



Study of Peripheral Artery Disease and its Association with Type 2 Diabetic Patients

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Abstract

Background: Type 2 Diabetes (T2D) is a metabolic disease that can be prevented through lifestyle modification, diet control, and control of overweight and obesity. Education of the populace is still key to the control of this emerging epidemic. Novel drugs are being developed, yet no cure is available in sight for the disease, despite new insight into the pathophysiology of the disease. Peripheral arterial disease (PAD) is a common complication and comorbidity of diabetes. Patients with diabetic foot ulcers have coexisting PAD at a proportion of approximately 50% and may suffer from chronic ischemic pain. Arterial brachial index (ABI) is a reliable method for identifying PAD and quantifying PAD severity. The value 0.9 has been used as a cutoff for signs of arterial occlusion. According to a clinical study, diabetic patients could have certain degrees of arterial occlusion at a higher ABI value because of calcified noncompressible arteries, and a possible consequence is the under diagnosis of PAD in this population. More specifically, another clinical study has shown that the cut-off value with the highest sensitivity and specificity for diabetic patients is between 1.0 and 1.1. Patients with PAD have a much higher rate of cardiovascular events. Reduced ABI has been identified as a risk factor for CVD events, cardiovascular death, and overall mortality. When compared to ABI equal to or higher than 0.9, ABI less than 0.9 was linked with a substantial increase in the primary composite endpoint of major cardiovascular events and the secondary endpoint of all-cause death in a retrospective study of approximately 450 patients with T2DM. The signs and symptoms of the peripheral arterial disease are based on the part of the body that is affected. About 66% of patients affected by PAD either do not have symptoms or have atypical symptoms. The American Diabetes Association (ADA) recommends an initial screening for PAD based on an exhaustive interview and a clinical examination including a history of decreased walking speed, leg fatigue, claudication, and the palpation of the pedal pulses.

Keywords: Peripheral Artery Disease, Type 2 Diabetes

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Introduction

T2D is a metabolic disease that can be prevented through lifestyle modification, diet control, and control of overweight and obesity. Education of the populace is still key to the control of this emerging epidemic. Novel drugs are being developed, yet no cure is available in sight for

the disease, despite new insight into the pathophysiology of the disease (1).

Many patients with T2D are asymptomatic. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. (2)



It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million. The number of people with T2D is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. It is estimated that 439 million people would have type 2 DM by the year 2030 **(3)**.

Peripheral arterial disease (PAD) is a common complication and comorbidity of diabetes. Patients with diabetic foot ulcers have coexisting PAD at a proportion of approximately 50% and may suffer from chronic ischemic pain. Arterial brachial index (ABI) is a reliable method for identifying PAD and quantifying PAD severity. The value 0.9 has been used as a cutoff for signs of arterial occlusion. According to a clinical study, diabetic patients could have certain degrees of arterial occlusion at a higher ABI value because of calcified noncompressible arteries, and a possible consequence is the under diagnosis of PAD in this population **(3)**.

More specifically, another clinical study has shown that the cut-off value with the highest sensitivity and specificity for diabetic patients is between 1.0 and 1.1. Another detrimental effect of DM concerning vascular function is worse revascularization outcomes **(2)**.

Patients with PAD have a much higher rate of cardiovascular events. Reduced ABI has been identified as a risk factor for CVD events, cardiovascular death, and overall mortality. When compared to ABI equal to or higher than 0.9, ABI less than 0.9 was linked with a substantial increase in the primary composite endpoint of major cardiovascular events and the secondary endpoint of all-cause death in a retrospective study of approximately 450 patients with T2DM.

Peripheral arterial disease (PAD) is one of the major complications of diabetes. Peripheral arterial disease is defined as an atherosclerotic narrowing of peripheral arteries of the legs, stomach, arms, and the head—most commonly involving arteries of lower extremities **(4)**.

Lower extremities PAD usually manifests in concordance with the systemic atherosclerotic process including coronary artery disease (CAD). Diagnosing PAD in patients with CAD can help to change the exercise regimen prescribed to these patients in a cardiac rehabilitation program to fit both pathologies, in addition to early treatment and/or intervention if required **(5)**.

Patients with PAD are either asymptomatic or complain of atypical symptoms. So screening is essential to reach the right diagnosis. Asymptomatic disease can progress to the symptomatic phase, with intermittent claudication, which could negatively affect the quality of life **(6)**.

Prevalence increases dramatically with age, The global disease burden exceeds 200 million persons worldwide, and PAD increased in prevalence by 23.5% between 2000 and 2010 **(4)**.

Signs and Symptoms

The signs and symptoms of the peripheral arterial disease are based on the part of the body that is affected. About 66% of patients affected by PAD either do not have symptoms or have atypical symptoms **(5)**.

The most common presenting symptom is intermittent claudication, which causes pain and severe cramping when walking or exercising. The pain is usually located in the calf muscles of the affected leg and is relieved by rest. This occurs



because during exercise the muscles of the leg need more oxygen. Normally, the arteries would be able to increase the amount of blood flow and therefore increase the amount of oxygen going to the exercised leg. However, in PAD, the artery is unable to respond appropriately to the increased demand for oxygen by the muscles, as a result, the leg muscles are overly saturated with lactic acid, resulting in pain in the muscle that only goes away with rest (4).

Epidemiology:

The prevalence of lower extremities PAD in the general population is 3–7%, affecting up to 20% of those over 70%–80% of affected individuals are asymptomatic; only a minority ever require revascularization or amputation. PAD affects one in three diabetics over the age of 50. In the US, it affects 12–20 percent of Americans age 65 and older. Around 10 million Americans have PAD. Despite its prevalence and cardiovascular risk implications, only 25% of PAD patients are undergoing treatment (7).

The Egyptian study by **Basyouni et al. (8)** revealed that the prevalence of undiagnosed lower extremities PAD in patients with CAD was 14.5%. These results were concordant with **Dieter et al. (9)** who assessed a total of 100 patients (66 men and 34 women) and found a 19% prevalence of undiagnosed PAD. However other studies found prevalence as high as **26.6% (10)**. The difference between results may be due to the variation in the number of studied patients and, different studied populations as well as the prevalence of risk factors in studied patients Risk

Factors and Mortality Rates:

Analysis of data from the National Health and Nutrition Examination Survey demonstrated

that the most significant lower extremities PAD risk factors are hypertension, diabetes mellitus, chronic kidney disease, hyperlipidemia, and smoking. The odds of having PAD increase with each additional risk factor, from a 1.5-fold increase with one risk factor to a 10-fold increased risk with three or more risk factors (11).

Pathophysiological Mechanisms of PAD

Intermittent claudication results from a diminished inflow of oxygen due to a reduced blood flow in the lower limbs during physical activity, which is a consequence of stenosis or obstruction of an artery irrigating the skeletal muscle. Many mechanisms contribute to the development of lower extremities PAD, in particular arterial stiffness, thrombotic abnormalities, low-grade inflammation, advanced glycation end-products, and oxidative stress (12).

Several studies have suggested the development of an acute inflammatory reaction in response to ischemia induced by exercise, with increased release of different biomarkers (thromboxane, IL-8, intercellular adhesion molecules, or von Willebrand factor) and vasoconstrictors including endothelin-1. Previously, **Nativel et al. (13)** reported an independent association between plasma concentrations of tumor necrosis factor- α receptor 1 (TNRF1) and ischemia modified albumin, inflammatory and redox status biomarkers, and an excess-risk of major lower extremities PAD in patients with T2D.



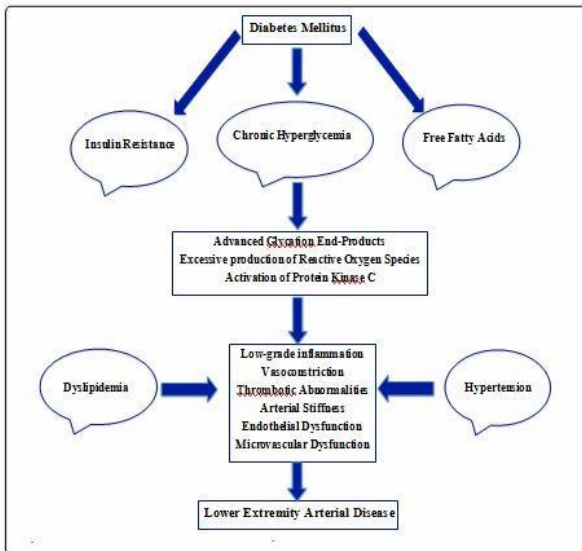


Figure (1): Principal mechanisms involved in the pathogenesis of lower extremity artery disease in patients with diabetes (13).

Clinical Presentation

Intermittent claudication is the hallmark of PAD and is defined as fatigue, discomfort, cramping, or pain of vascular origin in the calf muscles of the lower extremities that are consistently induced by exercise and consistently relieved within 10 minutes by rest (5).

In the general population, only about 10% of persons with known PAD have the classic symptom of intermittent claudication. Approximately 40% do not complain of leg symptoms at all, and 50% have a variety of leg symptoms different from classic claudication, such as exertional pain that does not stop the individual from walking, does not involve the calves, or does not resolve within

10 minutes of rest (4).

The 2016 American Heart Association/American College of Cardiology (AHA/ACC) guideline on the management of patients with lower extremity PAD recommends patients at

increased risk of PAD should be assessed for exertional leg symptoms, and ischemic rest pain, and non-healing wounds (14).

Classification of PAD

The two most commonly used methods to classify PAD are the Fontaine and the Rutherford systems of classification. The Fontaine stages were introduced by René Fontaine in 1954 to define the severity of chronic limb ischemia: (15).

- Stage I: asymptomatic
- Stage IIa: intermittent claudication after walking a distance of more than 200 meters
- Stage IIb: intermittent claudication after walking a distance of less than 200 meters
- Stage III: rest pain
- Stage IV: ulcers or gangrene of the limb

The Rutherford classification was created by the Society for Vascular Surgery and the International Society of Cardiovascular Surgery, introduced in 1986, and revised in 1997 (and known as the Rutherford classification after the lead author, Robert B. Rutherford). This classification system consists of four grades and seven categories (categories 0–6): (15).

- Grade 0, Category 0: asymptomatic
- Grade I, Category 1: mild claudication
- Grade I, Category 2: moderate claudication
- Grade I, Category 3: severe claudication

- Grade II, Category 4: rest pain
- Grade III, Category 5: minor tissue loss; ischemic ulceration not exceeding ulcer of the digits of the foot
- Grade IV, Category 6: major tissue loss; severe ischemic ulcers or frank gangrene
- Moderate to severe PAD classified by Fontaine's stages III to IV or Rutherford's categories 4 to 5, presents limb threat (risk of limb loss) in the form of critical limb ischemia **(16)**.

Recently, the Society for Vascular Surgery came out with a classification system based on "wound, ischemia and foot Infection" (WIFI). This classification system, published in 2013 was created to account for the demographic changes that have occurred over the past forty years including increased incidence of high blood sugar and evolving techniques and ability for revascularization. This system was created based on ischemia and angiographic disease patterns not being the sole determinants of amputation risk. The WIFI classification system is broken up into two parts: wounds and ischemia. Wounds are graded 0 through 3 on the presence of ulceration and/or gangrene and ischemia **(17)**.

- Grade 0: no ulcer, no gangrene
- Grade 1: small, shallow ulcer; no gangrene
- Grade 2: deep ulcer with exposed tendon or bone, gangrene limited to toes
- Grade 3: extensive, full-thickness ulcer; gangrene extending to forefoot or midfoot

Ischemia is graded 0 through 3 based on ABI, ankle systolic pressure, and toe pressure **(17)**.

- Grade 0: ABI 0.8 or higher, ankle
- Grade 1: arterial brachial index 0.6 to 0.79, ankle pressure 70 to 100 mm Hg, toe pressure 40 to 59 mm Hg
- Grade 2: ABI 0.4–0.59, ankle pressure 50 to 70 mm Hg, toe pressure 30 to 39 mm Hg
- Grade 3: ABI < 0.39, Ankle pressure < 50 mmHg

Toe pressure < 30 mmHg

The TASC (and TASC II) classification suggested PAD treatment is based on the severity of the disease seen on an angiogram **(15)**.

Clinical examination:

The American Diabetes Association (ADA) recommends an initial screening for PAD based on an exhaustive interview and a clinical examination including a history of decreased walking speed, leg fatigue, claudication, and the palpation of the pedal pulses **(18)**.

Diabetic neuropathy may hide symptoms of PAD and should be systematically screened as well. Distal diabetic neuropathy is also involved in medial arterial calcification that leads to incompressible arteries. The clinical presentation of PAD can be assessed according to Lerich and Fontaine or Rutherford classification. IC and rest pain are the most important signs to be evaluated, though they can be lacking or difficult to attribute exclusively to PAD. Any deterioration of walking quality or speed must be taken into account as well as fatigue, pain, cramps, discomfort, or burns in the buttocks, thighs, calf, or feet. Those symptoms are



especially suggestive of PAD when triggered by exercise and quickly relieved with rest. The clinical examination may also contain a careful evaluation of the general aspect of the skin, hairiness, and lower limb temperature. Pulse palpation (distal pedis, posterior tibial, popliteal, and femoral arteries), a simple and cheap clinical examination, should be systematically performed in all patients with diabetes (18).

Ankle-brachial index (ABI)

The ankle-brachial index (ABI) is an inexpensive and reproducible method for assessing lower extremity hemodynamics. The ABI is the ratio of the highest systolic pressure in each leg, obtained at the dorsalis pedis and posterior tibial recurrent arteries using a Doppler probe, to the higher the right or left arm brachial artery pressures. Interpretation of ABI results are outlined in Table 4 (19).

Table (1): Diagnostic Criteria for Lower Extremity Peripheral Artery Disease on Ankle and Toe-Brachial Testing

Ankle-brachial index	
1.0 to 1.3	Normal
0.9 to 1.0	Borderline
0.7 to 0.9	Mild
0.4 to 0.7	Moderate
< 0.4	Severe
Toe-brachial index (used when ankle-brachial index is noncompressible; > 1.3)	
> 0.7	Normal
0.4 to 0.7	Abnormal
< 0.4	Severe

Ultrasound and other imaging methods:

The Doppler ultrasound exam is an imaging method with a good lower extremity PAD diagnosis performance (sensitivity 93% and specificity 97%). It is a simple, non-invasive, and affordable method allowing anatomical and hemodynamic vascular assessments, regardless of medial arterial calcifications, but it remains dependent on the operator's experience. The Doppler waveform analysis provides further information; a triphasic waveform reflects a normal hemodynamic state and then the absence of lower extremity PAD. The presence of monophasic or biphasic waveforms has a good negative predictive value but her positive predictive value remains less consistent depending on the presence of peripheral neuropathy (20).

Interestingly, a previous study has shown that a semiquantitative score based on the ultrasonographic features of the lower limb arteries may help in the assessment of lower extremity PAD across different stages, as well as the evaluation of its associated cardiovascular risk. Computed tomography angiography, magnetic resonance angiography, and angiography permit a precise topographic diagnosis and are often performed in the pre-operative work-up when large arterial vessels are involved. The topography of lower extremity PAD is usually categorized as proximal (from the common iliac to the superficial femoral artery) and distal lesions (from the popliteal to the dorsal pedis artery). The distal localization has been shown to be more common than the proximal one in patients with diabetes (21).

Treatment/Management of PAD

Lower extremity PAD is considered a coronary artery disease risk equivalent, and patients with lower extremity PAD are at increased risk for



major adverse cardiac events (MACE), including myocardial infarction (MI), ischemic stroke, and cardiovascular death. They are also at risk for major adverse limb events, which include major amputations and acute limb ischemia.

Among patients with symptomatic lower extremity PAD, annual rates of MACE are 4% to 5%, and rates of major adverse limb events are 1% to 2% **(22)**.

Patients with lower extremity PAD should receive a comprehensive program of guideline-directed medical therapy, including structured exercise and lifestyle modification, to reduce MACE and major adverse limb events and to improve functional status. Smoking cessation is a vital component of care for patients with lower extremity PAD who smoke **(14)**.

A- Exercise

Current guidelines endorse supervised exercise therapy as a first-line treatment for all patients with lower extremity PAD **(19)**. Exercise therapy for patients with lower extremity PAD has typically involved walking to the point of significant claudication pain, then briefly resting until the pain subsides. For patients unwilling to endure repeated bouts of pain, modalities of exercise that avoid claudication or walking performed at intensities that are pain-free or that produce only mild levels of claudication can achieve health benefits comparable with walking at moderate or higher levels of claudication pain **(23)**.

B- Drug Therapy

1- Antiplatelet Therapy

Current AHA/ACC guidelines recommend antiplatelet therapy with aspirin alone (75 to 325

mg per day) or clopidogrel (Plavix) alone (75 mg per day) to reduce the risk of MI, stroke, and vascular death in patients with symptomatic lower extremity PAD **(14)**.

2- Anticoagulant Therapy

In the Cardiovascular Outcomes for People Using Anticoagulation Strategies trial, the addition of low-dose rivaroxaban (Xarelto; 2.5 mg twice daily) to aspirin in patients with coronary artery disease and symptomatic lower extremity PAD reduced MACE and major adverse limb events (absolute risk reduction = 1.0% for each; number needed to treat = 100), although it also increased the absolute risk of major bleeding by 1%. This combination therapy has not been approved by the U.S. Food and Drug Administration **(24)**

3- Statin Therapy

Substantial evidence supports the use of statin therapy in all patients with lower extremity PAD **(14)**.

One trial evaluating patients with lower extremity PAD found that atorvastatin (Lipitor) reduced the risk of long-term adverse limb outcomes (revascularization procedures and need for ischemic amputation) by 18% compared with those not receiving statins. High-intensity atorvastatin also improves pain-free walking distance and community based physical activity in those with intermittent claudication **(25)**.

4- Antihypertensive Therapy:



Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death (14).

Medications to Improve Circulatory Flow

Cilostazol (Pletal), a vasodilator with antiplatelet activity, is an effective therapy to improve symptoms and increase walking distance in patients with claudication. The usefulness of the drug is limited, however, by its adverse effect profile (e.g., dizziness, gastrointestinal symptoms) and its contraindication for use in patients with heart failure. Pentoxifylline (Trental), a drug that increases red blood cell deformability to improve circulatory flow, does not improve maximal walking distance in patients with lower extremity PAD, and guidelines do not recommend using it for the treatment of claudication (14).

C- Surgery

Revascularization is a reasonable treatment option for patients with lifestyle-limiting claudication who have an inadequate response to other guideline-directed therapies. Preoperative evaluation includes angiography to define the location and severity of vascular occlusion and to guide the selection of the appropriate surgical intervention (Figure 7). Commonly used interventions include bypass grafting, endarterectomy, and angioplasty with stenting (26).

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