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Editorial

Essential fatty acids and their metabolites in the pathobiology of (coronavirus disease 2019) COVID-19



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The pandemic disease of (coronavirus disease 2019) COVID-19 caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) can be lethal due to damage to the pulmonary vascular endothelial cells and of other vessels (termed *endotheliopathy*), alveolar exudative inflammation and interstitial inflammation, alveolar epithelium proliferation, and hyaline membrane formation resulting in respiratory failure due to acute respiratory distress syndrome. COVID-19 is associated with excess production of proinflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and possibly other cytokines. COVID-19 affects almost all vital organs in the body.

SARS-CoV-2 virus targets nasal and bronchial epithelial cells and pneumocytes by the binding of its spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor. SARS-CoV-2 virus uptake is promoted by the type 2 transmembrane serine protease (TMPRSS2) of the host cell, which cleaves ACE2 and activates the spike protein to assist the coronavirus's entry into the host cells [1]. Both ACE2 and TMPRSS2 are expressed by the host target cells. SARS-CoV-2 infects pulmonary capillary endothelial cells, inducing an inflammatory reaction (endotheliitis) that triggers thrombotic events in various blood vessels.

COVID-19 induces apoptosis of T lymphocytes to cause severe lymphopenia and impairs lymphopoiesis owing to a reduction in Bcl-6⁺ germinal center B cells that correlates with aberrant extrafollicular TNF- α accumulation in the spleen and lymph nodes [2]. Thus, high TNF- α levels seen in severe COVID-19 not only cause a "cytokine storm" but also suppresses immune response [3,4]. In this context, the proposals made by Torrinhas et al [5] and Sukkar and Bassetti [6] suggesting, respectively, the potential beneficial action of parenteral fish oil and induction of ketosis in COVID-19 are rather interesting.

Metabolism of essential fatty acids

The dietary essential fatty acids (EFAs) *cis*-linoleic acid (LA, 18:2 n-6) and α -linolenic acid (18:3 n-3) are metabolized by delta-6-desaturase, delta-5-desaturase, and elongases to form, respectively, γ -linoleic acid (GLA, 18:3 n-6), dihomo-GLA (DGLA, 20:3 n-6), and arachidonic acid (AA, 20:4 n-6); and eicosapentaenoic acid (EPA, 20:5 n-3); and docosahexaenoic acid (DHA, 22:6 n-3). DGLA

is the precursor of 1 series prostaglandins (PGs) such as PGE₁, whereas AA is the precursor of 2 series PGs, thromboxanes (TXs), and 4 series leukotrienes (LTs). EPA is the precursor of 3 series PGs, TXs, and 5 series LTs. Most of these PGs, TXs, and LTs are proinflammatory in nature, but 2 series PGs and TXs and 4 series LTs are more potent than 3 series PGs and TXs and 5 series LTs with regard to their proinflammatory action. Thus, PGE₂ is more potent than PGE₃ in inducing inflammatory events [7].

AA is also the precursor of lipoxin A₄ (LXA₄), a potent antiinflammatory compound, whereas antiinflammatory resolvins of E series are derived from EPA, and resolvins of D series, protectins, and maresins from DHA. LXA₄ inhibits the production of PGE₂ and LTs. GLA, DGLA, AA, EPA, DHA, PGE₁, PGE₂, LXA₄, resolvins, protectins, and maresins inhibit the production of IL-6 and TNF- α [7]. PGE₂ has both pro- and antiinflammatory actions. Adequate formation of PGE₂ is necessary for the optimal amount of inflammation to occur, which in turn initiates antiinflammatory events by augmenting LXA₄ formation [8,9]. Thus, AA metabolism is crucial to the inflammatory process. PGE₂ and LTs facilitate generation of M1 macrophages (which are proinflammatory in nature), whereas GLA, DGLA, AA, EPA, DHA, PGE₁, LXA₄, resolvins, protectins, and maresins favor generation of M2 macrophages [10,11] (which are antiinflammatory in nature).

Ketogenic diet and its clinical implications

The keto diet is a high-fat, moderate-protein, low-carbohydrate regimen. It results in the production of ketones, which are used as fuel by the body, and thus leads to faster metabolism, decreased hunger, and more efficient weight loss.

Initially, the keto diet was recommended for children with intractable epilepsy, though why it is effective is not clear. It is beneficial for those with type 2 diabetes mellitus, hypertension, and obesity. Sukkar and Bassetti [6] have proposed that the keto diet inhibits M1 macrophages, activates M2 macrophages, and enhances type 1 interferon (IFN) production that is mediated by augmented lactate production, and thus suppresses the "cytokine storm" seen in COVID-19.

EFAs and their metabolites in COVID-19

PGE₃ and LTs of the 5 series formed from EPA are less proinflammatory than PGE₂ and LTs of the 4 series formed from AA,

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implying that PGE₃ and LTs of the 5 series do not trigger inflammation of sufficient degree to initiate the inflammation resolution process. Hence, resolvins, protectins, and maresins may be inadequate to trigger an efficient inflammation resolution process even though they are antiinflammatory compounds. It is noteworthy that LXA₄ generation is enhanced by resolvins [12,13]. This implies that resolvins, protectins, and maresins may enhance the formation of LXA₄ to resolve inflammation. This is supported by previous studies showing that LXA₄ is more potent than resolvins and protectins at preventing the cytotoxic action of benzo[*a*]pyrene, streptozotocin, and doxorubicin [14–16]. AA and LXA₄ have potent antiinflammatory actions by suppressing IL-6 and TNF- α and expression of nuclear factor κ B [14–16], whereas AA enhances LXA₄ formation to bring about its antiinflammatory action.

PGE₂ and LXA₄ interact with each other to regulate inflammation and its resolution

AA supplementation to animals and humans enhances its tissue content with no change in PGE₂ levels but increases LXA₄ formation [17–19]. PGE₂ suppresses IL-6 and TNF- α production and alters macrophage polarization induced by mesenchymal stem cells [20,21]. At low concentrations, PGE₂ binds to EP₄, a high-affinity receptor, and enhances the production of interleukin-23 (IL-23), whereas high PGE₂ amounts bind to the EP₂ receptor to inhibit IL-23 production [22]. Furthermore, PGE₂ triggers the production of LXA₄ and inhibits LTB₄ synthesis by modulating the expression of 5- and 15-lipoxygenases, and thus induces resolution of inflammation [8,9].

AA is critical for inflammation resolution

A delicate balance is maintained between T_H1 (IL-2, IFN- γ) and T_H2 (IL-4, IL-5, IL-10, IL-13) cytokines to regulate inflammation. IFN- γ -producing CD4⁺ T_H1 cells and PGE₂ are needed to control invading microbial inflammatory stimuli to initiate and maintain the mononuclear inflammatory response. Formation of IL-17 (T_H17), a proinflammatory cytokine, is dependent upon IL-23 and PGE₂, which induce chemokine expression and recruitment of cells [11]. Once the purpose of inflammatory response is achieved, IL-10, IL-4, and LXA₄ are produced to initiate and induce resolution of inflammation [23]. Thus, PGE₂ and LXA₄ are crucial to initiating and resolving inflammation, respectively.

Resolvin E1 has actions similar to LXA₄ and suppresses IL-23 and IL-17 production in addition to its ability to inhibit IL-6 and TNF- α . Resolvin E1 promotes LXA₄ production [13,23], suggesting that cross talk occurs between the metabolism of n-3 and n-6 fatty acids.

Conclusions and therapeutic implications

The proposal by Torrinhas et al [5] is interesting but fails to consider the critical role of AA and its products PGE₂ and LXA₄ in inflammation and its resolution. Resolvins, protectins, and maresins are certainly important in the resolution of inflammation [11–16]. But the resolution of inflammation would not occur without optimal inflammation in the first place. This is so because PGE₂ triggers the production of LXA₄ and inhibits LTB₄ synthesis by modulating the expression of 5- and 15-lipoxygenases to induce resolution of inflammation [8,9,23]. Furthermore, resolvins enhance the synthesis of LXA₄ [12,13].

Inhibition of 15-prostaglandin dehydrogenase (a prostaglandin-degrading enzyme) not only enhances PGE₂ levels but also increases hematopoietic capacity [24]. Hence, administration of AA, the precursor of PGE₂, is expected to augment hematopoiesis

in those with COVID-19 who are known to have lymphopenia [25]. This implies that administration of appropriate amounts of AA/PGE₂/LXA₄ in a timely fashion could be of significant benefit in COVID-19.

Human cells exposed to SARS-CoV-2 or human coronavirus 229E (HCoV-229E) release significant amounts of AA and LA, which inactivate the viruses [26,27]. These results support my previous proposal [28–31] that AA and other fatty acids may inactivate SARS-CoV-2. Hence, it can be argued that release of inadequate amounts of AA and other fatty acids by infected cells may cause SARS-CoV-2 to survive, proliferate, and cause COVID-19. Mann et al [32] showed that in severe COVID-19, poor induction of the COX-2 enzyme occurs that may result in suboptimal PGE₂ production, whereas those with mild COVID-19 showed higher TNF- α and COX-2 expression. COX-2 expression remained low in individuals with severe COVID-19 throughout intensive care, but levels were restored to normal upon recovery in patients with mild cases. These results suggest that supplementation of AA may enhance COX-2 expression and PGE₂ formation that may be of benefit in severe COVID-19. On the other hand, supplementation of EPA/DHA in those with severe COVID-19 may further suppress PGE₂ formation, which may be unwarranted. Hence, caution needs to be exercised in recommending parenteral fish oil as an adjuvant pharmacotherapy in severe COVID-19.

It is known that calorie restriction enhances the activity of desaturases, especially delta-6-desaturase, and thus increases the formation of GLA, DGLA, AA, EPA, and DHA, which may lead to increased formation of LXA₄, resolvins, protectins, and maresins [33]. But whether such a change occurs with a keto diet needs to be confirmed. One of the concerns about the keto diet in those with COVID-19 is whether there is enough time to see the potential benefits (since COVID-19 progresses within 10–14 d from mild to severe), as well as the induction of ketosis, which may have some unintended adverse consequences.

It has been reported that those who are critically ill due to COVID-19 have much lower levels of cytokines compared to those who have sepsis [34]. In addition, patients with COVID-19 have a severe deficiency of vitamin C [35]. Vitamin C enhances formation of PGE₁ [36], an antiinflammatory, platelet antiaggregator, and modulator of the immune response [37]—functions that are remarkably like those of LXA₄. Insulin also has antiinflammatory actions [38,39]. This suggests that administration of adequate amounts of AA/EPA/DHA (in the right proportion), vitamin C, and insulin may be of significant benefit in COVID-19 and sepsis.

These proposals can be verified by studying whether GLA, DGLA, AA, EPA, DHA, LXA₄, resolvins, protectin, and maresins can inactivate SARS-CoV-2; and measuring activities of desaturases, COX-2, and 5-, 12-, and 15-LOX enzymes and different types of phospholipases in those with COVID-19 along with plasma levels of various EFAs and their metabolites.

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