Peripheral artery disease (PAD) usually refers to ischemia of the lower limb vessels. Currently, the estimated number of cases in the world is 202 million. PAD is the third leading cause of atherosclerotic cardiovascular morbidity. The measurement of the ankle-brachial index (ABI) is recommended as a first-line noninvasive test for screening and diagnosis of PAD. An ABI <0.90 is an independent predictor of cardiovascular events and this measurement is useful to identify patients at moderate to high risk of cardiovascular disease. However, there is insufficient evidence to assess the benefits and harms of screening for PAD with the ABI in asymptomatic adults. Lifestyle modifications, including smoking cessation, dietary changes and physical activity, are currently the most cost-effective interventions. Inverse associations with PAD have been reported for some subtypes of dietary fats, fiber, antioxidants (vitamins E and C), folate, vitamins B6, B12 and D, flavonoids, and fruits and vegetables. A possible inverse association between better adherence to the Mediterranean diet and the risk of symptomatic PAD has also been reported in a large randomized clinical trial. Therefore, a Mediterranean-style diet could be effective in the primary and secondary prevention of PAD, although further experimental studies are needed to better clarify this association.

Key Words: Mediterranean diet; Peripheral artery disease; Prevention

Peripheral atherosclerotic vascular diseases are defined by the American College of Cardiology/American Heart Association as a group of clinical disorders that includes abdominal aortic aneurysm, renal and mesenteric artery disease, extracranial carotid artery disease and lower extremity peripheral disease. The European Society of Cardiology uses the term peripheral artery disease (PAD) to include several vascular sites, including carotid, vertebral, upper extremity, mesenteric, renal, and lower extremity vessels but not the aorta. The guidelines of this society are focused on the atherosclerosis process that causes stenosis or occlusion of non-cerebral and non-coronary arteries, although there are different etiologies related to specific vascular territories.

The term PAD is frequently used to include only ischemia of the lower limb vessels including the aorta, iliac, femoral, popliteal, tibial, peroneal arteries and their major branches. Typically, only one-third of patients with PAD are diagnosed, although 50% of them have atypical leg symptoms and between 10% and 20% of these patients develop intermittent claudication characterized by discomfort or pain in the limbs while walking. A smaller percentage follows a gradual progression to critical limb ischemia, the most severe clinical manifestation of PAD, which is characterized by rest pain and ulcers or gangrene, and in some very severe cases, the critical limb ischemia eventually requires amputation.

The measurement of the ankle-brachial index (ABI) is recommended as a first-line noninvasive test for screening and diagnosis of PAD. The ABI is calculated as the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery. A sphygmomanometer cuff is placed just above the ankle and a Doppler instrument is used to measure the pressure of the posterior and anterior tibial (dorsalis pedis) arteries of each foot. Usually the highest ankle systolic pressure is divided by the highest brachial systolic pressure, resulting in a value of the ABI for each leg.

In healthy persons the ABI is >1.0 because the blood pressure wave amplifies as it travels distally from the heart and the result is a higher ankle than brachial systolic blood pressure. The majority of studies use an ABI of 0.90 as the threshold to define PAD and borderline ABI is between 0.91 and 0.99. The ABI has a high specificity but lower sensitivity to detect PAD. In a meta-analysis of 4 studies, the pooled specificity and sensitivity of using ABI ≤0.90 compared with angiography was 86% and 75%, respectively. This lower sensitivity is partially explained by some patients having a normal or high ABI (>1.30). This is frequently found in the elderly and patients with diabetes or endstage renal disease where peripheral arteries are calcified and noncompressible. In these cases there are alternative tests such as measurement of the toe-brachial index and values <0.70 are usually considered diagnostic of PAD. However, this cutoff is not strictly evidence-based and the diagnostic criteria are still ambiguous.
The mode of determination of ABI has important consequences for epidemiology studies. Variations are found in the technique of measurement, such as the method of pulse detection and whether the arm and ankle are measured bilaterally. A lack of standards for the measurement and calculation of ABI leads to discrepant results and affects the estimation of PAD prevalence within a population. A higher sensitivity has been found if the ABI numerator is the lowest pressure in the arteries of both ankles. For example, in the Multi-Ethnic Study of Atherosclerosis the lower pressure was used instead of the higher and the prevalence of PAD was almost 4-fold higher in women and 2.8-fold in men.

Relevance of PAD From a Public Health Perspective

The estimated number of PAD cases worldwide was 202 million in 2010. It is well known that PAD prevalence increases with age and the worldwide prevalence of PAD is approximately 5% at age 45–49 and 18% at age 85–89 years. PAD is likely to follow an increasing trend in the forthcoming 2–3 decades because of the expansion of the world’s aging population. In fact, the number of cases has increased by 23.5% globally from 2000 to 2010. Moreover, PAD is a global problem because almost 70% of cases is concentrated in low and middle-income countries. The result is that there is currently a global pandemic of PAD affecting millions of people of all ages.

Although a number of studies have shown that PAD prevalence is higher in males than in females, other more recent studies have found an increased prevalence of PAD in women. These differences may be explained by methodological differences but it is also true that women with PAD are more likely to present without symptoms and it is more probable that they have been underdiagnosed and undertreated. There are specific differences, such as hormone replacement therapy, which was associated with a reduction in PAD prevalence in a large population of postmenopausal women. In any case, a meta-analysis found that the PAD prevalence did not differ significantly by sex in high-income countries but was higher in women than in men in low and middle-income countries. A general recommendation for future studies of PAD prevalence and risk is to include sex as well as age-specific values.

The prevalence of PAD may also significantly differ by race and ethnicity. PAD was most prevalent in black women and least common in Asian women in a population of 3.3 million patients aged 40–99. A higher risk for non-Hispanic blacks was also found in a nationally representative sample of the US population. There are also ethnic differences in ABI among middle-aged adults without PAD. However, these differences must be taken with caution because they may not be a manifestation of higher risk of atherosclerosis but a physiological difference in stiffness of vessels or in wave reflection.

PAD is the third leading cause of atherosclerotic cardiovascular morbidity. The diagnosis of PAD in patients with chronic heart failure is associated with increased mortality, hospitalization and adverse outcomes. Moreover, both symptomatic and asymptomatic PAD are independently associated with an increased risk of cardiovascular disease and mortality. A cohort study with 6,880 patients ≥65 years found that the risk of all-cause mortality was similar in asymptomatic and symptomatic patients with PAD and significantly higher than in those without PAD. Similarly, the PANDORA study found that prevalence of asymptomatic PAD among patients not considered at high cardiovascular risk was not negligible.

A higher risk of coronary and cerebrovascular disease was associated with a low ABI (<0.9) in a low-risk Mediterranean population. Therefore, the ABI is used as an indicator of generalized atherosclerosis because a low ABI has been associated with higher rates of concomitant coronary and cerebrovascular disease. A meta-analysis of 16 population cohort studies showed that the ABI behaved as an independent predictor of cardiovascular events beyond the Framingham risk score.

Patients who are initially considered at low-risk of having a cardiovascular event may have undiagnosed PAD. In the Multi-Ethnic Study of Atherosclerosis (MESA), a low ABI (<1.00) was found in 9% of participants aged 45–84 years and without any traditional risk factors. A high prevalence of PAD (ABI ≤0.90) was found in Chinese hypertensive adults without cardiovascular disease, diabetes, or dyslipidemia. The majority of these patients would not typically be candidates for ABI assessment. However, a systematic assessment of the ABI in all patients having at least 1 cardiovascular risk factor (in addition to age) could help to identify an important percentage of the patients who are at high risk. Adding the ABI measurement is useful to identify patients at moderate to high risk of cardiovascular disease. A systematic review concluded that in population-based cohorts, a low ABI is highly specific but not very sensitive to predict future cardiovascular outcomes, so it should not be used as a generic screening test. In fact, there is some disagreement across current guidelines on PAD screening in asymptomatic adults and the US Preventive Services Task Force concluded that there was insufficient evidence to assess the benefits and harms of screening for PAD and cardiovascular disease assessment with the ABI in asymptomatic adults.

Control of Risk Factors for PAD and the Need for Primary Prevention

Risk factors for PAD include the same classical major determinants of atherosclerotic disease. Globally, the most important risk factors are smoking, diabetes, hypertension, and high low-density lipoprotein-cholesterol levels, although the magnitude of these associations is higher in high-income countries than in low and middle-income countries. Current evidence shows that the magnitude of the association between cigarette smoking and PAD is greater than that reported for coronary artery disease and that secondhand smoke is an independent risk factor for PAD. Moreover, there is a graded association between the number of modifiable risks factors and the prevalence of PAD, and a long-term association between risk profiles at baseline and the risk of PAD after almost 40 years of follow-up. The metabolic syndrome has also been associated with both incident low ABI and clinical PAD, as well as central and abdominal obesity. Poor sleep quality has also been identified as a risk factor in a cross-sectional study of Chinese hypertensive patients.

Other novel risk factors or biomarkers are low serum 25-hydroxyvitamin D levels, hyperhomocysteinemia, low levels of serum bilirubin, total adiponectin, and lipoprotein-associated phospholipase A2. The association with these factors can be explained because of the high proatherosclerotic risk profile in PAD, characterized by endothelial dysfunction and systemic low-grade inflammatory activity. Several markers of inflammation, such as C-reactive protein and interleukin-6, have been found to be associated with symptomatic PAD independently of traditional cardiovascular risk factors. Moreover, a graded direct dose-response relationship between inflammatory...
markers (C-reactive protein, fibrinogen and leukocyte count) and PAD has been found in a US adult population from the NHANES survey. A number of studies have also examined the association between environmental risk factors and PAD. A higher prevalence of PAD has been associated with greater exposure to polycyclic aromatic hydrocarbons, which are pollutants produced by the incomplete combustion of organic materials such as fuel, coal, tobacco smoking or food cooking. Bisphenol A, a chemical used in the manufacture of polycarbonate plastics and epoxy resins, has also been associated with PAD. A similar association has been reported for organochlorine pesticides.

Atherosclerotic PAD is also associated with genetic variants and it is known to have a heritable component. Factors associated with PAD include variation in the genetic code and epigenetic DNA modifications and these factors could enhance the capacity to detect susceptible subjects at risk for PAD. For

### Table. Nutrients and Dietary Patterns Showing Inverse Associations With Peripheral Artery Disease (PAD) in Observational Studies and 1 Randomized Trial

<table>
<thead>
<tr>
<th>Study name</th>
<th>Nutritional factor</th>
<th>Definition of PAD</th>
<th>Design</th>
<th>Year of publication</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greek study</td>
<td>Polysaturated fatty acids and dietary fiber</td>
<td>Diagnosed PAD</td>
<td>Case-control</td>
<td>1991</td>
<td>100 patients and 100 controls</td>
</tr>
<tr>
<td>The Edinburgh Artery Study</td>
<td>Fiber-containing foods, vitamin E and C</td>
<td>ABI ≤0.70 or symptomatic PAD</td>
<td>Cross-sectional</td>
<td>1993</td>
<td>1,592 participants aged 55–74 years</td>
</tr>
<tr>
<td>The Edinburgh Artery Study</td>
<td>Linoleic acid and α-linolenic acid</td>
<td>ABI ≤0.90</td>
<td>Case-control</td>
<td>1994</td>
<td>235 participants aged 55–74 years</td>
</tr>
<tr>
<td>Finnish α-Tocopherol, β-Carotene Cancer Prevention Study</td>
<td>Dietary carbohydrates, fiber, n-6 polysaturated acids and dietary antioxidants</td>
<td>Intermittent claudication</td>
<td>Cohort study</td>
<td>2000</td>
<td>26,872 male smokers aged 50–69 years</td>
</tr>
<tr>
<td>The Rotterdam study</td>
<td>Dietary beta-carotene, vitamins C and E</td>
<td>ABI ≤0.90</td>
<td>Cross-sectional</td>
<td>2001</td>
<td>4,367 participants aged 55–94 years</td>
</tr>
<tr>
<td>Italian study</td>
<td>Mediterranean diet pattern</td>
<td>Symptomatic PAD</td>
<td>Case-control study</td>
<td>2003</td>
<td>432 patients with type 2 diabetes</td>
</tr>
<tr>
<td>Health professionals follow-up study</td>
<td>Fruit and vegetables*</td>
<td>ABI &lt;0.80 or symptomatic PAD</td>
<td>Cohort study</td>
<td>2003</td>
<td>44,059 men free of cardiovascular disease and diabetes</td>
</tr>
<tr>
<td>Health professionals follow-up study</td>
<td>Folate, vitamins B6* and B12*</td>
<td>ABI &lt;0.80 or symptomatic/diagnosed PAD</td>
<td>Cohort study</td>
<td>2003</td>
<td>46,036 men aged 40–75 years</td>
</tr>
<tr>
<td>Health professionals follow-up study</td>
<td>Cereal fiber</td>
<td>ABI &lt;0.80 or symptomatic/diagnosed PAD</td>
<td>Cohort study</td>
<td>2003</td>
<td>46,032 men aged 40–75 years</td>
</tr>
<tr>
<td>English study</td>
<td>Dietary folate and vitamin B6</td>
<td>ABI &lt;0.90</td>
<td>Case-control study</td>
<td>2004</td>
<td>392 men &gt;50 years of age</td>
</tr>
<tr>
<td>InCHIANTI study</td>
<td>Vegetable lipid intake, vitamin E</td>
<td>ABI &lt;0.90</td>
<td>Cross-sectional</td>
<td>2006</td>
<td>1,251 participants, mean age 68 years</td>
</tr>
<tr>
<td>Study conducted in Greece in 1980</td>
<td>Flavonoids</td>
<td>Diagnosed PAD</td>
<td>Case-control study</td>
<td>2006</td>
<td>200 patients</td>
</tr>
<tr>
<td>Japanese-Brazilian Diabetes Study Group</td>
<td>Fiber from whole grains Linoleic acids</td>
<td>ABI &lt;0.90</td>
<td>Cross-sectional</td>
<td>2008</td>
<td>1,267 patients aged ≥30 years</td>
</tr>
<tr>
<td>National Health and Nutrition Examination Survey 2001–2004</td>
<td>Vitamin D</td>
<td>ABI &lt;0.90</td>
<td>Cross-sectional</td>
<td>2008</td>
<td>4,818 participants ≥20 years of age</td>
</tr>
<tr>
<td>National Health and Nutrition Examination Survey 1999–2004</td>
<td>Vitamins A, C and E, vitamin B6, folate, α-linolenic acid</td>
<td>ABI &lt;0.90</td>
<td>Cross-sectional</td>
<td>2008</td>
<td>7,203 participants ≥40 years of age</td>
</tr>
<tr>
<td>National Health and Nutrition Examination Survey 2001 to 2004</td>
<td>Vitamin D</td>
<td>ABI &lt;0.90</td>
<td>Cross-sectional</td>
<td>2008</td>
<td>4,839 participants ≥40 years of age</td>
</tr>
<tr>
<td>Japanese study</td>
<td>Eicosapentanoic acid</td>
<td>ABI ≤0.90</td>
<td>Cross-sectional</td>
<td>2013</td>
<td>238 patients with coronary artery disease</td>
</tr>
<tr>
<td>US National Health and Nutrition Examination Survey 1999–2004</td>
<td>Linolenic acid</td>
<td>ABI &lt;0.90</td>
<td>Cross-sectional</td>
<td>2012</td>
<td>6,352 participants ≥40 years of age</td>
</tr>
<tr>
<td>US National Health and Nutrition Examination Survey 1999–2004</td>
<td>Dietary fiber, folate, vitamins B6, C and E**</td>
<td>ABI &lt;0.90</td>
<td>Cross-sectional</td>
<td>2013</td>
<td>6,534 participants ≥40 years of age</td>
</tr>
<tr>
<td>PREDIMED randomized trial</td>
<td>Mediterranean Diet</td>
<td>Symptomatic PAD</td>
<td>Randomized primary prevention trial</td>
<td>2014</td>
<td>7,435 participants aged 55–80 years (men) or 60–80 years (women)</td>
</tr>
</tbody>
</table>

*No clear protective effect was found. **Association not statistically significant after adjusting for energy intake and physical activity. ABI, ankle-brachial index.
example, a case-control study has suggested that premature PAD may have a genetic basis. However, given the multifactorial nature of this disease, current results have only shown a minor contribution of specific gene polymorphisms in some cases. Until now, it has only been hypothesized that gene-environment interactions, epigenetic factors, or acquired mitochondrial genetic alterations could play an important role in the diagnosis and treatment of this complex disease.

Although PAD has common risk factors with other cardiovascular diseases, good clinical control of the disease is less frequently achieved in patients with PAD than in those with coronary or cerebrovascular diseases. In the Reduction of Atherothrombosis for Continued Health study, patients with symptomatic PAD did not achieve the same risk factor control as frequently as patients with coronary artery or cerebrovascular disease, despite comparable cardiovascular risk profiles. Therefore, primary prevention of PAD demands increased attention because of the global burden of this disease and the barriers for using ABI as a screening test for the general population. Lifestyle modifications are currently the most cost-effective interventions and there is compelling evidence to support smoking cessation, dietary changes and exercise.

**Prevention of PAD With Diet and Lifestyle: Role of the Mediterranean Diet**

Dietary changes are a strong determinant with a large capacity to ameliorate major traditional cardiovascular risks factors, including diabetes, hypertension and hyperlipidemia. Cumulative evidence exists to support the preventive role that some nutrients and foods have on the prevention of coronary and cerebrovascular diseases. However, there are important reasons to use dietary pattern analysis instead of looking at individual nutrients or foods. Several a priori-built dietary indexes, such as the DASH score, the Mediterranean diet, or the Healthy Eating Index, have been used in large prospective studies that have reported a substantial reduction in cardiovascular risk associated with increased adherence to these high-quality dietary patterns.

The main mechanisms that account for this protection are related to the effects of specific nutrients in decreasing endothelial function and through the reduction of low-grade inflammation and through the influence that these nutrients may exert on oxidative stress.

The role that nutrition, and specifically a dietary pattern, has on the primary prevention of PAD remains elusive. The Table shows the epidemiological studies that have found an inverse association between several nutritional factors or dietary patterns and PAD. Nutrients and foods showing inverse associations are some subtypes of dietary fats, fiber, antioxidants (vitamins E and C), folate, vitamins B6 and B12, vitamin D, flavonoids, and fruits and vegetables. A possible inverse association between antioxidant vitamins and a lower prevalence or incidence of PAD (Table). Although results from the PREDIMED randomized trial were consistent and robust in sensitivity analyses, only the occurrence of symptomatic PAD was studied and in an exploratory, non-prespecified analysis. Therefore, a new randomized trial specifically designed with PAD as the major endpoint is needed to establish a causal relationship between a Mediterranean diet and the primary prevention of both symptomatic and asymptomatic PAD.

Adopting a low-fat diet has been a frequently recommended option to prevent PAD. However, current evidence suggests that Mediterranean diets are superior to low-fat diets in the control of cardiovascular risk factors. In addition, it is well known that compliance with low-fat diets is more difficult to sustain in the long-term. Thus, a Mediterranean diet could be a good alternative to the traditional low-fat diet because it improves patients’ compliance through satiation and the palatability of the diet. Following and expanding the recommendations of the European Society of Cardiology for patients with PAD, a Mediterranean-style diet could be effective not only in the primary and secondary prevention of PAD but also in the reduction of cardiovascular risks factors.

**Disclosures**

Conflicts of interest: None.

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Primary Prevention of PAD


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