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# The Role of Fish Oil Feeding Rich in $\omega$ -3 Polyunsaturated Fatty Acids in Patients with Sepsis and Septic Shock

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## Abstract

Different clinical studies have demonstrated that fish oil, rich in the very-long-chain  $\omega$ -3 polyunsaturated fatty acids (PUFAs), has immunomodulatory effects, suppressing the production of pro-inflammatory cytokines in diverse groups of critically ill patients. Moreover, such compounds have been found to attenuate the inflammatory response within 2–3 days upon parenteral administration. Recent experimental data suggest that activation of the cholinergic anti-inflammatory pathway constitutes a novel mechanism of such immune-regulatory effects. Since enhanced vagal tone has been associated with decreased cytokine secretion, novel monitoring tools of its activity at the bedside are needed, in order to evaluate nutritional manipulation of inflammatory response in the critically ill. The present chapter provides an overview of the mechanisms of action through which  $\omega$ -3 PUFA modulates immune response in critically ill patients suffering from sepsis and septic shock. Furthermore, it summarizes the current evidence regarding clinical effects from administration of fish oil rich in  $\omega$ -3 PUFAs in septic patients. Finally, it presents data that suggest the existence of a continuous interrelation between immune status and autonomic nervous system during systemic inflammation and proposes novel tools of autonomic nervous system monitoring at the bedside, in order to assess pharmacological manipulation of immune response by  $\omega$ -3 PUFAs in acute illness.

**Keywords:**  $\omega$ -3 fatty acids, lipid emulsions, sepsis, heart rate variability, enteral, parenteral, nutrition, critical care, autonomic nervous system

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## 1. Introduction

Acute systemic inflammation is the host response to various insults, such as infection, trauma, hemorrhage, etc., and is mediated by the release in circulation of different cytokines, such as tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-1 (IL-1), IL-4, IL-6, or IL-10 [1, 2]. Such mediators possess both pro- and anti-inflammatory properties. Furthermore, they are capable to activate the hypothalamo-pituitary-adrenal (HPA) axis and both the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS), which subsequently may affect the immune response [1].

However, safety mechanisms do sometimes fail, leading to a new continuum of disease—sepsis, septic shock, and multiple organ dysfunction syndrome (MODS). In this respect, patients develop nutrient deficiencies, which are associated with an increased risk of developing infections, organ failure, and death [3]. Consequently, artificial nutrition via the enteral or parenteral route is considered as an integral part of standard care. Recently, the concept of pharmaconutrition has emerged as an alternative approach, considering nutrition an active therapy rather than an adjunctive care [4]. Thus, specific nutrients have been designed to modulate the host immune response and suppress systemic inflammation. Moreover, lipid components of parenteral nutrition have been found to provide powerful bioactive molecules that may act to reduce inflammatory responses [5].

Different clinical trials have shown that fatty acids from fish oil can be considered as powerful disease-modifying nutrients in patients with acute lung injury and sepsis [6, 7]. Particularly, feeding with fish oil rich in the very-long-chain,  $\omega$ -3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) has been found to attenuate the production of different cytokines, chemokines, and other effectors of innate immune response [8]. In addition, the recent discovery of resolvins generated by EPA and DHA has shed more light on resolution of inflammation, as a possible mechanism of the anti-inflammatory actions of  $\omega$ -3 PUFAs during systemic inflammation [9]. However, oral administration of these compounds is required for several weeks to affect metabolic and inflammatory pathways in humans. Nevertheless, it has been recently demonstrated that intravenous administration of fat emulsions rich in  $\omega$ -3 PUFAs can lead to their rapid incorporation into phospholipids of different cells, such as platelets or monocytes, within the first 2 days of feeding, reducing serum pro-inflammatory cytokines over the next 7–8 days [10–12]. This may affect membrane fluidity, ion channel opening, or different signal pathways, leading to decreased production of TNF- $\alpha$  and IL-6 [8, 10]. The bypass of the intestinal process of absorption that is significantly delayed during critical illness could be another reason for such immediate effects.

## 2. Anti-inflammatory mechanisms of $\omega$ -3 PUFA

There are two types of naturally occurring essential fatty acids (EFAs) which cannot be synthesized in the body and need to be obtained in our diet, the  $\omega$ -6 series derived from linoleic acid (LA) and the  $\omega$ -3 series derived from  $\alpha$ -linolenic acid (ALA). Both the  $\omega$ -6 and  $\omega$ -3

series are metabolized by the same set of enzymes to their responsive long-chain metabolites. In general, the term EFA includes all unsaturated fatty acids. In this respect, all EFAs are PUFAs, but all PUFAs are not EFAs [13]. The major metabolic pathways of  $\omega$ -3 include (1) incorporation into triglycerides that are found in circulating lipoproteins; (2) incorporation into phospholipids of either circulating lipoproteins as well or part of cellular membranes; (3) be circulated as free (nonesterified) fatty acids (FFAs) in the plasma, mostly bound in albumin; and (4) undergo oxidation generating substrates for ATP synthesis.  $\omega$ -3 PUFAs incorporated in membrane phospholipids are capable to affect membrane fluidity and membrane-associated protein function. Furthermore, they can be cleaved by different phospholipases, giving rise to FFAs that subsequently are further oxidized to form various metabolites that are called eicosanoids (such as prostaglandins and leukotrienes) [8, 13]. These eicosanoids derived from EPA through different cyclo- and lipo-oxygenases are generally considered less pro-inflammatory in relation with their counterparts derived from the very-long-chain  $\omega$ -6 PUFA, such as arachidonic acid (AA). The major PUFA-derived mediators are lipoxins, resolvins, and protectins which are highly active and are involved in different physiological and pathophysiological processes. In this respect, experimental studies have shown that protectin D1 (PD1) reduces inflammatory infiltration, enhances phagocytosis of apoptotic neutrophils by macrophages, and, finally, increases macrophage migration to sites of antigen presentation. As a result, these metabolites seem to both inhibit the initiation of an overwhelmed inflammatory response and accelerate at the same time its resolution [8, 13].

The  $\omega$ -3 PUFA can also inhibit the activity of nuclear factor  $\kappa$ B (NF- $\kappa$ B), which is considered a pivotal pro-inflammatory transcription factor and induces the expression of many pro-inflammatory genes, mediating through the production of different cytokines, the innate immune response [8, 9].

### 3. $\omega$ -3 PUFA, the autonomic nervous system, and heart rate variability

Different experimental studies have confirmed that there is a continuous cross talk between the brain and the immune response to different inflammatory insults during both an acute and chronic inflammation. In this respect, it has been postulated that the brain may coordinate and affect at the same time the immune response. The first mechanism is based on the activation of vagus nerve afferent fibers, which convey the information that an inflammatory response takes place, through different mediators, such as cytokines [14–16].

Cytokines can activate visceral vagus afferent fibers which terminate within the dorsal vagal complex (DVC) of the medulla oblongata. The nucleus tractus solitarius (NTS) and the dorsal motor nucleus (DMN) of the vagus are part of DVC and give projections to hypothalamic paraventricular nucleus (PVN) that is responsible for the synthesis and release of corticotropin-releasing hormone (CRH), with subsequent production of adrenocorticotropin hormone (ACTH) from the anterior pituitary. ACTH is the main inducer of the synthesis of immunosuppressive glucocorticoids from the adrenal cortex. DMN that is connected with NTS is believed to constitute the main site of origin of preganglionic vagus efferent fibers. NTS is also connected to rostral ventrolateral medulla (RVLM), which increases noradrenergic preganglionic neurons' depolarization in the spinal cord [17]. In conclusion, the brain may alter the

immune response through the activation of both the sympathetic (SNS) and parasympathetic nervous systems (PNS), as well as the activation of the HPA axis. In this respect, the SNS may induce local inflammatory response through  $\alpha_2$ -subtype adrenoreceptor stimulation by nor-epinephrine (NE), in the early stage of inflammation. Nevertheless, stimulation of  $\beta_2$ -subtype adrenoreceptor-cAMP-protein kinase A pathway can also reduce pro-inflammatory cytokine production [18–20], suggesting that SNS activation can both protect the organism from the detrimental effects of pro-inflammatory cytokines and increase at same time local inflammatory response [21, 22].

Apart from the SNS, a link between the PNS of the ANS and immunoregulatory processes has been suggested. Thus, acetylcholine is capable to decrease TNF- $\alpha$  production from human macrophage cultures and immune cells located in the spleen upon stimulation with endotoxin, leading to its reduced release into the circulation. This effect is mediated by the specific  $\alpha 7$ -subunit of the nicotinic acetylcholine receptor [23–25]. Acetylcholine is also effective in suppressing other pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and high mobility group box 1 (HMGB1) [26].

A novel anti-inflammatory mechanism of lipid-diet immunosuppressive effects has been recently described by Luyer and colleagues [27]. They demonstrated that high-fat enteral nutrition was able to lead to attenuation of systemic inflammation in rats subjected to hemorrhagic shock, through stimulation of cholecystikinin (CCK) receptors and subsequent activation of the cholinergic anti-inflammatory pathway.

In this respect, Tracey has suggested that for the development of new monitoring tools of the  $\omega$ -3 PUFA effects upon the cholinergic pathway in the clinic, new surrogate markers are needed [28], such as heart rate variability (HRV) analysis that is the variability of R-R series in the electrocardiogram (ECG). HRV reflects both sympathetic and parasympathetic inputs upon the heart and can be estimated via frequency domain methods, which calculate the different frequency components of a heart rate signal through a fast Fourier transformation (FFT) of an R-R time series [29]. The method displays in a plot at least three peaks—fast periodicities [high frequency (HF), 0.15–0.4 Hz] which are largely due to the influence of vagal tone—and has the largest impact on HRV. Recently, it has been found that central muscarinic cholinergic stimulation (usually in the context of balancing cytokine production) is also accompanied by activation of the HF component of HRV and an instantaneous increase in total variability [30]. Low-frequency periodicities (LF, 0.04–0.15 Hz) are produced by baroreflex feedback loops, affected mostly by sympathetic modulation of the heart, and very low frequency (VLF) periodicities (less than 0.04 Hz) are related to vasomotor activity. The LF/HF ratio has been considered as a surrogate marker of sympathovagal balance [29, 31].

Studying physiological signals of critically ill patients can easily identify “hidden” information, which can estimate variability and information content (entropy) as a measure of complexity, within time series [32]. It has been suggested that such measures are significantly altered during critical illness and may predict different outcomes of interest, such as the onset of septic shock and late organ dysfunction [33]. In addition, implementation of variability analysis of physiological signals at the bedside might give rise to new markers of disease. Such “physiomarkers” are generally considered more appropriate for better and more accurate early warning signs for patients, since they can be easily measured at the bedside. On the contrary, it has been repeatedly demonstrated that various “biomarkers” such as cytokines



exhibit marked interdependence, pleiotropy (multiple effects), and redundancy (multiple cytokines with the same effect). At the same time, their plasma concentrations fluctuate from day to day and correlate poorly with classic physiologic variables in septic patients [33, 34].

Both LF and HF frequency components and overall HRV are significantly reduced in septic patients, whereas the degree of attenuation has been found to be prognostic of survival [22, 35]. The reduction in instantaneous HRV has been associated with an overproduction of cytokines [36], whereas pharmacological stimulation of the efferent vagus nerve has been found to increase the HF component of HRV and inhibit at the same time TNF- $\alpha$  secretion in septic animals [37]. Many studies have shown that oral supplementation of  $\omega$ -3 PUFAs increases instantaneous HRV, reduces LF/HF ratio, and confers protection against ischemia-induced ventricular tachycardia and sudden cardiac death [38, 39]. In this respect, Christensen and colleagues [39] demonstrated that fish oil feeding can induce an incorporation of DHA into the membranes of granulocytes that is associated with a dose-response increase in HRV and may protect against serious ventricular arrhythmias. In a recent study [40], the intravenous administration of fish oil with  $\omega$ -3 PUFAs, before endotoxin injection in healthy volunteers, was able to blunt fever response and sympathetic stimulation and enhance vagal tone, estimated with HRV analysis. This reduction was associated with a significant decrease in plasma norepinephrine and adrenocorticotropin hormone (ACTH) levels. Such effects of fish oil reflect an enhanced efferent vagal activity via a central-acting mechanism due to a possible suppression of pro-inflammatory cytokines, which have been found to inhibit central vagal neurons [8, 41].

However, different interventional studies on  $\omega$ -3 PUFAs and HRV in patients with heart disease have found inconsistent results, with only 8 out of the 20 trials published so far, supporting a beneficial effect on HRV [42]. Thus, Mozaffarian et al. [43] found that individuals with the highest fish consumption ( $\geq 5$  meals/week) exhibited 1.5 ms greater HRV than those with the lowest fish consumption. Moreover, this modest reduction in HRV was associated with only a 1.1% reduction in the relative risk for sudden cardiac death. As we have stated elsewhere [44], "reasons for such inconsistency might include heterogeneous populations, limited sample sizes or different study protocols with variable administered doses of  $\omega$ -3 PUFA and length of intervention." Furthermore, "different methods of measurement of HRV with variable time of recordings could be an additional confounder" [42–44]. Another potential limitation of such measures could be associated with the fact that a reduction in pacemaker funny current rather than an alteration in autonomic neural output was found to be responsible for heart rate reduction and increase in HRV in an animal study with administration of  $\omega$ -3 PUFAs [45]. Nevertheless, a potential impact of autonomic tone on HRV cannot be evaluated in this study since experiments were performed in denervated hearts.

In conclusion, an association has been suggested between increased HRV and fish oil administration in different groups of patients with cardiovascular diseases [38, 39, 42]. However, the possible relationship between HRV changes and inflammatory markers during fish oil feeding has not been studied yet, in septic patients. Thus, we think that a promising approach could be the assessment of the relationship between vagal activity estimated with HRV and inflammatory markers in septic patients, during parenteral fish oil feeding. In this case, we assume a beneficial effect of  $\omega$ -3 PUFAs on HRV and cytokine response, early in the course of disease.

## 4. Clinical studies

In Europe there are currently three available lipid emulsions containing  $\omega$ -3 fish oil for IV administration: Omegaven (Fresenius Kabi, Germany) that is a 10% fish oil emulsion supplement; Lipoplus/Lipidem (B Braun, Germany) that contains a mixture of 50% medium-chain triglycerides (MCT) and 40% soybean oil (SO) that is rich in  $\omega$ -6 PUFA, such as LA and 10% fish oil; and Smoflipid (Fresenius Kabi, Germany) that is a four-oil mixture of 30% soybean oil, 30% MCT, 25% olive oil, and 15% fish oil [13].

Numerous studies in critically ill patients have found favorable effects of  $\omega$ -3 fish oil on different aspects of inflammatory response. Mayer and colleagues [10] randomized 21 septic patients requiring parenteral nutrition to receive an IV lipid emulsion rich either in  $\omega$ -3 (Omegaven) or  $\omega$ -6 (Lipoven) PUFAs. They were able to show that the first group within 2 days of infusion demonstrated a rapid incorporation of  $\omega$ -3 fatty acids into mononuclear leukocyte membranes. In addition, fish oil rich in  $\omega$ -3 was found to suppress generation of pro-inflammatory cytokines from mononuclear leukocytes upon ex vivo stimulation with endotoxin. Heller and colleagues [46] demonstrated that IV  $\omega$ -3 PUFA administration (Omegaven) in 661 surgical critically ill patients improved survival and reduced infection rates, antibiotic requirement, and length of stay in a dose-dependent manner. Moreover, IV fish oil was found safe, conferring significant clinical benefits when administered in doses between 0.1 and 0.2 gr/Kg/day. In two other studies evaluating fish oil parenteral administration in surgical patients admitted to the Intensive Care Unit (ICU), it was found that although a short-term (<5 days) administration influences immune parameters, postoperative administration may further reduce length of stay and infectious complications in the ICU [12, 47]. In this respect Braga et al. concluded that  $\omega$ -3 should be given prior to surgery in order to enhance their anti-inflammatory effects in the postoperative period [48].

Barbosa et al. [11] evaluated the effects of IV fish oil administration (Lipoplus) for 5 days in 25 septic ICU patients. They found a significant decrease in IL-6 plasma concentration, reduced hospital length of stay and amelioration in gas exchange during the sixth day of stay in the ICU.

In 2014, Manzanares and colleagues [49] after aggregating six randomized controlled trials (RCTs) evaluating the effects of parenteral fish oil on relevant clinical outcomes in a heterogeneous group of critically ill patients were able to demonstrate a significant reduction in mortality and duration of mechanical ventilation. In 2015, the same group of researchers, after analyzing data from 10 RCTs involving 733 patients, was not able to find any survival benefit from parenteral fish oil feeding in septic patients [50]. Nevertheless, a reduction in the incidence of infections and a trend toward reduced duration of mechanical ventilation and length of stay in ICU were reported. Furthermore, intravenous fish oil feeding exhibited a nonsignificant trend toward reduced mortality. Since conflicting data have been originated from other systematic reviews and meta-analyses [51, 52] “low sample size and heterogeneity of the cohorts included do not permit a final recommendation on the use of  $\omega$ -3 PUFAs as a pharmaconutrient strategy in septic ICU patients” [50].

The European Society for Clinical Nutrition and Metabolism (ESPEN) Guidelines on Parenteral Nutrition in Intensive Care has suggested that both EPA and DHA can affect cell membranes and,

subsequently, reduce the intensity of inflammatory response. As a result, fish oil-enriched lipid emulsions might decrease duration of hospitalization in critically ill patients [53]. Canadian recommendations also endorse the use of fish oil-enriched lipid emulsions when parenteral nutrition is indicated [54]. Finally, the American Society for Parenteral and Enteral Nutrition (ASPEN) in its recently published guidelines cannot recommend fish oil parenteral feeding in critically ill patients at this time, due to lack of availability on the market of these products in the United States, despite approval by the FDA in 2013 [55]. Nevertheless, it considers as appropriate its future administration either in patients with septic shock who are candidates for parenteral nutrition due to hemodynamic compromise, such as hypotensive (mean arterial blood pressure < 50 mm Hg); patients for whom catecholamine agents (e.g. norepinephrine, epinephrine) are being initiated and patients for whom escalating doses are required to maintain hemodynamic stability; or surgical postoperative patients who are not eligible for enteral nutrition (e.g. short bowel) [55].

Different studies have also assessed potential differences between SO and fish oil lipid IV fat emulsions in septic patients. In a recent systematic review of 12 RCTS including 806 patients by Manzanares and colleagues, no significant difference in outcome benefits was found [56]. In another meta-analysis of eight RCTS involving 391 patients by Palmer et al. [52], a significant reduction in hospital length of stay was demonstrated by nearly 10 days in those receiving  $\omega$ -3 fish oil in relation with either SO-based or SO + MCT-based lipid emulsions. However, no differences were seen between groups with regard to ICU length of stay, infectious complications, and mortality. The strongest evidence in favor of fish oil PUFAs than SO-based lipid emulsions comes from small observational studies [55]. In this respect, data collected from an International Nutritional Survey showed a significantly lower ICU length of stay, reduced duration of mechanical ventilation, and reduced ICU mortality in septic patients receiving fish oil PUFAs when compared with SO-based lipid emulsions [57].

Another issue that has been tested in different RCTs is associated with safety and tolerability. Recently, a meta-analysis of 23 trials involving 1503 patients receiving long-term parenteral nutrition with IV fish oil found no evidence of any deleterious effects [58]. Consequently, ESPEN Guidelines on Parenteral Nutrition in Intensive Care suggests that lipids and essential fatty acids should be an integral part of the regimen to provide energy and should be administered at a rate of 0.7–1.5 gr/Kg over 12–24 h [53].

Considering enteral administration of lipid emulsions rich in  $\omega$ -3 PUFAs in critically ill patients with sepsis and septic shock, strong evidence is still lacking. While early studies and meta-analyses suggested reduced infection rates, ICU length of stay, and duration of mechanical ventilation, in both medical and surgical patients in a general ICU [59], Heyland and colleagues found a modest reduction in hospital length of stay, particularly in medical patients [60]. Furthermore and according to ASPEN Guidelines, current evidence does not support the use of enteral fish oil administration, particularly in medical ICU patients, due to heterogeneity of studies, variety of experimental and commercial lipid formulations, variable dosage of individual components, and increased costs [55]. Finally, two recent meta-analyses showed that the effect of fish oil lipid emulsions on mortality in septic patients was not influenced by the route of administration (enteral vs. parenteral) [50, 61].



## 5. Conclusions

Many experimental studies have confirmed that  $\omega$ -3 PUFAs possess different anti-inflammatory properties. Either through effect on membrane fluidity with subsequent attenuation of cytokine production or through indirect activation of the cholinergic anti-inflammatory pathway (immunoreflex), fish oil lipids have demonstrated immune-regulatory activities in different experimental settings. As a result, different investigators have evaluated their role in different groups of patients exhibiting systemic inflammation, such as surgical or septic patients treated in the ICU. However, extreme heterogeneity in patients' populations, route of administration, doses and duration of therapy, as well as commercially available products limits generalizability of results derived from numerous systematic reviews and meta-analyses. Consequently and since the current evidence is still too weak and sparse to make recommendations about the role of fish oil in the treatment of the critically ill, we suggest that HRV could be adopted as end point for monitoring nutritional manipulation of inflammatory response at the bedside, helping translation of basic science results into successful randomized controlled trials. In this case, we assume that  $\omega$ -3 PUFAs upon parenteral administration will be rapidly incorporated into the phospholipid membranes of different immune cell types, reducing the inflammatory response and increasing HRV.

In this respect, 24 h recordings and longitudinal changes of HRV in two groups of septic patients with similar severity of disease and receiving parenteral nutrition with the same volume of glucose, nitrogen, and fat but different lipid composition could be tested. In the case that HRV metrics predict outcomes of interest, such as lower infection rate and/or attenuated organ dysfunction, such a study might identify a unique value of HRV analysis as a monitoring tool of inflammatory modulation by fish oil feeding, in septic patients. Another potential use of HRV in artificial nutrition of septic patients as has been suggested by Tracey [62] could be its adoption as a physiomarker to early identify patients with reduced vagal tone. In this case, a susceptibility to increased inflammation can be assumed, whereas HRV metrics might serve as an early alarm to identify patients who might benefit from pharmacological stimulation of the cholinergic anti-inflammatory pathway, such as  $\omega$ -3 PUFAs [62].

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