

Review

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Review

Potential Benefits of Omega-3 Polyunsaturated Fatty Acids (N3PUFA) on Cardiovascular Health Associated with COVID-19: An Update for 2023

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Abstract: Accumulating literature demonstrates that omega-3 polyunsaturated fatty acid (N3PUFA) can be incorporated into the phospholipid bilayer of cell membrane in the human body to positively affect the cardiovascular system, including improving epithelial function, decreasing coagulopathy, and attenuating uncontrolled inflammatory responses and oxidative stress. Moreover, it has been proven that the N3PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are precursors of some potent endogenous bioactive lipid mediators that mediate some favorable effects attributed to their parent substances. A linear dose-response relationship between increased EPA and DHA intake and reduced thrombotic outcomes have been reported. The excellent safety profile of dietary N3PUFA makes them a prospective adjuvant treatment for people exposed to a higher risk of cardiovascular problems associated with COVID-19. This review presented the potential mechanisms that might contribute to the beneficial effect of N3PUFA and the optimal form and dose applied.

Keywords: N3PUFA; EPA; DHA; omega-3; cardiovascular; coagulation; thrombosis; COVID-19; inflammation; oxidative stress.

1. Introduction

Coronavirus Disease-2019 (COVID-19), which causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), has been linked to 6.7 million deaths and 657.9 million reported cases of infection by January 2023 [1]. Mounting evidence of endothelial dysfunction in the autopsy of COVID-19 patients supports the hypothesis that there is an association between endothelial dysfunction (e.g., systemic hypertension, cardiovascular diseases, diabetes, and obesity) and the SARS-CoV-2 infection [2], as well as the post-manifestations of COVID-19 (a.k.a., long COVID-19) [3]. The endothelium is a single-cell sentinel layer that lines the innermost blood vessels with many functions, such as acting as a mechanical barrier between the blood and the basement membrane, regulating vascular toning, and modulating the immune system [4]. SARS-CoV-2 viral attack occurs through endothelial human angiotensin-converting enzyme 2 (ACE2) receptor, facilitated by host serine protease Transmembrane protease, serine 2 (TMPRSS2) priming, directly causes membrane disruption and damage to endothelial cells or indirectly leads to host inflammatory effects [5]. Both phenomena lead to endothelial dysfunction (i.e. endotheliitis, endothelialitis and endotheliopathy) [3], characterized by endothelial activation and decreased endothelium-dependent vasodilation,

hyperpermeability, and inflammation/leukocyte adhesion, resulting in proinflammatory, procoagulant, and proliferative state.

The increased risk of severe illness in patients with existing cardiovascular diseases (CVDs) and those developing CVDs without pre-existing comorbidities following COVID-19 infection is strongly linked to high levels of pro-inflammatory cytokines (a.k.a. "cytokine storm syndrome"); severe local vascular dysfunction caused by the extension of widespread alveolar and interstitial inflammation to the pulmonary vasculature; and the intense oxidative stress associated with COVID-19 infection [7–10]. Ongoing symptomatic COVID-19 (present from 4 weeks and up to 12 weeks) and post-COVID-19 syndrom (present for > 12 weeks and are not attributable to alternative diagnoses) have been identified based on available data [11]. Rezel-Potts et al. [12] evaluated the net long-term impacts of COVID-19 infection on cardiovascular and diabetes outcomes for a large population-based case-control study (428,650 COVID-19 cases vs 428,650 controls). They reported a 6-fold increase in overall cardiovascular diagnoses, an 11-fold increase in pulmonary embolism, a 6-fold increase in atrial arrhythmias, and a 5-fold increase in venous thromboses among acute COVID-19 patients with no pre-existing CVDs in the first four weeks after infection. Moreover, these risks increased for up to 3 months following the infection [12]. Although the risk of developing new CVDs declined to baseline in patients without pre-existing CVDs, as reported by Rezel-Potts and colleagues [12], another observational study by Knight et al. [13] reported the elevated risk of developing CVDs might persist for up to 49 weeks after COVID-19 infection.

The incident cardiovascular complications can be life-threatening in severe COVID illness. Because COVID-19's symptoms and severity are varied, medical interventions must be carefully balanced between benefits and risks. A healthy nutritional status is one of the most important factors that support immune homeostasis, particularly on COVID-19 days [14]. A deprived nutritional status due to low dietary quality could significantly contribute to an impaired immune system, especially since the continuous emergence of new variants constantly threatens vaccine-induced immunity [15]. A potential solution to health challenges in the COVID-19 era is enhancing patients' general immunity via dietary intervention and nutraceutical supplementation. Omega-3 polyunsaturated fatty acids (N3PUFA) and their metabolites play an important role in the synthesis of various inflammatory mediators, such as prostaglandin (PG), leukotrienes (LT), thromboxanes (TX), protectins, and resolving. Moreover, N3PUFA is essential in regulating lipid rafts and influencing cell membrane fluidity. They are capable of incorporating into the bi-phospholipid layers of the cell membrane of neutrophils, an essential part of the innate immune system and produce a range of lipid mediators with hormone-like actions (including prostaglandins, leukotrienes, and maresins) [16], primarily targeting the sites of tissue damage and infections. N3PUFA also improves the function of macrophages by provoking major alterations in gene regulation to regulate the production and secretion of cytokines and chemokines, blunting M1 macrophage polarization and promoting M2 polarization, promoting the ability of phagocytosis [16]. Other studies have reported the anti-inflammatory mechanisms of N3PUFA, including down-regulating Nuclear Factor- κ Beta (NF- κ B), a transcription factor involved in cell signaling that initiates an inflammatory response by the innate immune system [17,18]; inducing interferons (IFNs) that inhibit viral replication [19]; affecting the motility of CD4+ [20] and CD8+ T cells [21] and modifying their ability to reach target tissues, and thereby potentially modulate cytokine responses to viral attack.

The major causes of severe illness following COVID-19 infection are related to immune system overdrive leading to cytokine storms and, thereby, a potential cause of severe CVD. In 2022, a case-control study reported that lower N3PUFA intake was inversely associated with an increased likelihood of developing severe illness following COVID-19 infection after adjustment of confounders [22]. Increasing N3PUFA intake in the diet or through supplementation could potentially promote better immune function and decrease the severity of inflammatory response. As N3PUFA is abundantly available in marine resources and have GRAS (generally recognized as safe) status [23], they could be a relatively safe and convenient prophylactic and conjunctive supplementation or treatment approach for patients who have con-morbidity CVD. In light of this,

the current review aims to evaluate the role of N3PUFA in anti-inflammation and their potential health benefits in protecting cardiovascular health during and post COVID-19 infection.

2. Risk of cardiovascular health deterioration during and post COVID-19

2.1. Epidemiology evidence: endothelial dysfunction is linked to COVID-19 associated cardio dysfunction

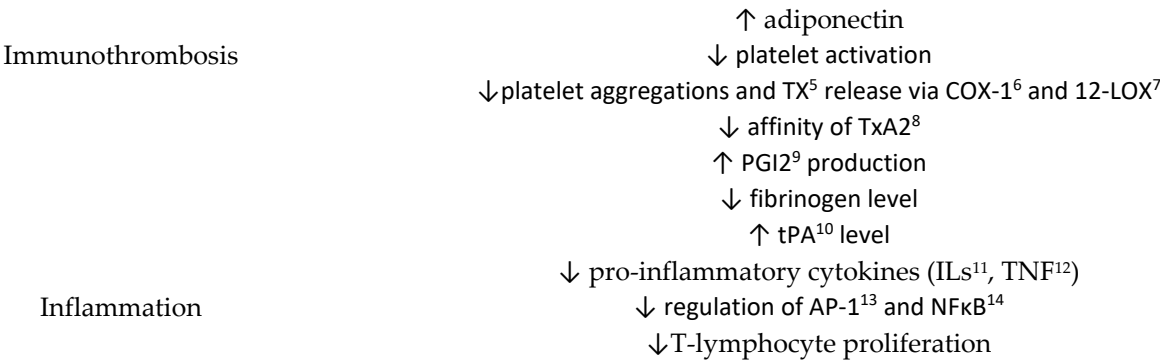
SARS-CoV-2 comprises four structural proteins: spike (S), membrane (M), nucleocapsid (N), and envelope (E) proteins. After binding to ACE2, the S protein changes its shape through the endosomal pathway (also known as proteolysis) and helps the virus and host cell fuse so that viral RNA can be injected into the host cell [24]. In the endoplasmic reticulum (ER), SARS-CoV-2 proteins assemble with viral RNA to form virions, which are then released from the host cells. While 81% of symptomatic individuals had the relatively mild disease after infection, 14% developed severe disease with dyspnea, hypoxia, or over 50% lung involvement by imaging, and 5% developed critical disease with respiratory failure, shock, and/or multiorgan dysfunction [25]. Since the early phases of the COVID-19 pandemic, the pathophysiologic traits, including severe endothelial injury [5], alveolar-capillary microthrombi [26], venous thromboembolism [27], systemic inflammatory response [28], and acute respiratory distress syndrome (ARDS) have been reported [29].

Particularly, cardiovascular disease shares a bidirectional relationship with the severity of COVID-19. Patients hospitalized with severe COVID-19 have a significantly higher rate of incidents of clinical cardiovascular complications [30,31], encompassing acute heart failure, arrhythmias, venous thromboembolism, cardiogenic shock, arterial thrombosis, myocardial ischemia or infarction, acute stroke and myocarditis. The early studies in 2020 reported a high incidence of venous thrombosis (33%) [32] and pulmonary embolism (20.6%) [33] among severe COVID-19 illness, whilst around 50% of patients who required intensive care had thrombosis [34–37]. The retrospective cohort study by Argenziano et al. [30] reported that during the early pandemic stage in New York, the most common clinical complications among the 1000 patients studied encompassed over 25% of thromboembolism, around 20% of arrhythmias and heart failure. Similarly, a significantly higher relative risk (RR) (up to 25%) of developing thrombotic complications was reported in the Netherlands after COVID-19 infection, in particular venous thromboembolism, when compared to influenza infection (11% increased RR) [38]. Numerous population-based studies also provided strong evidence that individuals with pre-existing cardiometabolic disease were prone to develop severe COVID-19 illness and a higher risk of life-threatening complications [39,40]. This can be potentially related to pre-existing subclinical pathophysiological abnormalities, such as endothelial dysfunction, procoagulation (platelet hyperreactivity and propensity to coagulopathy), and dysfunctional immune responses [41]. Furthermore, the invasion of SARS-CoV-2 on the endothelium of blood vessels can lead to direct endothelial damage and triggers a marked immune response that further causes additional endothelial dysfunction [5,42].

The endothelial dysfunction may continue after COVID-19. The 2022 population-based study in Sweden quantifies the increased risk of thromboembolic events among individuals who recovered from COVID-19 compared to controls without COVID-19 but matched for comorbidities and other risk factors [43]. The study reported that incidence rates were significantly increased for a first deep vein thrombosis up to 70 days after COVID-19, pulmonary embolism up to 110 days, and a bleeding event up to 60 days [43]. More studies have reviewed the potential causal factors that contributed to the elevated cardiovascular risks, which are directly linked to immunothrombosis, not only in acute but also post COVID-19 infections.

Table 1. Potential mechanism of anti-thrombotic effects of N3PUFA.

Pathological significance	Effects of N3PUFA ¹
Endothelial function	↑ NO ² and eNOS ³ activity ↓ endothelin-1 ↑ endothelium-mediated vasodilation ↑ VSMC ⁴ relaxation



¹ omega-3 polyunsaturated fatty acids. ² nitric oxide. ³ nitric oxide synthase. ⁴ vascular smooth muscle cell. ⁵ thromboxane. ⁶ cyclooxygenase-1. ⁷ 12-lipoxygenase. ⁸ thromboxane A2. ⁹ prostacyclin. ¹⁰ tissue plasminogen activator. ¹¹ interleukins. ¹² tumor necrosis factor- α . ¹³ Activator protein 1. ¹⁴ Nuclear factor kappa B.

2.2. Prothrombotic state in COVID infection

It has been hypothesized that the endothelial dysfunction caused by SARS-Cov-2 infection can lead to a prothrombotic state that encompasses increased immuno-thrombosis, coagulation, and decreased fibrinolysis [44]. (Table1)

Immuno-thrombosis is characterized as a mechanism by which monocytes and neutrophils activate the coagulation cascade as the host immune fights the viral invasion. The uncontrolled release of proinflammatory cytokines and chemokines responsible for the innate immune system, including Interleukin (IL)-6, IL-8, interferon (IFN)- γ and IL-2, can result in an increase in platelet production and activity. IL-6 also increases the expression of TF on monocytes and endothelial cells to further worsen under failure dysfunction [45]. IFN- γ can also impair the vascular endothelium to promote a prothrombotic effect, whereas IL-2 upregulates Plasminogen activator inhibitor-1 (PAI-1) to reduce fibrinolysis [46]. The elevated IL-8 attracts neutrophils to the infected cells, increasing the likely part of the formation of neutrophil extracellular traps (NETs) [45], which may lead to platelet-dependent NET-driven thrombosis. (Table1)

The platelet activation and recruitment to a site of endothelial injuries produce a platelet plug and act as an adhesion site for coagulation factors. Simultaneously, the activated platelets secrete bioactive compounds (e.g., the polyphosphates and other coagulation factors and immunological mediators (e.g., complement factors) to further promote the activation of coagulation factors by inhibiting Tissue factor pathway inhibitor (TFPI) and promoting fibrin polymerization [44].

The direct invasion of SARS-CoV-2 into endothelial cells damages the intercellular junctions of the endothelium to expose the prothrombotic subendothelial matrix collagen, which activates the intrinsic coagulation pathway, and tissue factor (TF), which activates the extrinsic coagulation pathway. Both pathways activate factor X to cleave prothrombin to form thrombin, which cleaves fibrinogen to increase the fibrin strands, stabilize platelet aggregates, and form a thrombus. A recent discovery of mechanisms linking SARS-CoV-2 infection to platelet hyper-reactivity indicates that the spike protein on the envelope of virions or on the surface of SARS-CoV-2 infected cells can activate the calcium-dependent chloride channel and scramblase transmembrane protein 16F (TMEM16F, aka., anctamin 6) expressed in platelets to activate the platelet adhesion and aggregation potentially [44]. (Table1)

The viral infection can also induce vascular injury leading to pyroptosis, which is a program to sell deaths thatch release various damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) [47]. The recognition of PAMPs by monocytes' toll-like receptors (TLRs) and CD14 receptors stimulates the transcription and expression of TF [47]. The cumulative response to the DAMPs and PAMPs is likely to accumulate the immune cell expression of prothrombotic proteins through inflammation and contributes to hypercoagulation [44].

Blocking the ACE2 receptor by SARS-CoV-2 viruses can also lead to increasing Ang II, which promotes the endothelial expression of an array of prothrombotic proteins, including P-selectin, TF, and von Willebrand factor (VWF). The raised combination of soluble thrombomodulin (i.e.,

endothelial glycoprotein) and the other prothrombotic proteins can directly activate the extrinsic coagulation pathway. An increase in inflammation in endothelial cells invaded by SARS-CoV-2 can induce the TF expression on macrophages and platelets, impair the TFPI, which inhibits the TF pathway, and further induce coagulation [48].

3. Beneficial potential of N3PUFA as conjunctive supplements for cardiovascular health in acute and post COVID-19

3.1. N3PUFA and endothelial function

N3PUFA has been shown to reduce the improve damaged endothelial function through various mechanisms. The most significant effect of N3PUFA on endothelial cells is to increase vasodilation nitric oxide (NO) availability, which is mediated by NO synthase (eNOS) activation [49], and enhance eNOS activity [50]. N3PUFA may mitigate the vasoconstrictive effect of endothelin-1. Experiments conducted on human endothelial cells in cultures exposed to eicosapentaenoic acid (EPA), EPA indicated a decrease in endothelin-1 production independent of the effects of EPA on NO [51]. Nevertheless, fish oil supplementation in healthy subjects did not affect plasma endothelin-1 levels over a brief period [52], potentially due to the lower dose. N3PUFA also demonstrated regenerative properties on the endothelium of the blood vessels that are mediated by stimulation of endothelial progenitor cells in healthy individuals and patients with a high CVD risk [53]. (Table1)

N3PUFA may also influence the activity of endothelium-mediated vasodilation and vascular smooth muscle cell (VSMC) function by stimulating the release of adiponectin with vasodilatory properties from perivascular adipocytes. It has been demonstrated that N3PUFA increased plasma adiponectin levels in subjects taking oral supplements of fish oil [54]. Randomized controlled trials (RCTs) examined the association between dietary N3PUFA and endothelium-dependent vasodilation remains inconclusive. However, whilst several RCTs did not establish an improvement in vasodilation [55–57], two studies have shown the beneficial effects of N3PUFA on triglyceride concentration and inflammatory markers [57,58]. (Table1)

3.2. N3PUFA and anti-thrombotic properties

Increasing evidence has supported the anti-thrombotic properties of N3PUFA. The 2018 epidemiology study observed that a diet including a high intake of marine N3PUFA was associated with a reduced risk of venous thromboembolism (VTE) following unprovoked index events [59]. Again, metaanalysis of prospective cohort studies confirmed N3PUFA's protective effect on VTE and recurrent VTE [60]. The 2020 meta-analysis by Zhang et al. [60] evaluated the overall multi-variable adjusted RR, reporting the significant inverse association between N3PUFA consumption and the risk of venous thromboembolism (VTE) (RR = 0.89, 95%CI: 0.80-0.98, P=0.024). The 2017 RCT by Bonutti and colleagues examined the anti-thrombotic effect of the daily consumption of 325 mg aspirin and 1g N3PUFA-rich fish oil for 90 days significantly reduced the VTE after surgery for primary total knee arthroplasty [61]. A more recent RCT compared the daily supplementation of 1g N3PUFA also reported significantly reduced deep vein thrombosis after 30 days [62].

There are several mechanisms by which N3PUFA can exert their anti-thrombotic effects. (Table1) One of the most well-studied mechanisms is their ability to inhibit the platelet-activating factor and other prothrombotic pathways [63]. Similar to other mammalian cell membranes, the platelet membrane has a lipid bilayer consisting of an outer leaflet of cholinephospholipids (primarily phosphatidylcholine and sphingomyelin) and an inner leaflet of negatively charged aminophospholipids (i.e. phosphatidylethanolamine (PE) and phosphatidylserine (PS)) [64]. Numerous aspects of platelet function rely heavily on the platelet phospholipid membrane [64]. Several enzymes dependent on calcium and adenosine triphosphate (ATP) control the asymmetric distribution of membrane phospholipids [65]. Upon platelet activation, this asymmetric orientation of membrane phospholipids is disrupted, leading to calcium-dependent exposure of PS on the platelet surface. It is well known that PS surface exposure is a crucial component of normal hemostasis because it facilitates platelet procoagulant functions. The formation of the

prothrombinase complex on the surface of platelet membranes facilitates the conversion of prothrombin to thrombin, thereby enhancing platelet activation [66,67].

Elevated levels of N3PUFA may alter platelet phospholipid membrane composition and platelet function, thereby influencing the progression and thrombotic complications of CVD. (Table1) EPA and docosahexaenoic acid (DHA) can act on the platelet membrane to reduce platelet aggregation and thromboxane (TX) release via cyclooxygenase-1 (COX-1) and 12-lipoxygenase (12-LOX), which metabolize fatty acids into a group of beneficial oxylipins in platelets that significantly regulate platelet function in hemostasis and thrombosis [68]. Even in healthy subjects, 4-week EPA supplementation successfully decreased platelet activation, an early step in platelet aggregation [69]. Particularly, as a COX substrate, it appears EPA is more active than DHA in altering platelet function, although the evidence is limited, whilst DHA appears to reduce the affinity of thromboxane A₂ (TxA₂) and increase the production of prostacyclin (PGI₂) [68]. TxA₂ is a pro-inflammatory molecule that promotes platelet aggregation and vasoconstriction, while PGI₂ is an anti-inflammatory molecule that promotes vasodilation and inhibits platelet aggregation. By reducing the production of TxA₂ and increasing the production of PGI₂, N3PUFA can help prevent blood clot formation. In platelet hyperactivity pro-thrombotic conditions, a higher dose of N3PUFA might be necessary to reduce platelet activation and aggregation [68]. In addition, N3PUFA have been shown to decrease the levels of fibrinogen, a protein involved in blood clot formation, and increase the levels of tissue plasminogen activator (tPA), an enzyme that breaks down blood clots. By reducing fibrinogen levels and increasing tPA levels, N3PUFA fatty acids can help to prevent the formation and promote the dissolution of blood clots [68].

These anticoagulant properties of n-3 PUFAs suggest possible effects on platelet aggregation in patients with severe COVID-19 illness. We can only speculate at this time as to whether n-3 PUFAs can mitigate the coagulopathy associated with severe COVID-19. More research is needed to fully understand the mechanisms by which N3PUFA fatty acids exert their anti-thrombotic effects and to determine the optimal dose and duration of N3PUFA fatty acid supplementation for preventing thrombosis.

3.2. N3PUFA and inflammation

During viral infection, inflammation induced by a relatively low level of oxidative stress (a low or medium concentration of reactive oxygen species (ROS) and reactive nitrogen species (RNS)) can be sufficient to generate an environment hostile enough to eradicate phagocytosed viruses (e.g., by pulmonary alveolar macrophages). Nonetheless, a prolonged or unresolved inflammatory process is associated with the overproduction of reactive oxygen species (ROS), which compromises the antioxidant activities of the body's defences, resulting in extensive cellular and tissue damage [70,71]. SARS-CoV-2 infection causes a significant increase in systemic oxidative stress and inflammation [72–74]. (Table1)

N3PUFA are metabolic substrates of lipoxygenase and cyclooxygenase, which produce "specific pro-resolving mediators" ((SPM) resolvins, protectins, and maresins) that end acute inflammatory responses. EPA competes with inflammatory arachidonic acid (AA), the metabolic precursor of proinflammatory and prothrombotic eicosanoids in cell membrane phospholipids, for the eicosanoids enzymatic route, reducing prostaglandins, leukotrienes, and thromboxanes [75]. (Table1)

N3PUFA SPM reduces proinflammatory cytokines, leukocyte migration, and macrophage activity at the inflammatory site [76]. If healthy participants ingest more than 2 g/day of N3PUFA, their primary mononuclear cells release less tumor necrosis factor- α (TNF- α), interleukin-1, and interleukin-6 during endotoxin stimulation [77]. N3PUFA also suppress interleukin-2 and T-lymphocyte proliferation, adhesion molecules, and platelet-activating factor's pro-thrombotic action [77]. (Table1)

Activator protein 1 (AP-1) and Nuclear factor kappa B (NF κ B) are downregulated by N3PUFA binding to G-protein receptor 120 [78]. NF κ B stimulates pro-inflammatory cytokines and adhesion molecules, while AP-1 activates TNF- α . Lastly, N3PUFA influences inflammasomes, the innate immune system sensor and receptor proteins that form intra-cytoplasmic complexes in response to

damaging stimuli. Infection, wounded cell host molecules, and cardiovascular risk factors such as advanced glycation end-products and oxidized low-density lipoproteins activate inflammasomes. EPA and DHA can suppress the NF κ B and stimulate inflammasome lysosomal autophagy [17]. (Table1)

4. N3PUFA form and bioavailability

Since 1994, N3PUFA has been investigated and established for its health benefits; amongst the most tremendous was to improve cardiovascular health. N3PUFA conferred cardiovascular benefits through reducing triglycerides, anti-inflammation, vasodilation, anti-hypertension, improving endothelial function, and reducing platelet aggregation [79]. N3PUFA was named based on the presence of the closest double bond to the methyl end of the hydrocarbon (acyl) chain being on carbon number three, counting the methyl carbon as number one. Within the N3PUFA family of polyunsaturated fatty acids, the most well-studied are linolenic acid (LNA) and its derivatives, including the plant-derived α -linolenic acid (ALA; 18:3n-3), and EPA (20:5n-3), DHA (22:6n-3) [15], and docosapentaenoic acid (DPA; 22:5n-3) that are derived from marine [80].

The metabolic conversion pathway of plant-derived ALA to bioactive EPA requires the help of Δ 6-desaturase to form Stearidonic acid, which then transforms to Eicosatetraenoic acid via elongation, then to DHA by desaturation with the involvement of Δ 5-desaturase. In human, the metabolism is influenced by various factors (e.g., age, sex, hormonal change, genetics, etc.), the conversion rate can be relatively low, and the health benefits of ALA is limited [81]. Only around 8% of dietary ALA is converted to EPA and less than 4% to DHA in healthy young males, whereas in healthy young females, 21% of dietary ALA is converted to EPA and 9% to DHA [82,83]. Moreover, ALA has low bioavailability due to a higher rate of oxidation. In comparison, DHA has more bioavailability owing to its characteristic as a poor β -oxidation substrate [14]. Marine-derived EPA and DHA are considered better N3PUFA sources.

Following ingestion, N3PUFA is hydrolyzed, like the other dietary lipids, in the intestinal to FFAs and monoglycerides, which can then be incorporated into micelles after bile salt emulsification and absorbed into enterocytes by passive diffusion into chylomicrons [84]. The chylomicrons containing FFAs are delivered to various organs through lymphatic circulation for further metabolism [84]. Absorption and, thus, bioavailability is affected by factors such as intestinal pH, bile secretion, microorganisms, type of chemical bond, concurrent food consumption, other components such as calcium [81], and the different forms of N3PUFA. N3PUFA exists in various forms, which are free fatty acids (FFAs, including free EPA, DHA, and DPA), triglycerides (TG), ethyl esters (EE), and phospholipids [82,84]. The unrefined fish oil contains mainly triglycerides with various amounts of N3PUFA (i.e., EPA, DHA, DPA as fatty acids) attached to glycerol in low concentration. Various purification methods have been adopted to increase the EE and TG forms of N3PUFA. Amongst all, the ethylating purification method removes the glycerol backbone of triglycerides to release the EPA and DHA, while removing the shorter-chain fatty acids. The FFAs are then esterified to an ethanol backbone to form ethyl esters (i.e., EE form N3PUFA). The alternative method to increase N3PUFA content is to break down concentrated EE form N3PUFA into FFAs and then esterify the FFAs to a glycerol alcohol backbone to form re-esterified TG forms of N3PUFA [85]. As EE form requires the extra hydrolysis step to separate the FFAs from the ethyl carrier in the human intestine [86], the FFAs and TG form N3PUFA have higher bioavailability ester. In an acute study, the absorption of EPA in TG form is 90% compared to 60% in EE form [85]. The 2-week study of 72 adults by [87] reported a higher bioavailability of 3.3 g of re-esterified TG from EPA and DHA (124%) compared to natural fish oil, whilst EE form (73%) was lower. The significantly lower bioavailability of EE forms compared to TG forms tended to be of short duration (8-12 hours) and provided that a large dose of N3PUFA (over 3 grams of EPA and DHA) was provided to participants. However, the results from long-term comparative studies suggest no significant difference in the absorption of EPA and DHA between TG or EE forms when N3PUFA is routinely consumed as dietary supplements. A long-term study [88] reported no significant difference in bioavailability between TG and EE forms after 9 healthy males consumed 1.1 gram EPA and 0.37 gram DHA over 3 month period. Sadovsky and Kris-

Etherton [89] pointed out that the beneficial effect of EE form on objective health parameters, such as decreasing plasma triglycerides, initiated at 1 month post supplementation and reached maximum effective at 2 month. A short-term statistically significant difference in absorption and bioavailability does not necessary reflect the overall bioavailability and clinical impact in the long-term.

5. High N3PUFA dose can be essential in protecting cardiovascular health in COVID-19

N3PUFA has conferred cardiovascular health by reducing inflammation, anti-oxidative stress, improving arterial and endothelial functions, and reducing platelet aggregation [79]. Since our body cannot synthesize N3PUFA, we highly rely on dietary intake to replenish them [83]. The epidemiological evidence reported that the intake of EPA and DHA from the diet is strongly associated with fatty fish consumption. In contrast, the intake of N3PUFA varies significantly among different populations and is generally lower than recommended 0.2 - 0.5 g/day for general adults [90–92] (depending on the various authorities making the dietary recommendation guidelines) in most Western countries of which the main protein source is meat instead of fish [93,94]. The inclusion of supplements that contain EPA and DHA is essential if the daily recommendation cannot be met through food intake only.

Particularly, the well-known biological parameter, triglyceride concentration, has demonstrated a dose-dependent relationship with N3PUFA. A significant reduction (20-50%) in blood TG was reported in patients with high baseline TGs after consuming 3 to 4 grams/day of EPA or a combination of EPA and DHA [95]. However, controversies surrounding the clinical trials involving various N3PUFA daily doses emphasize the importance of high-dosage N3PUFA in reducing CVD risks, including the combining stroke, MI, and death from CVD causes and major cardiovascular events. Therefore, to establish the dose that can demonstrate clinically significant cardiovascular benefit, review the previous RCTs that studied the association between N3PUFA and CVD. Although there is a lack of consensus among the scientists and clinicians, clear evidence from decades of studies is able to assist the recommendation.

Table 2. Characteristics of parallel-design RCTs of N3PUFA.

Year	Trial	Population	No. subjects	Age (yr)	Male (%)	Subjects	N3PUFA ¹ , dose	Control	Study period	Result
						characteristics				
1999	GISSI-P [96]	Italian	11,324	59	84.7	Surviving recent (≤3 months) myocardial infarction	N3PUFA, 1g/day	Vitamin E, 300 mg/day	3.5 yr	↓ RR ² of death = 10% (95% CI: 1 - 18%); ↓RR of CVD = 17% (95% CI: 3 - 29%)
2007	JELIS [97]	Japanese	18,645	Average 61	31.4	Total cholesterol ≥ 6.5 mmol/L	EPA ³ , 1.8g/day; statin	Statin only	5 yr	↓19% RR in major cardiovascular events
2008	GISSI-HF [99]	Italian	955	≥ 18	77.8	With chronic heart failure of New York Heart Association class II-IV,	N3PUFA, 1g/day	Placebo	3.9 yr	↓HR ⁴ of death = 0.91 (95% CI: 0.833 - 0.998); ↓HR of

						irrespective of cause and left ventricular ejection fraction				hospital admission for cardiovascular reasons = 0.92 (95% CI: 0.849 - 0.999) ↓HR of death = 0.57 (95% CI: 0.29 - 1.10); ↓HR of cardiovascular events = 0.86 (95% CI: 0.57 - 1.38)
2010	DOIT [99]	Norwegian	563	64–76	100	Without overt cardiovascular disease	N3PUFA, 2.4 g/day	Placebo (corn oil)	3 yr	
2010	SU.FOL.OM3 [100]	France	2,501	45-80	79.5	With a history of myocardial infarction, unstable angina, or ischaemic stroke	5-methyltetrahydrofolate, 560 µg/day, vitamin B6, 3 mg/day, vitamin B12, 20 µg/day; N3PUFA, 0.6 g /day	Placebo	4.7 yr	No significant effect on major cardiovascular events
2010	Alpha-OMEGA [101]	Netherland	4,837	60-80	78.0	Had a myocardial infarction, received state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy	N3PUFA, 0.376 g/day (EPA, 0.226 g/day; DHA ⁵ , 0.150 g/day)	ALA, 1.9 g/day	NA	→ HR of major cardiovascular events = 1.01 (95% CI: 0.87 - 1.17)
2010	OMEGA [102]	German	3,851	64	74.4	3 to 14 days after acute myocardial infarction	N3PUFA (EE form), 1g/day	Placebo	1 yr	No significant difference in sudden cardiac death, total

										10
										mortality, major adverse cerebrovascular and cardiovascular events → HR of time to death or admission to the hospital for cardiovascular causes, 0.97 (95% CI: 0.88 - 1.08)
2012	ORIGIN [103]	Canadian	12,536	≥ 50	40.0	At high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance, or diabetes with multiple cardiovascular risk factors or atherosclerotic vascular disease but not myocardial infarction	N3PUFA (EE form), 0.9g/day	Placebo	6.2 yr	→ HR of the rates of major cardiovascular event, 1.01 (95% CI: 0.93 - 1.10)
2013	R&P [104]	Italian	12,513	≥ 65	61.5	With stable, existing CVD (>12 months since initial event)	N3PUFA (EE form), 1g/day	Placebo	1 yr	→ HR of risk of CVD or secondary CVD outcomes, 0.95; 95% CI, 0.78-1.17
2014	AREDS-2 [105]	USA	4,203	50-85	56.8	With an acute MI	N3PUFA, 1g/day (EPA, 650 mg/day; DHA, 350 mg/day); lutein, 10 mg/day; zeaxanthin, 2 mg/day	Placebo	4.8 yr	↓ LVESVI ⁶ (-5.8%, P = 0.017); ↓ non-infarct myocardial fibrosis (-5.6%, P = 0.026)
2016	OMEGA-REMODEL [106]	USA	358	> 21	65.0	With diabetes but	N3PUFA, 4g/day (EPA, 465mg/day; DHA, 375mg/day)	Corn oil (Linoleic acid, no N3PUFA, 600mg/day)	6 mth	No significant
2018	ASCEND [107]	UK	15,480	≥ 40	62.6		N3PUFA, 1g/day	Olive oil, 1g/day	7.4 yr	

						without evidence of atherosclerotic cardiovascular disease					difference in serious vascular event or revascularization
											No significant difference in serious vascular event; ↓ HR of MI= 0.71 (95% CI:0.59–0.9)
2019	VITAL [108]	USA	25,871	> 50 (males) > 55 (females)	49.9	Healthy	N3PUFA, 1g/day; vitamin D3 2000 IU/day	Placebo	5.3 yr		
						With established cardiovascular disease or with diabetes and other risk factors, receiving statin therapy, fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter), a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter)	EPA (icosapent ethyl highly purified EPA formulation), 4g/day	Placebo	4.9 yr		↓ HR of major cardiovascular events = 0.75 (95% CI: 0.68 - 0.83)

¹ N3PUFA, n-3 polyunsaturated fatty acid; ²RR, relative risk; ³EPA, eicosapentaenoic acid; ⁴HH, hazard ratio; ⁵DHA, docosahexaenoic acid; ⁶LVESVI, left ventricular systolic volume index.

Since the first landmark clinical trial that investigated the cardiovascular protective effect of N3PUFA in 1999, controversies have been reported. The GISSI-P study in the Italian population was the first study that demonstrated the 1 g of N3PUFA (combination of EPA and DHA) supplement /day significantly reduced the RR of death by 10% (95% CI: 1 -18%) and severe cardiovascular events by 17% (95% CI: 3 - 29%) comparing to the control group who consumed 300 mg/day of vitamin E

[96]. The later GISSI-HF study again demonstrated a significant reduction in the hazard ratio (HR) of death and hospital admission for cardiovascular reasons after the subjects were on the same dose for 3.9 years [98]. The fundamental development in CVD treatment has been achieved, including aggressive therapy, since GISSI-P study was published. Yokoyama et al. [97] also demonstrated in the 2007 JELIS study that daily addition of 1.8 g EPA to standard statin medication /day significantly reduced related risk of major coronary events in Japanese subjects who had equal or higher than 6.5 mmol/L total cholesterol after 5 years follow-up. However, in the OMEGA study, where the majority of subjects received statin therapy at baseline, there was no significant improvement in sudden cardiac death, total mortality, or major adverse cerebrovascular and cardiovascular events (MACE) [102]. There is a possibility that the pre-clinical trial optimal medial therapy could contribute to the insignificant efficacy. (Table 2)

Notably, the study populations in large-scale studies that showed a significant reduction in CVD risk were from high seafood intakes regions, such as the Italian population in GISSI-P and GISSI-HF studies and the Japanese population in the JELIS study, who potentially have higher baseline N3PUFA concentrations due to high dietary supply (Table 1). Previous studies have raised the possibility that a threshold of endogenous level may be required to show the statistical significance of N3PUFA on CVD risk. Population with a higher baseline of N3PUFA reservation may need a lower dose of N3PUFA to show statistically significant improvement in cardiovascular health; on the opposite, Western populations with lower fatty fish consumption are likely to require a higher N3PUFA dose. A 2010 small RCT of elderly Norwegian males (n = 563) at high risk of developing CVD (72% without overt CVD), DOIT study, reported a tendency towards reduction of all-cause mortality and cardiovascular events that reaching statistical significance after the subject was on a doubled dose (2.4 g/day) despite the smaller sample size [99]. The VITAL study [108] has also shown that the subjects, who received the most cardiovascular benefit from the N3PUFA supplement, had the lowest baseline levels of N3PUFA concentration. (Table 2)

The findings from later studies using the low dose N3PUFA (0.376 – 1 g/day) failed to demonstrate its sufficiency for populations who have lower average fatty fish consumption to reach the same therapeutic benefit to lower cardiovascular risk [100–105,107,108] (Table 1), including the SU.FOL.OM3 study, Alpha-OMEGA study, OMEGA study, ORIGIN study, R&P study, AREDS-2 study, ASCEND study. Although the VITAL study of the US cohort found that daily administration of 2000 IU/day of vitamin D3 and 1 g/day of N3PUFA (combination of EPA and DHA) did not significantly reduce the risk of CVD when compared to the placebo group after 5.3 years of intervention [108], a statistically significant decrease in HA of MI was reported. It was until the OMEGA-REMODEL study found that high-dose N3PUFA (4g/day of EPA and DHA combination) appeared to be beneficial for 6 months after acute MI demonstrated a reduction in adverse left ventricular remodeling, non-infarct myocardial fibrosis and serum biomarkers of systemic inflammation beyond the current guideline-based standard of care [106]. The most recently conducted multi-center REDUCE-IT study reported that the high N3PUFA dose of 4 g/day (icosapent ethyl, highly purified EPA) significantly reduces major cardiovascular events in a multi-population, particularly in US participants who had low baseline N3PUFA level [109]. (Table 2)

Moreover, the findings from later studies using the low dose N3PUFA (0.376 – 1 g/day) failed to demonstrate its sufficiency for populations who have lower average fatty fish consumption to reach the same therapeutic benefit to lower cardiovascular risk [100–105,107,108] (Table 1). It was until the most recently conducted multi-center REDUCE-IT study reported that the high N3PUFA dose of 4 g/day (icosapent ethyl, highly purified EPA) significantly reduced the major cardiovascular events in a multi-population, particularly in US participants, who receive statin therapy [109]. The treatment cohort significantly reduced the primary endpoint (composite of CVD death, non-fatal MI, non-fatal stroke, CV revascularization or unstable angina) by 25% and the secondary endpoint MACE by 26% [109]. The sub-cohort of the US reduced the RR of all-cause mortality by 30% and the absolute risk by 2.6% [109]. (Table 2)

Recent meta-analyses have examined the potential sources of heterogeneity in the effect of N3PUFA on cardiovascular health. The 2019 meta-analysis by Hu and colleagues [110] conducted a

meta-regression of 13 RCTs, excluding REDUCE-IT, and concluded that marine N3PUFA supplementation was negatively associated with the risk of MI (RR = 0.92, 95% CI: 0.86, 0.99; P=0.020), CHD death (RR = 0.92, 95% CI: 0.86, 0.98; P=0.014), total CHD (RR = 0.95, 95% CI: 0.91, 0.99; P=0.008), CVD death (RR = 0.93, 95% CI: 0.88, 0.99; P=0.013), and total CVD (RR = 0.97, 95% CI: 0.94, 0.99; P=0.015). The negative association was further strengthened when the REDUCE-IT study was included [110]. Bernasconi and colleagues [111], in the updated 2020 meta-analysis, stated that N3PUFA of EPA and DHA combination statistically significantly reduced the risk of CVD and MI by 9% and 13%, respectively. Moreover, a dose-dependent association is reported between the reduction of MI risk (9% reduction) and an additional 1 g/day of N3PUFA [111], indicating that the higher dose provided significantly higher protection. One 2017 meta-analysis that reviewed the minimal dose required for a clinically meaningful change in triglyceride concentration suggested that the low dose of N3PUFA could explain the inconsistent results in previous RCTs (< 1.5 g/day of EPA and DHA combination) [112]. A recent update on the dose recommendation of N3PUFA reviewed the threshold of baseline N3PUFA index, and the supplementation dose has suggested that high-dose N3PUFA (4 g/day) appears to be more beneficial among the people with low baseline N3PUFA (< 8% N3PUFA index, a measurement of serum N3PUFA level). In contrast, the low dose (1 g/day) may only benefit people with a high baseline ($\geq 8\%$ N3PUFA index) [113]. Further work including clinical trials on high dose concentrated ethyl esters (i.e., EE form) N3PUFA will be conducted and funded by Pharma New Zealand PNZ Limited.

6. Conclusions

COVID-19 can cause a hyperinflammatory response that leads to the formation of blood clots, which can affect blood vessels throughout the body, including those that supply the heart. There is growing evidence that COVID-19-related immunothrombosis can increase the risk of CVD. Patients with pre-existing CVD are at a higher risk of experiencing complications from COVID-19. It is vital for healthcare providers to monitor COVID-19 patients for signs of CVD and provide appropriate treatment to reduce the risk of complications.

At this time, there are no clear studies that demonstrate the positive effects of N3PUFA on COVID-19 patients. However, high dose concentrated N3PUFA (4 g/day) have been shown to regulate and modulate certain negative immunological overreaction effects, limit coagulopathy, and influence cell signaling and gene expression. They are well-known to have antithrombotic, anti-inflammatory, and pro-resolving properties, which can be advantageous for COVID-19 patients. The ingestion of N3PUFA and/or their metabolites may prevent and manage cardiovascular and thrombotic issues in COVID-19 patients. It is, therefore, prudent to study the possible uses of fish oil/N3PUFA PUFAs supplementation as an adjuvant to medication in COVID-19 patients at risk for vascular thrombotic events.

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