EDITORIAL

Inflammation and its resolution in coronary artery disease: a tightrope walk between omega-6 and omega-3 polyunsaturated fatty acids

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RELATED ARTICLE
by Sut et al, see p. 117

Cardiovascular disease, the world's leading cause of death, is associated with increased and chronic inflammation, both systemically and locally. Epidemiological studies have identified a plethora of cardiovascular risk factors such as smoking, hypertension, abnormal lipid profile, and diet. In particular, diet is an important predictor of coronary artery disease (CAD) since it is modifiable and highly correlated with obesity, blood pressure, cholesterol levels, and diabetes. Adherence to the Mediterranean diet has been repeatedly associated with lower cardiovascular risk, in large part due to the abundance of omega-3 polyunsaturated fatty acids (PUFAs) in this cuisine.

This belief became popular almost 50 years ago when an epidemiological study revealed that the Inuits on the west coast of Greenland, characterized by a high fish consumption, had lower levels of plasma lipids compared with the Danish controls, which suggested that a high intake of omega-3 PUFAs was the reason for a reduced risk of cardiovascular events.[1] Since then, this scientific field has expanded to examine how omega-3 PUFAs may play a role in reducing the risk of inflammation-related cardiovascular events.[2]

In this issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Sut et al[3] report on the dietary PUFA intake in men with chronic coronary syndrome treated with percutaneous coronary intervention (PCI) and its association with inflammation severity, evaluated with the C-reactive protein (CRP), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) values. While subjects with a high dietary omega-3 PUFA intake exhibited a lower PLR, the CRP level did not differ between the groups. Importantly, stratifying the study population by a dietary ratio of omega-6 to omega-3 PUFAs revealed significantly higher CRP levels in subjects with the ratio higher than 4:1.[3] These results indicate that the relative intake of omega-6 and omega-3 PUFAs may reveal significant associations with inflammation in CAD. The latter assumption is supported by studies in healthy volunteers showing that a high omega-6 / omega-3 PUFA ratio is associated with increased levels of inflammatory biomarkers such as CRP or tumor necrosis factor α.[4] In contrast, polyphenol intake did not predict any of the inflammatory marker levels.[3]

A closer look at the downstream metabolism of PUFAs may provide additional insights into the role of the omega-6 / omega-3 PUFA ratio in coronary atherosclerosis. Indeed, omega-6 PUFAs are fatty acids responsible for the proinflammatory response, serving as a substrate for the production of the proinflammatory lipid mediators: leukotrienes and prostaglandins. On the other hand, omega-3 PUFAs are substrates for the generation of specialized proresolving lipid mediators (SPMs).[5] This family of molecules is composed of D-series resolvins, maresins, and protectins, which are formed from docosahexaenoic acid, and E-series resolvins, which are derived from eicosapentaenoic acid,[5] as depicted in FIGURE 1. The SPMs are responsible for inhibiting inflammation and restoring tissue homeostasis during the so called proresolution phase of the inflammatory response. This phase is mainly dependent on the active class switch of the mediators present in the system, changing from proinflammatory eicosanoids derived from omega-6 PUFAs to the omega-3 PUFA–derived SPM formation.[5]

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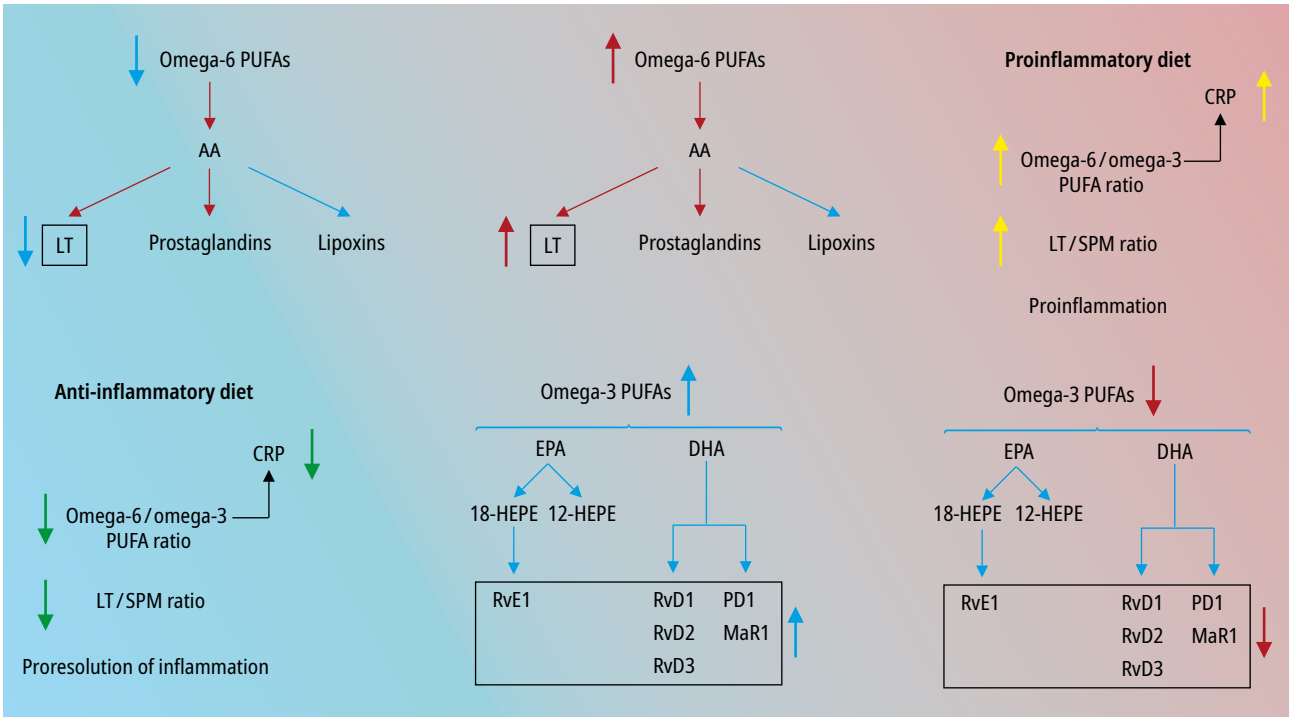

FIGURE 1 Expected impact of low and high dietary intake of omega-3 and omega-6 fatty acids on the balance of lipid mediators. The blue background means predominant proresolution of inflammation, and the red one, predominant proinflammation.
Abbreviations: ↓, decrease; ↑, increase; AA, arachidonic acid; CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HEPE, hydroxyeicosapentaenoic acid; LT, leukotriene; MaR, maresin; PD, protectin; PUFA, polyunsaturated fatty acid; RvD, D-series resolvin; RvE, E-series resolvin; SPM, specialized proresolving lipid mediator

The association of a higher ratio of dietary omega-6 / omega-3 PUFAs with inflammation reported by Sut et al[3] may hence potentially reflect an imbalance between proinflammatory and proresolving mediators derived from omega-6 and omega-3 PUFAs, respectively. Indeed, several downstream PUFA-derived lipid mediators have been shown to directly regulate the atherosclerotic process.[6] Indeed, the ratio of leukotriene B_4 to resolvin D1 serves as a biomarker for a nonresolving cardiovascular inflammation, for example, in subclinical atherosclerosis[7] and vulnerable plaques.[8]

The report by Sut et al[3] comes in a very interesting moment. Those observations, together with the positive results of the latest clinical trial on eicosapentaenoic acid supplementation at a dose of 4 g/d that showed a 25% reduction of cardiovascular events in the secondary prevention,[9] suggest that adherence to an anti-inflammatory diet rich in omega-3 PUFAs and low in omega-6 PUFAs may reduce inflammation and hence suppress the development of CAD. To support this assumption, it would be of importance to study the production of SPMs as the final bioproducts from omega-3 PUFAs and the ratio to the omega-6 PUFA-derived leukotriene levels (FIGURE 1).

The results from this study are promising. However, certain limitations should be considered before they can be fully applied to dietary advice and clinical practice. The multiparametric approach for determining dietary anti-inflammatory effects based on CRP, PLR, and NLR values, advocated by Sut et al,[3] must be further studied since the results were obtained in a cohort that included only men with previously diagnosed CAD. No control of known cardiovascular confounding factors (absence of multivariable / multivariate analyses) also weakens the intrinsic validity of the study. These problems can be solved with multiple statistical strategies. To minimize confounding, patients can be either matched across the strata or adjusted for clinical attributes that are known to confound the levels of inflammatory biomarkers. Furthermore, since a majority of patients with CAD are put on complex medication regimens, a possible drug-related interaction effect on protective PUFA characteristics should be further explored. Finally, it should be noted that the Food Frequency Questionnaire may have overestimated the PUFA intake, since the median omega-3 PUFA intake was reported to be 4.2 g/d,[3] which is remarkably high.

Taken together, the study by Sut et al[3] is an important contribution to the current knowledge on the dietary effects on inflammation in general and, in particular, on the role of the omega-6 / omega-3 PUFA ratio as

a biomarker of nonresolving inflammation. Future studies that would use highly dimensional datasets implementing artificial intelligence learning models could reveal the exact dietary predictors of inflammation in CAD.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Cardiac Society, or publisher.

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