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Diagnosis and Roles of Therapeutic Management of Peripheral Artery Disease: Review

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Abstract: **Peripheral artery disease (PAD) is underdiagnosed, undertreated, poorly comprehended, and a lot more typical than previously thought. Approximately 12% of the adult population has PAD, and the frequency is equal in men and women. This comprehensive review was aiming to discuss the peripheral artery disease (PAD), and especially the diagnosis procedures and treatment approaches to this disease. A comprehensive search was carried out through electronic databases; MEDLINE up to November 2016, and EMBASE and of reference lists to identify possible additional studies concerning the peripheral artery disease diagnosis and treatment. Possible studies for inclusion were independently assessed for suitability by authors and any lack of clarity or disagreement was resolved by discussion. PAD is a significant health issue and is related to increased cardiovascular morbidity and death. The ABI is an effective and simple test for identifying PAD. Management of PAD includes therapies to enhance measures and signs to reduce cardiovascular events. All patients with PAD need to receive an antiplatelet representative, statins to lower LDL below 100 mg/dL, and optimal therapy for hypertension and diabetes.**

Keywords: **Peripheral artery disease (PAD), diagnosis, treatment, MEDLINE, diabetes.**

1. INTRODUCTION

Peripheral artery disease (PAD) is underdiagnosed, undertreated, poorly comprehended, and a lot more typical than previously thought [(1,2)]. Approximately 12% of the adult population has PAD, and the frequency is equal in men and women [(3)]. A strong association exists in between advancing age and the frequency of PAD. Practically 20% of adults older than 70 years have PAD [(4)]. In an elderly hypertensive population from the Systolic Hypertension in the Elderly Program, the prevalence of PAD was 38% in black guys, 25% in white males, 41% in black ladies, and 23% in white females [(5)].

Awareness and treatment of PAD has actually been especially bad over the past 20 years. Enthusiasm has increased particularly because of recent endovascular advances in the treatment of peripheral arterial stenoses. As medical gadget companies have actually developed balloons, stents, cryoablation, and atherectomy instruments, a surge to screen, detect, and deal with these patients has actually begun. Board accreditation in vascular medicine is currently available through the American Board of Vascular Medicine, which offers accreditation evaluations in general vascular medication and endovascular treatment. The publication of the American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines on the Management of Patients with PAD further advances awareness and education with appropriate recommendations for the examination and treatment of patients with PAD [(5,6)]. Claudication is the symptomatic expression of PAD; nevertheless, it occurs less regularly than has actually been reported formerly. Patients might experience timeless claudication, atypical leg pain, rest pain, ischemic ulcers, gangrene, or no signs at all (**Table 1**) [(6)]. Asymptomatic disease might be present in up to 50% of patients with PAD (6). Of the 460 patients in the Walking and Leg Circulation Study, 19.8% had no exertional leg pain, 28.5% had irregular leg pain, 32.6% had traditional intermittent claudication, and 19.1% had pain at rest [(7)]. The Rotterdam Study recognized a 19.1% prevalence of PAD in their

associate population; nevertheless, claudication was reported in only 6.3% in the PAD group (8). In the Edinburgh Artery Study, the frequency of claudication amongst 1592 individuals aged 55 to 74 years was 4.5%, whereas asymptomatic PAD happened in 8.0% of enrollees [9].

The diagnosis of PAD need to not be ignored for 2 crucial factors. Patients with PAD may experience lots of problems, such as claudication, ischemic rest pain, ischemic ulcers, repeated hospitalizations, revascularizations, and limb loss [6]. These result in a poor quality of life and a high rate of depression [10,11]. Even patients who have no leg signs have a poorer practical performance, poorer quality of life, smaller calf muscle location, and greater calf muscle fat than an age-matched group of patients without PAD [12]. Second, patients with PAD have a greater probability of experiencing a myocardial infarction (MI), stroke, and cardiovascular death and have a higher rate of all-cause death compared to patients without PAD [13,14,15].

TABLE 1. **Distinct Modes of Presentation in Patients With Peripheral Artery Disease**

Classic claudication
Pain, discomfort, aching, heaviness, tiredness, tightness, cramping, or burning in the calf, thigh, hip, and buttocks that (1) is reproducible with a similar level of walking from day to day, (2) disappears after several minutes of standing, and (3) occurs at the same distance once walking has resumed
Atypical leg pain
Lower-extremity discomfort that is exertional but does not consistently occur at the same distance walked and may require a longer period of time to resolve or require the patient to sit down or change body position
Asymptomatic
Without obvious symptoms, but usually associated with functional impairment on formal testing

Objective:

This comprehensive review was aiming to discuss the peripheral artery disease (PAD), and especially the diagnosis procedures and treatment approaches to this disease.

2. METHODS

A comprehensive search was carried out through electronic databases; MEDLINE up to November 2016, and EMBASE and of reference lists to identify possible additional studies concerning the peripheral artery disease diagnosis and treatment. Possible studies for inclusion were independently assessed for suitability by authors and any lack of clarity or disagreement was resolved by discussion.

3. RESULTS

- **Diagnosis procedures of PAD:**

When patients present with grievances or obvious manifestations of an atherothrombotic occasion, diagnosing PAD is uncomplicated. In the asymptomatic patient, a thorough history and review of symptoms, asking particularly about exertional signs in the upper or lower extremities, is very important in detecting PAD. The classic symptoms of intermittent claudication are exertional pain or cramping in the legs, brought on by the same degree of effort and eased with rest. Just recently, more atypical functions of claudication have actually been explained and include lower extremity heaviness, generalized pain, or tiredness [16]. The existence of signs assists in classifying the patient with lower extremity PAD (**Table 2**) [17]. An evaluation of risk factors for developing PAD (previous or present tobacco use, diabetes mellitus,

dyslipidemia, high blood pressure, and obesity) is also crucial when diagnosing patients. Diabetic patients are at the greatest risk of progression of disease and require for limb-saving surgery. The importance of medical diagnosis and treatment of PAD cannot be highlighted any more than by keeping in mind that in patients with symptomatic PAD, the relative risk of death from cardiac causes is increased almost six-fold [18]. Diagnosis of PAD is finest helped by a detailed health examination. ACC/AHA standards offer a Class I recommendation for a detailed pulse evaluation for patients at risk for lower extremity PAD [6]. Blood pressure measurements in both arms need to be performed on all patients thought of having PAD. Left subclavian artery stenosis is under identified and frequently asymptomatic until the patient establishes a serious high grade stenosis. Auscultation for bruits in the neck, supraclavicular location, abdomen, flank, and groins should be done. In addition to an extensive history and physical exam, the ankle brachial index is a powerful, yet basic office-based tool to detect and figure out the severity of lower extremity PAD. It is highly precise in anticipating the associated risk of future cardiovascular events such as fatal myocardial infarction (MI), stroke (CVA), and vascular deaths [19].

Table 2: Classification of peripheral arterial disease [17]

Fontaine		Rutherford		
Stage	**Clinical**	**Grade**	**Category**	**Clinical**
1	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate-severe claudication	I	2	Moderate claudication
		I	3	severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		IV	6	Ulceration or gangrene

A. Exercise Treadmill Testing and ankle brachial index (ABI):

The ABI, segmental blood pressure, and pulse volume waveform analysis are the only strategies that provide physiologic info about perfusion in the limb. Using a hand-held constant wave Doppler ultrasound gadget, the higher systolic pressure determined from either the posterior tibial or dorsalis pedis (in each leg) is compared with the greatest brachial pressure taken from either arm (**Figure 1**) [3,6]. A regular ABI is 0.90 to 1.40. A decrease in the ABI indicates lowered blood circulation to the lower extremity [20,21]. Measurement of the ABI does not define the level of obstructive disease, however it is accurate, simple to acquire, and correlates with the severity of the perfusion irregularity but not with the practical problems that the patient might experience.

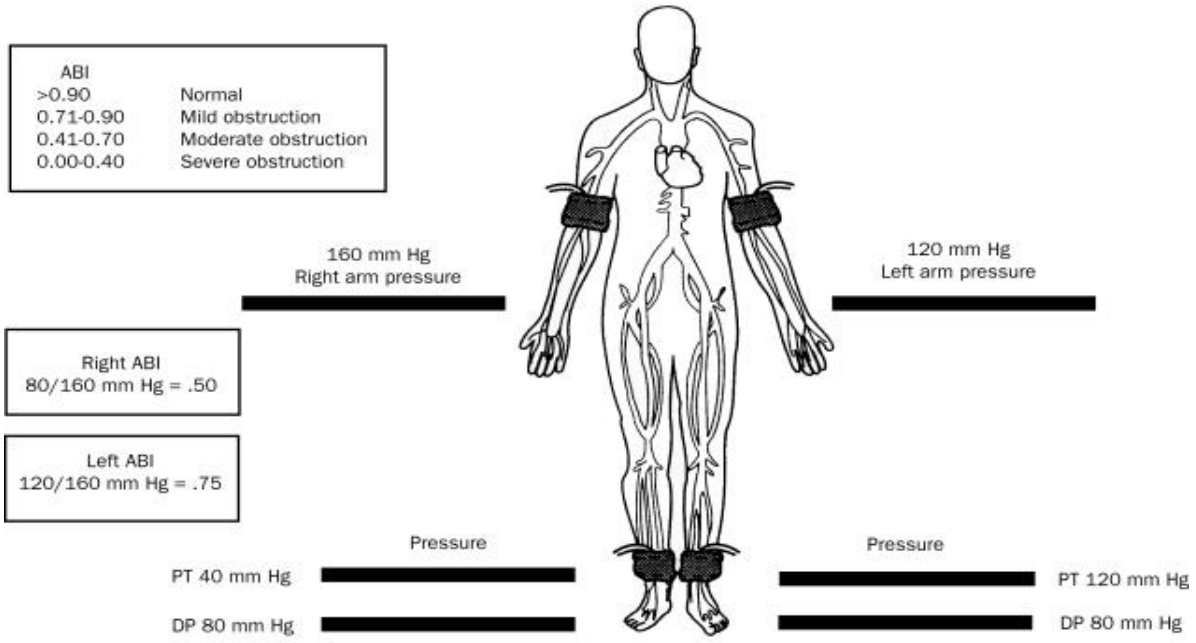

Figure 1: Calculation of the ankle brachial index (ABI). DP = dorsalis pedis; PT = posterior tibial artery. [3]

The diagnostic value of the ABI is limited in disease states that lead to noncompressibility of blood vessels (eg, patients with diabetes or renal failure). In these circumstances, the increase in ABI (>1.40) may be an artifact [6].

B. Duplex Ultrasonography:

Duplex ultrasonography is a safe and cost-efficient approach of accurately identifying the seriousness and place of stenosis and differentiating stenosis from occlusion. B-mode or gray-scale imaging shows a 2-dimensional picture of the artery wall and lumen, allowing a rough evaluation of the lesion and atheroma characteristics. Color flow Doppler and pulsed wave Doppler enable an evaluation of the stenosis severity on the basis of Doppler-derived velocity requirements [22]. Duplex ultrasonography is an accurate method for determining the degree of stenosis or length of occlusion of the arteries providing the lower extremity [23,24,25].

C. Magnetic Resonance Angiography (MRA:

MRA of the aorta and peripheral vasculature can be performed quickly with excellent image quality. A lot of vascular studies are performed with gadolinium-enhanced 3-dimensional MRA, which acquires angiographic-like images [26,27,28,29]. The quality of MRA is so good that it (or computed tomographic angiography [CTA] has actually virtually changed diagnostic angiography in determining exactly what kind of intervention is possible. The success of MRA in determining little runoff vessels satisfies or goes beyond that of conventional catheter-based angiography [30]. With existing technology, contrast-enhanced 3-dimensional MRA has a level of sensitivity of around 90% and a uniqueness of around 97% in the detection of hemodynamically significant stenoses in any of the lower-extremity arteries as compared to digital subtraction angiography [31].

D. Computed Tomographic Angiography (CTA):

Multidetector CTA provides high-resolution image quality rapidly [32]. Current multidetector-row scanners get approximately 250 synchronised interweaving helices. Computed tomographic angiography has numerous benefits over conventional angiography, consisting of volumetric acquisition, which allows visualization of the anatomy from multiple angles and in multiple airplanes after a single acquisition; enhanced visualization of soft tissues and other nearby anatomic structures; and less invasiveness and therefore less problems [31,33,34]. It also has several advantages over MRA, consisting of higher spatial resolution, absence of flow-related phenomena that might misshape MRA images, and the capacity to imagine calcification and metal implants such as endovascular stents or stent grafts. The uniqueness and sensitivities are greater than 95% for recognizing stenosis of greater than 50% and for properly identifying occlusions [45]. The primary downsides of CTA compared with MRA are direct exposure to ionizing radiation and the have to use an iodinated contrast agent [31,32].

- **Management of PAD:**

The primary goal in dealing with patients with PAD is twofold: the avoidance of future cardiovascular occasions in addition to maximal secondary preventive measures utilizing antiplatelet therapy and smoking cessation, and treating diabetes, hyperlipidemia, and high blood pressure mellitus. These steps will decrease the risk of future atherothrombotic events as these patients have a substantial increased risk of events (**Figure 2**) [6]. Adhering to an everyday regimen of workout and modifying the dietary intake of fat must be consisted of in this restorative plan.

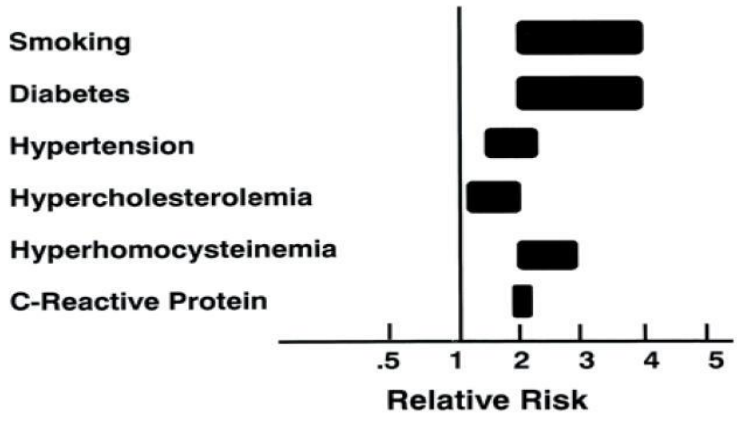

Figure 2: Risk of developing lower extremity peripheral arterial disease [6]

Smoking Cessation management:

It has been plainly shown that patients who effectively quit cigarette smoking have actually reduced rates of PAD development, crucial limb ischemia, amputation, MI, and stroke, as well as increased long-lasting survival [36]. The details of an efficient cigarette smoking cessation program are beyond the scope of this short article, it is important to communicate to the patient that discontinuation of smoking is incredibly essential to general well-being, conservation of the limb, and survival [37].

Lipid-Lowering treatment:

According to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), PAD is a CAD risk equivalent, and therefore the objective low-density lipoprotein cholesterol (LDL-C) level is less than 100 mg/dL (to transform to mmol/L, increase by 0.0259) [38]. Although numerous large-scale prospective medical trials on the efficacy of LDL-C decrease in patients with CAD and stroke have been conducted, no potential randomized trials have actually been conducted in patients with PAD [39,40,41]. Moreover, intensive cholesterol lowering in patients with LDL-C levels at a standard of less than 130 mg/dL (typical worth, 108 mg/dL) and increased C-reactive protein levels of greater than 2.0 mg/L (average worth, 4.2 mg/L) (to convert to nmol/L, multiply by 9.524) substantially lowered the occurrence of MI, stroke, revascularization, hospitalization for unsteady angina, or death from cardiovascular causes in patients without clinical proof of cardiovascular disease (hazard ratio, 0.56; P<.001).

In the Heart Protection Study, which randomized 20,536 high-risk participants to 40 mg/d of simvastatin or placebo, a 24% relative risk decrease was observed in newbie cardiovascular events in patients who received simvastatin [39]. The subgroup of patients with PAD had comparable cardiovascular benefits regardless of history of MI or CAD. Even the subgroup population who had LDL-C levels less than 100 mg/dL at baseline benefited from statin treatment [39].

Independent of cholesterol-lowering impacts, statin use enhanced walking distance and speed in patients with PAD [42]; certainly, patients with PAD who take statins have actually been revealed to have less yearly decline in lower-extremity efficiency than those who do not [43]. Several research studies have actually evaluated the role of statins on claudication signs and walking period and have shown that these representatives may have a modest impact at finest [44,45].The existing suggestions promote an objective LDL-C level of less than 100 mg/dL for patients with PAD; for very high-risk patients, the objective is an LDL-C level of less than 70 mg/dL.4 Because all patients with PAD are at extremely high risk, reducing the LDL-C level to less than 70 mg/dL in all patients with PAD is reasonable.

Hypertension Management:

Antihypertensive treatment must be administered to hypertensive patients with PAD to achieve a goal of less than 140/90 mm Hg for nondiabetic patients or of less than 130/80 mm Hg for patients with diabetes or persistent renal disease to decrease the risk of MI, stroke, congestive heart failure, and cardiovascular death [6].

Antithrombotic management:

Antiplatelet treatment has actually been shown in multiple research studies and meta-analyses to prevent the risk of occlusive arterial disease in patients with PAD [46]. The most commonly utilized antiplatelet representative is aspirin, which has been used for centuries. Aspirin blocks platelet activation by irreversibly preventing cyclo-oxygenase; this decreases the production of the powerful prothrombotic and vasoconstrictive representative, thromboxane A2. To this day, the biggest meta-analysis studying using aspirin was performed by the Antithrombotic Trialists' Collaboration, which showed marked decrease in vascular events in patients treated with aspirin [46]. This meta-analysis integrated information from 287 studies with over 13,500 high-risk patients with heart disease and compared the efficacy of anti-platelet treatment against control. Using anti-platelet representative's aspirin and ticlopidine resulted in a 22% decrease in negative cardiovascular occasions defined as MI, CVA, or vascular death [46]. Of the 287 research studies, 42 were randomized reports of almost 10,000 patients with PAD. Making use of aspirin in this subset of patients led to a significant 23% reduction in the incidence of non-fatal MI or CVA and deadly vascular death [46].

The secondary goal in the management of PAD includes the treatment of way of life and the restriction of signs in order to enhance lifestyle. PAD patients with periodic claudication represent the biggest group of symptomatic patients. Exercise therapy is suggested for all patients with claudication signs. A supervised exercise training program that is monitored by experienced personnel has actually been studied in many trials. Increase in walking abilities has been shown in large meta-analyses from the Cochrane Collaboration [47]. Drug therapy with cilostazol is shown to enhance strolling time and lower uncomfortable lower extremity claudication. The true mechanism of its action is unknown, cilostozol has

various actions consisting of anti-platelet activity, a vasodilatory result, and enhancement in HDL levels [48]. Use of this agent is restricted by its side-effects of headache, queasiness, palpitations, and dizziness. Due to its inhibition of phosphodiesterase III, the FDA has a black-box caution for use of cilostazol in patients with heart failure and left ventricular dysfunction [6]. Trental, a rheolytic representative with effects on platelet aggregation, can be considered as a 2nd alternative to cilostazol. Due to its unpredictable efficiency, the ACC/AHA practice standards give it a Class IIb sign [6].

4. CONCLUSION

PAD is a significant health issue and is related to increased cardiovascular morbidity and death. The ABI is an effective and simple test for identifying PAD. Management of PAD includes therapies to enhance measures and signs to reduce cardiovascular events. All patients with PAD need to receive an antiplatelet representative, statins to lower LDL below 100 mg/dL, and optimal therapy for hypertension and diabetes. Patients with PAD might experience claudication or vital limb ischemia or may have no signs at all. Both asymptomatic and symptomatic patients with PAD have actually a considerably increased rate of MI, stroke, and cardiovascular occasions. The 2 major strategies for treatment are: (1) to enhance symptoms and quality of life with medical therapy alone (workout, cilostazol) or surgical or percutaneous revascularization and (2) to prevent cardiovascular events with an extensive program that includes smoking cessation, a workout program, control of blood pressure, achievement of goal LDL-C, antiplatelet treatment, and control of diabetes.

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