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Omega-3 fatty acids: a novel resort against gastrointestinal injury

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Abstract. – The integrity of gastric barrier derives from the balance between defending and damaging factors. In particular, prostaglandins play a relevant role in the maintenance of gastric homeostasis and prevention of peptic disease, at different levels. Omega-3 fatty acids, particularly eicosapentanoic acid, are the precursors of the third series of prostaglandins (with anti-inflammatory properties), also reducing the formation of the second series of prostaglandins (pro-inflammatory ones). Such a pathophysiological rationale brought to the experimental application, both in animal models and, more recently, in humans, of omega-3 fatty acids against gastrointestinal damage.

Omega-3 fatty acids have shown interesting results in preventing different types of gastric damage in mouse models. A large retrospective case-control study on patients taking both anti-thrombotic therapy and eicosapentanoic acid showed (although only at unadjusted analysis) an inverse correlation between consumption of eicosapentanoic acid and gastrointestinal injury. Prospective, well-designed, comparative studies are warranted to clarify if omega-3 fatty acids may represent, or not, a novel resort against gastrointestinal injury.

Key Words:
Omega-3 fatty acids, Prostaglandins, Gastrointestinal injury, Gastric barrier, Cyclooxygenases.

Omega-3: General Considerations

Fatty acids are classified, according on the number of double bonds found in their side chain, in three groups: polyunsaturated, monounsaturated and saturated fatty acids. Polyunsaturated fatty acids include both omega-3 and omega-6 fatty acids. Overall, fatty acids have two ends, one, with a carboxylic acid (-COOH), considered the beginning of the carbon chain, so called "alpha", and another with a methyl (CH3) group, called "omega" to indicate the tail of the carbon chain. The position of the first double carbon bond, counted from the omega-end, indicates the nomenclature of fatty acids (e.g. omega-3, omega-6, et cetera).

Omega-3 fatty (also named n-3 or ω-3) acids are polyunsaturated fatty acids that display a double bond at the third position from the end of their carbon chain (C=C). The most important types of omega-3 fatty acids for humans are: alpha-linolenic acid (ALA), eicosapentanoic acid (EPA), docosahexaenoic acid (DHA). ALA can be converted to EPA and consequently to DHA by a desaturase enzyme[1].

DHA and EPA are commonly found in fish, squids, eggs, whereas common sources of ALA are represented by vegetable oils, especially those from sea-buckthorns, walnuts, clary, berry, algae, flax-seeds, chia, hemp). Food intake of omega-3 changes both among different populations and within the same Country[2]. Actually, common diet of Paleolithic man was higher in omega-3 content than now[3]. In Western dietary lifestyle, omega-3 fatty acids are indeed underrepresented compared to omega-6 (ratio 1:20)[2].

Omega-3 fatty acids have been widely investigated in mainstream medicine. Several guidelines suggest their introduction in diet to foster cardiovascular health[4,5]. Consumption of omega-3 fatty acids has been also associated with a lower prevalence of some types of malignancies[6,7]. As a consequence, several market claims advocate the dietary intake of omega-3 fatty acids for the prevention of both cardiovascular and cancer risk. However, the initial enthusiasm for omega-3 fatty acids is currently being curbed by recent evidences. In a recent meta-analysis, pooling together a large number of studies and patients, omega-3 fatty acids showed no efficacy in protecting from cardiovascular diseases[8]. Furthermore, a systematic review of literature found no evidence for a role of omega-3 fatty acids in cancer prevention[9].

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Omega-3 fatty Acids Against Gastrointestinal Injury: Pathophysiology and Rationale

The integrity of gastric barrier derives from the balance between defending and damaging factors. Protective mechanisms can be divided in three groups, depending on their site of action: pre-epithelial, epithelial, post-epithelial. Pre-epithelial barrier is constituted by gastric mucus, which is rich in bicarbonate and spreads out protecting the gastric mucosa from intraluminal content and harmful substances. Epithelial barrier is composed of intercellular junctions, particularly tight junctions, and epithelial cells. Post-epithelial barrier consists mainly of the endothelial microvascular blood flow, that carries nutrients and oxygenated blood, and of the proliferation of stem cells that provides the reconstitution of the epithelium; this mechanism is regulated by prostaglandin E2, survivin, and other growth factors. Other factors participate to the regulation of mucosal balance, including the vagal stimulation, several hormones and releasing factors (such as gastrin, ghrelin, steroids, cholecystokinin, thyrotropin-releasing factor, corticotropin-releasing factor)[10]. In particular, prostaglandins play a relevant role in the maintenance of gastric homeostasis and prevention of peptic disease, at different levels: first by the synthesis of bicarbonate and mucus, then by regulation of vessel permeability and blood flow. Prostaglandins derives from the oxidation of essential fatty acids (dihomo-γ-linolenic acid or DGLA, arachidonic acid or AA, eicosapentanoic acid or EPA) by cyclooxygenases. Prostaglandins are grouped in three series, depending on the number of double bonds in the fatty acid from which they derive. Both the first and the third series have an anti-inflammatory action, prevent platelet aggregation, enhance blood flow, whereas the second series plays a pro-inflammatory role. Both the first and the second series derive from omega-6 fatty acids: DGLA is the parent compound of the first series, whereas oxidation of its derivate AA by COXs brings to the formation of the second series of prostaglandins. Omega-3 fatty acids, particularly EPA, are the precursors of the third series of prostaglandins.

Cyclooxygenase-1 (COX-1) is known to be present in nearly all human tissues in health. In the gastrointestinal tract, it plays a gatekeeper role, through the production of anti-inflammatory prostaglandins. In reverse, cyclooxygenase-2 (COX-2) is involved in the regulation of inflammation by the formation of pro-inflammatory prostaglandins[12].

Inhibition of COX-1 activity and consequent reduction in the synthesis of prostaglandins represents indeed the main mechanism of gastric damage by nonsteroidal anti-inflammatory drugs (NSAIDs), although they can be harmful to our stomach also in a direct manner, through damage of epithelium. NSAIDs are, therefore, considered the second most important risk factor (after *H. pylori* infection) for the development of peptic disease worldwide[13]. Selective inhibitors of COX-2 have shown to reduce considerably, but not to erase totally, the risk of peptic ulcer development during chronic NSAIDs treatment[14].

Several points of evidence suggest omega-3 fatty acids as suitable protective agents against gastric damage. Generally, anti-inflammatory effects of omega-3 fatty acids are widely known. Both EPA and DHA have shown the ability to inhibit several proinflammatory interleukines, such as IL-1, IL-6, IL-12, TNF-alpha, and proinflammatory prostaglandins[15,16]. Anti-inflammatory properties of omega-3 have, therefore, been applied in several field of clinical medicine, especially rheumatology, with positive outcomes on joint pain[15,17].

More specifically, omega-3 fatty acids exert their anti-inflammatory role being directly involved in the metabolic pathway of prostaglandines. Both DHA and EPA, indeed, act as substrate for prostaglandins as well as arachidonic acid (an omega-6 fatty acid), with multiple protective effects[18]. First, they reduce the production of second series of prostaglandins, competing with arachidonic acid as substrate. Then, they drive directly the prostaglandin pathway to third series, that displays less mitogenic and proinflammatory properties than second series. Intake of fish oil resulted indeed in an increase of third series of prostaglandins in *in-vivo* studies[19-20]. Third series prostaglandins are less mitogenic and less efficient in inducing both COX2 and synthesis of IL-6[21].

Furthermore, oxidation of EPA reduces the expression of leukocyte adhesion receptor, through the activation of PPAR-alpha and the inhibition of NF-kB, preventing the interplay of leukocytes with the endothelium[22].

Such a pathophysiological rationale brought to the experimental application, both in animal models and, more recently, in humans, of omega-3 fatty acids against gastrointestinal damage.

Omega-3 Fatty Acids Against Gastrointestinal Injury: Current Evidences

Over the years, the role of omega-3 fatty acids in promoting the health of the gastric barrier has ben investigated, both in animal models and in human studies.

In 1992, Hunter et al[23] demonstrated that the chronic administration of fish oil (rich in eicosapentaenoic acid) is more effective than a control diet, in reducing the extent of gastric damage in a murine model of hemorrhagic gastritis induced by ethanol.

Also the acute administration of fish oil was protective against ethanol-induced gastric damage in rats[24].

Eicosapentanoic acid prevented epithelium damage also in a multiple mouse model of gastric injury, including mechanical (ligation of pylorus), chemical (NSAIDs and reserpine) and thermic stress[25].

Fish oil keeps the integrity of gastric epithelium both by inhibiting harmful factors (such as acid secretion) and by enhancing protective factors (mucus secretion, antioxidant enzymes activity)[26].

In a recent mouse model, docosahexaenoic acid in pure form showed comparable efficacy than omeprazole in preventing indomethacin-induced gastric damage. The protective effect of DHA appeared to be mediated by a decrease in gastric levels of B4 leukotriene[27].

According to Yu et al[28], omega-3 fatty acids may have a protective role for gastric mucosa also in counteracting apoptosis induced by oxidative stress, through the inhibition of apoptotic gene expression and the fragmentation of DNA.

Eicosapentanoic acid showed efficacy not only as a gatekeeper of the gastric mucosa, but also of the duodenum[29].

Collaterally, omega-3 fatty acids have shown to have a beneficial role against *H. pylori* infection. High dietary content in polyunsaturated fatty acids have been linked to the decrease of duodenal ulcer incidence[30]. Such phenomenon may have several explanations. Omega-3s also seem to have a role in gastritis *H. pylori*-related. In an *in-vitro* model, linolenic acid inhibited the growth of H. pylori in a temporary but significant fashion, and destroyed the bacterium at higher concentration[31]. Docosahexanoic acid showed similar results in a combined in-vitro/mouse model[32].

Also some data on humans are currently available. A large, retrospective, case-control Japanese study reviewed 3271 patients in anti-thrombotic treatment. Eighty-seven of them were taking eicosapentanoic acid at the same time. Overall, gastric damage (peptic ulcer or hemorrhagic gastritis) developed in 172 patients of which only 9 were taking eicosapentanoic acid. Such association was significantly protective at un-adjusted odds ratio (0.43; 95% CI = 0.20-0.84; p = 0.0207), although it has not been confirmed, however, by correcting the estimation based on multiple logistic regression (adjusted odd ratio = 0.62; 95% CI = 0:27-1:27, p = 0.2178)

Conclusions

Omega-3 fatty acids have been extensively investigated for both cardiovascular and cancer prevention, with unclear results. Because of their role in shifting prostaglandins production to anti-inflammatory avenues, they may play a role in protecting gastrointestinal epithelium against injuries. Several *in-vitro* and mouse models have showed excellent results in this direction. However, human studies lacks, and the way to go is long, although promising. Prospective, well-designed, comparative studies are warranted to clarify if omega-3 fatty acids may represent, or not, a novel resort against gastrointestinal injury.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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