Omega-3 Fatty Acids and Covid-19: Prevention or Adjuvant Therapy?

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Abstract
The mechanisms of COVID-19 complications are multifactorial, including long-term tissue damages from direct viral attack, dysregulation of both immunity and ren-in-angiotensin-aldosterone system and coagulation system, unresolved systemic inflammation and oxidative stress. Omega-3 polyunsaturated fatty acids (omega-3 or n-3 PUFAs) might have favorable effects on immunity, inflammation, oxidative stress at different stages of SARS-CoV-2 infection. Omega-3 and their metabolites including specialized proresolvin mediators, have shown effects in reducing pro-inflammatory cytokines, accelerating the resolution of chronic inflammation and restoring tissue homeostasis, and therefore offer a promising strategy against COVID-19. This article will discuss the inflammatory condition during COVID-19 pandemic, focus on the mechanisms that may contribute to the likely benefits of omega-3 and provide potential recommendations to promote strategies for wellness.

Introduction
Comorbidities may predispose individuals to high-risk infective diseases such as SARs-CoV-2, with more severe complications, making interventions more complicated. An important comorbidity prone to infectious diseases, particularly to SARs-CoV-2 infection and to COVID-19, is obesity, an alarming pandemic that predisposes them to comorbidities, such as diabetes mellitus, hypertension or metabolic syndrome and that adds a higher risk for poor outcomes and mortality in case of impact with novel viruses. Recent studies suggest that omega-3 PUFAs may interact at different stages of SARS-CoV-2 infection, particularly in contrasting the viral entry and replication phases, where persistent viral infection may be responsible for the sustained inflammatory state of long COVID.

There is growing evidence for the beneficial effects of omega-3 PUFAs and their metabolites, namely specialized pro-resolving mediators (SPMs), including amelioration of uncontrolled inflammatory
In infected patients it was observed that omental adipocytes are hyper-responsive to TNF-α, by decreasing the mRNA levels of adiponectin, which is the antago-nist adipokine with anti-inflammatory activity, is inversely linked to the amount of adipose tissue in obese subjects: a low adiponectin level is correlated to higher inflammation and obesity: in particu-lar, adipose tissue constitutes an autonomous endocrine organ, releasing large amounts of "adipokines", bioactive peptides with a central role in vascular homeostasis, regula-tion of appetite, glucose and lipid metabolism, and immunity. Adipokines can target dif-ferent organs and influence phlogosis responses and can exert pro-inflammatory or an-ti-inflammatory actions. Leptin is the leading adipokine; it promotes the displacement of local macrophages in the white adipose tissue (WAT) determining a shift toward a pro-inflammatory profile and decreases regulatory T-cells, also inducing Th17 polariza-tion. Hyperleptinemia is a typical obesity marker, with leptin resistance upsetting the endothelial signals, contributing to a pro-inflammatory microenvironment, and pre-disposing to cardiac and vascular complications. Adiponectin, which is the antago-nist adipokine with anti-inflammatory activity, is inversely linked to the amount of adipose tissue in obese subjects: a low adiponectin level is correlated to higher inflamm-atory mediators (particularly CRP and IL-6) levels and to several obesity-related meta-bolic diseases. Adipocyte hypertrophy is correlated to unbalanced intracellular signaling: the c-Jun NH2-terminal kinase (JNK) and the nuclear factor-kB (NF-kB) path-ways are activated; enlarged omental adipocytes are hyper-responsive to TNF-α, while increas-ing the levels of both pro-inflammatory genes (TGF, TNF-α, PAI-1, IL-1, IL-6, MCP-1) and hypoxia response genes (glucose transporter 1, HIF-1, VEGF): this exacerbates the in-flammation in adipose tissue, contributing to obesity-related implications. This chronic inflammatory state creates a natural background predisposing obese subjects to negative outcomes if an additional inflammatory stimulus (such as a virus) is introduced. In H1N1 a link between obesity and higher mortality was evidenced for body mass index (BMI)>45 kg/m² (OR 4.2; CI 1.9-9.4). Most recently, these findings were supported during the COVID-19 pandemic: obesity tripled the risk of hospitalization of those infected with SARS-CoV-2. More than 30% adult COVID-19 hospitalizations had obesity as a comorbid condition. In a healthcare cost model, 20.3% of patients with BMI>40 kg/m² needed intensive care treatment, including invasive mechanical ventilation compared with 6.6% of those with BMI <25 kg/m². In infected patients it was reported not only the presence of dysregulated inflammation but also a pro-thrombotic state, with evidence of ve-nous thrombocytopenia/thromboembolism, renal failure, and disseminated intravascular coagulation in many ARDS patients. The patients with microthrombi showed more comorbidities such as overweight/obesity (64%), hypertension (62%), and cardiovascular disease (53%). Endothelial hyper-activation enhances signaling pathways and leads to the generation of vascular adhesion molecules and proinflammatory cytokines, ad-dressing inflammatory cells to both endothelium and underlying tissues. Further, both endothelium and adipose tissue produce plasminogen activator inhibitor-1(PAI-1): a higher levels of PAI-1 is typical of obesity and can determine hypofibrinolysis, thus con-tributing to poor outcomes in these patients. 

The Role of Inflammation and Obesity as a Comorbid Condition
A persistent pathological inflammatory process is generated during some comorbiditi-ies, such as diabetes mellitus, hypertension, metabolic syndrome and obesity: in particu-lar, adipose tissue constitutes an autonomous endocrine organ, releasing large amounts of "adipokines", bioactive peptides with a central role in vascular homeostasis, regula-tion of appetite, glucose and lipid metabolism, and immunity. Adipokines can target dif-ferent organs and influence phlogosis responses and can exert pro-inflammatory or an-ti-inflammatory actions. Leptin is the leading adipokine; it promotes the displacement of local macrophages in the white adipose tissue (WAT) determining a shift toward a pro-inflammatory profile and decreases regulatory T-cells, also inducing Th17 polariza-tion. Hyperleptinemia is a typical obesity marker, with leptin resistance upsetting the endothelial signals, contributing to a pro-inflammatory microenvironment, and pre-disposing to cardiac and vascular complications. Adiponectin, which is the antago-nist adipokine with anti-inflammatory activity, is inversely linked to the amount of adipose tissue in obese subjects: a low adiponectin level is correlated to higher inflamm-atory mediators (particularly CRP and IL-6) levels and to several obesity-related meta-bolic diseases. Adipocyte hypertrophy is correlated to unbalanced intracellular signaling: the c-Jun NH2-terminal kinase (JNK) and the nuclear factor-kB (NF-kB) path-ways are activated; enlarged omental adipocytes are hyper-responsive to TNF-α, while increas-ing the levels of both pro-inflammatory genes (TGF, TNF-α, PAI-1, IL-1, IL-6, MCP-1) and hypoxia response genes (glucose transporter 1, HIF-1, VEGF): this exacerbates the in-flammation in adipose tissue, contributing to obesity-related implications. This chronic inflammatory state creates a natural background predisposing obese subjects to negative outcomes if an additional inflammatory stimulus (such as a virus) is introduced. In H1N1 a link between obesity and higher mortality was evidenced for body mass index (BMI)>45 kg/m² (OR 4.2; CI 1.9-9.4). Most recently, these findings were supported during the COVID-19 pandemic: obesity tripled the risk of hospitalization of those infected with SARS-CoV-2. More than 30% adult COVID-19 hospitalizations had obesity as a comorbid condition. In a healthcare cost model, 20.3% of patients with BMI>40 kg/m² needed intensive care treatment, including invasive mechanical ventilation compared with 6.6% of those with BMI <25 kg/m². In infected patients it was reported not only the presence of dysregulated inflammation but also a pro-thrombotic state, with evidence of ve-nous thrombocytopenia/thromboembolism, renal failure, and disseminated intravascular coagulation in many ARDS patients. The patients with microthrombi showed more comorbidities such as overweight/obesity (64%), hypertension (62%), and cardiovascular disease (53%). Endothelial hyper-activation enhances signaling pathways and leads to the generation of vascular adhesion molecules and proinflammatory cytokines, ad-dressing inflammatory cells to both endothelium and underlying tissues. Further, both endothelium and adipose tissue produce plasminogen activator inhibitor-1(PAI-1): a higher levels of PAI-1 is typical of obesity and can determine hypofibrinolysis, thus con-tributing to poor outcomes in these patients.

Nutrients in COVID-19 prevention and Treatment
COVID-19 patients often suffer from harmful consequences (Table 1), because of a prominent systemic inflammation, with the outcome of COVID-19 patients being closely related to their
nutritional status. In this respect, an adequate intake of nutrients can be helpful in order to prevent the infection and support the immune system during COVID-19 acute phase, but also in the post-acute phase, thus contrasting the various long-lasting symptoms typical of the so-called “long COVID”. For example, vitamin C contrasts inflammation and stimulates the immune response by regulating both cytokine secretion and histamine release, decreases oxidative stress, and regulates of T and B lymphocytes differentiation/proliferation. Numerous observational studies demonstrated that insufficient levels of vitamin D are related to COVID-19 severity, in addition, patients treated with a high-dose cholecalciferol supplementation displayed faster negativization, decreased access to intensive care and increased survival among COVID-19 hospitalized patients than those without supplementation. Similarly, the glycoprotein lactoferrin can modulate the inflammatory process by inhibiting the production of proinflammatory cytokines and by regulating the expression of iron homeostasis proteins (such as ferritin, ceruloplasmin and transferrin receptor 1). Among the most helpful nutrients in the prevention and treatment of COVID-19, omega-3 fatty acids can play a pivotal role, as well as in the therapy of many inflammation-related diseases. Among the physiological processes of phlogosis resolution is the enzymatic conversion of omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into specialized pro-resolution mediators (including resolvins and protectins) participating in the resolu-tion of phlogistic status and helping solve the cytokine storm and COVID-19 associated complications.

Overview and Potential Role of Omega-3 in Covid-19

Immunomodulating Effect
A weak and ineffectual immune system often provides the chance for pathogens to bring severe illness. Omega-3 fatty acids, present in walnuts, flaxseeds and seafood (such as sardines, halibut, tuna, salmon, mackerel, but also in marine sponges, algae, crusta-ceans and krill), are responsible for numerous cellular functions such as signaling and cell-to-cell interaction. An adequate dietary intake of these polyunsaturated fatty acids can modulate the immune answer, by improving omega-6 and omega-3 ratio. Their anti-inflammatory action is mediated by the inhibition of both 5-lipoxygenase/leukotriene B4-B5 pathway and NF-kB pathway with a reduced expression of cell surface adhesion mole-cules and a reduced production of interleukins (IL-1 and IL-6) from neutrophils. Omega-3 were displayed to decrease the generation of pro-inflammatory cytokines from macrophages infected with Pseudomonas aeruginosa and to increase phagocytic ca-pacity of macrophages: in fact, microorganisms-mediated activation of the macrophage TLR4 signaling cascade depends on membrane lipid composition whose structures change after the incorporation of EPA and DHA. A 45-days double blind randomized study divided the healthy adult volunteers in two groups: placebo versus 3g DHA daily supplementation. The supplemented group showed a minor post-exercise stress-induced IL-2 release from peripheral mononuclear cells, this is certainly helpful in the resolu-tion of upper respiratory tract infections. Similarly, a 45-days 1.6g-1.8g daily supple-mentation displayed to enhance NK cell activity, reduce prostaglandins E2 levels and stimulate interferon-gamma secretion with a substantial immune reinforcement, potentially able to prevent and to mitigate COVID-19 infection. In the same way, an in-creased intake of omega-3 determines their increased incorporation into cell membranes, thus replacing arachidonic acid: this mechanism may enhance inflammation resolution in athlete post-exercise as well as in COVID-19 patients. Additionally, some potential antiviral activities of DHA-derived mediators have been reported: protectin D1 (a member of the class of specialized proresolving mediators generated by the oxygenation of DHA) and 17-HDHA (an autoxidation product of DHA) demonstrated to inhibit respectively influenza A and H1N1 viral replication in mice. Similar results were displayed against Zika virus, coxsakievirus and enterovirus with a significant viral load attenuation in human cells.

Antinflammatory Effect
A plethora of anti-inflammatory mechanisms have been attributed to omega-3 (Table 1). Firstly, they modulate the expression of adhesion molecules and inflammatory cyto-kines by activating anti-inflammatory transcription factors (PPARα/y) and stopping TLR4-mediated activation of NF-kB. Secondly, omega-3 are metabolized into
leukotrienes (with anti-inflammatory activities) by cyclooxygenases and lipoxygenases. Additionally, their metabolism produces proresolving mediators (Figure 1) with powerful antiphlogistic activities, especially resolvins, protectins and maresins: they inhibit the migration of polymorphonuclear cells and the generation of both reactive oxygen species and chemo-kines, stimulating tissue regeneration and restoration of tissue homeostasis, which may be really helpful in limiting cytokine storm during COVID-19. Further, an intersection between innate immune inflammatory and mitochondria has also been reported: the mitochondrial dysfunction can trigger uncontrolled inflammatory answers determining the secondary injury aggravation in COVID-19. At the same time the hypersecretion of inflammatory mediators triggers further intracellular cascades, altering mitochondrial functions: IL-6 and IFN-γ stimulate mitochondrial ROS production and determine mitochondrial membrane permeabilization until cell death; IL-1β and TNF-α inhibit mitochondrial oxidative phosphorylation and ATP production with exacerbation of cell injury. In this respect, omega-3 displayed overabundance of beneficial effects against inflammation in many trials. Rats on n-3 PUFA enriched diet presented a reduction not only in pulmonary microvascular permeability and lung neutrophil accumulation but also decreased concentrations of arachidonic acid-derived metabolites (such as prostaglandin E2 and thromboxane B2) in alveolar macrophages, compared to n-6 PUFA enriched diet. In another study, pre-incubation with DHA of rhinovirus-infected epithelial cells decreased the release of IL-6 and IFN-γ-inducible protein, and suppressed the virus-induced inflammation. In intensive care unit patients (with severe sepsis or septic shock requiring mechanical ventilation), a DHA enriched diet significantly ameliorated clinical outcomes with a lower mortality rate, in comparison to the control groups. Similarly, a high-dose EPA diet (9 daily grams for 7 days) was evaluated in early-stage sepsis. This meta-analysis evidenced a noticeable improvement in oxygenation of ventilated patients with acute respiratory distress syndrome. Further studies defined the benefit of EPA and DHA supplementation (from 4 to 6 grams per day) in severe COVID-19, inhibiting cytokine secretion and mitigating the inflammatory state. This anti-inflammatory activity could be particularly precious in high-risk populations with underlying health conditions, such as diabetes, obesity, hypertension, oncologic diseases and old age, which could trigger the detrimental outcome often associated with severe COVID-19.

![Fig.1](image)

**Fig.1**: The connection n-3 PUFAs, inflammation and COVID-19 outcomes: N-3 PUFAs can replace the pro-inflammatory arachidonic acid in cell membranes or be metabolized to specialized pro-resolving mediators (SPMs): this down-regulates the NF-kB pathways and inhibits the synthesis of pro-inflammatory cytokines.
Anti-Arrhythmic, Vasodilator and Anti-Thrombotic Effect

While systemic inflammation, respiratory complications and multi-organ dysfunction determine a noticeable morbidity and mortality, cardiovascular complications (such as myocarditis, acute myocardial infarction, dysrhythmias and thromboembolic accidents) during COVID-19 can also occur typically in older subjects with comorbidities. However numerous cases of large vessels occlusion were reported also in young patients because of significant coagulation anomalies, such as increased d-dimer, prolonged prothrombin time, and abnormal platelet levels. Omega-3 are known to contrast car-diovascular risk factors, such as hypertension, hyperlipidemia and abnormal heart rhythm reducing the risk of cardiac death for both hemorrhoidal or atrial fibrillation patients and healthy subjects without anamnestic cardiovascular diseases. In fact, they penetrate into cell membranes altering the lipid raft structure and function: this leads to improved intracellular organelle and cellular functions, higher arrhythmic thresholds, modified autonomic tone and attenuated hypertension. Their anti-arrhythmic action can be explained by different mechanisms: the modulation of L-type calcium, sodium and potassium channels, the inhibition of thromboxane generation, the capability to lower the plasmatric concentration of non-esterified fatty-acids, which had previously dis-played proarrhythmic activities. Additionally, omega-3 inhibit chemotactic answer of immune cells and adhesion molecules interaction/ expression on endothelial cells, thus contrasting the development of blood clots in vessels: this mechanism, together with the anti-inflammatory activity, can explain the anti-thrombotic properties of omega-3 (Table 1). These mechanisms, responsible for omega-3 anti-atherogenic effects, may contrast the development of blood clots in arteries during COVID-19, considering its pro-coagulant status and high risk of thromboembolic complications. Another research in a Japa-nese population evidenced that higher fish intakes were inversely associated with intrac-erebral hemorrhaging. Omega-3 may influence membrane fluidity, interacting with Peroxisome Proliferator-Activated Receptors (PPARs) and represent a substrate for lipoygenase, cyclooxygenase and cytochrome P450. As a result, n-3 PUFAs can induce he-modynamic modifications, improve endothelial function and arterial compliance, de-crease arrhythmias risk, and inhibit inflammatory pathways. Strong evidence suggests that DHA is more efficient in decreasing blood pressure, heart rate, platelet aggregation, and improving both the endothelial health and HDL/LDL ratio thus decreasing global cardiovascular risk, so that the daily supplementation of omega-3 can be recommended for cardiovascular prevention.

Impact on Respiratory System

The role of omega-3 in respiratory affections has already been evidenced in asthma and exercise-induced bronchoconstriction where the presence of epithelial injury and phlogosis in the airways was found. A decreased bronchial phlogosis due to an omega-3 dietary supplementation was clearly reported. For example, the low in-cidence of asthma and other chronic respiratory diseases in Eskimos may be due to the great intake of fat fish among this population. More specifically, a daily administra-tion of 3.2 grams of EPA and 2.0 grams of DHA for 3 weeks decreased the concentration of pro-inflammatory cytokines (IL-1β and TNF-α) in the sputum also displaying that both fish oil and anti-leukotrienes medication were independently effective in mitigating hy-perpnea-induced and exercise-induced bronchoconstriction as well as airway inflamma-tion. A randomized clinical trial evidenced that a high daily omega-3 dietary intake mitigated lung inflammation with a meliorated oxygenation in critical acute lung injury: the meta-analysis of outcome data displayed that the use of an inflammation-modulating diet in patients with acute respiratory distress syndrome increased ventilator-free days and significantly decreased mortality at 28-day interval. Similarly, an open-label trial showed the efficacy of parenteral nutrition with fish oil in modulating inflammatory re-sponse and cytokine production in patients with respiratory distress during sepsis: after 3 days the omega-3/omega-6 ratio was reversed with EPA and DHA prevalent over arachi-donic acid, and omega-3 incorporation into mononuclear leukocyte membranes. Addi-tionally, critical patients with acute lung injury and acute respiratory distress syndrome are prone not only to a major risk of sepsis but also to cardiac arrest: omega-3 can promote resolution of inflammation and precondition the heart against septic cardiomyopathy be-cause of their antioxidant and immuno-modulating activity.
Effect on the Renin Angiotensin Aldosterone System

Renin Angiotensin Aldosterone system (RAAS) has been focused on for several years because of its pivotal role in the physiology and pathophysiology of cardiovascular disease: it is involved in blood pressure regulation, fluid, and electrolyte balance through action on kidney and blood vessels. Angiotensin converting enzyme (ACE), is a critical regulator of RAAS by converting Angiotensin I (Ang-I) to Angiotensin II (Ang-II), which is the most powerful biologically active product of RAAS. Ang-II increases blood pressure stimulates aldosterone secretion, which results in sodium reabsorption and potassium excretion. However, a second ACE (ACE2) is a negative regulator of RAAS: it opposes the effect of ACE in the heart, kidneys, and lungs and converts Ang-II to Angiotensin, which is a vasodilator, antihypertrophic, antithrombotic peptide.\(^7\) In fact, in almost all the cardiovascular pathological conditions there is a disturbance in ACE/ACE2 ratio, usually due to a down-regulation in ACE2 levels.

Additionally, ACE2 serves as a receptor for SARS-CoV-2 entry into target cells by binding of the spike protein to ACE2 and a specific transmembrane serine protease 2 (TMPRSS2) required for the spike protein priming, which also leads to down-regulation of ACE2.\(^8\) Interestingly, poor outcomes of COVID-19 have been observed in patients with pre-existing cardiovascular diseases, who have already deficiency in ACE2 and increased ACE/ACE2 ratio.\(^8\)

Omega-3 supplementation was associated to a significant decrease in serum levels of both ACE/ACE2 ratio and ACE (Table 1), displaying that they may reduce susceptibility to COVID-19 and reduce disease severity and its complication.\(^8\)

### Table 1: Potential molecular mechanisms of omega-3 PUFAs on COVID-19 complications

<table>
<thead>
<tr>
<th>Target</th>
<th>Mechanisms</th>
<th>Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Specialized proresolving mediators Reduction of cytokine storm Reprogramming peripheral blood cell transcriptome</td>
<td>Phlogosis resolution</td>
<td>49-54</td>
</tr>
<tr>
<td>Immune dysregulation</td>
<td>Tissue damage</td>
<td>Innate immunity enhancement</td>
<td>38,40,41</td>
</tr>
<tr>
<td>Viral invasion</td>
<td>Inhibition of platelet aggregation</td>
<td>Reduced exacerbation of cell injury</td>
<td>52</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Inhibition of angiotensin-converting en-zyme Reduced angiotensin II formation Activation of endothelial nitric oxide synthase generation Suppression of TGF-beta expression</td>
<td>ACE2/Ang1-7 re-balance Ameliorated vasodilatation</td>
<td>79-81</td>
</tr>
<tr>
<td>ACE2/Ang1-7 imbalance</td>
<td>Increase of antioxidant enzyme</td>
<td>Antioxidant effects</td>
<td>78</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>Release of neurotransmitters with hy-potalamus-pituitary-adrenal axis effects</td>
<td>Reduction of chronic fatigue, depression and post-traumatic stress disorder</td>
<td>83</td>
</tr>
<tr>
<td>Psico-social impact</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

This review highlights the molecular mechanisms of omega-3 PUFAs mediated resistance against COVID-19 based on available evidence. In addition to preserving or repairing the brain structure and function by interacting with phospholipid metabolism and the known shift in the pattern of lipid metabolites to a more anti-inflammatory metabolite profile, omega-3 PUFAs and/or their biologically active metabolites have the potential to improve oxidative stress, and immune dysregulation; maladaptation of the RAAS and coagulation system; and psychosocial stress from changes in health, financial status, or social life. Despite these promising effects of omega-3 PUFAs, additional epidemiological, experimental, and RCTs are needed to test, validate, and translate these proposed effects in the context of long COVID.

The administration of omega-3 fatty acids in COVID-19 patients aims to target both the improvement of health status and the prevention of potential complications: their anti-inflammatory action can stimulate macrophage phagocytic effort, disable enveloped virus, modulate cell signaling, attenuate coagulopathy, shift the lipid metabolites towards an anti-inflammatory pattern and globally mitigate an uncontrolled immune response secondary to the infection.

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Conflicts of Interest

The authors declare no conflict of interest.

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