

Review Article

Role of OMEGA-3 Fatty Acid Supplementation in COVID-19 Patients: A Narrative Review

Zoia Akram^{1*}, Alekhya Allenki², Sindhu Kishore³, Dolly Ogwu⁴, Olufunlola Titilayo Adefalu⁵,
Antonia Lisseth Valle Villatoro⁶, Janet Adebukola Omole⁷, Giass Uddin⁸, Shwetha Gopal⁹,
Abdurrahman Mir Khan¹⁰, Maham Nuzhat Lodi¹¹, Tarab Shahbaz¹², Noor Ul Huda Nabeel¹³,
Lisandra Vega¹⁴, Usman Tariq¹³, Mireille B Nkongho¹⁵

¹Allama Iqbal Medical College (AIMC), Pakistan

²Nizam' Institute of Medical Sciences, India

³Jinnah Sindh Medical University (JSMU), Pakistan

⁴University of Benin, Nigeria

⁵Windsor University School of Medicine, Saint Kitts and Nevis

⁶Universidad de El Salvador, El Salvador

⁷Allsaints University College of Medicine, Saint Vincent

⁸Chittagong Medical College, Bangladesh

⁹Davao Medical School Foundation, Philippines

¹⁰Army Medical College, Pakistan

¹¹Jinnah Sindh Medical University (SMC), Pakistan

¹²Lahore Medical and Dental college (LMDC), Pakistan

¹³Bahria University Medical and Dental College (BUMDC), Pakistan

¹⁴American University of Antigua, College of Medicine, Antigua & Barbuda

¹⁵Saint James School of Medicine (SJSM), Saint Vincent

***Corresponding author:** Zoia Akram, Department of Internal Medicine, Allama Iqbal Medical College (AIMC), Pakistan

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Abstract

Novel coronavirus 2019 (CoV-2019), also known as acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic in early 2020. Since then it has continued to spread unabated and has essentially crippled humanity. The nutritional status of a person plays a huge role in his defense against viral infections. Given the evidence of the beneficial effects of n3-PUFAs on the immune system, we aimed to examine the impact of omega-3 supplementation in patients with COVID-19 and gathered data from PubMed. Limited data is available on the association between the two. We have discussed in detail the beneficial effects of n3-PUFAs on the immune system, focusing on their role in critically ill patients with COVID-19. Furthermore, we have also elaborated on the results of a RCT study aimed to see the association between PUFA use and COVID patients outcomes. We conclude that PUFA should be used as a supplementation in COVID patients. However, further studies are needed to fully understand the association.

Keywords: Novel Coronavirus 2019; Omega-3 Fatty Acids

1. Introduction

Novel coronavirus 2019 (CoV-2019), also known as acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic in early 2020 [1]. Since then it has continued to rage unabated and has essentially crippled humanity. Coronavirus is being considered a respiratory virus but other presentations are also possible, and some are frequently emerging [2]. The case fatality varies by age, with the most deaths occurring in patients over 70 years [3]. It has not only affected the mental health of the general public but has

also adversely affected the mental health of physicians involved in the care of these patients [4]. Studies have demonstrated that fulminant systemic inflammatory pathology and an accompanying coagulopathy instigated by SARS-CoV-2 infection, both contribute to severe disease [3], while hyper inflammation induced by COVID-19 is the main cause of death or end-organ dysfunction [5]. A pair of studies have shown unbridled viral replication, loss of ACE2 expression via shedding or retraction, antibody-dependent enhancement (ADE), imbalanced pro-inflammatory cytokine production, and dysfunctional cellular immunity to be the most prominent factors responsible for these lethal manifestations [6]. Hence, it is very important to understand the role immune modulation can play in decreasing the mortality and morbidity associated with COVID-19. Omega-3 fatty acids (OM3FAs) have a significant role in modulating immune pathways and they are postulated to play a role in modulating the immune system [7] that can help with COVID-19 infection.

Omega-3 fatty acids (OM3FAs) are unsaturated fatty acids. They have one double bond located between the third and fourth omega end carbon. These fatty acids mostly originate from plant sources but can also be found in fish, nuts, leafy green vegetables, and beans [7]. Omega-3 polyunsaturated fatty acids (PUFAs) that are most commonly used clinically include α -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). OM3FAs are approved by FDA for treatments of hypertriglyceridemia but studies are being conducted to evaluate their role in type 2 diabetes, cancer, dementia, and cardiovascular diseases. Multiple mechanisms are put forward that can explain their beneficial role in these diseases but

previous research has demonstrated that OM3FAs have anti-inflammatory actions [7]. These anti-inflammatory properties can modulate or inhibit several pathways such as those of leukocyte chemotaxis, adhesion molecule expression, cyclooxygenase (COX) activity, and its subsequent eicosanoid production like leukotrienes and prostaglandins from arachidonic acid, pro-inflammatory transcription nuclear factor kappa B (nuclear factor-kB) activation and proinflammatory cytokines (e.g., TNF-alpha, IL-1, IL-6) production. Inhibition or decreased production of these pro-inflammatory substances can decrease the inflammatory process. Similarly, OM3FAs are also known to activate additional pathways that can decrease the inflammatory process. These include increased production of inflammation settling resolvins, maresins, lipoxins, and protectins; activation of anti-inflammatory transcription factor NR1C3, PPARs and activation of G protein-coupled receptor-120 (GPCR-120).

Thus, OM3FAs have a significant role in modulating immune pathways and they can prove beneficial in viral diseases with the tendency of increased cytokine storms such as that with COVID-19. Omega-3 polyunsaturated fatty acids (n3-PUFAs) can also amplify anti-inflammatory responses [5]. Given the evidence of the beneficial effects of n3-PUFAs on the immune system, we aimed to examine the impact of omega-3 supplementation in critically ill patients with COVID-19. We gathered data from previously published randomized controlled trials and case reports for our review article.

2. Role of PUFA in Inflammation and Immune System

The nutritional status of a person plays a huge role in his defense against viral infections. A couple of studies have pointed out that malnourished individuals are more likely to get various infections. Proper nutrition makes

our immune system stronger. Nutritional deficiencies affect the immune response and lead to oxidative stress in the host which can change the genome of the pathogen so that a benign pathogenic virus can convert into a highly virulent one [8]. Omega-3 polyunsaturated fatty acids (n3-PUFAs) are moderators of inflammation and acquired immune responses and can amplify anti-inflammatory responses. Essential PUFAs that come from diet participate to control acute and chronic inflammations. They are metabolic precursors of pro-resolving lipid mediators (SPMs) and omega-3 long-chain polyunsaturated fatty acids (omega-3 LC-PUFAs) and help to improve the inflammatory balance. Omega-3 LC-PUFAs interact at different stages of the viral infection, notably on the virus entry and replication. Therefore, the nutritional status of PUFAs is particularly important in tissue inflammatory status and overall immune response [9]. Hence, it can be said that supplementing omega-3 LC-PUFAs to COVID patients can play a role to control inflammation. Omega-3 LC-PUFAs can help in the prevention of the cytokine storm, by decreasing the intensity of inflammation, and thus can reduce the risk of mortality in COVID-19 patients.

3. Use of PUFA as Adjunctive Therapy in COVID Patients

A total of four cases [10,11] were identified in the literature where any form of PUFA was given to the patients diagnosed with COVID-19. The first three cases [10] describe the use of icosapent ethyl (IPE) as a component of supportive treatments in ICU patients with moderate to severe COVID-19 pneumonia. The fourth case [11] describes a mother-daughter duo who developed COVID-19. Looking at the results, it can be said the PUFA should be considered with regular treatment of COVID as it is likely to have favorable outcomes. Cases are described as follows: A 75-year-old patient presented for an abscess but during hospital admission became COVID positive and developed

ARDS (acute respiratory distress syndrome) secondary to COVID-19. Two days after administration of icosapent ethyl (PUFA), inflammatory markers improved, and he was moved out from the ICU. With icosapent ethyl and antibiotics alone, the patient improved remarkably; quantitatively assessed by a reduction in levels of creatinine and CRP (C-reactive protein) and with the resolution of his tachycardia, tachypnea, and hypoxia [10]. In the second case, a 23-year-old man presented with ARDS and respiratory failure, secondary to COVID-19 infection. Inflammatory markers began trending down after administration of antiviral therapy, immunosuppressive therapy, and convalescent plasma but the patient was still being considered for intubation before administration of icosapent ethyl. Interestingly, 3 days after the addition of icosapent ethyl as an adjuvant, the patient's chest X-ray findings improved, and acute-phase reactants declined to near baseline levels. The patient benefitted initially with an immunosuppressive and antiviral regimen, followed by complete resolution of his chest X-ray findings and level of acute-phase reactants near baseline just 3 days after the addition of icosapent ethyl [10].

In the third case, a 24-year-old man was intubated for ARDS secondary to COVID-19. His case is notable in that he only demonstrated improvement primarily while taking icosapent ethyl as an adjunct during his ICU stay.

[10]. In the fourth case, a 53-year-old woman presented to the clinic after exposure to COVID-19. Her 21-year-old healthy daughter was also exposed at the same time. They did not have any symptoms at the initial presentation. Four days after being exposed, both patients developed fever up to 101F. Sore throat, nasal congestion, and cough developed the next day (2nd symptom day) and anosmia on the fourth day (4th symptom day) after the onset of fever. The patient was started on oral IPE (2g twice daily) on the 2nd symptom day. Her daughter declined IPE. They otherwise received only symptomatic care that did not differ between the two. Interestingly, fevers began to subside on the 2nd symptom day (SD2) in the mother, however, symptoms persisted on till SD4, and anosmia was also resolved on SD7. On the other hand, her 21-year-old daughter continued to experience sore throat, nasal congestion, and anosmia through SD18. She only had partial relief of symptoms on SD18. By that time, her mother's symptoms were completely resolved. This case presentation signifies the importance of PUFA in modulating the disease course. The two patients with similar genetic backgrounds were exposed in the same manner to COVID-19 and developed similar symptoms. The one treated with IPE as an adjuvant experienced much less severe symptoms later on and the symptoms resolved much earlier in the disease course [11]. Table 1 summarizes these case presentations.

Gender	Age	Pre-morbid	Initial presentation	Dose	Outcome
Male	75	Hyperlipidemia, Hypertension, Diabetes mellitus type 2 requiring insulin, Obesity, Benign prostatic hyperplasia	--	Icosapent ethyl 2 g twice a day by NG tube	Creatinine and CRP improved and pt was discharged from ICU in 2.5 days.
Male	23	Obesity, Diabetes	Presented to the ICU with acute	Icosapent	AKI resolution with

			kidney injury (AKI) and respiratory failure secondary to COVID-19.	ethyl 2 g twice a day by NG tube	improvement in overall status.
Male	24	Autism	Admitted to the ICU and intubated for respiratory distress and developed ARDS in the setting of COVID-19 pneumonia.	Icosapent ethyl	IPE appeared to be responsible for his improvement from septic shock, and ventilatory requirements were significantly decreased in just 3.5 days.
Female	53	Hyperlipidemia	Four days after being exposed to a confirmed COVID-19 case, both patients developed persistent fevers up to 101F and later sore throat, nasal congestion, and cough on 2 nd symptom day (SD2) and anosmia on SD4.	Oral IPE (2g twice daily).	Symptoms resolved faster and the condition improved in the patient treated with IPE.

Table 1: Illustrates four COVID patients treated with OMEGA fatty acids.

4. A Randomized Controlled Trial Assessing the Beneficial Effect of PUFA on COVID Patients

To the best of our knowledge, there is only one randomized clinical trial [8] that has been performed to study the effect of omega-3 fatty acids on COVID patients. It was carried out in Iran from May to July 2020 in critically ill patients infected with COVID. 128 patients were included in the study. The intervention group received one capsule of 1000 mg omega-3 daily, containing 400 mg EPAs and 200 mg DHAs for 14 days. This supplement was added to their enteral formula. Results of the study revealed that the intervention group had a significantly higher 1-month survival rate and higher levels of arterial pH, HCO₃, and Be (base excess). Furthermore, it also supports the hypothesis that omega-3 supplementation can improve the level of indicators of kidney function including BUN, Cr, K, and urine volume. The results also indicated a statistically insignificant increase in

lymphocyte count and GCS (Glasgow Coma Scale). The results are elaborated as follows:

- Effects of omega-3 supplementation on arterial blood gas (ABG) parameters
After 14 days, the levels of arterial pH (7.30 vs 7.26, F = 19.11, P = 0.01), HCO₃ (22.00 vs 18.17, F = 10.83, P = 0.01), and Be (-4.97 vs -3.59, F = 23.01, P = 0.01) were significantly higher in the intervention group compared with the control group. However, there were no significant differences in PO₂ and PCO₂ between the two groups [8].
- Effects of omega-3 supplementation on 1-month survival rate
The intervention group had a significantly higher 1-month survival rate compared with the control group (21% vs 3%, P = 0.003). About 21% (n = 6) of the participants in the intervention group and only about 3% (n = 2) of

the participants in the control group survived at least for 1 month after the beginning of the study [8].

- Effects of omega-3 supplementation on kidney function

Levels of BUN (35.17 vs 43.19, $F=4.76$, $P=0.03$) and Cr (1.29 vs 1.68, $F=5.90$, $P=0.02$) were significantly lower and the amount of urine excreted (2101 vs 1877 ml, $F=12.26$, $p=0.01$) was significantly higher in the intervention group compared with the control group [8].

Hence, it can be safely said that Omega-3 supplementation improved the levels of several parameters of respiratory and renal function in critically ill patients with COVID-19.

5. PUFA, COVID, and Kidneys

Renal abnormalities occur in the majority of moderate-severe COVID-19 patients. Mostly, a prothrombotic state in these patients leads to microemboli in renal vessels. Moreover, hypertension is induced by pro-inflammatory status, increasing IFN- γ , IL-6, and IL-17 expression, and CD8+T cells in the kidney. Angiotensin II-induced hypertension and the endothelial dysfunction caused by the innate immune response seem to be involved in kidney injury [8]. Hence, it is very important to identify therapies that can improve kidney function in patients with severe COVID-19. The RCT study found that the administration of omega-3 PUFAs significantly decreased BUN, Cr, and K and increased urine volume in ICU patients infected with COVID-19. These findings suggest that omega-3 supplementation may be protective against the progression of renal impairment. Other studies performed in non-COVID patients have also demonstrated that higher dietary intake of PUFAs may improve creatinine clearance [12]. In contrast, some studies have shown opposite findings. Higashihara et al.

assessed the effects of omega-3 PUFAs on kidney function in 41 patients. He confirmed that omega-3 supplementation did not alter kidney function, assessed using 24-h urine creatinine clearance. These are yielded contradictory results, which may reflect differences in study duration, the dosage of omega-3, route of administration, and type of omega-3 fatty acids [8].

6. Conclusion

Many severely or critically ill COVID-19 patients have been reported to develop severe metabolic and respiratory acidosis indicating possible microcirculation dysfunction. RCT has identified that omega-3 supplementation improved arterial PH, HCO_3 , and Be. These findings can be associated with the effect of omega-3 supplementation on microcirculatory function. The case presentations mentioned in our review also state the importance of using PUFA. The outcomes in these critically ill patients were promising. Looking at the results, it can be said the PUFA should be considered with regular treatment of COVID as it is likely to have favorable outcomes. However, further research is required to fully explore the efficacy of IPE as a treatment for COVID-19.

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