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APPROACH TO THE PATIENT WITH DIABETES MELLITUS AND ATHEROMATOUS DISEASE IN OTHER TERRITORIES: LOWER LIMBS

ABORDAGEM DO PACIENTE COM DIABETES MELLITUS E DOENÇA ATEROMATOSA EM OUTROS TERRITÓRIOS: MEMBROS INFERIORES

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ABSTRACT

Diabetes mellitus (DM) has an incidence of 2 to 5% in Western populations, and 40 to 45% of all amputees are diabetic. DM is a risk factor for atherosclerosis and presents with a high prevalence of occlusive arterial disease. Macroangiopathy is more diffuse, more severe, and presents at an earlier age, depending on the mechanisms: changes in lipids and lipoproteins, changes in platelet function and changes in endothelial function. The clinical symptoms are variable and depend on the level of vascular and nerve involvement, and may range from intermittent claudication to critical ischemia (resting pain and trophic lesion). Anamnesis and physical examination are sufficient to determine the arterial lesion, the degree of peripheral neuropathy and whether or not there is infection. Complementary exams are important for planning the therapeutic management: ultrasound flow detector for measuring the ankle brachial index (ABI), Doppler ultrasound, magnetic resonance angiography, angiotomography and arteriography. Treatment is based on the clinical symptoms, and may range from clinical treatment, wound treatment, and surgical treatment to limb revascularization.

Keywords: Diabetes mellitus; Peripheral arterial disease; Intermittent claudication.

RESUMO

O diabetes mellitus (DM) tem incidência de 2 a 5% nas populações ocidentais, além disso, 40 a 45% de todos os amputados são diabéticos. O DM consiste em fator de risco para aterosclerose e apresenta alta prevalência de doença arterial oclusiva. A macroangiopatia é acometida de forma mais difusa, mais grave e em idade mais precoce, conforme os mecanismos: alteração dos lipídeos e lipoproteínas, alteração da função plaquetária e alteração da função endotelial. O quadro clínico é variável e depende do nível de acometimento vascular e nervoso, podendo variar de claudicação intermitente à isquemia crítica (dor de repouso e lesão trófica). A anamnese e o exame físico são suficientes para determinarem a lesão arterial, o grau de neuropatia periférica e se há ou não infecção. Os exames complementares são importantes para o planejamento da conduta terapêutica: detector ultrassônico de fluxo para mensuração de índice pressórico tornozelo-braço (ITB), ecografia doppler, angiorressonância nuclear magnética, angiotomografia e arteriografia. O tratamento é baseado no quadro clínico e pode variar entre tratamento clínico, tratamento das feridas e tratamento cirúrgico para revascularização do membro.

Descritores: *Diabetes mellitus; Doença arterial periférica; Claudicação intermitente.*

INTRODUCTION

The incidence of diabetes mellitus (DM) is between 2% and 5% in Western populations, and 40% to 45% of individuals with an amputated lower limb have diabetes.[1] DM is characterized by a high prevalence of occlusive arterial disease (5–10 times higher than patients without diabetes), manifested alone or combined with other complications. Trophic lesions are commonly found in the feet, with or without severe infection. They interfere with the life of patients with diabetes for longer periods, and they frequently result in limb loss.[2-4]

Patients with diabetes with peripheral arterial occlusive disease present a 10 times higher chance of amputations than patients without diabetes who experience the same disease.[1] Approximately 20% of hospitalizations and 50% of surgical admissions of patients with diabetes are due to foot problems. Thus, understanding the pathophysiology and treatment is crucial for reducing mortality and morbidity.[5]

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ETIOPATHOGENESIS

A higher risk factor for DM is the development of atherosclerosis, which affects the entire body, particularly in the lower limbs. The characteristic of vascular complications is arterial occlusion, which can be of two types: those compromising large-caliber vessels, such as coronaries and peripheral circulation (macroangiopathy), and those compromising small vessels, such as capillaries and arterioles of the kidneys, retina, and peripheral nerves (microangiopathy).

Microangiopathy

Microangiopathy is characterized by an increased thickness of the intimal layer of the arteriolar wall, mainly observed in the arterioles and capillaries. The thickness of the basal membrane of the capillaries has been observed using microscopy. This is accompanied by hyaline material deposition, whose nature remains to be understood, although they are considered by many authors as the glycosylation products of circulating proteins.[6]

Macroangiopathy

Diabetic macroangiopathy is more diffuse and severe and manifests early. It typically affects the infra-popliteal vessels (40% of patients with diabetes and gangrene have a palpable popliteal pulse); however, it can also affect the abdominal aorta and iliac and femoral arteries.

Several theories have been proposed to explain the appearance of the atherosclerotic plaque, and two hypotheses are mainly accepted.[7] The theory of insudation or infiltration of lipoproteins through the endothelium is based on experimental studies of intravenous injections of vasoactive substances (histamine, adrenaline, and others) that trigger intimal edema of the arterial wall, facilitating the insudation of low-density lipoproteins (LDL) in the affected areas. In turn, the endothelial lesion theory is based on the appearance of an atheroma in places of the arterial tree subjected to greater tension by the dynamics of blood flow. The thickening of the endothelium occurs in response to aggression, facilitating the deposition of lipids in these areas.

In normal individuals, there is a balance between lipid concentrations in plasma and arterial wall; an endothelial membrane is found between both. Individuals become more predisposed to develop atherosclerosis when one of two components change. All patients with diabetes present changes, which explains the occurrence of diffuse and frequent atherosclerotic lesions based on the following mechanisms:

1. Lipid and lipoprotein changes

The concentrations of low-density proteins (LDL and VLDL) are high in patients with poorly controlled diabetes. In addition, products resulting from platelet aggregation induce VLDL modifications. The non-enzymatic glycolysis of lipoproteins changes their biological activity, reduces fibroblast–VLDL degradation, and extends their half-life in the plasma.[8] VLDL presents with an abnormal composition, which would make them highly atherogenic, in patients with diabetes. Thus, the relationship between diabetes and atherosclerosis can be explained by the quantitative and qualitative changes in lipoproteins.

2. Change in platelet function

The reaction to trauma on the arterial wall also includes the deposition of fibrin and platelets on the endothelial surface. Platelets produce platelet derived growth factor (PDGF) for the development of smooth muscles in tissue cultures, and this factor could be responsible for the appearance of smooth muscle fibers as an atheroma component.[7] Changes in platelet function were shown in patients with diabetes; however, relating them properly to the origin of the atheroma is still not possible.

In vitro studies demonstrated an increased sensitivity of platelets, collected from patients with diabetes, to aggregating agents (ADP, adrenaline, collagen, and arachidonic acid). These changes are detected before the occurrence of arterial occlusion, suggesting they are induced by metabolic changes.

In vivo studies showed increased concentrations of platelet factor 4 and plasma thromboglobulins, substances that are produced in a second aggregation phase, and also demonstrated that the half-life of the platelet is reduced in patients with diabetes.[8]

3. Changes in the endothelial function

The levels of the von Willebrand factor is increased in patients with diabetes. The von Willebrand factor is a plasma glycoprotein produced by the endothelial cells, and it is related to platelet adhesiveness and permeability changes.

Peripheral atherosclerosis presents characteristics of those observed in patients with diabetes, mainly regarding its location. Medium and large arteries, from the aorta to popliteal vessels, are commonly affected, similar to those in any patient with atherosclerosis. However, leg arteries are also involved in patients with diabetes, or the individual develops tibioperoneal occlusive disease (TPOD). Foot arteries are often spared from occlusive lesions.[9]

The atheroma starts to develop with lipid deposition and evolves to a fibrous phase. Smooth muscle cells proliferate and migrate into the intimal layer. These cells are then responsible for the collagen deposition in the lesion.[10] The evolution of fibrous or soft atheroma may occur based on three types of progression. A slow progression, implying the accumulation of lipids and other tissues within the arterial wall, leads to a chronic decrease of the arterial lumen diameter; a sharp reduction of the arterial lumen diameter caused by intraplaque hemorrhage; and, finally, a secondary thrombosis, which can be restricted to an arterial wall lesion or be more widespread.[11,12]

We often observe peripheral occlusion reaching distal levels, such as in leg arteries, which is caused by the spread of the secondary thrombosis to parietal disease, restricted to the iliac–femoral level.

CLINICAL PICTURE

The clinical picture may vary, depending on the level of vascular and nerve involvement.

At the beginning, the clinical picture usually reflects a complaint of intermittent claudication (IC), characterized by pain for making effort while walking. This often affects the calf, and briefly improves, once effort is stopped. This pain may evolve, according to the different times investigated. Pain may be experienced even when efforts are very small, and the appearance of ischemic rest pain usually

accompanies complaints of limb cooling, pallor, and muscle atrophy, skin, and attachments.[4]

IC intensity varies depending on the extent of the affected arterial segment and the capacity developed by collateral circulation. The distances walked without pain and the recovery time after these walks depend on the severity of the ischemia. In aortoiliac and femoro-popliteal occlusions, the most frequent location for the perception of pain is the calf. If the arterial occlusion affects the aortoiliac segment, besides the calf, the pain can also manifest in the thigh and gluteal region. Claudication can manifest in the plantar region in the distal occlusion of leg arteries. Despite pain suggesting the level of occlusion, variations can be found due to the presence of collateral circulation.[13]

At later stages, the pain starts to be continuous and does not improve at rest. The pain is intense, located in the ischemic region of the limb, usually in the fingers or distal portions of the foot, and increases at night.[14]

Ischemic rest pain is most often accompanied by trophic lesions of the limb, which are characterized by ulcers and gangrenes. This causes a risk of limb loss.[15] In an attempt to reduce pain, the patient adopts positions with the leg suspended, thus causing venous stasis edema (aggravating factors for ischemia and stiffness). In addition, many patients have constantly reported to have cold and wet limbs.

Depending on the evolutionary stage of OAD, patients may present changes in skin color, which can be permanent or caused by the adoption of certain positions. When the affected limb is elevated, the skin becomes livid and pale, depending on the severity of the ischemia. If the leg is suspended, the skin becomes hyperemic, which can cause erythrocyanosis. The speed for the appearance of hyperemia, its extent, and intensity possibly depend on the development of a collateral circulation and indicate the degree of ischemia clinical compensation caused by trunk arterial occlusion. Intense erythrocyanosis and rapid reaction suggest good compensation, whereas slow and poor hyperemic reaction indicate poor compensation.

Trophic changes occur during the evolution of chronic arterial insufficiency. Skin atrophy is more severe in the feet and legs, where it becomes thin and poorly resistant to traumas and infections. Besides muscle atrophy, hair fall from the legs and dorsum of the foot have also been observed.

Gangrene characterizes the most severe phase of the disease. It appears spontaneously or is caused by traumas or infections. Ulcers are atonic, deep, surrounded by a halo of ischemic skin, and covered by necrotic crusts. They are very painful and can be very large. Gangrene is limited, in these cases, to the toes and metatarsal region, and rarely reaches the more proximal parts of the lower limbs. It can be dry or wet, when edema or secondary infection is present (Figure 1).

Figure 1. Patient with DM and infected trophic lesion.

DIAGNOSIS

Anamnesis and physical examination are sufficient to determine arterial lesion, degree of peripheral neuropathy, and the presence of infection. Performing complementary examination is important in planning the therapeutic strategy.[16]

The reduction of a pulse amplitude indicates the presence of complete stenosis or occlusion of the proximal artery, associated with the presence of a well-developed collateral circulation. Lack of pulse usually indicates complete vessel occlusion. The presence of a systolic murmur during auscultation or of tremor when palpating the artery is also indicative of arterial stenosis.

In cases of mild IC, clinical signs may not be evident or even absent. In this situation, physical examination at rest can be normal, but signs of OAD can appear immediately after making a physical effort.

1. Ultrasonic flow detector to measure the ankle–brachial index

Based the ratio between measurements of blood pressure in the lower and upper limbs, the ankle–brachial index (ABI) is assessed using an ultrasonic flow detector. In patients with diabetes, these blood pressure measurements may lose their value in presence of arterial calcification, which prevents attaining real values for this index. The systolic pressure measured in these limbs may be falsely higher than that in the upper limbs, even in the presence of a decreased flow.[17-22]

2. ABI in stress test

ABI is measured after making a physical effort of controlled intensity. Physical exercise causes muscle vasodilation and a proportional increase in flow in the lower limbs. Arterial stenosis also causes an increased flow in this region and in the collateral circulation. However, the loss of energy reduces the systolic pressure in the arterial segments that are distal to the lesion.

This effect allows the physician to assess the importance of arterial occlusion on the overall condition of the patient, enabling the distinction of whether the limitations to this physical examination are caused by OAD or other causes, which are frequent comorbidities in patients with DM.

3. Doppler ultrasound

Doppler ultrasound combines real-time B-mode ultrasound with pulsed Doppler, allowing the examination of the arterial wall, lumen, and adjacent structures and demonstration of the blood flow pattern.

Currently, this method has a high accuracy, which may be comparable to angiography. In the routine evaluation of IC patients, arterial lesions can be identified and quantified, and studying their evolution during clinical follow-up is possible.

Although this is a useful test, the evolutionary change of their results does not necessarily imply changes in the symptoms. There are individuals that present an increased

severity of arterial stenosis, although they can walk greater distances. In contrast, others cannot walk greater distances, although they present a stable injury.

4. Magnetic resonance angiography

Magnetic resonance angiography is a noninvasive examination, providing information about arterial wall morphology, adjacent structures, and arterial flow physiology, without exposing the patient to the adverse effects of radiation, radiopaque contrasts, and arterial catheterization punctures.

It is based on gadolinium's (paramagnetic contrast) ability to increase the signal emitted by the blood flow, providing better images than non-contrast examination in long vessel segments (50 cm) in short periods of time.[23]

5. Angiotomography

Angiomotography can accurately assess the abdominal aorta, iliac arteries, and lower limb arteries in the same examination with the same contrast injection. It reliably characterizes the degree of stenosis and the extension of the affected segment. Bone anatomical references are better visualized with angiomotography than with magnetic resonance angiography. The evaluation of the more distal leg arteries is more limited, particularly in presence of a significant atheromatous calcification. Therefore, it provides information required for decision and therapeutic planning, thereby functioning as diagnostic arteriography.[24]

6. Arteriography

Arteriography is used when surgery is indicated. It aids in surgical planning. Visualization of the trunk arteries, small muscles, and collateral branches is possible, enabling the assessment of minimal changes. The objective of this test is to verify proximal artery conditions and distal to the occlusion.[25,26] Because arteriography provides the best images of the arterial lumen, it is still considered the standard of comparison (gold standard) for other imaging modalities (Figure 2).[27]

7. Measurements to evaluate the walking distance

Objective evaluation of walking distances is one of the most important points of the IC study.[28]

There are two types of walking test: track and treadmill.

7.1. Track test

In the track test, the patient walks at a constant speed on a flat ground where distances are measured objectively. It is a suitable method, with good reproducibility indices. However, it depends entirely on a specialized examiner and appropriate place.

7.2. Treadmill test

In the treadmill test, the patients walk at predetermined speeds and time on a motorized treadmill until patients complain of maximum pain, and maximum walking distance is subsequently measured.

Two types of treadmill tests are used in patients with IC: fixed-loading (treadmill tests) (12-degree slope at a speed of 2 miles per hour, as recommended by the American Society of Vascular Surgery) and progressive-loading (performed in a treadmill with fixed speed but progressive slope elevation. It has better reproducibility than the previous one).

Figure 2. Arteriography of a patient with DM and POAD, showing multiple occlusions and stenosis of infra-popliteal arteries, with extensive collateral network.

Because numeric values to assess the improvement and worsening of symptoms have not been objectively established yet, they are arbitrary and defined by each researcher.

TREATMENT

The treatment of patients with diabetes depends on the recognition of vascular and neurological complications, with the purpose of controlling or even reverting clinical manifestations caused by these changes.[9,29]

1. Treatment of IC

The treatment of occlusions without severe ischemia (IC) initially consists of forcing the patient to walk, which often turns claudication to be less restrictive. In worsening situations, patients need to be treated surgically (revascularization) after a minimum period of 6 months of treatment.[30,31]

The objective of the clinical treatment in IC is to increase the walking distance by performing physical exercises. Walking should be daily, lasting at least 40 min. In these sessions, the patient walks until submaximal pain is felt, which is when the exercise must be interrupted. Subsequently, there is a progressive relief of pain until the patient can start walking again. Walking training protocols up to or beyond the point where pain starts usually offer better results. In addition, the patient should take good care of the feet, which is important for the prophylaxis of severe ischemia. This is because limbs are associated with an overall decrease in blood flow; thus, trauma can lead to decompensation of the clinical picture and the progression of the disease to severe ischemia.[32,33]

The patient should be instructed to keep the feet and legs in good hygiene conditions and prevent or treat early skin infections, interdigital mycoses, and traumas. Care is recommended with nails and the use of shoes that are sufficiently loosened to not compress the ischemic skin of the feet. The patient is advised to protect himself against low temperatures because coldness determines vasoconstriction, which aggravates peripheral circulatory conditions. Hence, the patient needs to protect not only the extremities, but also all body surfaces.

Two types of pharmacological treatment for IC have been empirically used: peripheral arterial vasodilators and hemorrheologic agents.

Vasodilators have not been confirmed to date as effective in the treatment of IC. This is because there is no vasoconstriction in ischemic tissues, preventing any justification for the use of these drugs. Probably, vasodilators still divert blood to normal tissues and have the capacity to vasodilate them. This could lead to an even greater reduction of arterial flow to ischemic tissues because there is no vasoconstriction in the ischemic tissues. Hemorrheologic agents act to reduce blood viscosity and decrease its influence on arterial flow. Their efficacy has been proven, to a greater or lower extent, in several studies. The most representative drug in this group is pentoxifylline. However, the data available to justify their use are not yet sufficiently robust.

2. Treatment of severe ischemia

In a patient with severe ischemia (trophic injury or resting ischemic pain), surgical treatment becomes mandatory because the natural course of limb loss is inevitable.

2.1. Local wound treatment

The manipulation of ulcers and gangrenes and the resection of necrotic tissues should be performed with extreme care, avoiding traumatizing areas of healthy skin to prevent the progression of necrosis. Topical medication should be applied with care, reducing the use of ointments to minimum, particularly those containing antibiotics or sulfa drugs that often cause local sensitization, and those with local anesthetics, which are phagedenic. The lesions should preferably be treated with occlusive dressings moist with saline solution or diluted with Dakin solution.

With regard to the infectious component of the trophic lesion of the lower limb, some therapeutic knowledge and attitudes are well established:

a. In patients with DM and PAD, the pathogenic flora are usually mixed, which are composed of Gram-positive, Gram-negative, and possibly anaerobic bacteria, leading to the use of antibiotics or a combination of antibiotics with a broad spectrum.
b. The infection process of the lower limb with trophic lesion and accumulation of purulent material should always be drained, without exception, as early as possible. Frequently, amputation of the fingers and performing large and deep incisions in the feet during debridement are necessary (Figure 3 and 4).
c. If the infectious process already poses a risk to the patient's life, or if the extension of the necrotic-infectious lesion turns the limb unfeasible, primary amputation is required in the leg or thigh level, open, accompanied by antibiotic therapy.

2.2. Surgical treatment

Correction of occlusion or subocclusion of the artery responsible for the reduction of blood flow to the limb should be used to treat patients with severe ischemia. The atherosclerosis of patients with diabetes tends to be disseminated, although more prevalent in the infrainguinal region.

Even considering some specific peculiarities of patients with DM, the same techniques of conventional and endovascular surgery are used in these patients.[34]

For the aortoiliac region, the most common stent surgeries are aortoiliac and aortofemoral grafts. These surgeries are individually considered for the needs of each patient, depending on the location, extent of the disease, and

Figure 3. Patient with DM and infected trophic lesion.

Figure 4. Immediate post-operative debridement of an infected trophic lesion in a patient with DM.

associated risks. Endovascular options are represented by balloon angioplasty with or without stent. They are generally indicated for a more focal disease.[35]

For the infrainguinal and infrapopliteal area, the use of the saphenous vein or other autogenous veins, as an arterial replacement in derivations continues to be highly used. There is an option to use other replacements, such as PTFE, which requires shorter surgical time and fewer incisions; however, function is not comparable to that of the saphenous vein in the infrapopliteal territory. Endovascular therapy with angioplasty and stent balloon is also an option increasingly used. It has the advantage of shorter surgical time, the possibility of local anesthesia, and to repeat the procedure in relapse. However, some lesions, such as very extensive occlusions, do not usually have good results with this technique.[5,34]

PREVENTION

Diabetic education decreases the incidence of these complications.

Patients should be informed regarding the risks of these complications once they are diagnosed with diabetes. Strict control of blood glucose seems to decrease the risk in the development of neuropathy, but the same cannot be said about the development of peripheral arterial occlusive disease.[2,8,36]

Trauma is the major triggering factor of foot and leg ulcers. The use of suitable shoes, allowing good plantar support, avoiding callosities formation, and care when cutting toenails should be emphasized.

The rehabilitation of the amputated patients with diabetes is difficult because of concomitant visual problems in the contralateral limb and, at this stage, care must be reinforced.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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