Dietary intake of fish oil and serum levels of omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been shown to be inversely correlated with cardiovascular morbidity and mortality of coronary artery disease (CAD) in many epidemiological studies. (n-3) PUFAs have suppressive effects on the initiation and progression of atherosclerosis mainly through their anti-inflammatory properties.

At the initiation of atherosclerosis, injured endothelium expresses adhesion molecules and produces cytokines, growth factors and vasoactive molecules, leading to the infiltration of monocytes and T lymphocytes into the sub-endothelial space. These inflammatory cells release enzymes, cytokines, chemokines, eicosanoids, and growth factors followed by chronic inflammation within the vascular wall. In this way, inflammation plays pivotal roles in the onset and/or progression of atherosclerotic diseases. Under stimulation, arachidonic acid (AA) is released from membrane phospholipids of inflammatory cells and metabolized by cyclooxygenase (COX) or lipoxygenase (LOX) to produce pro-inflammatory eicosanoids, such as prostaglandin E2 and leukotriene B4. On the other hand, n-3 PUFAs prevent the conversion of AA into pro-inflammatory eicosanoids by serving as an alternative substrate for COX or LOX, resulting in the production of biologically weaker pro-inflammatory eicosanoids, such as prostaglandin E3 and leukotriene B5 (Figure). In addition, resolvin, protectin, and maresin, which are derived from eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) via COX and LOX pathways, were shown to have anti-inflammatory properties in cell culture and animal studies.

At the advanced stage of atherosclerosis, these inflammatory cells secrete matrix metalloproteinases (MMPs) and cysteine proteases which could thin and weaken the fibrous cap, making the plaque vulnerable. A randomized placebo-controlled trial in patients who underwent carotid endarterectomy showed that n-3 PUFAs are incorporated into advanced atherosclerotic plaques after dietary supplementation of both EPA and DHA, followed by a reduced number of macrophages infiltrating into the plaques, suggesting n-3 PUFAs have a plaque-stabilizing effect. Also, the follow-up study OCEAN (Omacor Carotid EndArterectomy iNtervention) reported that mRNA levels of MMP-7, MMP-9 and MMP-12 were lower in carotid plaques in patients who had received EPA and DHA supplementation.

In a cross-sectional study, Shimada, et al. first reported that low serum EPA levels were independent risk factors for multiple vessel disease in patients with ST elevation myocardial infarction (STEMI). A total of 507 STEMI patients who had undergone emergency percutaneous coronary intervention were classified into 3 groups; one-vessel disease, two-vessel disease, and three-vessel disease/left main trunk disease. In this study, the relationship between serum PUFAs and extent of vessel disease was evaluated without distinction between culprit and non-culprit lesions. Also, in non-ACS patients, a lower serum content of n-3 PUFA was significantly associated with lipid-rich plaques.
Mechanisms for anti-inflammatory properties of n-3 PUFAs.

1) (n-3) PUFAs prevent the conversion of arachidonic acid into pro-inflammatory eicosanoids.
2) (n-3) PUFAs serve as an alternative substrate for cyclooxygenase or lipoxygenase, resulting in the production of biologically weaker pro-inflammatory eicosanoids.
3) Resolvin, protectin, and maresin derived from n-3 PUFAs via cyclooxygenase and lipoxygenase pathways have anti-inflammatory properties. (Quoted from Endo J, et al. J Cardiol 2016; 67: 22-7.)

As a gold standard to explore the vulnerability of coronary atherosclerotic plaques, invasive imaging modalities, such as IVUS, OCT, coronary angiography, and coronary computed tomography are currently performed. Using IVUS and OCT, culprit plaques for ACS were shown to have a thinner fibrous cap as compared with non-culprit plaques. In ACS patients, a non-culprit plaque is likely to become the culprit lesion for the near term recurrence of ACS. Further studies are needed to clarify the association between the serum levels of PUFAs and vulnerability of coronary atherosclerotic plaques in ACS patients with distinction between culprit and non-culprit lesions, enabling us to verify the clinical usefulness of serum n-3 PUFAs levels as a reliable and non-invasive marker for vulnerable plaques in coronary arteries.

Disclosures

Conflicts of interest: None.

References

7. Merched AJ, Ko K, Gotlinger KH, Serhan CN, Chan L. Atherosclerotic lesions. Recent investigations using intravascular ultrasound (IVUS) or optical coherence tomography (OCT) demonstrated that low serum levels of n-3 PUFAs were associated with lipid-rich plaque in culprit lesions for stable angina. The association of low serum levels of n-3 PUFAs and vulnerable plaques in non-culprit lesions detected by IVUS in patients with stable angina who had undergone at least 8 months of lipid-lowering therapy with a statin was also reported. Consistent with these findings in non-ACS patients, the inverse association between serum n-3 PUFA levels and extent of vessel disease identified in Shimada’s study might imply an inverse correlation of serum n-3 PUFA levels and the amount of vulnerable coronary atherosclerotic plaques, whether culprit or non-culprit.
15. Cawood AL, Ding R, Napper FL, et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. Atherosclerosis 2010; 212: 252-9.