Review

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Overview and potential role of omega-3 in COVID-19

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Abstract

Obesity is a modifiable inflammatory commodity that has been linked to higher morbidity and mortality to those that contract novel viruses, such as H1N1 and SARS-CoV-2. Loss of life and the high cost of obesity highlights the need to focus on preventative measures. This article will discuss obesity as a crucial comorbid 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. ***Clin Ter 2024; 175 (5):346-351 doi: 10.7417/CT.2024.5124***

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Introduction

Comorbid conditions can predispose an individual to high-risk infectious diseases such as SARs-CoV-2, with increased severity in complications that make interventions more complex (1). An important comorbidity that has been linked to infectious diseases, particularly to SARs-CoV-2 infection and to COVID-19, is obesity (2). Obesity is a worldwide preventable and modifiable epidemic (3) with widespread long-lasting implications. The problem is escalating. Between 1975 and 2019, the prevalence of obesity increased in every country in the world. Obesity-related noncommunicable diseases account for over 5 million deaths globally each year, with over half occurring under the age of 70. The World Health Organization reported that the prevalence of overweight or obese children and adolescents aged 5–19 years increased more than four-fold from 4% to 18% globally from 1975 to 2019 (4). The multifactorial and chronic nature of overweight and obesity leads to economic impacts for individuals and nations. This alarming epidemic predisposes children and adults to additional comorbidities that include diabetes mellitus and hypertension that add a higher likelihood for poor outcomes and mortality with the introduction of novel viruses (1). Protective and supportive therapies may be helpful to improve COVID-19 patients' prognosis. In this respect, the beneficial effect of omega-3 PUFA (n-3 polyunsaturated fatty acids, n-3 PUFA) includes the reduction of uncontrolled inflammatory reactions, oxidative stress and coagulopathy as well. In the light of their favorable safety profile, it is rational to consider n-3 PUFAs as a potential preventive strategy or adjuvant therapy in order to improve COVID-19 patients' outcomes.

Obesity as a comorbid condition: the role of inflammation

Obesity seems to create a persistent pathological inflammatory process: adipose tissue constitutes an independent endocrine organ, releasing a great amount of "adipokines" (5), bioactive peptides with a pivotal role in vascular homeostasis, regulation of appetite, glucose and lipid metabolism, and immunity. Adipokines can target different organs and influence phlogosis responses and can exert proinflammatory or anti-inflammatory actions (6). Leptin is the leading adipokine; it promotes the migration of resident macrophages in the white adipose tissue (WAT) determining their shift toward a proinflammatory profile and decreases regulatory T-cells, also inducing Th17 polarization (7, 8). Hyperleptinemia is a typical obesity marker (9), with leptin resistance upsetting the endothelial signals, contributing to a proinflammatory microenvironment, and predisposing to cardiovascular complications (10). Adiponectin, which is the antagonist adipokine with antinflammatory activity, is inversely linked to the amount of adipose tissue in obese individuals (11): low adiponectin levels are associated with elevated inflammatory mediators (particularly C-Reactive Protein CRP and IL-6) and with numerous obesity-related metabolic diseases (12-15). Adipocyte hypertrophy is correlated to unbalanced intracellular signaling: the nuclear factor-kB (NF-kB) and the c-Jun NH2-terminal kinase (JNK) pathway are activated; enlarged omental adipocytes are hyper-responsive to TNF-α, determining adipokines over-excretion (16, 17). Also, oxidative stress and hypoxia (due to hypoperfusion of the expanding adipose tissue) contribute to the obese

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proinflammatory microenvironment (18, 19) by decreasing the mRNA levels of adiponectin, while increasing those of proinflammatory genes (PAI-1, TGF, TNF-α, IL-1, IL-6, MCP-1) as well as those of hypoxia response genes (HIF-1, glucose transporter 1, VEGF): these events exacerbate the inflammatory response in adipose tissue and contribute to obesity-related complications. This chronic proinflammatory state present in adipose tissue creates a natural background predisposing obese patients to poor health outcomes when another inflammatory condition (such as a virus) is introduced. In patients with H1N1, Louie et al (2) found a link between obesity and poor outcomes and higher mortality for those with body mass index (BMI) above 45 kg/m2 (OR 4.2; CI 1.9-9.4). Most recently, these findings were supported during the COVID-19 pandemic. The Centers for Disease Control and Prevention (CDC) reported that obesity tripled the risk of hospitalization of those infected with SARs-CoV-2.6 More than 30% adult COVID-19 hospitalizations had obesity as a comorbid condition (20). In a healthcare cost model, authors found that 20.3% of patients with BMI>40 kg/m2 required intensive care treatment, including invasive mechanical ventilation compared with 6.6% of those with BMI <25 kg/m2 (21). In infected patients it was reported not only the presence of dysregulated inflammation but also a pro-thrombotic state (22), with evidence of venous 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%) (23). Endothelial hyper-activation enhances signaling pathways and leads to the generation of vascular adhesion molecules and proinflammatory cytokines, addressing inflammatory cells to both endothelium and underlying tissues (24, 25). Further, both endothelium and adipose tissue produce plasminogen activator inhibitor-1(PAI-1): high levels of PAI-1 are typical of obesity and can determine hypofibrinolysis, thus contributing to poor outcomes in these patients (26, 27).

Nutrients and nutritional status in COVID-19

An adequate intake of nutrients can be helpful in preventing the infection and supporting the immune system during both COVID-19 acute and post-acute phase: some nutrients modulate the innate and acquired immune systems, thus playing a pivotal role in the relationship between immunity, infection, inflammation and tissue damage. In particular, a correlation between different dietary patterns and COVID-19 disease outcomes was observed (28, 29). The main nutrients used in the supplementation of the patient with COVID-19, for their function on the immune system and on the microbiota are: arginine (substrate essential for lymphocyte function), glutamine (activator of T lymphocytes), omega-3 fatty acids (with anti-inflammatory activity for the inhibition of NF-κB activity), nucleotides (activators of the phagocytic function of macrophages, useful for a correct synthesis of DNA and RNA), vitamins D, A, E and C, and the trace elements of selenium, copper and zinc, with anti-inflammatory activity (30,31). In a double-blind clinical trial on 43 COVID-19 patients, assuming 200 ml/day of a standard high-protein normocaloric supplement for 7 days or 200 ml/day of an immunonutrient enriched supplement with L-arginine, nucleotides, and omega-3 fatty acids for 7 days, they observed that in the experimental group, there was a greater reduction in C-reactive protein levels (23.6 (± 7.5) mg/L versus 14.8 (± 12.1) mg/L) than in the control group (32). In another study, 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 (33,34). 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) (35).

Impact of omega-3 PUFA in COVID-19

Immunomodulating and Antiphlogistic Effect

Anti-inflammatory medications, such as glucocorticoids and non-steroidal anti-inflammatory drugs, control mediators of inflammation but not without side effects, while an increase in molecules that promote endogenous resolution of aberrant inflammation, like the powerful resolvins, which are derived from omega-3 fatty acids, avoids the side effects. The omega-3-derived metabolites can regulate the native immune response of B and T lymphocytes and their cytokines, decreasing interleukin (IL)-2, tumor necrosis factor alpha (TNF-κ) and interferon-gamma (IFN-κ) secreted by CD8 positive T cells, control the differentiation of CD4+ T-cells into T-helper 1 (Th1) and Th17, and increase IgG production by B cells. The VITAL study (36) revealed that taking omega-3 fatty acids in combination with vitamin D can lead to a decrease in autoimmune diseases, as the two nutrients can work synergistically to reduce inflammation.

An adequate dietary intake of these polyunsaturated fatty acids present in walnuts, flaxseeds and seafood (such as sardines, halibut, tuna, salmon, mackerel, but also in marine sponges, algae, crustaceans and krill), improving omega-6 and omega-3 ratio, can modulate the immune answer (37). Their anti-phlogistic action is mediated by the inhibition of both 5-lipoxygenase/ leukotriene B4-B5 pathway and NF-κB pathway with a reduced expression of cell surface adhesion molecules and a reduced production of interleukins (IL-1 and IL-6) from neutrophils (38). Omega-3 PUFA were displayed to decrease the generation of pro-inflammatory cytokines from macrophages infected with Pseudomonas aeruginosa (39) and to increase phagocytic capacity 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 (40). 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 (41); this is certainly helpful in the resolution of upper respiratory tract infections (42). Similarly, a 45-days 1.6g-1.8g daily supplementation displayed to enhance NK cell

activity (43), reduce prostaglandins E2 levels and stimulate interferon-gamma secretion (44) with a substantial immune reinforcement, potentially able to prevent and to mitigate COVID-19 infection. In the same way, an increased intake of omega-3 PUFA determines their increased incorporation into cell membranes, thus replacing arachidonic acid: this mechanism may enhance inflammation resolution in athlete post-exercise (45) 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 (46). Similar results were displayed against Zika virus (47), coxsakievirus and enterovirus with a significant viral load attenuation in human cells (48). Omega-3 are metabolized into leukotrienes (with anti-inflammatory activities) by cyclooxygenases and lipoxygenases. Additionally, their metabolism produces proresolving mediators with powerful antiphlogistic activities, expecially resolvins, protectins and maresins: they inhibit the migration of polymorphonuclear cells and the generation of both reactive oxygen species and chemokines, stimulating tissue regeneration and restoration of tissue homeostasis (49), 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 (50) determining the secondary injury aggravation in COVID-19 (51). 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 (52). In this respect, omega-3 PUFA 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 (53). 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 (54). 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 (55). 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. The lower rates of organ failures and severe sepsis development were associated to reduced levels of CRP, IL-6 and procalcitonin (56) with a reduction of intensive care stay by about two days (57). 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 (58). This antinflammatory activity could be particularly precious in high-risk populations with underlying health conditions, such as diabetes, obesity, hypertension, oncologic diseases and old age (59), which could trigger the detrimental outcome often associated with severe COVID-19.

Recent studies of viral diseases, including COVID-19, clearly displayed improvement in symptom severity, recovery prognosis, and probability of survival with the use of omega-3 PUFA. The improvement on metabolic diseases associated with aging is also persuasive: their consumption improves lipids, fatty liver disease, obesity, cognitive function, and cardiovascular complications of chronic kidney disease. Omega-3 PUFA have also been shown to support an anti-inflammatory effect in older age and to have favorable effects on age-related disease's complications, frailty, and mortality. A healthy Omega-6/3 PUFA ratio should be targeted for the modulation of low-grade inflammation, as well as for the prevention of immune dysregulation and complications of uncontrolled inflammation triggered by infections, development, and progression of autoimmune disorders, and the consequences of oxidative stress due to aging.

Impact on Cardiovascular System

It is now well recognized that COVID-19 affects extrapulmonary organs, particularly the cardiovascular system. For example, cardiogenic shock has been increasingly observed in patients with COVID-19, owing to the various mechanisms involved and the affinity of the SARS-CoV-2 virus to cells comprising the cardiovascular system. The SARS-CoV-2 virus is known to cause direct myocardial injury and induce arrhythmias and acute coronary syndromes leading to acute heart failure: specifically, injury to the myocardium, as evidenced by elevated cardiac biomarkers, has been reported in up to 30% of hospitalized COVID-19 patients and up to 55% in those with pre-existing cardiovascular disease. Interestingly but not surprisingly, the magnitude of troponin elevations in these hospitalized patients is associated with poorer outcomes (61). Once the SARs-CoV virus enters myocytes, viral inclusions, and inflammatory cells such as macrophages, neutrophils, and lymphocytes follow. This viral-mediated infiltration can cause myocardial edema or myocarditis coupled with necrosis, resulting in dilated cardiomyopathy and heart failure. Studies have shown that myocarditis is present in up to 30% of patients with COVID-19 and those with myocarditis have poorer prognoses. The first case reports on cardiogenic shock in otherwise healthy males with a diagnosis of COVID-19 suggest that shock is induced by direct viral-mediated myocardial injury (62).

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 (63). Omega-3 PUFA are known to contrast cardiovascular risk factors, such as hypertension, hyperlipidemia and abnormal heart rhythm reducing the risk of cardiac death for both hemodialysis or atrial fibrillation patients and healthy subjects without anamnestic cardiovascular diseases (64). Their anti-arrhythmic action can be explained by different mechanisms: the modulation

of L-type calcium, sodium and potassium channels (65), the inhibition of thromboxane generation (66), the capability to lower the plasmatic concentration of non-esterified fatty-acids, which had previously displayed pro-arrhythmic properties (67). Additionally, omega-3 PUFA inhibit chemotactic answer of leukocytes and adhesion molecules interaction/expression on endothelial cells, thus contrasting the development of blood clots in vessels: this mechanism, together with the antinflammatory activity, can explain their anti-thrombotic properties. These mechanisms, responsible for omega-3 PUFA anti-atherogenic effects (68), may contrast the development of blood clots in arteries during COVID-19, considering its pro-coagulant status and high risk of thromboembolic complications (69). Another study in a Japanese population found that high intake of fish was inversely associated with death caused by intracerebral hemorrhaging (70). EPA and DHA can influence membrane fluidity, interact with Peroxisome Proliferator-Activated Receptors (PPARs) and other transcription factors and sterol regulatory element binding proteins, and are substrates for enzymes such as COX, lipoxygenase, and cytochrome P450 (71). As a result, n-3 PUFAs can induce hemodynamic changes, improve endothelial function and arterial compliance, decrease arrhythmias risk, and inhibit inflammatory pathways.

Impact on lung health

A decreased bronchial phlogosis due to an omega-3 dietary supplementation was clearly reported (73). A longitudinal study found that higher omega-3 fatty acid levels were associated with attenuated lung function decline in 15,063 participants, with the largest effect sizes for the most metabolically downstream omega-3 fatty acid, docosahexaenoic acid. An increase in DHA of 1% of total fatty acids was associated with attenuations of 1.4 ml/yr for FEV1 and 2.0 ml/yr for FVC and a 7% lower incidence of spirometry-defined airway obstruction (74). More specifically, a daily administration 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 hyperpnea-induced and exercise-induced bronchoconstriction as well as airway inflammation (75). A randomized clinical trial evidenced that a high daily omega-3 PUFA 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 (76). Similarly, an open-label trial showed the efficacy of parenteral nutrition with fish oil in modulating inflammatory response 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 arachidonic acid, and omega-3 PUFA incorporation into mononuclear leukocyte membranes (77). Additionally, critical patients with acute respiratory distress syndrome are also prone to cardiac arrest: omega-3 PUFA can promote resolution of inflammation and precondition the heart against septic cardiomyopathy (78).

Conclusion

Undoubtedly, nutrition is a key determinant of maintaining good health. Key dietary components such as vitamins C, D, E, zinc, selenium and especially omega 3 fatty acids have well-established immunomodulatory and anti-inflammatory effects, with benefits in infectious disease. The supplementation of these nutrients may be used as therapeutic modalities potentially to decrease the morbidity and mortality rates of patients with COVID-19, shifting towards an anti-inflammatory pattern of lipid metabolism and globally mitigating an uncontrolled inflammatory answer secondary to the infection.

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Conflicts of Interest

The authors declare no conflict of interest.

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