The Potential Beneficial Effect of EPA and DHA Supplementation Managing Cytokine Storm in Coronavirus Disease

Zoltán Szabó 1*, Tamás Marosvölgyi 2, Éva Szabó 3, Péter Bai 4,5,6, Mária Figler 1,7 and Zsófia Verzár 1

1 Faculty of Health Sciences, Institute of Nutritional Sciences and Dietetics, University of Pécs, Pécs, Hungary; 2 Medical School, Institute of Bioanalysis, University of Pécs, Pécs, Hungary; 3 Department of Biochemistry and Medical Chemistry, Medical School, University of Pécs, Pécs, Hungary; 4 Department of Medical Chemistry, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; 5 MTA-DE Lendület Laboratory of Cellular Metabolism, Debrecen, Hungary; 6 Faculty of Medicine, Research Center for Molecular Medicine, University of Debrecen, Debrecen, Hungary; 7 2nd Department of Internal Medicine and Nephrology Centre, Clinical Centre, University of Pécs, Pécs, Hungary

Keywords: COVID-19, DHA – 22:6n-3, EPA - 20:5n-3, supplementation, IL-6 (Interleukin 6), IL-18

In the recent COVID-19 (caused by SARS-Cov-2 virus) pandemic a subgroup of patient death is attributed to the so-called “cytokine storm” phenomenon (also called cytokine release syndrome or macrophage overactivation syndrome) (Mehta et al., 2020). To date, the molecular events that precipitate a “cytokine storm” or the applicable therapeutic strategies to prevent and manage this process is not elucidated because of the complex nature of this problem (Tisoncik et al., 2012).

Recent articles suggest that specific nutrients such as vitamin B6, B12, C, D, E, and folate; trace elements, including zinc, iron, selenium, magnesium, and copper may play a key role in the management of cytokine storm (Calder et al., 2020; Grant et al., 2020; Muscogiuri et al., 2020).

Among these micronutrients LC-PUFAs (long chain polyunsaturated fatty acids) such as EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are noteworthy because of their direct influence in the immunological response to viral infections (Calder et al., 2020; Messina et al., 2020).

In this paper, we would like to draw the attention to the possible beneficial effect of EPA and DHA supplementation in SARS-CoV-2 infection and urge the medical community for further investigations and conduction of clinical trials.

Evidence suggests that n-3 LC-PUFAs can modulate the immune response and function in many ways (Calder, 2007, 2013; Zivkovic et al., 2011; Maskrey et al., 2013; Tao, 2015; Allam-Ndoul et al., 2017). Among these complex immunomodulatory effects, interleukin-6 (IL-6) and interleukin-1β (IL-1β)—because of the suspected central regulatory role in the “cytokine storm”—should be highlighted. These cytokines can be affected by dietary EPA and DHA intake (Figure 1). In addition, poly(ADP-ribose) polymerase enzymes that have anti-inflammatory properties, translatable to human COVID-19 infection were shown to improve tissue levels of DHA and EPA, as well as the downstream anti-inflammatory metabolites of EPA and DHA (Kiss et al., 2015; Curtin et al., 2020) further underscoring the applicability of DHA and EPA in COVID-19.

IL-6 blockade using Tocilizumab monoclonal antibody has been identified as a feasible therapeutic target in SARS-CoV-infections (Liu et al., 2020), nevertheless, reducing the expression of additional proinflammatory cytokines (e.g., IL-1β, IL-38) may have beneficial effects (Conti et al., 2020).
Both EPA and DHA can decrease the secretion of inflammatory cytokines in vitro and animal studies (Gutierrez et al., 2019). Pre-supplementation with DHA (400 mM) significantly decreased the release of IL-6 and IP-10 by Calu-3 cells infected with Rhinovirus RV-43 and RV-1B (Saedisomeilia et al., 2009).

Based on the results of a randomized, controlled study published in 2018, high-dose (1.5 g/day EPA and 1.0 g/day DHA) n-3 supplementation can reduce plasma levels of both IL-6 and IL-1β (Tan et al., 2018). The anti-inflammatory effect of EPA and DHA supplementation seems consistent with most of the previous clinical findings (Fritsche, 2006; Vedin et al., 2008; Kiecolt-Glaser et al., 2012; Muldoon et al., 2016; Calder et al., 2020) (Table 1).

A DHA metabolite (17-hDHA) can reduce IL-6 secretion in human B cells (Ramon et al., 2012).

The triglyceride-lowering effect of n-3 LC-PUFA supplementation is well-known (Yanai et al., 2018; Zhou et al., 2019; Abdelhamid et al., 2020). Lower levels of triglyceride present a lower risk of developing a “cytokine storm” based on the score from the available sHLH score system (Mehta et al., 2020). This approach represents another standpoint for the promotion of n-3 LC-PUFA supplementation in COVID-19 disease.

In addition, evidence suggests that in non-viral infected critically ill patients n-3 LC-PUFA supplementation can be helpful but data are highly limited (Rangel-Huerta et al., 2012). A recent meta-analysis reported the effects of omega-3 fatty acids and/or antioxidants in adults with acute respiratory distress syndrome in which the authors concluded that any beneficial effect in the duration of ventilator days and ICU length of stay or oxygenation at day 4 seems uncertain because of the very low quality of evidence (Dushianthan et al., 2019). To date there is no direct evidence of any beneficial or deleterious effect of immunonutrition with EPA and DHA in COVID-19 patients.

EPA and DHA supplementation can alter many biological pathways which may have direct influence in the outcome of COVID-19 (Fenton et al., 2013; Duvall and Levy, 2016; Curtin et al., 2020).
TABLE 1 | The effects of DHA and EPA supplementation on cytokine production.

| References           | Type          | Supplementation | Subjects                        | Effects                      |
|----------------------|---------------|-----------------|---------------------------------|-----------------------------|
| Ramon et al. (2012)  | in vitro      | 50 nM 17-hDHA   | CD19+ B cells                   | IL-6 ↓ 44%a, IL-10 ↓ 49%a, IL-10 ↓ 54%b, TNF-α ↓                        |
|                      |               | 100 nM 17-hDHA  |                                 |                             |
| Allam-Ndoul et al. (2017) | in vitro          | 1.0 µM DHA       | THP-1 acute monocytic leukemia cell line | IL-6 ↓ 12%; 19%; 30%; 6%; 13%; 24%; TNF ↓ 6%; 12%; 15%; 18% |
|                      |               | 0.5 µM DHA      |                                 |                             |
|                      |               | 0.75 µM DHA     |                                 |                             |
|                      |               | 1.0 µM EPA      |                                 |                             |
|                      |               | 0.5 µM EPA      |                                 |                             |
|                      |               | 0.75 µM EPA     |                                 |                             |
| Saedisomeolia et al. (2009) | in vitro          | 200 µM DHA       | Airway epithelial cells (Calu-3) with RV-43 | IL-6 ↓ 16%b, IL-8 ↓ |
|                      |               | 400 µM DHA      |                                 | IP-10 ↓ 28%b                 |
|                      |               | 200 µM EPA      |                                 | IL-6 ↓ 13%; 29%b             |
|                      |               | 400 µM EPA      |                                 | IL-8 ↓                      |
| Tan et al. (2018)    | RCT           | 1.5 g/day DHA 4th weeks | Plasma of patients with chronic venous leg ulcers | IL-6 ↓ 12%; 22%b; IL-10 ↓ 28%b; IL-8 ↓ |
|                      |               | 1.5 g/day DHA 8th weeks |                                 | IP-10 ↓ 24%b; TNF-α ↓ 12%; 23% |
| Vedin et al. (2008)  | RCT           | 1.7 g/day DHA   | Blood mononuclear leukocytes of Alzheimer disease patients | IL-6 ↓ 43%; IL-18 ↓ 35% |
|                      |               | 0.6 g/day EPA   |                                 | TNF-α ↓                      |
| Kiecolt-Glaser et al. (2012) | RCT          | 2.5 g/day n-3 PUFAs | Serum of healthy adults | IL-6 ↓ 4%; TNF-α ↓ 23% |
|                      |               | 1.25 g/day n-3 PUFAs |                                 |                             |
| Zhou et al. (2019)   | RCT           | 3.6 g/day EPA + DHA | Peripheral blood mononuclear cells (PBMCs) in Hypercholesterolemic Adults | TG ↓ 20%; 13%b; IL-6 ↓ 37%b; |
|                      |               | 1.8 g/day EPA + DHA |                                 | TNF-α ↓                      |
| Muldoon et al. (2016) | RCT           | 0.4 g/day DHA   | Serum of healthy adults          | IL-6 ↓                      |
|                      |               | 1.0 g/day EPA   |                                 |                             |

% change in the expression of cytokines upon DHA and/or EPA supplementation were either calculated from original data or reproduced from given publications, where available. A ↓ notation stands for a statistically significant decrease in the measured levels of the examined cytokines. Identical superscripts both in the “Supplementation” and “Effects” columns (a, b, c, d, e, f) denote the published effect(s) of the given supplementation group/dose.

The safety of EPA and DHA supplementation should be also highlighted. Although, the US Department of Health & Human Services National Institutes of Health Office of Dietary Supplements (ODS) concluded that a daily intake of EPA+DHA of up to 3.0 g/d is safe (Usdhhs N. I. O. H. and Office of Dietary Supplements, 2019), the European Food Safety Authority (EFSA) stated that the long-term consumption of EPA and DHA supplements at combined doses of up to about 5 g/day appears to be safe for the general public (EFSA, 2012). In addition some evidence suggest that long-term supplementation of EPA and DHA may have side effects such as increasing risk of certain types of cancers, but the results are conflicting (Gerber, 2012; Alexander, 2013; Serini and Calviello, 2018). It should be also noticed that the usage of algae- or plant-based sources of EPA and DHA seems more preferable than marine or animal-based sources (Doughman et al., 2007; Lane et al., 2014; Harwood, 2019).

Summary: Based on the available data, the supplementation of EPA and DHA in COVID-19 patients appears to have potential beneficial effect in managing the “cytokine storm.” Therefore, the use of EPA and DHA supplementation should be considered as both a supportive therapy and a prevention strategy in SARS-Cov-2 infection.

**AUTHOR CONTRIBUTIONS**

ZS, TM, and ÉS drafted the manuscript. TM, PB, and ZS designed the figure and the table. MF, ZV, and ÉS substantial contributions to the conception by supervising all the processes. PB, MF, ZV, and ÉS revised the manuscript critically for important intellectual content. TM and ZS proofread the final manuscript. All authors agree that our work is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

**ACKNOWLEDGMENTS**

TM and ÉS was supported by grants from NKFIH K120193. PB work was supported by grants from NKFIH (K123975, GINOP-2.3.2-15-2016-00006), the Momentum fellowship of the Hungarian Academy of Sciences and the University of Debrecen. The research was financed by the Higher Education Institutional Excellence Programme (NKFIH-1150-6/2019) of the Ministry of Innovation and Technology in Hungary, within the framework of the Biotechnology thematic programme of the University of Debrecen.
REFERENCES

Abdelhamid, A. S., Brown, T. J., Brainard, J. S., Biswas, P., Thorpe, G. C., Moore, H. J., et al. (2020). Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst. Rev. 12, CD003177. doi: 10.1002/14651858.CD003177.pub3

Alexander, W. (2013). Prostate cancer risk and omega-3 fatty acid intake from fish oil: a closer look at media messages versus research findings. P T 38, 561–564.

Allam-Ndoul, B., Guenard, F., Barbier, O., and Vohl, M. C. (2017). A study of the differential effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on gene expression profiles of stimulated Th-1 macrophages. Nutrients 9:424. doi: 10.3390/nu9050424

Calder, P. C. (2007). Immunomodulation by omega-3 fatty acids. Prostaglandins Leukot. Essent. Fatty Acids 77, 327–335. doi: 10.1016/j.plefa.2007.10.015

Calder, P. C. (2013). n-3 fatty acids, inflammation and immunity: new mechanisms to explain old actions. Proc. Nutr. Soc. 72, 326–336. doi: 10.1017/S0033584913001031

Calder, P. C., Carr, A. C., Gombart, A. F., and Eggersdorfer, M. (2020). Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients 12:1181. doi: 10.3390/nu12041181

Conti, P., Ronconi, G., Caraffa, A., Gallenga, C. E., Ross, R., Rydias, I., et al. (2020). Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J. Biol. Regul. Homeost. Agents. 34, 2313–2322. doi: 10.23812/JBRA.F. [Epub ahead of print].

Curtin, N., Banyai, K., Thaventhiran, J., Le Quesne, J., Helyes, Z., and Bai, P. (2020). Repositioning PARP inhibitors for SARS-CoV-2 infection (COVID-19): a new multi-pronged therapy for ARDS? Br. J. Pharmacol. doi: 10.1111/bph.15137. [Epub ahead of print].

Doughman, S. D., Krupanidhi, S., and Sanjeevi, C. B. (2007). Omega-3 fatty acids for nutrition and medicine: considering microalgae oil as a vegetarian source of EPA and DHA. Curr. Diabetes Rev. 3, 198–203. doi: 10.2174/1573990781388998

Dushianthan, A., Cusack, R., Burgess, V. A., Grocott, M. P., and Dushianthan, A. (2019). Immunomodulation for acute respiratory distress syndrome (ARDS) in adults. Cochrane Database Syst. Rev. 1:CD012041. doi: 10.1002/14651858.CD012041.pub2

Duval, M. G., and Levy, B. D. (2016). DHA- and EPA-derived resolvents, protectins, and maresins in airway inflammation. Eur. J. Pharmacol. 785, 144–155. doi: 10.1016/j.ejphar.2015.11.001

EFSA (2012). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion Related to the Tolerable Upper Intake Level of Eicosapentaenoic acid (EPA), Docosahexaenoic Acid (DHA) and Docosapentaenoic Acid (DPA). P. European Food Safety Authority (Efsa). Italy. EFSA Jounra.

Fenton, J. I., Hord, N. G., Ghosh, S., and Gurzelli, E. A. (2013). Immunomodulation by dietary long chain omega-3 fatty acids and the potential for adverse health outcomes. Prostaglandins Leukot. Essent. Fatty Acids 89, 379–390. doi: 10.1016/j.ejphar.2013.09.011

Fritsche, K. (2006). Fatty acids as modulators of the immune response. Annu. Rev. Nutr. 26, 45–73. doi: 10.1146/annurev.nutr.25.050304.092610

Gerber, M. (2012). Omega-3 fatty acids and cancers: a systematic update review of epidemiological studies. Br. J. Nutr. 107(Suppl. 2), S228–S239. doi: 10.1017/S0007114512001614

Grant, W. B., Lahore, H., Mcdonnell, S. L., Baggerly, C. A., French, C. B., Aliano, J., et al. (2020). Evidence that vitamin D supplementation could reduce the outcome of COVID-19: a hypothesis of work. Int. J. Mol. Sci. 21:3104. doi: 10.3390/ijms2103104

Muldoon, M. F., Laderian, B., Kuan, D. C., Sereika, S. K., Marsland, A. L., and Manuck, S. B. (2016). Fish oil supplementation does not lower C-reactive protein or interleukin-6 levels in healthy adults. J. Intern. Med. 279, 98–109. doi: 10.1111/joim.12442

Muscogiuri, G., Barrea, L., Savastano, S., and Colao, A. (2020). Nutritional recommendations for CoVID-19 quarantine. Eur. J. Clin. Nutr. 74, 850–851. doi: 10.1016/s1460-7441(20)3062-8

Ramon, S., Gao, F., Serhan, C. N., and Phipps, R. P. (2012). Specialized proresolving mediators enhance human B cell differentiation to antibody-secreting cells. J. Immunol. 189, 1036–1042. doi: 10.4049/jimmunol.1103483

Rangel-Huerta, O. D., Aguiler, C. M., Mesa, D. M., and Gil, A. (2012). Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials. Br. J. Nutr. 107(Suppl. 2), S159–S170. doi: 10.1017/S0007114512001559

Saeedioneolaei, A., Wood, L. G., Garg, M. L., Gibson, P. G., and Wark, P. A. (2009). Anti-inflammatory effects of long-chain n-3 PUFA in rhinovirus-infected cultured airway epithelial cells. Br. J. Nutr. 101, 533–540. doi: 10.1017/S0007114508025798

Serini, S., and Calviello, G. (2018). Long-chain omega-3 fatty acids and cancer: any cause for concern? Curr. Opin. Clin. Nutr. Metab. Care 21, 83–89. doi: 10.1097/MCO.0000000000000439

Tan, A., Sullenbarger, B., Prakash, R., and Medanian, J. C. (2018). Supplementation with eicosapentaenoic acid and docosahexaenoic acid reduces high levels of circulating proinflammatory cytokines in aging adults: a randomized, controlled study. Prostaglandins Leukot. Essent. Fatty Acids 132, 23–29. doi: 10.1016/j.ejpled.2018.03.010

Tao, L. (2015). Oxidation of polyunsaturated fatty acids and its impact on food quality and human health. Adv. Food Technol. Nutr. Sci. 1, 135–137. doi: 10.17140/AFTNSOJ-1-123

Tisoncik, J. R., Korth, M. J., Simmons, C. P., Farrar, J., Martin, T. R., and Katze, M. G. (2012). Into the eye of the cytokine storm. Microbiol. Mol. Biol. Rev. 76, 16–32. doi: 10.1128/MMBR.00515-11

Usdhhs N. I. O. H. and Office of Dietary Supplements (2019). Omega-3 Fatty Acids Facts Sheet for Health Professionals [Online]. US. Department of Health & Human Services, National Institutes of Health Office of Dietary Supplements: Office of Dietary Supplements (ODS) Available online at: https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/?fbclid=IwAR3KUXuQhfDzOvrgnueLocJGowShiv1KsV8YQIuLwvke_ 4GrwppSU1IKAU (accessed June 1, 2020).

Veldhuis, J. C., Cederholm, T., Freid, Levi, Y., Basun, H., Garlind, A., Faxen Irving, G. S., et al. (2008). Effects of docosahexaenoic acid-rich n-3 fatty acid supplementation on cytokine release from blood mononuclear leukocytes: the OmegaAD study. Am. J. Clin. Nutr. 87, 1616–1622. doi: 10.1093/ajcn/87.6.1616
Yanai, H., Masui, Y., Katsuyama, H., Adachi, H., Kawaguchi, A., Hakoshima, M., et al. (2018). An improvement of cardiovascular risk factors by Omega-3 polyunsaturated fatty acids. *J. Clin. Med. Res.* 10, 281–289. doi: 10.14740/jocmr3362w

Zhou, Q., Zhang, Z., Wang, P., Zhang, R., Chen, C., Zhang, C., et al. (2019). EPA+DHA, but not ALA, improved lipids and inflammation status in hypercholesterolemic adults: a randomized, double-blind, placebo-controlled trial. *Mol. Nutr. Food Res.* 63, e1801157. doi: 10.1002/mnfr.201801157

Zivkovic, A. M., Telis, N., German, J. B., and Hammock, B. D. (2011). Dietary omega-3 fatty acids aid in the modulation of inflammation and metabolic health. *Calif. Agric.* 65, 106–111. doi: 10.3733/ca.v065n03p106

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Copyright © 2020 Szabó, Marosvölgyi, Szabó, Bai, Figler and Verzár. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.**