetes Study)* [20, 21].

ABI values < 0.9, and > 1.3 define the presence of PAD. ABI values > 1.3 in diabetic patients are due to the presence of calcified vessels, and due to pathologically higher values of tibial and dorsopedal blood pressure. ABI values < 0.9 and > 0.7 represent mild leg ischemia, values < 0.7 and > 0.5 moderate ischemia, and those with value < 0.5 indicate severe (critical) ischaemia.

According to the American Diabetes Association (ADA) statement a diabetic patient older than 50 yrs is recommended for PAD screening by performing an ABI. If the ABI is normal, the Doppler test should be repeated after 5 years, or in the case of the appearance of PAD symptoms. If the patient
complains of claudication and does have ABI values within 0.9–1.3, AHA/ACC recommends the treadmill test for diagnosis.

ABI indicates the presence of systemic atherosclerosis in a population. The explanatory mechanism for the prognostic value of ABI is that its low values define the extent and severity of vascular disease and identify those patients at risk of thrombotic complications. This is related to an increased risk of cardiovascular events, including death [22]. Its prognostic value is shown in populations which have diabetes type 2 subgroups [23, 24]. The studies *Malmo* and *Mayo Clinic* showed an increased rate of death of 50–70% in a population with type 2 DM and the presence of PAD, defined as ABI [25]. Compared to other studies, our study results showed that ABI gives information on death rates in diabetic patients with CAD (Figure 2).

![Hazard Function](image)

*Figure 2 – Cumulative all-cause mortality in pts with type 2 DM stratified by pathological ABI*

Clinical symptomatology of intermittent claudication has been found in 50% of type 2 diabetic patients over 10–15 years follow-up. Diabetic PAD is accompanied with faster impairment of functional capacity and early development of critical leg ischaemia [26].

There is general agreement that diabetic atherosclerosis appears at an earlier age, it is diffuse, and clinically more severe, which complicates planned revascularization compared with non-diabetic people [27, 28, 29–32].

Angiographically assessed PAD in diabetic patients has a more distal location, characterized by tortuous, irregular arterial walls and the presence of calcifications [33]. Morphological assessment of peripheral arteries is necessary in the context of planning a revascularization procedure and includes noninva-
sive procedures (Echo-Doppler sonography, CT or MR angiography) and angiography according Seldiner, as well.

Treatment modalities

There are no confident results for a positive effect of anticoagulation drugs Cilostazol and pentoxyphillin derivates in patients with stable claudication, and in revascularized patients with non-stable claudication and in critical limb ischaemia in diabetic and non diabetic populations. There is an evidence for the use of Clopidrogel and Aspirin in diabetic patients with PAD to improve functional status and to lower cardiovascular risk (CAPRIE, CURE) [34, 35].

Control of hyperglycaemia is the basis of treatment for patients with PAD and DM. Thiazolidinediones could control hyperglycaemia and insulin resistance in diabetic pts, but without effect on the prognosis of patients with PAD [36].

After the HOT and ABDC trials’ results were published, ADA and the Joint National Committee 7 (JNC 7) have supported aggressive control of blood pressure in diabetic patients with arterial hypertension and PAD. Treatment of dyslipidaemia with statins in diabetic patients is associated with a significant reduction in future events, and that is why it is mandatory [37, 38]. An evidence-based approach to the treatment of modifiable risk factors in patients with PAD and DM is presented in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Target</th>
<th>Evidence level</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Abstinence</td>
<td>1 Level A</td>
<td>Clear</td>
</tr>
<tr>
<td>Platelet Inhibition</td>
<td>Aspirin or Clopidogrel</td>
<td>1 Level A</td>
<td>Clear</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>LDL &lt; 100 mg/dl (2.6 mmol/L)</td>
<td>1 Level A</td>
<td>Clear</td>
</tr>
<tr>
<td>Hypertension</td>
<td>BP &lt; 130/80 mmHg</td>
<td>1 Level A</td>
<td>Clear</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>HbA1c &lt; 7%</td>
<td>IIa Level B</td>
<td>Likely Beneficial</td>
</tr>
</tbody>
</table>

Although extremity survival after surgical vascular reconstruction is lower in diabetic patients compared with non-diabetic people, especially in those with marked neuropathy, a surgical approach is used in both populations [39].

Percutaneous transluminal angioplasty of the iliac-femoral vascular tree shows a lower patency rate, and higher restenosis rates in diabetic patients with intermittent claudication than in those without diabetes. In patients with critical limb ischaemia and diabetes, the rate of extremity salvage is lower despite the same patency and restenosis rates [40].
AHA/ACC recommendations for revascularization for diabetic patients and symptomatic PAD are shown in Table 2 [57].

Table 2

**Indications for revascularization in symptomatic PAD patients**

**Surgery (bypass)**

Class I for Lifestyle limiting claudication with...

1. ...infra-inguinal disease  
   Level of Evidence A
2. ...aorto-iliac obstruction  
   Level of Evidence B

**Endovascular Approach (percutaneous transluminal angioplasty)**

Class I for Lifestyle limiting claudication with...

1. ...aorto-iliac obstruction  
   Level of Evidence A
2. ...with stenoses less than 3 cm in iliac  
   or femoro-popliteal arteries  
   Level of Evidence B

Class IIa

1. Stents or other adjunctive endovascular techniques in salvage therapy for suboptimal  
   results from balloon dilatation of the femoral, popliteal, and tibial arteries  
   Level of Evidence C

Class IIb

1. Treatment of femoro-popliteal lesions by atherectomy, laser, thermal devices is not  
   well established  
   Level of Evidence A

Class III

1. Primary Stent placement in popliteal or tibial arteries.  
   Level of Evidence C

**Prognostic implications**

Duration of DM and its glycometabolic control are independent predictors for PAD development and progression [41–43]. The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) defined dyslipidaemia, especially HDL-cholesterol, arterial hypertension (value of systolic blood pressure), and microangiopathy as independent predictors for PAD progression in DM type 2 patients [44].

The pathophysiology of PAD in diabetic patients is identical to that in non-diabetic populations. However, the presence of platelet hypercoaguability,
Inflammation, endothelial dysfunction and diabetic neuropathy are additional predictors for its development and progression [45].

Patients with PAD and DM type 2 have a severely impaired quality of life, impaired functional capacity and increased probability of local leg infections [40].

Prognosis of PAD depends on the prediction of future cardiac and cerebrovascular events as well as the progression of critical leg ischemia. The relative risk of future cardiovascular events in diabetic people with PAD is two to four times higher compared to non-diabetic people with PAD, and in those with critical limb ischemia it is twice as high compared to the group with intermittent claudication. This high rate of morbidity and mortality in diabetic patients with PAD is connected to the high probability of polyvascular involvement of the coronary and carotid vascular territory [46]. There is a high frequency of future cardiovascular events (20%) and critical limb ischemia (30-40%) in diabetic patients with PAD, estimated over a period of five years (Framingham study) [47, 48]. Compared to non-diabetic people, patients with DM type 2 have a 10–15 times higher risk of amputations [49]. Mortality in diabetic patients with PAD is 86% for 13 years, and 60% for 2 years in patients with critical limb ischemia [50].

Clinical entities associated with peripheral arterial disease

Critical limb ischaemia

Chronic Critical Limb Ischaemia (CLI) is an "end stage" condition of peripheral arterial disease. Rest pain, and/or leg ulcers/necrosis together with ABI value < 0.5 define critical limb ischaemia (Picture 1).

Picture 1 – Necrosis of 1st and 2nd toes of foot
Despite much more frequently used revascularization methods and rigorous control of risk factors, CLI has still been referred with a high rate of amputation and mortality. 20% of this population died within 6 months, 35% of patients went to amputation [52].

There is a difference in CLI onset among the non-diabetic and diabetic populations with PAD: an incidence of 8% and 34% respectively [53]. It is probably explained by specific features of diabetic atherosclerosis which tends to be more diffuse and more severe than in non-diabetic people. The coexistence of neuropathy and infections, to which diabetic patients are more prone, complicate the problem of PAD and CLI in diabetes [54].

There is sufficient data on the influence of modifiable factors on PAD prognosis in the general population. Definite data on the influence of modifiable risk factors on the development of CLI in diabetic patients is lacking.

In the Vascular Centre at the University Cardiology Clinic Skopje, a cross-sectional study on the PAD population was done as a part of the VAS European Study. Among them (127 patients) 63 patients had diabetes mellitus and 64 patients were non-diabetic. Seventeen patients had CLI. Our results estimated by multiple regression models indicated differences in predictors of the onset of CLI between diabetic and non-diabetic subjects with PAD.

A previously measured ankle-brachial index below 0.5 and prostanoid treatment are predictors of the development of CLI in diabetic people (OR 3.39 CI 95% 0.28–40.78 for the first and OR 12.98 CI 95% 1.76–95.58 for the second parameter). Critical limb ischaemia in diabetic patients is not only a "large artery disease". the presence of microvascular complications is a predictor of PAD prognosis in diabetic patients (OR 12.98 CI 95% 1.76–95.58). Understanding concomitant heart failure as a predictor for the onset of CLI among diabetic patients (with a predictive value OR 3.14 CI 95% 0.61–16.09), and confirming smoking as a prognostic factor for non-diabetic people, could have important clinical usefulness in the risk assessment of peripheral arterial disease for better limb salvage and cardiovascular survival.

**Diabetic foot**

Diabetic foot, which is a typical clinical manifestation of DM, is caused not only by ischaemia (macro and/or microangiopathy), but also by neuroischaemic or mixed etiology [55]. This syndrome could also incorporate structural bone changes, the presence of artropathy (Sharcot) and skin lesions and infections.

Classification of diabetic lesions and their treatment modalities are given in Table 3 [56].
Table 3

*Wagner-Brodsky Classification of diabetic foot syndrome and lesions due to depth and ischaemia*

<table>
<thead>
<tr>
<th>Depth</th>
<th>Status</th>
<th>Treatment modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Foot with risk, no ulceration</td>
<td>Education of patients, accommodative footwear</td>
</tr>
<tr>
<td>1</td>
<td>Superficial ulceration, no infection</td>
<td>Offloading with contact cast (TCC), walking brace, special footwear</td>
</tr>
<tr>
<td>2</td>
<td>Deep ulcerations involving tendons and joints</td>
<td>Surgical debridement, wound care, offloading, culture-specific antibiotics</td>
</tr>
<tr>
<td>3</td>
<td>Extensive ulceration or abscess</td>
<td>Debridement, amputation, offloading, antibiotics</td>
</tr>
</tbody>
</table>

Ischemia

<table>
<thead>
<tr>
<th>Ischemia</th>
<th>Status</th>
<th>Treatment modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Not ischaemic</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Ischaemia without necrosis</td>
<td>Entry to vascular laboratory and consultation with vascular specialist if symptomatic</td>
</tr>
<tr>
<td>C</td>
<td>Partial gangrene</td>
<td>Consultation with vascular specialist</td>
</tr>
<tr>
<td>D</td>
<td>Complete foot gangrene</td>
<td>Major extremity amputation and consultation with vascular specialist</td>
</tr>
</tbody>
</table>

Conclusion

Several factors are known to differentiate PAD in patients with diabetes from PAD in non-diabetic patients: Patients with *diabetes mellitus* have a 3-fold increased risk of developing PAD compared to the general population, and PAD is a marker of general atherosclerosis in these patients. The last factor may provide clues to the difference in prognosis for patients with PAD and diabetes.

Diabetic patients, especially those with a long duration, poor glycolmetabolic control and the presence of risk factors are candidates to be screened for asymptomatic peripheral arterial disease. Patients with symptomatic peripheral arterial disease should be aggressively treated for risk factor modification, improvement of their functional capacity and coexistent coronary or carotid arterial involvement. Revascularization and restoration of blood flow is recommended if suitable. In order to reach these conclusion remarks aimed towards patients with PAD and DM, multidisciplinary approaches are required.
REFERENCES


 Peripheral arterial disease and diabetes


Резиме

ПЕРИФЕРНА АРТЕРИСКА БОЛЕСТ И ДИЈАБЕТЕС

Бошевски М.

Универзитетска клиника за кардиология,
Медицински факултет Скопје, Р. Македонија

За заемното дејство на периферната артериска болест (ПАБ) и на дијабетесот од значење се: прво, големата преваленци на ПАБ кaj паациентите со дијабетес во однос на општата популација, и, второ, што ПАБ е маркер на поливаскуларната болест.
Основната цел на овој ревијален труд е да ги опише факторите на ризик, дијагностичкиот пристап и терапевтските модалитети на оваа болест, позната уште како дијабетска ангиопатија.

Ключни зборови: периферна артериска болест, дијабетес.

Corresponding Author:
Marijan Bosevski
Faculty of Medicine
University Cardiology Clinic
Skopje, R. Macedonia

E-mail: marijanbosevski@yahoo.com.