

## Editorial

# Synergistic Action of Fish Oil and Olive Oil

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The essential Polyunsaturated Fatty Acids (PUFAs) are mainly represented by Linoleic Acid (LA; C18:2 $\omega$ -6) from the -6 family, responsible for the formation of Arachidonic Acid (AA; C20:4 $\omega$ -6) and  $\alpha$ -Linolenic Acid (ALA; C18:3 $\omega$ -3), Eicosapentaenoic Acid (EPA; C20:5 $\omega$ -3) and Docosahexaenoic Acid (DHA; C22:6 $\omega$ -3), that belong to the  $\omega$ -3 family. LA is present in vegetable oils such as soybean, corn (maize) and sunflower. ALA is found in flaxseed and canola oil, while the main source of EPA and DHA in fish oil present in marine fish fat [1,2].

ALA may be converted to EPA and DHA. In mammals, this conversion occurs slowly, while in plants, as well as marine algae, it occurs efficiently. When fish consume seaweeds, they incorporate EPA and DHA in their tissues [3,4].

EPA, DHA and AA comprise phospholipids of cell membranes and are precursors of eicosanoids, which include Prostaglandins (PGs) and Leukotrienes (LTs) [5]. The eicosanoids formed by the AA, such as PGE<sub>2</sub> and LTB<sub>4</sub>, act as inflammatory mediators, while the eicosanoids formed by the EPA, as PGE<sub>3</sub> and LTB<sub>5</sub>, have less inflammatory activity [2].

Western diets are characterized by a higher intake of  $\omega$ -6 fatty acids compared to  $\omega$ -3 fatty acids, increasing the  $\omega$ -6/ $\omega$ -3 ratio. The high consumption of  $\omega$ -6 fatty acids increases the proportion of AA in membrane phospholipids and hence the formation of AA-derived eicosanoids such as PGs, LTs, Lipoxins and Thromboxanes (TX), resulting in a proinflammatory, prothrombotic and proaggregatory physiologic state [6].

The increased intake of  $\omega$ -3 fatty acids from fish oils or other seafoods has been associated to anti-inflammatory, hypolipidemic, antithrombotic and vasodilatory properties. When fish or fish oil is ingested, the EPA and DHA are incorporated into cell membranes, partially replacing the  $\omega$ -6 fatty acids, such as AA. EPA competes for the enzyme cyclooxygenase pathway and 5-lipoxygenase and inhibits the production of eicosanoids from AA, leading to a decrease in PGE<sub>2</sub>, LTB<sub>4</sub>, and TXA<sub>2</sub> (a potent platelet aggregator and vasoconstrictor) and an increase in PGE<sub>3</sub> and LTB<sub>5</sub> [5-7].

Olive oil is rich in oleic acid (C18:1 $\omega$ -9), a  $\omega$ -9 Monounsaturated Fatty Acids (MUFA). Oleic acid is converted to Eicosatrienoic Acid (ETA; C20:3 $\omega$ -9), which may also be incorporated into the phospholipid membrane, and is another substrate for the enzyme 5-lipoxygenase pathway forming LTA<sub>3</sub>, a strong inhibitor of the synthesis of LTB<sub>4</sub>. Oleic acid is known to modify immune and inflammatory responses [2].

Olive oil has numerous beneficial health effects that are not associated only to the oleic acid mechanisms of action, but also to its minor components, especially when the extra virgin olive oil is used. Extra virgin olive oil is produced under conditions that do not alter its properties (cold press), and retains important components such as tocopherols, polyphenols and bioflavonoids, which are known to have anti-oxidant, anti-inflammatory and anti-atherosclerotic properties. Refined olive oil loses much of these minor components during the process steps [8-12].

Diets rich in olive oil and marine oils have both been associated with reduced cardiovascular risk factors [13,14]. Moreover, recent studies have shown additional benefits in various health conditions when these oils are used in combination, indicating that olive oil could provide a favorable ambience for fish oil treatments.

In an animal model using apolipoprotein E-deficient mice, Eilertsen et al., 2011 [15] studied the antiatherogenic effect of extra virgin olive oil in combination with seal oil. The authors found that the combination produced a significant inhibition of atherosclerotic plaque formation in the aorta of female mice. In the male mice, the antiatherosclerotic effect was only significant in the thoracoabdominal region of the aorta. Although the authors did not study the effect of the oils individually, it was hypothesized that a synergistic effect occurred between marine PUFAs and the antioxidant compounds present in extra virgin olive oil. The authors also demonstrated that olive oil remarkably prevented the oxidation of n-3 PUFAs. The authors concluded that the co-supplementation inhibited arterial plaque formation and progression, particularly in female apoE-deficient mice [15].

Although sparse, some studies have been performed in humans. Vognild et al. [16], 1998 studied the effects of dietary marine oils and olive oil on fatty acid composition, platelet membrane fluidity, platelet responses and serum lipids in healthy subjects. The authors concluded that the combination of cod liver oil and olive oil could produce better effects on platelet function than the oils given separately [16].

Ramírez-Tortosa et al., 1999 found a significant decrease in plasma triglycerides and a protective effect on the LDL susceptibility to oxidative modifications after a 3-month intervention with extra virgin olive oil and fish oil in male patients. The authors hypothesized that phenolic antioxidants, such as  $\alpha$ -tocopherol present in olive oil could protect n-3 PUFA LDL from oxidation, which could occur in a setting of high consumption of n-3 PUFA alone [17].

Camuesco et al., 2005 studied the combined effect of olive oil and fish oil in colonic inflammation of rats with Dextran Sulfate Sodium (DSS-induced colitis). The authors found that the incorporation of fish oil, significantly decreasing colonic TNF- $\alpha$  and LTB<sub>4</sub> levels increased the beneficial effects of olive oil. The attenuation of colonic injury induced by DSS was more evident in the group treated with both fish oil and olive oil than the attenuation observed for the olive oil group [18].

Our group studied this synergistic effect initially in patients with rheumatoid arthritis [8] and thereafter in patients with metabolic syndrome [19].

Berbert et al., 2005 found that improvements in several clinical parameters related to rheumatoid arthritis were more evident and precocious when fish oil supplements were used in combination with olive oil, rather than receiving fish oil alone. The authors hypothesized that olive oil provided additional decrease in inflammatory activity since minor components of the oil such as tocopherols and polyphenols have high antioxidant and anti-inflammatory potentials [8].

Venturini et al., 2015 conducted a 90-day trial to verify if the combined intake of fish oil and olive oil had synergistic effects on lipid profile and oxidative stress parameters in patients with the metabolic syndrome. The authors found a significant decrease in LDL-C and TC/HDL, LDL/HDL ratios in the group receiving both fish oil and olive oil. The group receiving fish and olive oils also showed an increase in the antioxidant defenses, measured by an increase in the total antioxidant plasma capacity and a decrease in the prooxidant state, measured by an increase in lipid peroxidation and Advanced Oxidation Protein Products levels (AOPP). The results indicated a synergistic effect between fish oil and olive oil. The authors associated the decrease in prooxidant markers to a decrease in the proinflammatory status provided by the fish oil supplementation in addition to the antioxidant effects of polyphenols present in the olive oil [19].

Although some studies suggest that olive oil may act synergistically with fish oil by increasing the incorporation of n-3 fatty acids in cell membranes [20,21], there is a clear need for more basic studies to verify the molecular pathophysiological mechanisms behind this synergistic action.

Studies investigating the co-supplementation of olive oil and fish oil remain scarce. Therefore, more randomized, placebo controlled clinical trials are needed to confirm a synergistic effect between the two oils and the mechanisms of action involved. However, the available studies collectively indicate that fish oil and olive oil have complementary mechanisms that result in better effects on than the oils given separately.

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