Review Article

Effect of omega-3 polyunsaturated fatty acids on inflammatory status, lipid levels, and severity of peripheral artery disease measured using ankle-brachial index - A review

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ABSTRACT

Peripheral artery disease (PAD) is a buildup of plaques causing blockage inside the arteries of the legs which is characterized by either partial or complete obstruction of the arteries of the lower limb, it is one of the common manifestations of atherosclerosis. Various factors such as smoking, diabetes, high blood pressure, and increased cholesterol levels contribute in developing PAD. It has been postulated that PAD is strongly associated with increased serum lipid levels and inflammatory status, which increases a high risk of cardiovascular disease among these patients. A non-invasive procedure for screening PAD or measuring the disease severity is done using ankle-brachial index (ABI). ABI value <0.9 indicates PAD. An increased omega-3 polyunsaturated fatty acid (n-3 PUFA) intake has been shown to reduce mortality and complications in PAD patients. The cardiac benefits of n-3 PUFAs are attributed to its antiarrhythmic properties; however, it also has some of the additional effect that generally contributes its cardiovascular action. Due to its inflammation resolution phase, it can be used in PAD. Hence, the beneficial effects of n-omega-3 fatty acid for patients with PAD are the focus of this review. If the n-3 PUFA is associated with circulating markers of inflammation, lipid levels, and ABI in patients with PAD, then, a better understanding of this relationship could help guide future treatment of these patients (i.e., nutritional recommendations or supplementation) in an effort to lower disease severity and improve their vascular function.

KEY WORDS: Ankle-brachial index, Omega-3 polyunsaturated fatty acids, Peripheral artery disease

INTRODUCTION

Peripheral artery disease (PAD) is a common disease, but it is highly neglected by medical professionals. It does not just only affect the arteries of limb but also the life as well, it is known to affect the quality of life (QOL) in patients' badly.[1,3] Atherosclerosis is the narrowing or blockage of the arteries with the formation of fatty deposits/plaque[2] also known as atheroma which is the most common cause of PAD.[4] The main symptom of PAD is intermittent claudication or may be associated with critical limb ischemia, whereas majority of patients mainly elderly people remain asymptomatic.[5,7] The prevalence of this disease increases with age [8,11] and if the modifiable risks are treated, such as cessation of cigarette smoking, control over diabetes, dyslipidemia, and hypertension in people with PAD,[9,13] the QOL can be improved in PAD patients.

Patients with PAD have a high risk of infection in the affected area that contributes to increased chance of getting affected with gangrene. If such occurs, amputation is the only solution in such patients.[6,10] PAD also increases cerebral vascular disease and coronary heart disease risks in patients impairing the QOL.[14]

ANKLE-BRACHIAL INDEX (ABI) AND ITS SIGNIFICANCE IN PAD

ABI is an effective, simple non-invasive screening tool for PAD in patients. It assesses arterial perfusion. A diminished ABI (<0.9) is the diagnostic criteria for PAD.[15]

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Classification of Pad According to ABI Value

ABI	PAD Severity
1–1.3	No PAD
0.91–0.99 (Acceptable)	This range and below also indicates increased cardiovascular risk [105], including stroke, coronary diseases, or cardiovascular death
≤0.9	Presence of PAD
0.7–0.9	Mild
O.4–0.69	Moderate
<0.4	Severe

ABI: Ankle-brachial index, PAD: Peripheral artery disease

ABI is highly sensitive and specific in nature, but it does not show accuracy in certain people. Elderly people, diabetes and renal disease patients generally have calcified and highly incompressible arteries (ABI > 1.3) that may lead to poor sensitivity of ABI test in PAD patients.[17,18]

A single ABI test may not be sufficient even in the symptomatic patients, at least two or more values should be taken for proper diagnosis of PAD, whereas in some cases, patients are left to exercise, and then, ABI test is carried out for acquiring a specific ABI value.[19]

MEASUREMENT OF ABI

The ABI is measured using systolic blood pressures of the brachial in the upper limbs, posterior tibial and dorsalis pedis arteries for lower limbs bilaterally. For each lower extremity, the highest systolic pressure of the two pedal pulses should be divided with the highest systolic pressure of the two brachial arteries to achieve an accurate ABI value.[20]

EFFECT OF OMEGA-3 POLYUNSATURATED FATTY ACID 3-PUFA IN PAD

An increased omega-3 polyunsaturated fatty acid (n-3 PUFA) intake has shown reduction in mortality in both healthy subjects and patients with the previous history of myocardial infarction.[7] The cardiac benefits of n-3 PUFAs are mainly attributed to their antiarrhythmic properties; however, several additional effects may contribute to the protective cardiovascular action of these molecules.[7,8] These supplements tend to reduce triglyceridemia and inflammatory status, thus improving the endothelial function. Thereby, interfering with fundamental mechanisms promoting atherogenesis and inhibiting the development of new plaques, they retard the growth of established plaques and contribute to plaque stabilization.[7,8]

n-3 PUFAs, namely eicosapentaenoic acid (EPA), alpha-linolenic acid, and docosahexaenoic acid (DHA), are responsible for the above effect. They are enzymatically converted into lipid mediators which show stereospecificity and have receptor-mediated biological actions.[21,33] Specifically, lipid mediators generated from EPA and DHA are actively involved in the resolution phase of inflammation as they display anti-inflammatory properties where they compete with arachidonic acid reducing pro-inflammatory eicosanoids.[22]

INFLAMMATION AND ITS ROLE IN PAD

Inflammation plays a very important role in PAD, it leads to initiation and progression of the disease enormously.[23] Various inflammatory markers are known to possess pro-atherogenic properties which may be involved in any step during the process of the inflammation.[23] Strongest risk factors for the development of PAD are cigarette smoking and diabetes mellitus.[24] They promote oxidative stress which directly or indirectly enhances inflammatory pathways.[25]

Inflammation can be one of the factors for arterial hypertension.[26] Angiotensin II evokes the production of highly reactive oxygen species and triggers the endothelial cells to express several cell adhesion molecules (CAMs), mainly CAM-1.[27] They even act on arterial smooth muscle cells causing increased expression of pro-inflammatory cytokines such as interleukin (IL)-6 and monocyte chemoattractant protein-1.[28,29]

Many studies showed that the significant increase in baseline C-reactive protein (CRP) concentration may increase the risk of developing PAD which is independent of other factors that can cause atherosclerosis which is a hallmark for PAD.[30]

ASSOCIATION OF CRP IN THE DEVELOPMENT OF PAD

CRP is a marker of inflammation. It is derived from leukocytes and releases endothelium monocyte chemoattractant protein-1 in response to IL-6 stimuli, these proteins attract monocytes to the endothelium, leading to upregulation of tissue factor and pro-inflammatory cytokines such as tumor necrosis factor-α, inhibition of nitric oxide.[30] CRP causes induction of endothelial adhesion molecules such as intracellular CAM and vascular CAM-1 which leads to adhesion of monocytes to the endothelium.[31] Many studies showed that inflammatory markers mainly CRP are associated with slow or short walking.

ABI is intensively associated with CRP levels. It is inversely proportional to ABI value, i.e., its increased level shows lesser ABI value. Thus, CRP is an independent factor that leads to PAD. People with 2-fold increase in CRP levels have a higher risk of developing PAD and its complications.[30]

Omega n PUFA has shown inflammation resolving effect. As mentioned above, omega n-PUFA gets converted into lipid mediators that have stereospecific and receptor-mediated biological actions which are actively involved in the resolution phase of inflammation by affecting the activity of membrane proteins and physical membrane characteristics.[21,33] Mainly DHA has shown anti-inflammatory action by significantly decreasing the concentration of CRP in serum.[32]

HALLMARK OF PAD-ATHEROSCLEROSIS

Atherosclerosis is attributed as the hallmark of PAD. They generally represent several series of cellular and molecular responses which may result in inflammation.

Specialized pro-resolving lipid mediators (SPMs) are derived from the n-3 PUFAs. These are specific biochemical signals which cause resolution of inflammation rather than a passive decrescendo of inflammatory cytokines.[33]

The process by which n-3 PUFA shows its impact on inflammation begins with the incorporation of EPA and DHA into cellular membranes.[34] Once incorporated, they affect the activity of membrane proteins and alter the physical membrane characteristics of the cell. They are converted into wide variety of bioactive lipid mediators, also known as SPMs which shows the anti-inflammatory property.[35] Simultaneously, the circulating unesterified n-3 PUFA which has not been corporate into cell arrives at the site of inflammation and gets directly converted into lipid mediators.[35]

The omega-3 index is a validated biomarker. It is used to define the red blood cell (RBC) content of EPA and DPA. Identifying the percentage contribution of EPA and DHA to total identified RBC fatty acids allows precise reflection of plasma and tissue levels of EPA and DHA. Low level of omega-3 index has been seen in patients with PAD.[36]

DYSLIPIDEMIA AND EFFECT OF n-3 PUFA ON LIPID LEVELS

Dyslipidemia can activate inflammatory process by modifying the oxidation of low-density lipoproteins (LDLs) and very LDLs (VLDLs) which is one of the primary causes for PAD.[37]

Omega-3 PUFA reduces serum triglycerides (TGs) and also apoB-48 which is the apolipoprotein of chylomicrons (CMs).[38] Thus, decreased CM particle sizes and increased pre-heparin lipoprotein lipase (LPL) suggest n-3 PUFA activity against lipids. It accelerates CM-TG clearance by increasing LPL activity.[38] CM remnants possess direct atherogenic properties.[39] The n-3 PUFA was reported to significantly decreased apoB-48 secretion in the basal state.[40] Reduced secretion of apoB-48 may reduce production of CM and may also induce a decrease of CM remnants which is beneficial in preventing atherosclerosis. EPA has shown its effect on lipoproteins by decreasing their serum levels. Mechanism of this process has not been completely understood. Briefly, n-3 PUFA reduces atherogenic CM remnant by increasing the LPL activity and reducing the levels of apoB-48 secretion.[41]

Omega-3 PUFA significantly produces a decrease in VLDL-C and hepatic secretion of VLDL apoB - which is apolipoprotein of VLDL that may produce a significant reduction of VLDL production.[42]

Omega-3 PUFAs elicit hypotriglyceridemic effects by suppressing hepatic lipogenesis through reducing the levels of sterol receptor element-binding protein-1c (SREBP-1c), hence, upregulating fatty acid oxidation in the liver and skeletal muscle.[38]

Omega-3 PUFAs, especially DHA, increase the level of high-density lipoprotein (HDL).[40] HDL is formed by catabolism of TG-rich lipoproteins such as VLDL or intermediate-density lipoprotein (IDL) by LPL.[4] Therefore, increased LPL activity reduces IDL and VLDL and increases HDL levels.[38] An increase of HDL due to Omega-3 PUFA can be explained by an increased activity of LPL, which may be associated with increased TG hydrolysis of VLDL. Omega-3 PUFA reduces VLDL-C, by reduction of hepatic secretion of apoB-100, decrease of SREBP-1c, and an increase of LPL activity.[41] However, EPA has shown non-significantly reduction of LDL levels in serum. DHA reduces more VLDL than EPA.[38]

DHA decreases the concentrations of fasting and postprandial TG, small dense LDL particles, remnant-like chylomicron particles, and inflammatory markers and EPA reduces LDL levels.[32]

CONCLUSION

Omega-3 PUFA is known to show its effect on lipid levels, inflammatory marker, and ABI, thereby decreasing the disease severity in patients with PAD and improving the QOL of such patients. Omega n-PUFA can be a boon for treating PAD as a nutritional supplement that avoids the side effects which are related with the conventional treatment of the disease. The understanding of the disease and the use of omega n-PUFA to improve the vascular function and QOL in PAD can be a nutritional guidance for such patients.

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