Letter to the Editor in relation to Bistrian BR. Parenteral fish oil emulsions in critically ill COVID-19 emulsions [published online ahead of print, 2020 May 8]. JPEN J Parenter Enteral Nutr. 2020;10.1002/jpen.1871.

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Abstract

In this letter we discuss the proposition of Bristian BR (2020) to use the intravenous administration of fish oil emulsions in critically ill COVID-19. We consider that immune modulatory properties of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, rapidly provided in high amounts by fish oil emulsion, may be important to change the course of COVID-19's death pathway. Prescriptions should be based on body weight (e.g. 0.2 g pure FOLE/kg body weight/day) and also should consider combining the parenteral administration of fish oil emulsion to low oral aspirin intake, in order to trigger resolvin synthesis from EPA and DHA.

Dear Editor,

We have read with great interest the letter "Parenteral fish oil emulsions in critically ill COVID-19".[1] As researchers in the field, we recognize the potential benefit of intravenous fish oil lipid emulsion (FOLE) for hospitalized patients affected by Coronavirus Disease 2019 (COVID-19).[2] This approach will allow rapid delivery of high amounts of bioactive forms of omega-3 fatty acids, with helpful immune-modulatory properties, to become available immediately to cells and tissues.[3]

We propose that not only obese patients, as suggested by Bistrian[1], but also several other types of infected patients may benefit from FOLE. Most high-risk populations severely compromised by COVID-19 (elderly, obese, diabetic, hypertensive, oncologic) have a disturbed inflammatory component (e.g. chronic low grade inflammation).[4-7] We suspect this pre-existing condition may be important in triggering the detrimental hyperinflammation associated to severe COVID-19 phenotypes, which may be attenuated by the omega-3 fatty acids in FOLE.

Eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, provided by FOLE, have the ability to decrease the synthesis of inflammatory cytokines by modulating gene transcription factors.[3,8] These include the activation of peroxisome proliferator activated receptor (PPAR), suggested as a therapeutic target to attenuate the cytokine storm in COVID-19.[8-10] Furthermore, these highly unsaturated fatty acids have shown to destabilize rigid membrane lipid rafts.[11] SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) to enter human cells, a cell receptor located at membrane lipid rafts.[12] Importantly, the cytokine storm observed in severe COVID-19 may be a consequence of an impaired inflammatory resolution. The observation that neutrophil extracellular traps (NETs) seem a marker of the disease severity supports this

impression.[13] EPA and DHA are essential precursors of resolvins, protectins and maresins, which highly orchestrate the resolution of inflammation.[14]

All together, the immune modulatory properties of EPA and DHA may be important to change the course of COVID-19's death pathway. Therefore, as suggested by Bistrian[1], the use of FOLE as an adjuvant immune-pharmaco-nutrient in COVID-19 seems clinically relevant.[2]. We believe FOLE should be provided on a per body weight basis (e.g. 0.2 g pure FOLE/kg body weight/day) in order to avoid that underweight individuals receive very high amounts of EPA and DHA and that obese individuals receive too low amounts of EPA and DHA. This approach was safe in patients with sepsis and in general critically ill elderly populations.[15,16]

Whether disturbances in systemic metabolism triggered by hyperinflammation may increase the use of EPA and DHA to other purposes than immunomodulation (e.g. energy generation) is unknown. In this sense, it also should be considered to associate low oral aspirin intake in patients with COVID-19 receiving intravenous FOLE. Aspirin can trigger resolvin synthesis from EPA and DHA, so its exogenous supply may aid COVID-19 patients to resolve inflammation.[17] Furthermore, similarly to EPA and DHA, aspirin may have a desirable anticoagulant effect for COVID-19 patients. In a Dutch ICU enrolling 184 patients with COVID-19, 38% abnormal blood clotting and 33% formed clots were reported, probably due hyperinflammation.[18,19] In a model of arteriosclerosis, less aortic plaque lesions and proinflammatory lipid mediators were observed when combining oral fish oil with aspirin than just oral fish oil.[20] In patients with cardio or cerebrovascular ischaemic diseases, this practice was safe and did not affect the risk of upper gastrointestinal complications (e.g. bleeding).[21]

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