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REVIEW

LOWER EXTREMITY PERIPHERAL ARTERY DISEASE: IMPLICATIONS FOR PHYSIOTHERAPY

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Peripheral artery disease (PAD) is more prevalent among the elderly and is a predictor of cardiovascular mortality causing high morbidity. It is commonly associated with other illnesses such as diabetes mellitus, cerebrovascular and coronary heart disease. Even when asymptomatic, PAD patients are often treated by a physiotherapist, either specifically for lower extremity PAD or during rehabilitation for other clinical conditions, where PAD is a comorbidity. As such, physiotherapists need to better understand the clinical presentation of the disease, treatment options and precautions to be adopted when treating these patients. The objective of this brief review is to synthesize data regarding PAD epidemiology, consensus on lower extremity PAD treatment, precautions for assessing and handling PAD patients and present information on new PAD treatment options under evaluation. The supervised exercise/rehabilitation program for PAD should be the mainstay of patient treatment, owing to its clinical effectiveness demonstrated in several studies; however, there is paucity of data about long-term effects of exercise programs for PAD patients on mortality or incidence of revascularization and amputations. New PAD treatments, such as cell therapy, appear promising.

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INTRODUCTION

Cardiovascular diseases cause high mortality rates worldwide and are one of the world's greatest public health problems[1;2]. Among the most prevalent are those with similar pathophysiology, such as ischemic heart disease and peripheral artery disease (PAD) of the lower extremity. Both clinical conditions share common risk factors, predominantly diabetes, arterial hypertension, hypercholesterolemia and smoking (particularly for PAD), in addition to others such as increased c-reactive protein, hyperhomocysteinemia, being overweight, metabolic syndrome, physical inactivity and psychological stress (which likely exert great influence on coronary disease)[3].

Peripheral artery disease (PAD) can be defined as partial or total obstruction of the peripheral arteries caused by atherosclerosis. This reduces perfusion of tissue irrigated by these arteries and may progress to clinical symptoms and eventual necrosis. With the exception of coronary arteries, the term applies to several arterial beds such as renal and mesenteric arteries; however, this article discusses only peripheral artery disease of the lower limbs.

PAD is most common among the elderly population[4-7] and is commonly associated with other disorders, including diabetes mellitus[8;9] and coronary disease[10-13]. Even when asymptomatic, PAD patients are treated by physiotherapy, whether for vascular or other diseases. It is therefore necessary to have a better understanding of the pathophysiology of the disease, its clinical presentation, consensus on PAD treatment and precautions to be considered for these patients. This article presents a brief review of PAD, focusing on the implications and precautions of the physiotherapy approach when treating these patients.

Clinical characteristics of PAD patients

Although time elapsed between the initial endothelial lesion and the appearance of symptoms is relatively long in the development of atherosclerosis, non-invasive techniques may identify the presence of PAD, even during the asymptomatic phase, thereby facilitating disease management. In fact, most PAD sufferers do not exhibit the classic symptoms expected for the disease, as reported by Fowkes et al. (1991, The Edinburgh Artery Study)[4]. The authors described PAD prevalence greater than 20% in the general population between the ages of 55 and 74, while prevalence of intermittent claudication was only 4.5%. Other authors also found a low percentage of individuals with classic PAD symptoms among those diagnosed with the disease, based on assessment using the ankle brachial index (ABI)[5;6]. It is estimated that approximately 20-50% of those suffering from lower extremity PAD are asymptomatic[7]. This indicates a deficit in limb perfusion, even though specific symptoms are not present during the patient's everyday activities. This means they do not seek medical attention, making it impossible to specifically treat the disease in its initial stages.

PAD may progress to the symptomatic phase, where signs appear that indicate a perfusion deficit. Symptoms exhibited are intermittent claudication (pain experienced in the affected muscles, typically in the calf muscle, similar to a cramp or "burning pain" when walking), which may progress to pain in the area when at resting. Signs that may accompany the disease include dry skin and sparse body hair; nail changes; reduced peripheral pulse, paleness or cyanosis, lower temperature in the body segment, less muscle trophism and eventual tissue damage. The disease can advance to critical limb ischemia, defined as the presence of pain at rest, ulceration or gangrene, placing the patient at high risk of losing the limb[14]. This progression may worsen when associated with diabetes, which in addition to influencing micro and macrovascular lesions[15;16], can cause sensorimotor polyneuropathy in the affected area[17].

PAD predominately affects the elderly. Prevalence studies depend, in part, on PAD diagnosis methodology. In general, studies use the ankle brachial pressure index (ABI), a non-invasive, practical and relatively easy-to-use diagnostic tool. According to recommendations of the American College of Cardiology (ACC) and American Heart Association (AHA)[18;19], the index is calculated by dividing the highest systolic blood pressure in the ankles, measured in the posterior tibial and dorsalis pedis arteries, by the greatest systolic blood pressure value in the brachial arteries of the arms. Both measurements are taken using an appropriate blood pressure cuff and Doppler probe, with patients at rest in a supine position, and the index is calculated for both sides. PAD is present when the index value is ≤ 0.9. Progressively lower values are associated with greater functional limitation, with severe PAD diagnosed when ABI values are below 0.4-0.5, in accordance with the authors[20;21]. Values above 1.3 were

used to classify non-compressive arteries, more common in diabetes patients and requires additional diagnostic methods to confirm or exclude PAD diagnosis [18;22]. However, in a recent publication, the ACC and AHA updated PAD recommendations and modified normal and abnormal ABI values so that an index higher than 1.4 is classified as noncompressible arteries[19]. This recommendation is in accordance with that already described by the Inter-Society Consensus for managing peripheral artery disease-TASC II[7]. In addition, values between 0.91 to 0.99 are considered "borderline".

It is possible to perform the ABI after physical exertion, such as walking on a treadmill, in order to assess the severity of PAD. As per TASC II guidelines, this is undertaken on a treadmill at a speed of 3.2 km/h (2mph) and incline of 10%-12%, until the onset of claudication (or for a maximum of 5 minutes), at which time pressure in theankle is measured again to establish the ABI. Consensus determines that a decrease of 15%-20% in ABI is considered a diagnostic criterion of PAD. Variants of the treadmill test are the use of stairs or walking along a flat corridor. Table 1 displays ABI classification recommendations as per ACC/AHA guidelines[19] and by Arain and Cooper, 2008[21] applied for ABI testing after exercise. According to the ACC/AHA, the ABI should be measured when assessing suspected PAD patients for those who: (1) experience pain in lower limbs during exertion, (2) present with unhealed ulcers, (3) who are 65 years and older; (4) who are 50 years and older with a history of diabetes or smoking[19].

PAD prevalence is typically below 5% among those under 60 years, increases progressively with age and can exceed 20% in individuals aged 70 years or older [6;8;18].

Overall worldwide prevalence is estimated at 3% - 10%; however, frequency of intermittent claudication is around 3% above 40 years old and can rise to 6% in those aged 60

Table 1. Ankle brachial index classification at rest and after exercise

Recommendations ACC/AHA, 2011		**Arain and Cooper ABI after exercise**		
ABI	**Severity**	**ABI**		**Severity**
		At rest	After exercise	
>1.4	Noncompressible			
1.00-1.40	Normal	>0.9	>0.9	Normal
0.91-0.99	Borderline			
0.41-0.90	Mild to moderate	0.8-0.9	0.5-0.9	Mild
		0.5-0.79	0.15-0.49	Moderate
0.00-0.40	Severe	<0.5	<0.15	Severe

Rooke et al., 2011[19] and Arain and Cooper, 2008[21].

years or older[7]. Individuals classified as at risk of contracting PAD are those (1): older than 50 years who present diabetes mellitus (DM) and another atherosclerosis risk factor (smoking, dyslipidemia, hypertension or hyperhomocysteinemia), (2) aged between 50 and 69 years, that have a history of smoking or DM, (3) aged 70 years and older, (4) exhibiting ischemic pain when at rest or have symptoms in the lower limbs during exercise (suggesting claudication), (5) with abnormal peripheral pulse exam, (6) suffering from coronary, carotid or renal atherosclerotic disease[7;18.] As previously mentioned although predominance of the disease reaches 20% in the elderly population, most patients experience no symptoms. It is the responsibility of health care professionals, including physiotherapists, to observe possible signs of the disease, the presence of symptoms during therapeutic activities (for example, limitation during submaximal effort testing) or alterations in clinical tests during evaluation. The presence of the signs described above could indicate PAD and may require referral for investigation and diagnosis.

Moreover, since worldwide (and Brazilian) life expectancy has increased and due to the significant prevalence of PAD risk factors, a substantial portion of the population currently requires treatment intervention and, particularly, secondary intervention. As described further on, supervised physical activity is fundamental, and essential to managing these patients. With regard to this population and the necessity for a wide range of therapeutic techniques to contemplate their needs, which are

restricted not only to physical and functional difficulties caused by PAD, but also to those resulting from cardiac and musculoskeletal limitations, physiotherapists play a significant role in managing these patients.

PAD: impact for the patient and correlation with coronary and cerebrovascular disease

In addition to causing significant morbidity[10], PAD also results in high mortality, mainly from coronary and cerebrovascular disease[12;13;23;24]. In a study following the progression of patients for 10 years after PAD diagnosis, relative risk of mortality from cardiovascular disease was 5.9 and from coronary disease was 6.6[11]. The aggravating factor is that relative risk of mortality due to cardiovascular disease was present even in asymptomatic individuals (relative risk of 4.7). Patients experiencing intermittent claudication had a mortality rate of approximately 70% over 15 years[7].

Another important observation is that those diagnosed with PAD are either at substantial risk of developing cardiovascular or cerebrovascular disease, or these conditions are already present requiring special or precautionary attention during physiotherapy. In fact, the occurrence of coronary disease among PAD sufferers is high and can reach 90% depending on the evaluation method used, such as angiography (for a review, see Golomb et al., 2006) [25]. In accordance with revised inter-society consensus guidelines for managing peripheral artery disease-TASC II, 40%-60% of PAD patients suffer simultaneously from coronary artery and cerebrovascular disease, and it is estimated that 10%-30% of individuals with coronary artery disease also present with PAD7. This carries several implication for physiotherapists, including but not restricted to: (1) patients treated for PAD may experience difficulty in prescribed exercise as a result of coronary disease, (2) individuals suffering from coronary artery disease may be limited during exercise due to PAD, (3) identifying and treating asymptomatic PAD patients may potentially reduce the risk of cardiac or cerebrovascular events in this population and could reduce or slow progression of the disease, 4) during the course of treatment for PAD, cardiac symptoms previously due to exercise limitations, may emerge as a result of improved exercise capacity.

A criterion proposed by the ACC/AHA is that patients beginning an exercise program be submitted to a detailed evaluation that includes a treadmill test. This test is conducted in order to determine an individual´s exercise capacity and possible limitations other than those caused by lower extremity vascular disease, such as those resulting from cardiac disorders. This allows the physiotherapist to more accurately determine exercise intensity, and it increases awareness of the need not only to supervise, but also to monitor exercise through an electrocardiogram (ECG), for example. This initial assessment will also establish variables such as distance walked until the onset of claudication, when present, and maximum distance walked, which are important parameters when determining the progression and effectiveness of patient treatment.

In general, patients experiencing intermittent claudication are expected to exhibit symptoms that will limit physical activity before they reach an exercise level that may cause imminent risk of a cardiac event. Nevertheless, it is important to consider that, among asymptomatic subjects or those with a serious cardiac pathology, the intensity of exercise below the pain threshold may not be advisable at that particular moment of rehabilitation.

Another important element to observe is that during treatment, total distance walked and distance walked until claudication begins to increase with tolerance to greater exercise intensity. This may also subject the individual to a higher level of effort than that tolerated in initial assessment, resulting in the emergence of symptoms not previously exhibited, such as angina and dyspnea. It is vital that the physiotherapist be aware of these situations and re-evaluate prescribed exercise conditions for these patients. This reinforces the importance of a supervised exercise program (suggested as the initial choice for treating patients with intermittent claudication)[7;26]; however, it is also essential to be aware of symptoms reported by patients when carrying out prescribed activity at home and perform a medical reassessment to adjust treatment accordingly.

Additionally, the six-minute walk test can also be used in conjunction with treadmill testing to evaluate PAD patients starting an exercise program, and particularly to monitor treatment progress[18].

PAD and Diabetes Mellitus

Diabetes Mellitus (DM) is considered one of the major risk factors for developing PAD. Due to the characteristics of this population, for example, in regard to other clinical conditions associated with motor and autonomic neuropathies, diabetic patients require special attention during physiotherapy care to treat PAD. Investigating PAD among patients with diabetes is essential, given that macrovascular disease is common in these individuals[27]. Among diabetic patients, PAD is the greatest risk factor for amputation of lower limbs and also has a potentially adverse effect on quality of life and functionality[9].

For diabetic patients diagnosed with PAD, the TASC II7 recommends that blood glucose levels be controlled, aiming at a glycated hemoglobin level - HbA1c < 7%22, or close to 6%. Certain lifestyle changes are also proposed, including giving up smoking, losing weight, proper nutrition and physical activity[7].

Exercise combined with a proper diet, in diabetic individuals, has beneficial effects in preventing and treating both diabetes and PAD. The advantages of physical activity in these patients include better glycemic control, alterations in body composition, improved cardiorespiratory fitness, reduced cardiovascular risk (and possible PAD progression) and improvements in functionality[28].

The Brazilian Diabetes Society[29] recommends physical activity for diabetic patients in order to improve glycemic control, lower glycated hemoglobin levels, decrease cardiovascular risk, reduce body weight and improve self-esteem. Both the Brazilian Diabetes Society[29] and the AHA30 have similar guidelines with respect to exercise time and intensity. According to their recommendations, aerobic exercises such as walking, swimming, cycling, running and dancing should be performed 3 to 5 times a week for at least 30-60 minutes, or a total of 150 minutes per week. They should be performed at moderate intensity, that is, between values corresponding to 50%-70% of maximum VO_2, since this produces a positive effect on controlling glycated hemoglobin levels.

For those diagnosed with diabetes and PAD, exercise must take into account the presence of sensory changes caused by neuropathy, such as paresthesia or numbness in the lower limbs (in extreme cases, even analgesia in some areas of the foot), as well as the existence of claudication. This requires that clinical examinations include a sensory assessment of the lower limb, primarily the feet, as proposed by Boulton et al.[31]. Certain precautions are also vital, such as prescribing low-impact activities, wearing comfortable or adapted shoes, instructing patients on caring for their feet and routinely examining them before and after exercise. Another possible situation among diabetic patients is the presence of cardiac autonomic neuropathy, which may interfere in prescribing and especially monitoring exercise (for example, when monitoring increased HR during exercise), making it essential to monitor the subject's perceived exertion in order to limit exercise intensity. Table 2 shows a summary of some considerations to be adopted when implementing a physical activity program for diabetic individuals, according to Brazilian Diabetes Society recommendations[32].

PAD and Diabetes Mellitus are typically related to individual lifestyle. Educating patients and lifestyle changes are fundamental to the success of therapy and to avoid the emergence of secondary conditions. It is therefore important that physiotherapists become key players in education and developing programs that favor the prevention of complications and provide a multifactorial approach to the problem, thereby preventing impairment in quality of life and functionality among patients.

BASES FOR TREATMENT, PHYSIOTHERAPY INTERVENTIONS AND NEW FORMS OF TREATMENT.

Functional limitations caused by PAD establish a vicious cycle where physical inactivity favors worsening risk factors for cardiovascular and cerebrovascular disease, as well as promoting progression of the peripheral artery disorder itself. Some of these factors are overweight/obesity, dyslipidemia, hypertension and glucose intolerance. Thus, patients suffering from limited exercise capacity are not only predisposed to PAD progression, but are also at greater risk of cardiovascular and cerebrovascular disease.

Appropriate treatment would therefore be to modify risk factors and promote interventions that reverse or reduce limited functional capacity[7;18;22;30].

Table 2. General exercise recommendations for diabetic patients

• Monitor blood glucose, particularly in DM1 and long duration exercise
• Exercise is contraindicated for hyperglycemia > 250mg/dl with ketosis and in patients suffering from proliferative retinopathy (aerobic and high intensity resistance exercise)
• If insulin therapy is used, the amount of insulin must be adjusted by the physician prior to activity, especially for DM1, since hypoglycemia may occur even hours after physical activity
• Patients treated with insulin or secretagogue (sulfonylurea, glyburide) should be supplemented with simple carbohydrates (isotonic solutions, juice, candy) when blood glucose is < 100mg/dl.
• Use of appropriate footwear and clothing and self-examination of the feet before and after activity.
• An option for patients with peripheral neuropathy is exercise that reduces weight supported by the feet, such as hydrotherapy, swimming and exercise bicycles.

General exercise recommendations for diabetic patients, based on guidelines of the Brazilian Society of Endocrinology and Metabolism, 2006[32]. DM1 – Diabetes mellitus type I.

Modifying risk factors requires educational and pharmacological intervention, such as those centered on controlling glycemia, total cholesterol and its fractions, as well as blood pressure[22].

Although elevated serum concentration of homocysteine is an independent PAD risk factor, supplementation with vitamin B is not recommended due to doubts regarding its

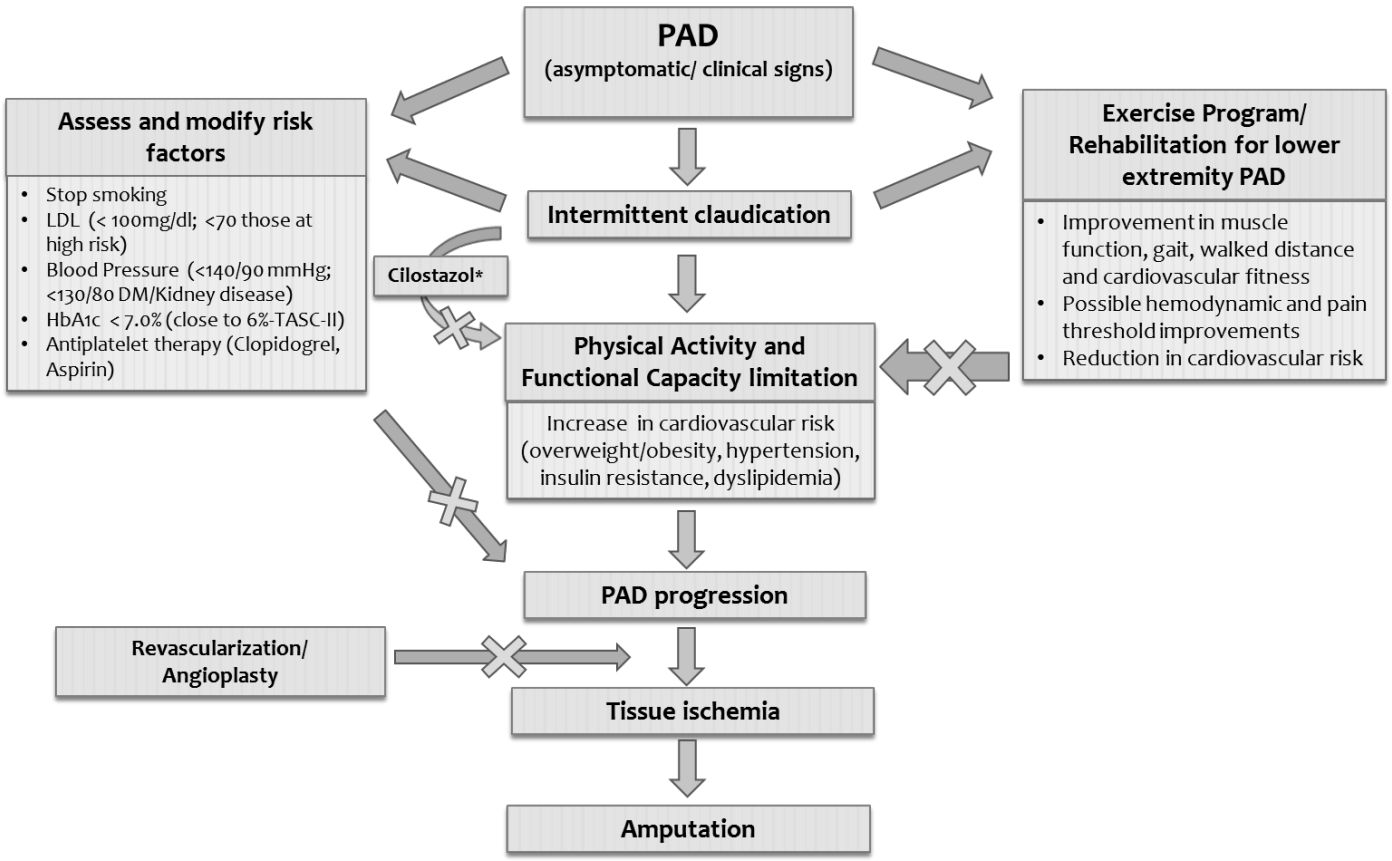

Figure 1. Functional limitation caused by PAD, disease progression and therapeutic options. The left column represents treatment recommendations according to the TASC-II[7]. *Cilostazol is the pharmacological option recommended by the ACC/AHA[18] and TASC-II[7]; however, second-line drugs differ according to guidelines, with pentoxifylline for the former and naftidrofuryl for the latter.

efficiency[7]. Occasionally, anti-platelet drugs may be prescribed and drugs such as cilostazol, a phosphodiesterase III inhibitor that causes less cAMP degradation, consequently lowering platelet aggregation and relaxing vascular smooth muscle, are used to treat PAD patients[7;18].

Nevertheless, physical activity is still the first and most fundamental recommendation when treating individuals with PAD, although in clinical practice this has not been standard practice[7]. Exercise programs for PAD can increase the walking capacity of patients when compared to pre-treatment values[7;18;26;33-38]. The average rise in maximum distance walked varies according to parameters used for treatment, such as training period. However, mean increases reported are close to 120% in relation to baseline values[34], at times even exceeding 200%[33;37;38]. When compared to using only prescribed medication for PAD, such as cilostazol and pentoxifylline, supervised exercise programs are more effective, for example, in maximum distance walked. Exercise was shown to be approximately three times more effective than cilostazol and almost seven times more effective than pentoxifylline (a drug with hemorheology properties that interferes in platelet aggregation and blood viscosity) in comparison with the percentage increase in maximum distance walked[36]. Although the effects of unsupervised activity programs are positive, supervised exercise is more beneficial and when possible, this should be the first recommendation for PAD patients[7;18;26]. Supervised training improves the functional capacity of individuals with intermittent claudication39 and positively impacts their quality of life[35]. Van Asselt et al.[38] recently demonstrated that even though supervised exercise incurs higher economic cost, its cost-benefit is greater than home-based training when considering that the effect on maximum distance walked is superior for supervised activity. The impact of these PAD training programs has been associated with histological and biochemical alterations of the skeletal muscles[40;41], changes in inflammatory markers[42], endothelial function variations[43-45], altered mobility of the lower limbs and gait46, and improved cardiorespiratory capacity[47-51]. Figure 1 depicts an organizational chart describing functional limitations caused by PAD, disease progression and therapeutic options. Whether symptomatic or not, that is, displaying abnormal ABI values and no intermittent claudication, PAD patients would ideally benefit from a supervised exercise program[35]. Routine walking seems to reduce the progression of PAD in these patients[52]. Exercise for individuals with claudication is a well-defined prescription[7;18;35;36;47]. Physiotherapists play a vital role in this intervention since, in addition to providing patients with the necessary exercise program, these professionals can assess and intervene in other physical and functional limitations that patients may experience and which can interfere in the conduct and/or prescription of certain exercise modalities and intensities (for example, in the case of heart disease or patients with associated musculoskeletal disorders, which is common in the elderly population with a high prevalence of PAD). This is significant given that initial and concomitant treatment of these conditions could enable patients to confidently begin and continue and exercise programs centered on improving lower limb muscle conditioning and cardiovascular fitness.

Within supervised exercise programs, studies have been conducted to evaluate exercise performed below the pain threshold and those proposing intensity that causes claudication. Intervals of rest are applied until symptoms cease and exercise resumes, which in these cases typically consists of walking on a treadmill or a flat surface. The two most widely used international norms (ACC/AHA, TASC II)[7;18] suggest exercise intensity that provokes claudication. Table 3 summarizes recommendations for exercise programs among patients with PAD and intermittent claudication, as per the ACC/AHA[18].

It is important to note that an initial treadmill-based exercise capacity test is recommended, in order to analyze whether claudication is the limiting factor for exercise, to establish the safety of the program and determine whether limitation is present under exertion as a result of a condition other than PAD. Furthermore, supervised physical activity allows for monitoring and identification of possible cardiac signs and symptoms (including arrhythmia, angina, electrocardiographic changes requiring special attention and that, when present, indicate the need for reassessment to identify cardiovascular disease that may previously have been hidden due to exercise limitation imposed by PAD).

The main problem of prescribing exercise-using parameters described above is that they trigger symptoms

(pain) in the lower limbs, often discouraging continued exercise and adherence to the training program.

Table 3. Recommendations for exercise prescription by ACC/AHA, 2006[18]

Modality:	Aerobic exercise on treadmill or track walking. Resistance training is complementary.
Intensity:	Speed and grade that elicit symptoms (claudication) within 3-5 minutes Keep workload until moderate severity claudication followed by a period of rest (standing or sitting) to permit symptoms to resolve then restart walking
Duration:	Initially equal to 35 minutes of intermittent walking. Step increases of 5 min per session until reach 50 minutes
Frequency:	3 to 5 times a week
Period:	12 weeks

A number of recent studies have drawn attention to the use of aerobic exercise in the upper limbs as a viable and more comfortable alternative (since it does not cause pain) for treating lower extremity PAD with physical activity (and occasionally for amputees who cannot walk or experience difficulty with this activity)[47-49;51].In a randomized controlled clinical trial, Zwierska et al.[47] showed that aerobic exercises for upper limbs, performed on a cycle ergometer, exhibited effectiveness comparable to lower limb aerobic exercise when assessing functional capacity improvement, represented by maximum distance walked, distance walked until claudication and peak VO_2 in individuals with intermittent claudication. Previous results presented by the same authors suggested the usefulness of upper limb exercise for individuals suffering from claudication[49]. This systemic effect may be a consequence of improved vasomotor control due to systemic cardiovascular adaptations involving neurohumoral control. Similar findings regarding the effectiveness of upper limb exercise in PAD patients were described by Treat-Jacobson and colleagues[51].

Recent studies have raised the hypothesis of cell and gene therapy treatment for PAD. Tateishi-Yuyama et al.[53] investigated cell therapy through intramuscular autologous implantation (gastrocnemius) of mononuclear bone marrow cells in ischemic members of PAD sufferers. Using patients with bilateral ischemia and injecting circulating blood mononuclear cells as a control into one limb, the authors recorded increased ABI after 4 weeks, as well as greater transcutaneous O_2 pressure, improved collateral circulation and less pain at rest. These alterations persisted when patients were re-evaluated at 24 weeks. Subramaniyam et al. (2009)[54] treated PAD patients using injections (subcutaneous, 3 times a week) of cytokine GM-CSF (GM-CSF-granulocyte macrophage colony-stimulating factor) to stimulate mobilization of progenitor cells from bone marrow, inducing neovascularization.

The researchers observed improvements (intragroup) in treadmill walking times until claudication and in total time walked. Another form of treatment for severe PAD (patients exhibiting skin lesions, even when minimal) is gene therapy, with intramuscular injection of DNA to codify expression of fibroblast growth factor type 1 (FGF1), favoring revascularization of the limb (TAMARIS-TRIAL)[55]. Studies of phase 2 clinical trials showed promising results; however, when the investigation was widened to phase 3 in a high quality multicenter trial, findings did not confirm therapeutic benefit. Although disappointing, these results should not exclude gene therapy as an option, but denote the need for improvements in various stages of treatment, as suggested by the authors, including selection of appropriate vectors, dose and treatment frequency.

Final Considerations

PAD has great clinical importance since it provokes high morbidity and is an independent predictor of mortality resulting from cardiovascular causes. This indicates the need for earlier diagnosis and implementation of rehabilitative and preventive treatment to reduce the consequences of disease progression. The supervised exercise/rehabilitation program for PAD should be the mainstay of patient treatment, owing to its clinical effectiveness demonstrated in several studies, and its prescription should be intensified. Research assessing the impact of exercise programs for PAD patients on mortality or incidence of revascularization and amputations should be implemented to analyze their long-term effects. New PAD treatments, such as cell therapy, appear promising.

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