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Review Article

Nutrition Section

Omega-3 Fatty Acids as an Adjunct Therapy in Sepsis: Insights and Implications: A Narrative Review

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ABSTRACT

Sepsis is a severe condition that affects a vast number of people globally, irrespective of their underlying health status. Sepsis arises from a disproportionate immune response to infection, leading to life-threatening organ dysfunction. This dysfunction is assessed using scoring systems like the Sequential Organ Failure Assessment (SOFA), where a score increase of two points or more signifies a high mortality risk in infected patients. Despite advances in critical care, mortality rates remain high, emphasising the need for novel therapeutic strategies. Inflammation, marked by mitochondrial dysfunction, oxidative stress and cytokine release, is central to sepsis, causing cellular damage and organ failure. Omega-3 Fatty Acids (FAs), Polyunsaturated Fatty Acids (PUFAs) essential for human health, have emerged as potential candidates due to their anti-inflammatory and immunomodulatory properties. Omega-3 FAs can positively influence SOFA scores. The mechanisms underlying the therapeutic effects of omega-3 FAs in sepsis are complex and multifaceted. These FAs may exert their beneficial effects by modulating the inflammatory response, attenuating oxidative stress, improving endothelial function. Neurological outcomes, such as improved Glasgow Coma Scale (GCS) scores, have also been reported. Importantly, it is associated with shorter hospital stays and reduced time on Mechanical Ventilation (MV). In conclusion, omega-3 FAs appear to be promising adjunct therapy for sepsis. While further research is needed to fully elucidate their mechanisms of action and to establish optimal dosing strategies, the available evidence suggests that these FAs may improve outcomes in patients with sepsis.

Keywords: C-reactive protein, Immune response, Inflammation, Length of stay, Organ dysfunction, Therapeutic agent

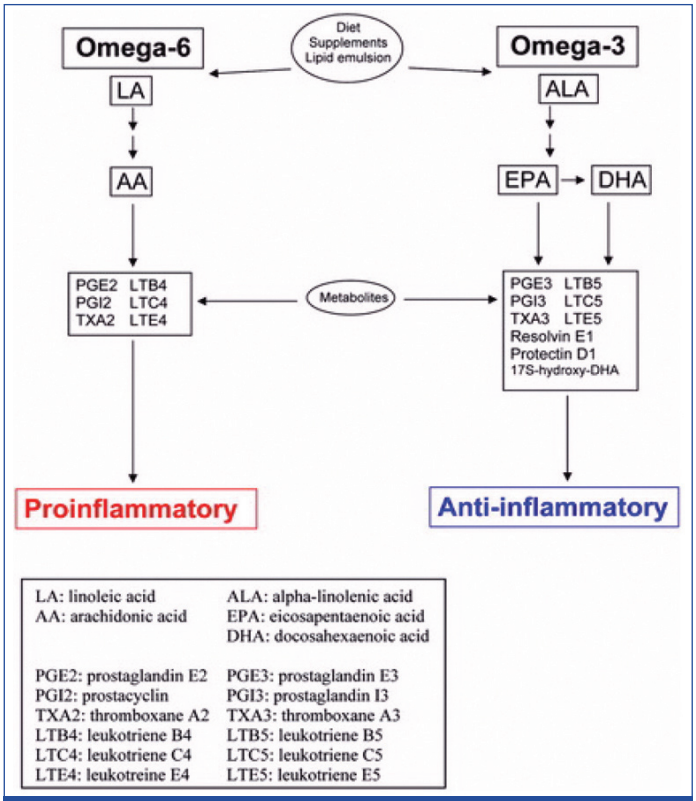
INTRODUCTION

Sepsis is a critical condition that adversely affects many lives regardless of any underlying health problems. In 2017, 48.9 million sepsis cases and 11 million related deaths were estimated, which was attributed to almost 20% of deaths worldwide [1]. Weiss SL et al., reported a global prevalence of 8.2% and 15.3% in Asia [2]. It is an inflammatory syndrome leading to aberrations in biochemical, pathological and physiological functions. As per sepsis 3 guidelines, sepsis is a condition characterised by life-threatening dysfunction of organs, stemming from an unbalanced body response to infection [3]. The severity of this dysfunction is evaluated by a scoring system that measures abnormalities based on clinical observations, laboratory results, or therapeutic intervention. Organ dysfunction manifests as a significant increase of two points or more in SOFA scores following the onset of infection [3]. The "SOFA score" is supposed to be zero in patients without any pre-existing organ dysfunction. A "SOFA score" of two points or more shows approximately 10% of the overall mortality risk in a patient with infection. An adapted and validated tool with age-adjusted parameters for severely ill paediatric patients was the "Paediatric SOFA (pSOFA)" score [4]. The hallmark of sepsis is inflammation characterised by mitochondrial dysfunction, oxidative stress and inflammatory cytokine release, leading to cellular damage and organ dysfunction [5]. During sepsis, pathogenic incursion of the bloodstream causes inflammation due to the circulating high levels of inflammatory cytokines. C-Reactive Protein (CRP), is considered a robust proinflammatory and anti-inflammatory that, helps in the eradication of pathogens [6].

Xiao C et al., stated the most prevalent dysfunction is the respiratory system which is 76.7%, followed by infected site, the abdomen, and the Central Nervous System (CNS) by 37.6%, 24.5%, and 12.7%, respectively [7]. On the other side, Weiss SL et al., and Watson RS et al., noted the respiratory system (40 and 37.2%) and haematologic system (19 and 25%) as the most common sites of infection [2,8], whereas, Jacobs RF et al., reported meningitis (49.7%) as the foremost root cause of sepsis [9]. The mortality rate remains high among the respiratory system (65.6%), cardiovascular system (30.5%) and renal system dysfunctions (18.3%) [10]. Implementations of large-scale clinical trials are necessary to improve early diagnosis, treatment and clinical management. Along with various medical and clinical interventions, nutrition intervention, plays a critical role in patient recovery and overall outcomes. Adequate energy, protein and micronutrients are essential for supporting the body's immune response, promoting tissue repair, and improving overall outcomes. Early nutritional intervention, enteral feeding whenever possible and individualised plans are key strategies to ensure optimal nutrition in sepsis patients. Many nutrients such as vitamins A, C, E, B6, and folic acid iron, copper, zinc and selenium, play an important role in sepsis, among them are omega 3 FAs [6,11].

Omega-3 FAs are polyunsaturated because their chain comprises several double bonds. The naming convention of FAs is determined by the position of its first double bond, starting from the tail. For omega-3 FAs, the initial double bond occurs between the third and fourth carbon atoms from the tail end. This essential nutrient should be consumed regularly through food. It can be found in fish such as sardines, salmon, tuna, halibut and other seafood such as algae and krill [12]. Omega-3 FAs have the potential to mitigate inflammation and could contribute to reducing the risk of chronic conditions such as cancer, heart disease, arthritis, diabetes, Alzheimer's Disease (AD) and stroke [13]. It also regulates blood pressure, haematic clotting, glucose tolerance and nervous system development and functions. Among omega-3 FAs, there are α-Linolenic Acid (ALA), Eicosapentaenoic Acid (EPA), and Docosahexaenoic Acid (DHA). Omega-3 FAs are also named vitamin F from FAs [12].

Research in critical care regarding the clinical and biological effects of lipids has emerged and intervened enterally as well as parenterally during critical illness, especially Omega-3 FAs which have anti-inflammatory properties [14]. These lipid emulsions have mainly omega-3 i.e., EPA and DHA with small amounts of omega-6 and arachidonic acid [Table/Fig-1] [15]. Over the last decennary, there has been increasing attention on the function of Omega-3 FAs and their influence on the formation of inflammatory cytokines and eicosanoids, particularly in septic patients. New studies have shown that omega-3 PUFAs can enhance the stability of cell membranes, regulate immune function, inhibit hyperinflammatory responses, and decrease the occurrence of Systemic Inflammatory Response Syndrome (SIRS), Multiple Organ Dysfunction Syndrome (MODS), and infection-related complications [16-18].



[Table/Fig-1]: Omega-6 and omega-3 FAs metabolites [15].

This review aims to address this gap by comparing the effects of omega-3 FAs on different organ systems and across various sepsis conditions. Additionally, it will provide valuable insights for developing evidence-based guidelines for omega-3 FAs supplementation in sepsis patients. Therefore, this review study has been conducted to explore the potential of omega-3 FAs in modulating immune function, reducing inflammatory cytokines, and improving different organ functions involved in sepsis including the Length of Stay (LOS). The present study focused on exploring the effect of Omega-3 FAs on different organs involved in sepsis and other related outcomes such as SOFA score, LOS and CRP.

Sepsis and its Complications

Sepsis is a life-threatening condition caused by a dysregulated host response to infection, leading to widespread inflammation, immune dysfunction and potential organ failure. Its complications impact various organ systems, including Acute Respiratory Distress Syndrome (ARDS) in the lungs, Acute Kidney Injury (AKI), cardiovascular dysfunction with septic shock and hepatic dysfunction due to impaired perfusion and inflammation. These effects are mediated by an exaggerated release of proinflammatory cytokines, endothelial dysfunction and microvascular thrombosis [3,19,20]. Omega-3 FAs, such as EPA and DHA, exhibit potent anti-inflammatory and immunomodulatory properties. Their mechanism of action involves modulating membrane phospholipids to produce less-inflammatory lipid mediators like resolvins and protectins while reducing proinflammatory cytokines [21,22]. These effects mitigate sepsis-induced organ damage by preserving endothelial integrity, reducing oxidative stress and enhancing immune resolution. Emerging evidence supports omega-3 supplementation as an adjunctive therapy in managing sepsis, although further clinical studies are needed to confirm its therapeutic efficacy [22,23].

Benefit of Omega 3 FAs on Hospital Length of Stay (LOS)

In a meta-analysis by Koekkoek WK et al., trials examining omega-3 FAs-enriched enteral nutrition in critically ill patients revealed significant reductions in both Intensive Care Unit (ICU) LOS and duration of ventilation. High-quality trials demonstrated a marked decrease in ICU LOS, whereas low-quality trials showed only a trend toward reduction. Importantly, neither overall nor subgroup analyses found significant effects on mortality. Two meta-analyses have independently assessed the methodological quality of the included studies in their meta-analysis using a 14-point scoring system based on Cochrane Collaboration criteria where key assessment components included random-sequence generation, allocation concealment, blinding, completeness of outcome data and selective reporting. Studies scoring between 9 and 14 were classified as high quality (level I), while those scoring 0 to 8 were categorised as low quality (level II). Any disagreements in assessment were resolved through consensus [19].

In a systematic review by Pradelli L et al., the use of omega-3 FAs-containing Parenteral Nutrition (PN) was compared to standard PN and was linked to notable reductions in the Relative Risk (RR) of infection, Hospital LOS (HLOS) and ICU LOS for critically ill ICU patients. Moreover, the overall costs of hospital episodes were lower with omega-3 FAs-containing PN than with standard PN. These findings underscore the significant statistical and clinical enhancements in patient outcomes associated with omega-3 FAs-containing PN [20].

Impact of Omega 3 FAs on C-Reactive Proteins (CRP) and SOFA Score

The SOFA score is a widely used tool to assess the severity of organ dysfunction in critically ill patients, particularly those with sepsis according to sepsis-3 definition [3]. It is a six-point scoring system that evaluates the dysfunction of six major organ systems: Respiratory system (PaO_2/FiO_2 ratio); Cardiovascular system {Mean Arterial Pressure (MAP), platelets and vasopressors}; Renal system (Creatinine); Liver system (Bilirubin); Coagulation system; CNS (GCS score). Each organ system is assigned a score based on the degree of dysfunction, with higher scores indicating more severe organ failure. The total SOFA score is used to predict the risk of mortality, with higher scores associated with a higher risk of death. SOFA score <2 gives Low risk of mortality, SOFA score 2-3 for Intermediate risk of mortality while SOFA score ≥4: High risk of mortality [5]. Omega 3 FAs have been reported to have the potential to reduce the SOFA scores as per the recent research data.

In a 2013 study by Hosny M et al., the potency and safety of omega-3 FAs and antioxidants in septic patients were investigated. Group-A intervened with a high dose of omega-3 FAs along with a fixed dose of antioxidants, Group-B received a lower omega-3 FAs dosage for seven consecutive days, and the control group received conventional sepsis treatment only. Follow-up was performed for all groups for inflammatory markers, SOFA scores, the necessity for organ supportive measures, ICU LOS, 28-day mortality, final outcomes and complications. In comparison to the control group, patients in Group-A exhibited significantly lower levels of CRP, IL6, and Procalcitonin (PCT) on day 7. Additionally, Group-A patients demonstrated significantly reduced requirements for and shorter durations of MV, and a decreased incidence of severe sepsis as indicated by mean and peak SOFA scores, with no notable

differences in the need for vasopressors and haemodialysis. However, comparing the low dose of omega-3 FAs plus antioxidants group to the control group using the same parameters yielded insignificant results [21].

Ibrahim ES, studied the impact of enteral omega-3 FAs on critically ill septic patients and it was found that during ICU stay the CRP levels and leukocytic count were high in the control group. A lesser incidence of organ and haemodynamic failure was observed in the experimental group. The ICU SOFA score was elevated, and the length of ICU stay was also prolonged in the control group. However, post-ICU hospital stays were similar in both groups. There was no variation in the count of patients requiring MV. Similarly, there were no distinctions observed in terms of ICU and hospital survivors [22].

Role of Omega 3 FAs on Organ System Involved in SOFA Score

Cardiovascular system: Cardiovascular dysfunction is a common sequel of sepsis. It is commenced by the mediators of sepsis causing abnormalities of the cardiac physiology and additional disruption to the normal homeostatic and reflex responses. MAP refers to the average pressure within the arteries throughout one cardiac cycle, derived from both systolic and diastolic blood pressure measurements. It is regarded as a superior indicator of perfusion to vital organs compared to systolic blood pressure.

Mechanisms are in place to ensure that the MAP remains at least 60 mmHg in adults so that blood can effectively reach all tissues [Table/Fig-2] [15,16,23-46], Doaei S et al., and Greer J, [16,23] for MAP only. Arrhythmogenesis is a feature of cardiovascular dysfunction in sepsis [23].

Consuming marine/fish omega-3 FAs consistently demonstrates antiarrhythmic effects. This intake enhances cellular membrane fluidity, inhibits L-type calcium channels and decreases the likelihood of arrhythmic events during vulnerable periods. Evidence indicates that maintaining an omega-3 FAs index of approximately 8%, achievable by consuming omega-3-rich seafood up to five times weekly or ingesting over three grams of EPA and DHA daily, offers the most effective protection against arrhythmic events [24]. In a randomised double-blind clinical trial, Continuous Ambulatory Peritoneal Dialysis (CAPD) patients were randomly assigned to either the omega-3 FAs or the placebo group. The conclusion of this study indicates that omega-3 reduced BP significantly but had no impact on lipid profile in the CAPD patients. There were no notable variances among the two groups in mean changes in serum triglyceride, total cholesterol, high-density lipoprotein and low-density lipoprotein [25]. The result of epidemiological studies shows that omega-3 FAs decrease the risk of coronary heart disease, hypertension, and stroke, and their complications [47,48]. Omega-3 FAs exert pleiotropic cardiometabolic effects with a diverse range of actions including effects on lipids, blood pressure, cardiac and vascular function, eicosanoids, coagulation and immunological responses [26]. In a case-control study done by Pedersen J et al., the intake of EPA and DHA as reflected in adipose tissue content is inversely associated with the risk of myocardial infarction [27].

Larsen B et al., study demonstrated the impact of lipid emulsion incorporating Fish Oil (FO) on inflammatory markers and LOS. The 32 newborns planned for open-heart surgery with cardiopulmonary bypass, were intervened with an intravenous lipid emulsion with

Author name	Place/Year of study	Study design	Sample size	Intervention	Findings
Cardiovascular system					
Greer J, [23]	USA, 2015	Review	N/A	Observed cardiac dysfunction in sepsis	Cardiovascular dysfunction in sepsis often includes arrhythmogenesis; Omega-3 FAs exhibit antiarrhythmic properties and stabilise heart rhythm.
Dinicolantonio JJ and O'Keefe JH [24]	USA, 2019	Review study	N/A	Omega-3 FAs intake from marine sources	Antiarrhythmic effects by reducing calcium channel activity, with optimal intake reducing arrhythmic risk.
Naini AE et al., [25]	Iran, 2015	Randomised double-blind clinical trial	40 CAPD patients	Omega-3 supplementation vs. placebo	Omega-3 FAs reduced blood pressure significantly, but no effect on the lipid profile in CAPD patients.
Simopoulos AP, [26]	USA, 2002	Epidemiological study	N/A	Omega-3 FAs in diet	Omega-3 FAs reduces the risk of coronary heart disease, hypertension, and stroke, impacting blood pressure and cardiovascular function.
Pedersen J et al., [27]	Greece, 2000	Case-control study	100 myocardial infarction caes and 98 controls	EPA/DHA intake	EPA/DHA levels in adipose tissue were inversely associated with myocardial infarction risk.
Larsen B et al., [28]	Denmark, 2012	Randomised controlled trial	32 newborns	Lipid emulsion with/without Fish Oil (FO)	EPA/DHA-enriched lipid emulsion reduced TNF-α levels and shortened Length of Stay (LOS) in critically ill newborns undergoing heart surgery.
Doaei S et al., [16]	Iran, 2021	Randomised controlled trial	120 COVID-19 patients	Omega-3 supplementation	No significant effect on Mean Arterial Pressure (MAP) in COVID-19 patients aged 35-85 years.
Respiratory system					
Sheu C et al., [29]	Taiwan, 2010	Experimental study	736 ARDS cases	Analysis of sepsis and neutrophil function	Neutrophil accumulation, vascular hyper-permeability, and impaired oxygenation contribute to ARDS in sepsis-related cases.
Mayer K et al., [30]	Germany, 2003	Randomised controlled trial	28 critically ill patients	Parenteral Nutrition (PN) with EPA and DHA	Significant improvement in neutrophil function in patients receiving omega-3 enriched PN.
Doaei S et al., [16]	Iran, 2021	Randomised controlled trial	120 COVID-19 patients	Enteral Nutrition (EN) with EPA and DHA	No significant effect on O_2 saturation or neutrophil count after omega-3 supplementation.
Langlois PL et al., [31]	USA, 2019	Meta-analysis (12 RCTs)	N/A	Omega-3 FAs in enteral immune-modulatory diets	Improved PaO_2/FiO_2 ratios, reduced ICU LOS, and decreased Mechanical Ventilation (MV) duration in ARDS patients.
Abbasi E et al., [32]	Iran, 2021	Systematic review and meta-analysis	N/A	Omega-3 FAs, Gamma-Linolenic Acid (GLA), and antioxidants in ARDS patients	Significant improvement in pulmonary gas exchange, trends towards reduced ICU LOS, and MV duration in critically ill ARDS patients.
Kim JS et al., [33]	USA, 2020	Meta-analysis of population-based cohort studies	N/A	Higher DHA intake	Higher levels of DHA correlated with reduced hospitalisation risk due to ILD, lower mortality, and fewer lung abnormalities on CT scans.

Blood clotting function and Cell Blood Count (CBC)					
Doaei S et al., [16]	Iran, 2021	Randomised controlled trial	120 COVID-19 patients	Omega-3 FAs supplementation	Marginal improvement in lymphocyte count (p-value=0.05); no significant differences in Partial Thromboplastin Time (PTT), haemoglobin levels, or platelet count.
Alioglu B et al., [34]	Turkey, 2013	Prospective study	62 Children (aged 2-12 years)	FO supplementation	Increased platelet aggregation and secretion in children after FO supplementation, showing hyperaggregation.
Bach RR et al., [35]	USA, 1989	Double-blind placebo-controlled study	30 healthy adults	2.52 g/day omega-3 FAs vs. 1.26 g/day for 5 weeks	Decreased red blood cell rigidity, plasma viscosity, and systolic blood pressure in higher-dose omega-3 group.
Golanski J et al., [36]	Poland, 2021	Review	N/A	FO (6 g of EPA/day) vs. vegetable oil	Significant reduction in platelet adhesion; contradictory results in the effectiveness of omega-3 FAs in influencing coagulation. Higher doses may be needed.
Liver function					
Lee S et al., [37]	USA, 2007	Review study	N/A	Omega-3 FAs balancing n-6/n-3 ratio in sepsis	Suggests balancing omega-6/omega-3 ratio reduces inflammatory cytokine production, with potential benefits for cholestasis in viral hepatitis and sepsis-induced liver dysfunction.
Schmocker C et al., [38]	USA, 2007	Animal study (fat-1 mice)	N/A	Omega-3 FAs supplementation	Fat-1 mice with a balanced n-6/n-3 ratio showed reduced liver inflammation, decreased TNF-α levels, and less severe liver damage, suggesting the anti-inflammatory effects of Omega-3.
Lee SI et al., [15]	USA, 2009	Prospective cohort study	77 infants (18 on fish oil, 59 on soy oil)	FO-based lipid emulsion for PN-associated cholestasis	Significant reduction in triglyceride levels in infants receiving FO, while those on soybean oil had no change. FO was associated with improved liver function markers.
Badia-Tahull M et al., [39]	Spain, 2015	Retrospective study	53	FO-based PN in ICU patients with sepsis	Improvement in GGT, ALP, and ALT with FO-based PN supplementation. A positive association between FO and liver function improvement was observed.
Central Nervous System (CNS)					
Dighriri IM et al., [40]	Saudi Arabia, 2022	Systematic review	N/A	Omega-3 FAs ingestion	Omega-3 FAs increase brain blood flow by enhancing haemoglobin oxygen saturation and total haemoglobin concentrations. They also help inhibit neuronal cell death and reduce inflammation.
Erdman JW et al., [41]	USA, 2011	Review study	N/A	Omega-3 FAs (DHA and EPA) supplementation	Omega-3 FAs (especially DHA) serve as precursors to resolvins and protectins, which possess anti-inflammatory and neuroprotective properties that can reduce inflammation in the brain.
Serhan CN, [42]	USA, 2007	Review study	N/A	Omega-3 FAs-derived bioactive molecules (resolvins, protectins)	Resolvins and protectins are potent mediators that resolve inflammation, suggesting a therapeutic role for Omega-3 FAs in controlling inflammation and neuroprotection during sepsis.
Renal system					
Lauretani F et al., [43]	Italy, 2009	Population-based epidemiological study	N/A	Omega-3 FAs levels and creatinine clearance correlation	Low plasma PUFA levels correlated with a more significant reduction in creatinine clearance in dialysis patients over a 3-year follow-up.
Chung H et al., [44]	South Korea, 2015	Animal models	N/A	Omega-3 FAs supplementation	Omega-3 FAs supplementation reduced renal inflammation and fibrosis in animal models, suggesting a protective effect against kidney damage.
Doaei S et al., [16]	Iran, 2021	Randomised controlled trial	128	Omega-3 FAs supplementation	Creatinine levels significantly lower and urine output significantly higher in the intervention group, suggesting benefits for kidney function.
Hu J et al., [45]	China, 2017	Meta-analysis of 9 randomised controlled trials (RCTs)	444 CKD patients	High-dose omega-3 FAs supplementation	Lower risk of proteinuria and decreased risk of end-stage renal disease, though negligible effects on creatinine clearance and eGFR were observed.
Pluta A et al., [46]	Poland, 2017	6-month supplementation study	90 CKD patients, stages 1-3	Omega-3 FAs supplementation	Significant reduction in urinary MCP-1 excretion, suggesting a positive effect on kidney inflammation; no significant changes in eGFR, CRP, or serum MCP-1 levels.

[Table/Fig-2]: The influence of Omega-3 FAs on multiple organ functions during sepsis [15,16,23-46].
CAPD: Continuous ambulatory peritoneal dialysis; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; ARDS: Acute respiratory distress syndrome; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase (ALT); CRP: C reactive protein; MCP: Monocyte chemoattractant protein-1; eGFR: Estimated glomerular filtration rate

(experimental group) or without (placebo group) EPA and DHA. This study signified that EPA and DHA-enriched lipid emulsion decreases Tumour Necrosis Factor-α (TNF-α) levels in newborns and also showed a reduction in LOS with a significant time in the treatment group. Providing EPA and DHA in lipid emulsions may enhance the inflammatory response in critically ill newborns [28]. Doaei S et al., found no noteworthy effect on the MAP after the supplementation of omega-3 FAs was done on COVID-19 patients of age between 35 and 85 years [16].

Respiratory System

Lung dysfunction, known as ARDS or Acute Lung Injury (ALI) is frequently associated with sepsis. Sepsis-related ARDS is linked to a poorer outcome than non sepsis-related ARDS [29]. Neutrophils have been demonstrated to contribute in the dysfunction of organs. Neutrophil-mediated tissue injury, apoptosis and autophagy are also involved in sepsis-induced tissue injuries that are linked to ARDS. Vascular hyper-permeability and neutrophil accumulation lead to impaired oxygenation [49].

Mayer K et al., showed that EPA and DHA containing PN significantly improved neutrophil functions [30]. However, in Doaei S et al., study EN containing EPA and DHA had no significant impact on the O_2 saturation and neutrophil after the supplementation of omega-3 [16].

In a meta-analysis comprising 12 randomised control trials, the clinical benefits of omega-3 fatty intervention on gas exchange and patient clinical outcomes with ARDS were assessed. Langlois PL et al., concluded that incorporating omega-3 FAs into enteral immune-modulatory diets for critically ill ARDS patients may mitigate disease severity by enhancing both early and late ratios of arterial oxygen partial pressure (PaO_2) to a fraction of inspired oxygen (FiO_2). Additionally, marginal but substantial improvements were observed in ICU LOS and duration of MV [31]. A systematic review and meta-analysis by Abbasi E et al., found that omega-3 FAs with Gamma-Linolenic Acid (GLA) and antioxidants significantly improve pulmonary gas exchange and are related to a trend towards reduced ICU LOS and MV duration in critically ill ARDS patients [32]. In meta-analysis of population-based cohort studies, higher levels of DHA were correlated with a reduced risk of hospitalisation due to Interstitial Lung Disease (ILD), reduced mortality rates, and fewer lung abnormalities detected on computed tomography scans [33].

Blood Clotting Function and Cell Blood Count (CBC)

Activation of coagulation frequently occurs in severe infection and sepsis and may develop thrombosis. Supplementation with Omega-3 FAs may impact blood clotting function and CBC [50]. In a study, the lymphocyte count improved in the omega-3 FAs-supplemented group compared to the control group, although this outcome was marginally significant (11.59 vs. 11.80, F=4.08, p-value=0.05). However, no considerable differences were found in these groups in terms of Partial Thromboplastin Time (PTT), haemoglobin levels and platelet counts [16].

The platelet function in the paediatric age group was analysed by Alioglu B et al., the platelet aggregation tests were induced by a high dose of Adenosine Diphosphate (ADP), children aged between 2 and 12 years taking FO supplementation. The values were remarkably high in comparison with the values measured before the intervention of FO. The FO-supplemented group's values exhibited hyperaggregation and increased the secretion of platelets [34].

The antithrombotic and anti-inflammatory activity of omega-3 FAs has been observed in patients at risk of Venous Thrombo-Embolism (VTE) in a double-blind placebo-controlled study in 30 healthy subjects taking 2.52 g/day of omega-3 FAs as compared with 1.26 g/day for five weeks, the group with a higher dose of omega-3 PUFAs displayed decreased red blood cell rigidity, plasma viscosity and systolic blood pressure [35]. A study performed on healthy adults reported that FO (equivalent to 6 g of EPA/day), in compression to vegetable oil, significantly reduced platelet adhesion. In this research, they have focused on FAs and their metabolites on various components of the haemostatic system, in particular on blood platelets and endothelium. The results were contradictory, and some of them failed to report the beneficial effects of supplementing omega-3 FAs in the diet. A potential explanation could be the need to use higher doses of omega-3 FAs and a proper ratio of omega-3 and omega-6 FAs [36].

Liver Function

Sepsis-associated hepatic dysfunction is clinically recognised by jaundice or cholestasis and is caused by various underlying mechanisms such as the impairment of energy-dependent bile and bile acid transport by hypoxia, hypoperfusion, and overproduced cytokines. Sepsis triggers cholestasis through the release of inflammatory cytokines mediated by endotoxins, which disrupt cellular biliary transport. While preventing the infectious source is not always feasible, treating the resulting complications with omega-3 FAs could be beneficial. Balancing the omega-6/omega-3 ratio closer to 1:1 in cellular membranes could reduce substrate availability for inflammatory cytokine production, favouring anti-inflammatory mediators. This approach extends beyond sepsis-induced cholestasis; viral hepatitis, often marked by cholestasis, fibrosis and cirrhosis, may also benefit from omega-3 FAs, both directly and during acute inflammatory episodes [37].

In an animal study, Schmocker C et al., demonstrated milder inflammatory liver injury in fat-1 mice, which possess a balanced n-6/n-3 PUFA ratio. This was reported by a decrease in serum alanine aminotransferase levels and less severe histological liver damage. The diminished inflammatory response is interrelated with decreased plasma TNF-α levels and reduced hepatic gene expression of TNF-α, IL-1beta, IFN-gamma, and IL-6 in fat-1 mice. Consequently, there was a decreased rate of apoptosis in the livers of fat-1 animals, as indicated by DAPI-staining (diamidino-2-phenylindole). These results support the inflammation-suppressing effects of omega-3 FAs in the context of liver inflammation [38].

Lee SI et al., examined the effects of different lipid emulsions on PN-associated cholestasis in infants. Patients with PN-associated cholestasis who received treatment with a FO-based lipid emulsion (n=18) were prospectively monitored for triglyceride, direct bilirubin and albumin levels and compared to patients maintained on a soy-based lipid emulsion (n=59). It was observed that FO reduced the triglyceride levels after 20 weeks of intervention while there was no change in infants receiving soybean lipid emulsion. The impact of FO-based lipid emulsion on serum triglyceride, bilirubin and albumin levels in children with PN associated liver disease was observed. Omega-3 FAs are metabolised through beta-oxidation and typically broken down locally into short-chain FAs in the liver [15].

Badia-Tahull M et al., conducted a retrospective study in which variation of Liver Function Tests (LFT) was defined as the variation among values just before the first administration and values in the end of administration of FO. A multiple linear regression was carried out to study the association between PN-lipids (FO or vegetable) and the variation of each LFT. The following variables were used to adjust the lipid's effect in sepsis, and LOS in the ICU. There was Gamma-glutamyl Transferase (GGT), Alkaline Phosphatase (ALP) and Alanine Aminotransferase (ALT) improvement with FO PN-supplementation [39].

Central Nervous System (CNS)

While the full range of neurological problems in septic patients is not fully understood, dysfunction of the CNS caused by sepsis seems to be just as critical a sign of increased mortality as problems with the kidneys or lungs. Several potential causes of septic encephalopathy have been suggested, including tiny abscesses in the brain, imbalances in amino acid metabolism, changes in brain chemicals (neurotransmitters), and reduced blood flow and oxygen use in the brain.

In a systematic review by Dighriri IM et al., ingestion of omega-3 FAs exhibited an increase in blood flow in the brain as it leads to higher haemoglobin oxygen saturation and total haemoglobin concentrations, thus, suggesting an improvement in blood circulation in the brain. In the same review, they also focused on studies demonstrating dietary shortages of omega-3 FAs and how a decrease in brain DHA might cause changes in the neuronal membrane, change enzyme activity and electrophysiological qualities and change neurotransmission. Omega-3 FAs help to inhibit neuronal cell death. Moreover, they lower inflammation and affect brain functions [40].

EPA and DHA are also the precursors for resolvins, which bring about a programmed resolution of the inflammatory process. DHA serves as the precursor for synthesis of protectins that have anti-inflammatory and neuroprotective activities [41]. These chemical mediators, resolvins and protectins, are potent stereoselective agonists that control the duration and magnitude of inflammation, Serhan CN, reached to conclude that bioactive molecules open

new avenues and approaches to therapeutic interventions via accelerated resolution of inflammation [42].

Renal System

Sepsis can affect the kidneys in two ways. The first is if the infection that caused the sepsis begins in the kidney through a kidney infection or a bladder infection. The second is if the cascade of events from sepsis causes kidney injury. Sepsis has been recognised as the leading cause of AKI in critically ill patients. The diagnosis of AKI is currently based on an increase serum creatinine concentration and/or a decrease in urine output.

Lauretani F et al., conducted a population-based epidemiological study, examining the correlation between total plasma omega-3 FAs levels and changes in creatinine clearance. They enrolled older adult dialysis patients and concluded that patients with low total plasma PUFA levels experienced a more significant reduction in creatinine clearance on follow-up of over three years [43]. In animal models, recent studies showed that there may be an association between PUFA and the progression of Chronic Kidney Disease (CKD). Omega-3 FAs supplementation has been shown to reduce renal inflammation and fibrosis [44]. Doaei S et al., showed in their study that creatinine (1.29 vs 1.68, F=5.90, p-value=0.02) was significantly lower and the amount of urine excreted (2101 vs 1877.02, F=12.26, p-value=0.01) was significantly elevated in the intervention group as compared to the control group [16].

Hu J et al., conducted a study assessing the benefits and risks of omega-3 FAs supplementation in CKD patients. Many studies assessed parameters such as proteinuria, serum creatinine clearance rate, Glomerular Filtration Rate (GFR), and the occurrence of end-stage renal disease. The study comprises nine randomised controlled trials of 444 CKD patients, with follow-up durations ranging from 2 to 76.8 months. Comparing high-dose omega-3 FAs supplementation with no or low-dose supplementation, the analysis revealed a lower risk of proteinuria but negligible effects on serum creatinine clearance rate and eGFR. However, high-dose supplementation was associated with a decreased risk of end-stage renal disease. In summary, omega-3 FAs supplementation considerably lowers the risk of end-stage renal disease and slows down disease progression in CKD patients [16,44,45].

A study done to assess the effect of 6-month supplementation with omega-3 FAs on selected markers of inflammation in patients with CKD stages 1-3. A significant decrease in urinary Monocyte Chemoattractant Protein-1 (MCP-1) excretion in CKD (p-value=0.0012) and in the reference group (p-value=0.001) was found. CRP, serum MCP-1, and WBC did not change significantly. An increase in ALA was seen. The eGFR, EPA, and DHA did not change remarkably in the CKD group. The reduction of urinary MCP-1 excretion in the absence of MCP-1 serum concentration may suggest a beneficial effect of omega-3 supplementation on tubular MCP-1 production [46].

CONCLUSION(S)

This review concludes that supplementing Omega-3 FAs in critically ill patients with sepsis can significantly reduce mortality rates and help mitigate the progression of sepsis-related organ dysfunction. Therefore, Omega-3 FAs could be a valuable addition to the therapeutic strategies employed to manage sepsis, potentially leading to better survival rates and reduced organ dysfunction in affected patients. While existing research on omega-3 FAs in sepsis shows promise, limitations exist. Studies vary widely in methodology, patient populations, and interventions, potentially impacting results. Additionally, small sample sizes in some studies limit their conclusions. Future research should focus on larger, randomised controlled trials to establish optimal dosage, timing, and duration of supplementation. This will help clinicians make informed decisions and improve patient outcomes.

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