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THE PATHOPHYSIOLOGY OF PERIPHERAL ARTERY DISEASE IN THE DIABETIC POPULATION

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Diabetes mellitus (DM) is a major risk factor for all forms of cardiovascular disease, this includes peripheral artery disease (PAD). Thus, vascular complications causes an increased risk of adverse cardiac and limb events and impaired quality of patients life. Diabetes patients have worse peripheral artery disease below the knee than nondiabetics. Peripheral arterial disease is characterized by arterial stenosis and occlusions in the peripheral arterial bed. The abnormal metabolic state of diabetes induces vascular dysfunction that predisposes to atherosclerosis. Proatherogenic changes increases the vascular inflammation and alterations in multiple cell types. Early diagnosis and treatment of PAD in patients with diabetes is important in order to reduce the risk of cardiovascular events, minimize the risk of long-term invalidity, improve quality of life and reduce the risk of lower extremity amputation. The diagnosis of PAD is established with the measurement of the ankle-brachial index (ABI) described by Winsor in 1950. ABI is an indicator of atherosclerosis and can serve as a prognostic factor for cardiovascular events and functional impairment, even in the absence of symptoms of PAD.

Keywords: diabetes mellitus; risk factors; CRP; ABI; PAD.

INTRODUCTION

PAD affects more than 8.5 million people in the United States, up to 30% of these patients have diabetes. More than 50% of PAD is caused by tobacco, smoking and diabetes. Among patients with DM who have chronic limb-threatening ischemia in one lower extremity, nearly one half will develop limb-threatening ischemia in the contralateral lower extremity within five years[1].The disease is often asymptomatic; peripheral neuropathy may alter pain perception. The absence of peripheral pulses and the presence of claudication, are inadequate diagnostic indicators. The systolic ankle-brachial index (ABI) is used for asymptomatic PAD. Even before reaching a diagnostic threshold for DM, 20 percent of patients with dysglycemia alone have an abnormal ankle-brachial index (ABI) compared with only 7 percent of patients with normal glucose homeostasis[2]. The measured ankle pressures may be elevated if the vascular wall is less compressible, in particular in the case of medial arterial calcification, known as Mönckeberg's sclerosis (independent of the atherosclerosis process)[3].

The ABI is a comparison of the higher posterior tibial or dorsalis pedis systolic blood pressure in each leg divided by the higher of the right or left arm systolic blood pressure (SBP). In order to obtain an accurate ABI, the patient should rest for 15 to 30 minutes prior to measuring the ankle pressure[4]. A low ABI can lead to a higher risk of coronary heart disease, stroke, transient ischemic attack, progressive renal insufficiency, which increases mortality rates. The ABI is generally, but not absolutely, correlated with clinical measures of lower extremity function such as walking distance, speed of walking, balance, and all physical activities. The normal ABI is >0.91 to as high as 1.3. Normally, the pressure is higher in the ankle than in the arm. Arterial occlusive disease is generally excluded by a normal ABI test. False negative tests can be produced by mild diseases and arterial entrapment syndromes[5]. A resting ABI of less than 0.9 (mild obstruction) generally is associated with stenosis of 50% or more and is 95% sensitive and 99% specific for angiographically documented PAD. An ABI above 1.3 is suspicious

for calcified vessels that may occur in diabetes mellitus or end-stage kidney disease and may also be associated with leg pain[6]. The American Diabetes Association has recommended that a screening ABI should be performed in patients >50 years of age with DM and, if normal, should be repeated every five years[7]. A screening ABI should be considered in diabetic patients <50 years of age who have other PAD risk factors (hypertension, smoking, hyperlipidemia, or duration of diabetes >10 years).

Diabetes and PAD are complicated by neuropathy and foot ulceration, which increases the risk of gangrene and amputation[8].

PATHOPHYSIOLOGY

The diabetic and non-diabetic population experience similar pathophysiology of PAD. Often times the peripheral atherosclerosis distribution is more distal in patients with diabetes and PAD than those without, most commonly involving the tibial vessels. The underlying metabolic abnormalities in DM enhance vascular inflammation, endothelial dysfunction, vasoconstriction, platelet activation, and thrombotic risk, processes important to the pathogenesis of PAD among patients with DM[9]. In addition to atherogenic effects from the diabetes-related dyslipidemia many clinical and experimental studies reveal that high levels of insulin precede development of arterial diseases[10]. Hyperinsulinemia could promote macrophage foam cell formation and thus may contribute to atherosclerosis in patients with type 2 diabetes[11]. Atherosclerosis and type 2 diabetes share similar pathological mechanisms, including elevation in cytokines like interleukin-6 (IL-6) and monocyte chemotactic protein (MCP)-1, which contribute to underlying inflammation of both[12]. One of the earliest events in the pathogenesis of atherosclerosis is lipid accumulation in the arterial wall and formation of foam cells through uptake of modified or oxidized low density lipoprotein by monocyte-derived macrophages[13]. Monocyte activation and transformation into macrophages are key steps in the atherosclerotic and inflammatory process[11].

INCREASED INFLAMMATION

Elevated levels of C-reactive protein (CRP) is known to be a risk factor for systemic cardiovascular disease, including PAD. DM is a hyperinflammatory state, with elevated levels of CRP and other markers of systemic inflammation[12]. CRP has procoagulant effects related to its enhancement of tissue factor expression[14]. Hyperglycemia from DM also leads to overproduction of mitochondrial reactive oxygen species via the protein kinase C (PKC) pathway[15]. PKC has been associated with perturbations in vascular cell homeostasis such as increases in permeability, contractility, extracellular matrix synthesis, cell growth and apoptosis, angiogenesis, leukocyte adhesion, and cytokine activation and inhibition[14].

ENDOTHELIAL DYSFUNCTION

Nitric oxide (NO), which is a potent vasodilator that inhibits platelet activation, is synthetized by endothelial cells. Diabetes impairs NO-mediated vasodilatation. Increased synthesis of vasoconstrictors and prostanoids will also contribute to endothelial dysfunction in diabetes. The effects of endothelial cell dysfunction increase arterial susceptibility to atherosclerosis[15].

ENHANCED VASOCONSTRICTION

Diabetes increases the production of vasoconstrictors, such as endothelin-1 (ET-1), a peptide released by endothelial cells, leading to enhanced vasoconstriction and platelet aggregation. Activation of smooth muscle cell mitogenesis and leukocyte adhesion done by ET-1 may contribute to this process[16].

ENHANCED THROMBOSIS

For diabetics the whole coagulation cascade is dysfunctional. Increased fibrinogen levels and plasminogen activator inhibitor (PAI)-1 together with platelets function abnormalities are prothrombotic state characteristics. Platelets thrombotic potential is enhanced due to increased expression of glycoprotein Ib and IIb/IIIa receptors, the platelets aggregating and adhering to vascular endothelium more readily for type 2 diabetes patients compared to a healthy individual. The natural antagonist of platelet hyperactivity is insulin since it enhances endothelial generation of PGI2 and NO while also sensitizing the platelet to PGI2[17].

DIAGNOSIS

The main reasons to diagnose PAD in diabetic individuals are to initiate therapies that decrease the risk of atherothrombotic events, improve quality of life, and decrease the risk of amputation[10]. A medical

history and physical examination are the most important in evaluating a diabetic person for the presence of PAD. Symptoms of leg pain, the development of ulcers, and functional impairments can be due to PAD[18]. Typical history of claudication, while having a high specificity for PAD, it has a low sensitivity[9].

The clinical stage of symptomatic PAD can be classified using the Fontaine staging system. Fontaine stage I are asymptomatic; stages IIa and IIb include patients with mild and moderate-to-severe intermittent claudication; those with ischemic rest pain are classified in Fontaine stage III; distal ulceration and gangrene represent Fontaine stage IV.

Physical examination should include blood pressure measurement, palpation of peripheral pulses: femoral, popliteal, and pedal vessels. The absence of both the dorsalis pedis pulse and the posterior tibial pulse strongly suggests the presence of PAD[19].

ABI screening. In PAD, the ankle systolic blood pressure is less than the brachial systolic blood pressure, and the ABI is reduced to <0,9 and correlates with a higher risk of cardiovascular events[20]. It is important to remember that vascular wall calcification does not imply that occlusive arterial disease is present, although these two conditions frequently coexist. If vascular calcification is present, stenotic vascular disease cannot be detected by ABI[21]. Other non-invasive tests such as measurement of the toe-brachial index (TBI) or Doppler waveform analysis may enable detection of occlusive disease despite a falsely elevated ABI[4].

CONCLUSIONS

The prevalence of DM increases with age, as does the prevalence of PAD in those with, as well as those without, DM. PAD is a common cardiovascular complication in patients with diabetes. The risk of developing PAD is much higher in patients with diabetes, and the disease is more severe and progresses more rapidly than in non-diabetic individuals[22]. DM also increases the incidence of limb ischemia manifested as ischemic rest pain or ulceration among patients with PAD[23].

Risk factor management includes lifestyle modifications, smoking cessation, blood pressure control, diet and exercise, foot care and treating associated conditions (diabetes, dyslipidemia, and hypertension), and preventing ischemic events with aggressive antiplatelet therapy[20].

In the cases of patients for whom risk factor change and pharmacological treatment are inadequate, revascularization has an important role[9].A preventive foot care and intervention program, when needed (infection drainage, surgery, revascularization) can help prevent major amputations[24].

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