# Advancing beyond the "heart-healthy diet" for peripheral arterial disease

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***Objective:*** **Peripheral arterial disease (PAD) is a burdensome cardiovascular condition that results from chronic inflammatory insults to the arterial vasculature. Key risk factors include age, gender, type 2 diabetes mellitus, hypertension, hypercholesterolemia, hyperhomocysteinemia, smoking, lack of physical fitness, and poor diet, the latter three being modifiable in the development and progression of PAD. A growing body of evidence indicates that imbalanced nutrient intake may contribute to the development and progression of PAD. The purpose of this review is to summarize current knowledge about nutritional patterns among patients with PAD and to ascertain whether certain health-promoting foods and nutrients could benefit patients with this condition.**

***Methods:*** **We conducted a comprehensive literature review to examine primary source evidence for or against the nutrients that are commonly associated with PAD and their potential utility as therapies.**

***Results:*** **We summarized nine categories of nutrients, as well as four diets endorsed by the American Heart Association that may be prescribed to patients with or at risk for PAD. The nutrients reviewed included omega-3 polyunsaturated fatty acids (*n*-3 PUFAs), folate and B-series vitamins, and antioxidants. The diet plans described include the Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean diet, low-fat diet, low carbohydrate diet, Dr Dean Ornish's Spectrum Diet and Dr Andrew Weil's Anti-Inflammatory Diet.**

***Conclusions:*** **PAD is a chronic inflammatory condition that is associated with longstanding poor nutrition habits. We advocate for an intensified use of diet in PAD therapy, and we specifically recommend following eating patterns that are rich in nutrients with anti-inflammatory and antioxidant properties. (J Vasc Surg 2015;61:265-74.)**

Peripheral arterial disease (PAD) is a burdensome cardiovascular condition that results from chronic inflammatory insults to the arterial vasculature.[1,2] Key risk factors include age, gender, type 2 diabetes mellitus, hypertension, hypercholesterolemia, hyperhomocysteinemia, smoking, lack of physical fitness, and poor diet,[2,3] the latter three being modifiable in the development and progression of PAD.

An insidious asymptomatic period typically makes PAD an underdiagnosed condition. PAD is a common disorder affecting up to 12 million Americans and 20% of patients in primary care; nearly one-third of patients aged ≥70 will suffer from PAD,[3] which significantly affects their quality of life and longevity. In light of recent reports that PAD is a global disease affecting >200 million individuals, with an incidence that has increased by nearly a quarter in the last decade,[4] stronger efforts need to be focused on primary and secondary risk reduction. Among the most concerning sequelae of advanced PAD are impaired ambulation, loss of functional capacity, pain, nonhealing wounds, and limb loss.[5-9] Despite the available medical therapies, patients with PAD continue to have a higher risk for cardiovascular events compared with patients with coronary artery disease (CAD)[10-12] and a threefold to fivefold increased risk of cardiovascular mortality compared with age-matched controls.[13] Hospitalizations and treatment associated with PAD impart a significant financial burden on the health care system. Each year >$21 billion is spent on PAD treatment in the United States.[14] Mainstays of treatment include medical therapies, exercise, vascular bypass operations, and endovascular procedures. Although these interventions are often helpful, it is not uncommon that patients experience postoperative complications, have recurrent symptoms, or require repeat treatments, which further increase the costs associated with PAD.[15]

A growing body of evidence indicates that imbalanced nutrient intake may contribute to the development and progression of PAD.[16-24] Promoting better nutrition may reduce oxidative stress, enhance endothelial cell function, and improve erythrocyte deformability, blood viscosity, and oxygen perfusion in atherosclerosis-induced muscle ischemia, all of which could lead to improvements in clinical outcomes.[25] A primary prevention approach incorporating nutritional therapy may be advantageous in decreasing rates of PAD, whereas a secondary prevention approach may be useful in treating symptoms of PAD or slowing its progression. The purpose of this review is to summarize current knowledge about nutritional patterns among patients with PAD and to ascertain whether certain health-promoting foods and nutrients could benefit patients with this condition. This review is meant to provide a comprehensive overview of primary source evidence

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rather than an exhaustive presentation of studies pertinent to this field.

## CURRENT DIETARY GUIDELINES AND RECOMMENDATIONS

The 2013 composite American Heart Association (AHA) and American College of Cardiology (ACC) Task Force Guidelines[26] address nutrition-focused risk reduction strategies for cardiovascular disease in a broad context, with the aim of improving public health. The guidelines endorse a "Heart Healthy Lifestyle"[26] and provide a general framework for incorporating healthy nutrition into lifestyle management to improve blood pressure and lipid control. They emphasize broad nutrient categories that are associated with better cardiovascular outcomes (eg, fruits and vegetables, whole grains, legumes, etc), although an important limitation is that particular nutrients that may benefit patients with advanced cardiovascular disease are not explicitly identified. The most specific suggestions are embedded in recommendations for lowering low-density lipoprotein cholesterol: the task force advises obtaining a maximum of 5% to 6% of total calories from saturated fat, reducing dietary monounsaturated fats (eg, oleic acid found in olive oil), and minimizing intake of foods rich in *trans*-fats (found in milk, animal fats, and some vegetable oils).

The AHA/ACC Task Force Guidelines are significant for incorporating the latest high-quality clinical trial evidence and promoting preventive strategies for the general population as a means of improving cardiovascular health. However, we remain without specific direction in regards to PAD, a disease at the severe end of the atherosclerotic syndromes. Compared with healthy individuals and those with mild coronary disease, individuals with PAD tend to have a greater systemic inflammatory burden, higher blood pressure, higher triglyceride levels, and deficiencies in various antioxidants and minerals.[16,27] Furthermore, our own experience demonstrates that the mortality rate among patients with PAD is double that of patients with CAD only.[28] We, therefore, advocate that beneficial nutrients have a stronger role in cardiovascular risk prevention for people at risk for or with diagnosed PAD.

Studies published on nutrition as a means of prevention often have conflicting results, and when disseminated in mass media, they may spark confusion about which nutrients are actually beneficial or which diet is most healthy. The most recent example pertains to reports that saturated fats[29,30] may have relatively neutral effects on cardiovascular disease, a notion that directly conflicts with the current AHA/ACC guidelines. A more valuable approach in advising patients with PAD would be to promote a diet that is specialized to address the nutritional alterations associated with this condition and that promotes intake of anti-inflammatory and antioxidant rich foods. In fact, recent reports have demonstrated that therapies specifically focused on nutrition and weight reduction in PAD may lead to improvements in functional impairment and ischemic outcomes.[16]

Nutritional intake and average dietary patterns among patients with PAD have previously been evaluated. Gardner et al[31] demonstrated that PAD and the presence of claudication are associated with a diet high in saturated fat, sodium, and cholesterol and low in fiber, vitamin E, and folate intake. In another study by Antonelli-Incalzi et al,[32] similar patterns were evident: PAD patients had lower consumption of vegetables, fiber, vitamins C and E, folate, and long-chain polyunsaturated fatty acids (PUFAs) compared with individuals without PAD. Notably, these cross-sectional studies had relatively small sample sizes and their data were derived from self-reported answers to dietary questionnaires. Despite these limitations, these studies are still instructive and help to inform our understanding of an average nutritional profile in patients with PAD.

Larger analyses using population-based data have also been conducted. In their study of the United States National Health and Nutrition Examination Survey (NHANES) data, which included 7200 patients, Lane et al.[21] found that consumption of vitamins A, C, E, $B_6$, and $B_{12}$ were associated with a lower odds of having PAD. Further analysis indicated that intake of fiber, vitamins A, C, E, $B_6$, folate, and *n*-3 PUFAs correlated with a reduced prevalence of PAD. Most recently, Naqvi et al[33] analyzed the associations between PAD (ankle-brachial index $<0.9$) and nutrient intake among participants from the NHANES. They found inverse associations between the incidence of PAD and intake of folate and vitamins A, $B_6$, C, and E, affirming the results observed by Lane et al[21] and the smaller cross-sectional studies described previously. However, after adjusting for energy intake and physical activity, odds ratios between the PAD and non-PAD groups were no longer statistically significant.

Knowledge about specific nutritional deficiencies can help guide therapeutic efforts. Achieving a better understanding of diet in PAD may also facilitate the design and execution of prospective and randomized trials with clinical outcomes such as major adverse cardiovascular events and limb-related end points such as claudication distance, limb revascularization, and amputation. Furthermore, if physicians and health professionals have a better understanding of specific nutrients and their effects on atherosclerotic progression, they can be better equipped to give advice about healthful nutrition. The chief nutrients that have been associated with atherosclerosis include *n*-3 PUFAs, folate and B-series vitamins, and antioxidants (Table I), each of which is reviewed below. Additional nutrients, in particular sodium, saturated fats, and fiber, have also been strongly linked to atherosclerosis risk—these have been extensively evaluated in prior studies in relation to cardiovascular outcomes, are associated with strong (grade I) recommendations from the AHA/ACC and will not be discussed here.[34] To identify primary sources, we searched PubMed/MEDLINE and the Cochrane database and we considered studies for inclusion if they were published in 1990 or more recently.

**Table I.** Nutrient recommendations based on the 2013 American Heart Association/American College of Cardiology (*AHA/ACC*) National Guidelines for Cardiovascular Disease

| *Nutrient* | *Recommendation* | *Organization affiliated with recommendation* | *Strength of evidence*[a] | *Level of evidence*[b] |
|---|---|---|---|---|
| *n*-3 PUFAs | • Daily 1.6 grams EPA + DHA | IOM[c] | | |
| | For primary prevention: | AHA/ACC[d] | | |
| | • Consume fatty fish (eg, salmon, tuna, mackerel) 2× week. Each fish portion should be 55-85 g and supply ≥500-1000 mg EPA + DHA | | IIa | A |
| | • Alternative: daily *n*-3 PUFAs supplements containing 1 g EPA + DHA | | IIb | B |
| | Secondary prevention: | | | |
| | • For individuals who do not typically eat fish, daily *n*-3 PUFAs supplements containing 1 g EPA + DHA may be beneficial | | IIb | A |
| Folate, vitamins $B_6$ and $B_{12}$ | • Daily intake of 400 g/1.7 mg/2.4 μg | IOM | | |
| | • Folic acid, vitamin B supplements not recommended for primary or secondary prevention of cardiovascular disease | AHA/ACC | III | A |
| Vitamin C | • No recommendations for antioxidant vitamin supplements to prevent or treat cardiovascular disease | AHA/ACC | III | C |
| Vitamin D | • Daily intake of 700 IU | IOM | | |
| | • No supplementation recommendation for cardiovascular disease prevention in individuals with normal vitamin D levels. | AHA/ACC | III | C |
| | • Correction of low vitamin D levels may reduce cardiovascular disease morbidity and mortality | | IIb | B |
| Vitamin E | • No recommendations for antioxidant vitamin supplements to prevent or treat cardiovascular disease | AHA/ACC | III | C |
| Coenzyme Q10 | • No specific recommendations regarding primary or secondary risk reduction | AHA/ACC | III | B |
| | • Long-term effects of supplementation in patients with congestive heart failure and/or taking statins not yet established Therefore, supplementation with coenzyme Q10 not recommended in these patients | | IIb | B |
| | • Short-term coenzyme Q10 supplementation may lead to mild blood pressure improvement and increases in ejection fraction in patients with CHF | | | |
| Saturated fat | • Reduce saturated fat intake to 5-6% of total daily caloric intake | AHA/ACC | I | A |
| Sodium | • Daily maximum: 1250 mg | IOM | | |
| | • Daily sodium intake should be restricted to 2.3 g (~6 g/d salt) | AHA/ACC | I | B |
| Dietary fiber | • Daily 30 g intake | IOM | | |
| | • Recommended dietary fiber intake is 14 g/1000 kcal, or 25 g for adult women and 38 g for adult men | AHA/ACC | IIa | B |
| | • Recommended to increase dietary fiber intake in order to reduce blood LDL-C and glucose | | I | A |

*CHF,* Congestive heart failure; *DHA,* docosahexanoic acid; *EPA,* eicosapentaenoic acid; *LDL-C,* low-density lipoprotein; n-*3 PUFA,* omega-3 polyunsaturated fatty acid.

[a]Strength of statement/recommendation: Class I—Evidence and/or general agreement that a given statement and/or recommendation is beneficial; Class II—Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the statement and/or recommendation; Class IIa—Weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb—Usefulness/efficacy is less well established by evidence/opinion; Class III—Evidence or general agreement that the treatment is not useful/effective and, in some cases, may be harmful.

[b]Levels of evidence: A—Data derived from multiple randomized clinical trials or meta-analyses; B—Data derived from a single randomized clinical trial or large non-randomized studies; C—Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

[c]IOM: the Institute of Medicine's Food and Nutrition Board, a branch of the National Academy of Sciences (2010); provides general dietary reference not based on disease states; retrieved from https://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables.

[d]AHA/ACC: the American Heart Association and American College of Cardiology, composite guidelines for lifestyle management, 2013; source: Eckel et al.[26]

## LONG-CHAIN *N*-3 PUFAS

Long-chain *n*-3 PUFAs, especially from marine sources, are among the nutrients that have been shown to reduce systemic inflammation[35] and protect against endothelial damage and atherosclerosis.[36] In a recent meta-analysis,[37] which evaluated the long-term effects of *n*-3 PUFAs on secondary prevention of cardiovascular events, authors found that prolonged supplementation (at least 1 year) with a minimum 1 g/d eicosapentaenoic (EPA) and docosahexanoic (DHA) acids was protective against death from cardiac causes, sudden death, and myocardial infarction. They did not observe a benefit for all-cause mortality or stroke. However, recent clinical trials have yielded conflicting data on the effects of *n*-3 PUFAs in cardiovascular diseases in general,[38-40] results that are likely related to both the relatively low dose supplemented (averaging 1.5 g/d) and the heterogeneous cohorts examined.[32] Very few studies have been conducted in the symptomatic PAD population.[41]

Table II summarizes the most recent clinical studies related to the role of *n*-3 PUFAs in PAD. *n*-3 PUFAs, and primarily EPA and DHA, have been shown to contribute to primary and secondary cardiovascular disease protection by reducing blood triglyceride concentration, decreasing production of inflammatory cytokines and mediators, lowering blood pressure, increasing nitric oxide (NO) production and endothelial relaxation and vascular compliance, and decreasing thrombosis and cardiac arrhythmias.[2,41] Greater consumption of *n*-3 PUFAs is associated with changes in cell membrane composition, which in turn affects membrane structure and alters membrane protein function.[2] It also leads to a relative decrease in inflammatory signals and monocyte adhesion in the endothelial cells compared with *n*-6 PUFAs.[42] Furthermore, *n*-3 PUFAs compete with *n*-6 PUFAs, saturated, and *trans*-fats for insertion into cell membrane and produce less potent inflammatory mediators than *n*-6 PUFAs,[25] thereby reducing inflammation within the vessel wall.[43]

The improvements in endothelial function in particular are likely due to effects of *n*-3 PUFAs on ameliorating the damage caused by exposure to oxidative stress. Increased dietary intake of fish or supplementation with *n*-3 PUFAs could lead to recovery of endothelial synthesis of NO and prostaglandin $I_2$, as well as vascular smooth muscle cell sensitivity to NO. These mechanisms are especially relevant to patients with PAD, many of who have a long history of smoking or elevated adiposity, or both, and have proinflammatory profiles as a result.

In addition to their direct influences on inflammation and endothelial function, *n*-3 PUFAs yield potent derivatives, namely protectins, lipoxins, resolvins, and maresins,[44] which exert homeostatic effects. These lipid mediators stimulate and activate endogenous pathways to terminate and promote the resolution of inflammation.[2,45] In the near future, novel anti-inflammatory treatments may incorporate such resolution-directed therapies,[45] which could be particularly beneficial for patients with PAD.

To date, investigations evaluating the role of *n*-3 PUFAs in PAD have yielded encouraging but mixed results. Some clinical studies that looked at the effects of supplementation in PAD have demonstrated functional improvements[35] Our group recently conducted clinical trial randomizing patients with intermittent claudication to 4.4 g EPA and DHA or placebo (The Effects of Omega-3 Fatty Acids Supplementation on Endothelial Function and Inflammation [OMEGA-PAD] I Trial [NCT01310270]) for 1 month. High-dose *n*-3 PUFA supplementation altered the lipid metabolome of PAD patients with a significant increase in the production of downstream metabolites of *n*-3 fatty acids including 18-, 15- and 5-hydroxy eicosapentaenoic acids and 4-hydroxy docosahexaenoic acid. Furthermore, there was a significant improvement in triglycerides in the *n*-3 PUFAs treated group.[46] We are currently enrolling patients for the Effects of Omega-3 Fatty Acids on Peripheral Arterial Disease (OMEGA-PAD) II trial, where *n*-3 PUFAs supplementation will take place over a longer duration (3 months) and the main observations will focus on functional outcomes among claudicant patients with regards to walking performance (NCT01979874).

Still other trials have found minimal or no benefits. In a Cochrane review by Sommerfield et al[47] evaluating patients who had intermittent claudication and comparing placebo with *n*-3 PUFAs supplementation, there did not appear to be improvements in quality of life, pain-free walking distance, maximal walking distance, ankle-brachial index or angiographic findings. Reasons for the lack of positive findings may be the large range of supplementation duration or insufficient dosing. Because systemic inflammation is increased in patients with PAD, they may require higher and more potent dosing, as well as longer (if not lifelong) therapy to experience biochemical, symptomatic, and mortality benefits. For primary prevention among the general population, the AHA/ACC guidelines recommend eating fish twice weekly, and each fish portion should range from 55 to 85 g and supply a minimum of 500 to 1000 mg of EPA plus DHA.[34] For individuals with cardiovascular disease, the guidelines state that those who do not regularly eat fish may consider taking fish oil supplements that contain 1 g of EPA plus DHA, based on supplementation studies in these patients.[34] Given the conflicting results regarding *n*-3 PUFAs in PAD at this point, specific dosing recommendations in PAD cannot yet be made. More randomized trials are warranted that are designed with adequate dosing schedules, commensurate to the increased inflammatory profile observed in this patient group.[16]

In addition to EPA and DHA, another dietary *n*-3 PUFA that is nutritionally essential is α-linolenic acid. Some rich sources for α-linolenic acid include flaxseed, chia seed, walnuts, and soybeans. Flaxseed, in particular, is increasingly being evaluated as a supplement for cardiovascular disease prevention due to its potent antiarrhythmic, antiatherogenic and antiinflammatory effects.[48]

**Table II.** Previous studies evaluating supplementation with omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) in peripheral arterial disease (PAD)

| *First author (year)* | *Type of study* | *Patients* | *No.* | *Treatment* | *Variables measured* | *Findings* |
|---|---|---|---|---|---|---|
| Leng et al (1998)[78] | Double-blind, randomized, placebo-controlled | M/F, IC | 120 | 1.95 g/d × 2 years (1.68 γ-linolenic acid + 0.27 g EPA) | Serum cholesterol lipoprotein concentrations, hemostatic and rheologic variables, walking distance, SBP, ABI, nonfatal coronary events, death | No change in lipids, higher hematocrit in treatment group, lower SBP |
| Conway and Evans (2005)[79] | Double-blind, randomized, placebo-controlled study | M/F, IC | 50 | 10 g/d fish oils × 16 weeks (1.7 g EPA +1.15 g DHA) | QOL, ABI, pain-free walking distance, walking distance | No change in QOL, ABI or absolute walking distance, increase initial walking distance |
| Luu et al (2007)[80] | Prospective study | IC and controls | 16 | 6 g/d × 12 weeks (1.02 g EPA + 0.69 g DHA) | Monocytes ability to induce recruitment using monocyte (from PAD patients) and endothelial cell cocultures | No change in recruitment of monocytes in PAD. Less recruitment of monocytes in controls after dietary supplementation |
| Madden et al (2007)[35] | Prospective study | M, IC | 16 | 6 g/d × 12 weeks (1.02 g EPA + 0.69 g DHA) | Walking distance, ABI | Increase in walking distance to first pain and total walking distance, increase in ABI |
| Schiano et al (2008)[81] | Single-blinded, randomized trial | M/F, IC | 32 | 2 g/d × 3 months (EPA:DHA 0.9:1.5) | Endothelial function, inflammatory function (CRP, myeloperoxidase) | Improvement in FMD, reduction in soluble thrombomodulin. No change in inflammation |
| Madden et al (2009)[82] | Prospective study | M, IC, and Controls | 205 | 6 g/d × 12 weeks (1.02 g EPA + 0.69 g DHA) | CD44 and CD22v3 expression | Reduction in CD44, increase in CD44v3 |
| Flock et al (2013)[83] | Randomized, placebo-controlled, double-blind, parallel group study | M/F | 115 | 0 mg, 300 mg, 600 mg, 900 mg, 1800 mg fish oil/d × 5 months | Omega-3 Index (O3I) | O3I increased in a dose-dependent manner |
| Singhal et al (2013)[84] | Randomized, placebo-controlled, double-blind | M/F | 328 | 1600 mg DHA/d × 16 weeks | FMD, O3I, triglycerides, distensibility, carotid intima-media thickness | Significant decrease in FMD of experimental group |
| Ruiz-Canela et al (2014)[85] | Randomized, blinded | M/F w/o PAD, w/T2DM | 7477 | Med. diet + extra virgin olive oil; Med. diet + nuts | Incidence of PAD | Lower incidence of PAD in Med diet + extra virgin olive oil group vs Med diet + nuts or control group that received only dietary counseling. |

*ABI,* Ankle-brachial index; *CRP,* C-reactive protein; *DHA,* docosahexanoic acid; *EPA,* eicosapentaenoic acid; *F,* females; *FMD,* flow-mediated vasodilation; *IC,* intermittent claudication; *M,* males; *Med,* Mediterranean; *QOL,* quality of life; *SBP,* systolic blood pressure; *T2DM,* type 2 diabetes mellitus.

Flaxseed also contains lignans, which have strong antioxidant properties, and fiber, which is associated with lowering cholesterol levels, and may therefore be beneficial for counteracting the inflammatory and oxidative stress states that prevail in PAD.[49]

Supplementation with *n*-3 PUFAs at high doses may cause mild gastrointestinal symptoms, namely a "fishy burp," that can be mitigated by refrigerating fish oil capsules before ingestion or consuming them with cool foods or beverages.[50] High intake of *n*-3 PUFAs has also been

**Table III.** Diet patterns recommended for primary and secondary prevention of cardiovascular disease

| *Diet pattern* | *Nutritional recommendations* | *Strength of evidence*[a] | *Level of evidence*[b] |
|---|---|---|---|
| DASH diet | Recommended to prevent hypertension and lower blood pressure. The diet emphasizes sodium restriction, reduction of fat intake, and alcohol avoidance | I | A |
| Mediterranean diet | A Mediterranean diet has been shown to improve quality and life expectancy in patients with cardiovascular disease, as well as those who have type 2 diabetes or are overweight | IIa | A |
| | Mediterranean diets have been found to be preferable to a low-fat diet in increasing HDL-C blood levels, reducing triglyceride levels, and improving insulin sensitivity | IIa | A |
| Low-fat diet | A low-fat diet has been shown to improve quality and life expectancy in people with cardiovascular disease, as well as in states of obesity and type 2 diabetes | IIa | A |
| Low-carbohydrate diet | A low-carbohydrate diet is effective at reducing triglyceride levels and increasing HDL-C blood levels, especially when compared with a low-fat diet | IIb | A |
| | Low-carbohydrate diets, which include 30%-40% of calories from carbohydrates and are low in saturated fat and high in monounsaturated fat, were found to be safe in healthy and overweight individuals at follow-up up to 4 years | IIa | A |
| Ornish Spectrum Diet | Emphasizes comprehensive lifestyle management, including diet (low-fat, whole foods, plant-based), exercise, stress management, and social support for reversal of coronary heart disease and minimizing risk for those with cardiovascular disease risk factors | No specific recommendation from national guidelines | |
| Weil Anti-inflammatory diet | http://www.drweil.com/drw/u/ART02012/anti-inflammatory-diet | No specific recommendation from national guidelines | |
| | Daily caloric intake should be between 2000 and 3000. The distribution of calories should be as follows: 40%-50% from carbohydrates, 30% from fat, and 20%-30% from protein | | |
| | Individuals are encouraged to consume carbohydrates, fat, and protein with each meal | | |
| | Specific recommendations on sources for carbohydrates, protein, saturated fats, vitamins/minerals, and supplements | | |

*DASH*, Dietary Approaches to Stop Hypertension; *HDL-C*, high-density lipoprotein cholesterol.

[a]Strength of statement/recommendation: Class I—Evidence and/or general agreement that a given statement and/or recommendation is beneficial; Class II—Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the statement and/or recommendation; Class IIa—Weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb—Usefulness/efficacy is less well established by evidence/opinion; Class III—Evidence or general agreement that the treatment is not useful/effective and, in some cases, may be harmful.

[b]Levels of evidence: A—Data derived from multiple randomized clinical trials or meta-analyses; B—Data derived from a single randomized clinical trial or large nonrandomized studies; C—Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

linked to a theoretical concern for increased bleeding risk. This potential side effect has been evaluated in large cohorts, and the aggregate results have not shown an association with clinically significant vascular effects or risk.[51,52]

## FOLATE, VITAMINS $B_6$ AND $B_{12}$

Deficiencies in folate or these critical B-series vitamins may disrupt homocysteine homeostasis and yield an accumulation of homocysteine. Such a state of hyperhomocysteinemia (when blood levels exceed 14 mmol/L) is associated with an increased risk of PAD,[16,53] as well as an increased risk of myocardial infarction and stroke. Because folic acid and vitamins $B_{12}$ and $B_6$ are involved in homeostatic metabolism, it has been postulated that supplements could theoretically lead to a resolution of normal physiologic levels and thereby reduce cardiovascular risk. Some studies that evaluated supplementation among individuals with hyperhomocysteinemia have shown biologic benefit.[54,55] However, other investigations have failed to show a clinical benefit from supplementation with folic acid and B-series vitamins.[26,56-59] Furthermore, a recent meta-analysis of folic acid supplementation in patients with chronic kidney disease, a condition that is often comorbid with advanced PAD, failed to show a beneficial effect in cardiovascular outcomes.[59] Although folic acid supplementation is generally not associated with detrimental effects, excessive intake may carry the risk of enhancing development of premalignant lesions, particularly in the colorectal tract.[60]

## ROLE OF VITAMINS IN PAD

Vitamin C is thought to exert protective effects on endothelial cells and vascular smooth muscle cells during the early steps in atherosclerosis by preventing endothelial dysfunction and promoting type IV collagen synthesis.[61] The vitamin diminishes recruitment and proliferation of vascular smooth muscle cells in regions of vascular damage, thereby lessening the oxidative stress that results from macrophage activation.[61] Following on these biochemical observations, inverse associations have been made between blood levels of vitamin C and inflammatory biomarkers, most notably C-reactive protein, in large observational population studies.[62,63] Vitamin C levels have been observed to be relatively low in PAD in several cohorts.[32,64] Despite this observation, there is a lack of prospective trials examining the clinical effects of vitamin C supplementation in this patient population or for cardiovascular risk prevention. In certain populations, high doses of vitamin C supplementation may even be related to detrimental cardiovascular mortality outcomes.[65] The 2013 AHA/ACC Task Force Guidelines, therefore, do not currently have recommendations for vitamin C.[26]

Vitamin D deficiency has also been associated with PAD.[16,26,66] Despite the association with a vitamin D-deficient state in PAD, no interventional studies have reported clinically significant effects of vitamin D supplementation (with or without calcium) on cardiovascular events, including myocardial infarction, stroke, and other cardiac and cerebrovascular outcomes.[26,67] In fact, the Women's Health Initiative trial found that combined vitamin D and calcium supplementation may have a nearly significant detrimental effect.[68] At this time, the AHA/ACC guidelines do not recommend screening blood vitamin D levels for cardiovascular disease prevention, although they do state that correction of decreased levels may improve cardiovascular disease morbidity and mortality rates. Taking these findings together, it is evident that vitamin D deficiency is a critical factor in PAD, although it is unclear whether specific recommendations can be made for supplementation. Ongoing studies such as the Vitamin D and OmegA-3 Trial (VITAL) trial[69] may yield critical information on the role of vitamin D supplementation in vascular health. Of note, toxicity from excessive vitamin D intake may lead to increased calcium deposition in the vasculature and thereby promote atherosclerosis as well as negative cardiovascular sequelae, such as atrial fibrillation.[70]

Vitamin E, also called α-tocopherol, is the only cell membrane-bound lipid-soluble antioxidant, and deficiencies have been observed in PAD.[31,32] Lower levels of this antioxidant are thought to impair tolerance to ischemia and worsen intermittent claudication.[25] However, a 2000 Cochrane review[71] that evaluated the effects of vitamin E supplementation on intermittent claudication found that the available data were inconsistent to favor recommending vitamin E in PAD patients. Importantly, caution should be used in recommending vitamin E supplementation to patients taking anticoagulants, such as warfarin, due to the synergistic effects of vitamin E with these medications and the increased risk for hemorrhagic events.[72] The 2013 AHA/ACC Task Force Guidelines support not recommending supplemental vitamin E.[26]

## COENZYME Q10

Formerly known as ubiquinone, coenzyme Q10 is another physiologic antioxidant that has been shown to positively affect cardiac performance in patients with congestive heart failure and ischemic heart disease and to exert a clinically significant blood pressure-lowering effect.[73] Although its exact mechanism of action is unclear, it is thought that this potent antioxidant may promote improved endothelial function. This hypothesis sparked the design and execution of several supplementation trials.[74-76] A recent meta-analysis[73] incorporated five randomized controlled trials evaluating the effect of coenzyme Q10 on arterial endothelial function and found that endothelial function (as assessed by endothelium-dependent flow-mediated vasodilation) significantly improved. The authors concluded that supplementation is warranted in patients with and without cardiovascular disease, although exact dosages are not established. In addition to a low number of aggregate studies, an important limitation to this analysis is that the studies reviewed incorporated patient groups with varying cardiovascular disease severity, including those with hyperlipidemia, type 2 diabetes mellitus, and CAD. Furthermore, no supplementation studies in PAD have been published. It is therefore difficult to draw conclusions about the role of coenzyme Q10 in primary prevention of cardiovascular disease as well as its role in secondary prevention in patients with PAD. Side effects associated with coenzyme Q10 are uncommon, but those reported include nausea, vomiting, diarrhea, and abdominal discomfort. In addition, coenzyme Q10 may have an antiplatelet effect and lead to an increased bleeding risk.[77] Supplementation studies in patients with PAD to evaluate the potential effects of the antioxidant are warranted.

Our review of primary evidence did not show a clear indication for routine testing of the nutrients presented above and therefore, our group does not have a practice of doing so in our vascular clinic. Despite this, our research has raised a higher awareness of nutrition issues in patients with PAD and the importance of a healthy diet is emphasized when discussing lifestyle modifications in our patients. Further well-conducted, large, multicentered, and double-blinded investigations are warranted to see if correction of deficiencies may improve clinical outcomes. If these findings are observed in prospective studies, then routine testing may be incorporated into clinical practice in the future.

## TYPES OF DIETS

From the available evidence and the recent AHA/ACC Task Force Guidelines, Eilat-Adar et al[34] proposed a healthy lifestyle plan that can serve as a good foundation

for dietary change. They recommended including eating fresh or frozen food without added sugars, minimizing intake of salt or high-calorie sauces, and using cooking methods that preserve the original nutrients. The diet should also include a diversity of vegetables, fruits, whole grains, soluble fibers, and legumes. Cooking with certain vegetable oils, particularly olive and canola oils, but not coconut and palm oils, is preferred over animal fat. They also propose eating at least two servings of fatty, oily fish (eg, salmon, tuna, and mackerel) weekly, with each portion size amounting to 55 to 85 g and supplying a minimum of 500 to 1000 mg EPA and DHA.

Further steps that physicians can take to help curb associated disability and mortality include instructing patients about diet plans designed for and studied in cardiovascular disease, such as the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets, and connecting them with resources that promote healthful nutrition. The AHA and ACC highlight four studied dietary plans that have been shown to improve cardiovascular disease risk factors and outcomes in the setting of diagnosed cardiovascular disease (Table III). Also included in Table III are two additional noteworthy diets that have been designed specifically for individuals with CAD or cardiovascular disease risk factors: Dr Dean Ornish's Spectrum Diet and Dr Andrew Weil's anti-inflammatory diet. Although these diet plans maintain different aims, they all exemplify the general task force recommendations and a few even go further by promoting more personalized nutrition to decrease disability and promote survival.[34]

Future studies that assess nutrition in PAD should compare the AHA/ACC recommended diet plans, as well as the Spectrum diet and the anti-inflammatory diet, in this patient population to determine their utility, feasibility, and effects on cardiovascular outcomes. Also, because PAD is a complex and multifactorial disease, prospective therapeutic efforts should incorporate a variety of nutrients and evaluate whether long-term supplementation affects claudication or survival, rather than focusing on singular nutrients.

## CONCLUSIONS

PAD is a chronic inflammatory condition that is associated with, among other risk factors, longstanding poor nutrition habits. Owing to the systemic nature of atherosclerotic burden in PAD and the high risk of ischemic events, patients with this condition should be considered candidates for secondary prevention strategies that emphasize lifestyle change, and particularly an improvement in dietary habits. We advocate for an intensified use of diet in PAD therapy and specifically recommend following a diet that is rich in nutrients with anti-inflammatory and antioxidant properties. Primary prevention for individuals with associated risk factors is also critically important and can be optimized by comprehensively evaluating an individual's long-term nutritional patterns, which provide clues about risk prediction for PAD and cardiovascular disease in general. Enhancing public awareness about PAD is imperative, as is making societal efforts to promote better nutrition to reduce the impact associated with this condition.

## AUTHOR CONTRIBUTIONS

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