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Modulation of inflammation and immunity by Omega-3 fatty acids: a possible role for prevention and to halt disease progression in autoimmune, viral, and age-related disorders

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Abstract. **Omega-3 polyunsaturated fatty acids (PUFA) have demonstrated anti-inflammatory properties, while Omega-6 have pro-inflammatory effects, and the balance between the two is an important aspect of healthy nutrition. Over the last 30 years, however, the Western diet has shifted largely from Omega-3 to Omega-6 consumption. Uncontrolled aberrant and chronic inflammation is a leading component of many common diseases, including arthritis, cardiovascular diseases, neurodegenerative diseases, cancer, obesity, autoimmune diseases, and infective diseases. Eicosanoids derived from Omega-6 participate in the inflammatory process, while Omega-3 PUFA have the opposite effect. Many favorable effects of Omega-3 are believed to result from their anti-inflammatory properties, but eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) also have inhibitory effects on immune cells and reduce proinflammatory cytokine release. All these mechanisms can be beneficial in autoimmunity. No effective preventions or definite cures for autoimmune diseases are yet known because pathophysiology is also unclear. Omega-3 fatty acid supplementation is associated with a significant reduction in disease activity in several autoimmune diseases, like type 1 diabetes (T1D), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and multiple sclerosis (MS). Studies of viral diseases, including COVID-19, show improvement in symptom severity, recovery prognosis, and probability of survival with the use of Omega-3. Finally, the evidence of the beneficial effect of Omega-3 on metabolic diseases associated with aging is persuasive; various studies have demonstrated that their consumption improves lipids, fatty liver disease, obesity, cognitive function, and cardiovascular complications of chronic kidney disease (CKD). Omega-3 PUFA have also been shown to support an anti-inflammatory effect in older age and to have favorable effects on age-related disease's complications, frailty, and mortality. A healthy Omega-6/3 PUFA ratio should be targeted for the modulation of low-grade inflammation, as well as for the prevention of immune dysregulation and complications of uncontrolled inflammation triggered by infections, development, and progression of autoimmune disorders, and the consequences of oxidative stress due to aging. There is still a need for randomized clinical studies to validate current evidence supporting supplementation with correct doses of Omega-3 PUFA in autoimmune and chronic disease prevention.**

Key Words:
Omega-3 fatty acids, Inflammation, Autoimmune diseases, Age-related disease, Viral diseases.

Definition and Function

Polyunsaturated fatty acids (PUFAs) represent a type of fat molecule predominantly found in lipid constituents like triglycerides, consisting of approximately 20 hydrocarbon units that possess a minimum of two carbon atoms connected by double or triple bonds, resulting in an incomplete saturation by hydrogen atoms. There are two primary categories of PUFAs: Omega-3 and Omega-6. The primary distinction between them is the placement of their double bonds on the carbon chain, either at position 3 or 6. The three major Omega-3 PUFAs are α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Mammals are unable to produce the essential Omega-3 fatty acid known as a-linolenic acid. However, they could synthesize EPA and DHA from alpha-linolenic acid, even though less than 5% and 1% can be metabolized into EPA and DHA, respectively[1]. Consequently, mammals depend on obtaining these fatty acids through their diet. Some Omega-6 are also essential fatty acids, like linoleic acid (LA), others are not, like arachidonic acid (AA).

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Diet Source

Nutritional sources of PUFA are mainly nuts and fish, particularly small oily fish, like anchovy, sardine, or mackerel. ALA is found in vegetable sources, nuts, and seeds, while EPA and DHA are the main components of fish oil. Omega-6, like LA and AA, are found in refined vegetable oils, meat, poultry, eggs, and milk[2]. Omega-3 has anti-inflammatory properties, while Omega-6 has pro-inflammatory effects, but the balance between the two is the most important part of healthy nutrition. The Western diet has changed dramatically in the last 30 years, in many deleterious ways, including a shift toward a higher Omega-6/Omega-3 ratio. In fact, foods consumed in industrialized countries are now dominated by Omega-6 PUFAs and contain only small amounts of Omega-3 PUFAs, with the ratio of Omega-6/Omega-3 reaching as high as 20-30, which has been linked to chronic inflammation. Consuming less seafood and less whole foods decreases Omega-3 intake. The lower consumption of seafood, particularly fresh and rich in Omega-3 PUFA seafood like salmon, trout, crabs, oysters, and mussels, may be partially related to the lower affordability of this diet[3]. Canned fish retains a portion of its Omega-3 PUFA content, although processing can reduce it to some extent. Likewise, frying fish leads to a decrease in the amount of Omega-3 PUFA present. Indigenous populations like the Eskimos, known for their high fish consumption, experienced remarkably low occurrences of autoimmune and inflammatory conditions such as type 1 diabetes, asthma, multiple sclerosis, and psoriasis[4]. Research conducted on Greenland Eskimos indicated that a diet rich in Omega-3 polyunsaturated fatty acids might contribute to decreased instances of these inflammatory diseases by modifying eicosanoid precursors and influencing other related pathways. Due to the alarmingly elevated Omega-6 to Omega-3 ratio commonly found in individuals who regularly consume a modern Western diet, initiatives have been undertaken to integrate Omega-3 fatty acids into the food supply, given their numerous health advantages; farm animals are also fed marine products. Despite its potential benefits, this process is expensive and time-consuming, and its feasibility is constrained by the number of available resources. Maintaining a favorable Omega-3 fatty acid status is achievable even with a vegetarian diet, by regularly incorporating reliable sources of alpha-linolenic acid (such as walnuts, flaxseeds, chia seeds, and their oils) while restricting the consumption of linoleic acid (found in corn and sunflower oils)[5]. If a return toward dietary styles containing less inflammatory foods (immunonutrition) and rich in Omega-3, micronutrients, and fibers, is going to be a difficult and slow process of social nutrition, taking a long-term supplement of Omega-3 (immunoceutical) can be an easily available, convenient, and relatively inexpensive way to reduce chronic inflammation. Most inflammatory diseases improve by increasing dietary intake of Omega-3, which can be associated with benefits throughout life[6].

Inflammation and Omega-3 Fatty Acids

While acute inflammation is self-limited, protective and necessary for restoring homeostasis in the affected tissues, chronic uncontrolled aberrant inflammation is a significant contributing factor to many common diseases; examples of such diseases include arthritis, inflammatory bowel diseases, periodontal diseases[7], cardiovascular diseases, neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, asthma, cancer, obesity and metabolic syndrome, diabetes and autoimmune diseases. Eicosanoids derived from Omega-6, such as prostaglandin (PG), thromboxane (Tx), leukotriene (LT), are participating in the inflammatory process; the Omega-3 PUFA instead are not metabolized to these pro-inflammatory molecules and actually seem to have the contrary effect, as described below. Anti-inflammatory medications, such as non-steroidal anti-inflammatory drugs (NSAIDs), control mediators of inflammation like PGs, but not without side effects, sometimes severe, especially if used chronically. Some anti-inflammatory therapies may even become damaging in the long term because they are immunosuppressive, like glucocorticoids for example, while instead an increase in molecules that promote endogenous resolution of aberrant inflammation, like the powerful resolvins, which are derived from Omega-3, avoids the side effects and in particular the immunosuppressive effect. The Omega-3-derived metabolites are able to regulate the native immune response of B and T lymphocytes and their cytokines, decreasing interleukin (IL)-2, tumor necrosis factor alpha (TNF-α) and interferon-gamma (IFN-γ) secreted by CD8 positive T cells, control the differentiation of CD4+ T-cells into T-helper 1 (Th1) and Th1[7], and increase IgG production by B cells.

Randomized controlled trials have shown improvements in clinical manifestations of rheumatoid arthritis (RA), systemic lupus erythematosus, and psoriasis with Omega-3 fatty acids but definite long-term studies proving the prevention of autoimmunity are lacking, or results are not clear, as it is possible that many years of Omega-3 intake, in the context of a generally healthy and anti-inflammatory diet, are necessary to demonstrate an advantageous effect. If that could be demonstrated, though, an inexpensive and simple strategy may give a valuable opportunity to implement this supplementation broadly in the general population, especially in high-risk subjects, and prevent the onset and progression of inflammatory and autoimmune diseases. Our hypothesis is that maintaining Omega-3 levels elevated, in relation to Omega-6, may help the body to restore the innate capacity to modulate hyperinflammatory and hyperimmune reactions that become lost when autoimmunity's trigger factors, viral diseases or age-related degenerative diseases, that have in common an inflammatory underlying state, happen.

Dietary marine-derived long-chain Omega-3 fatty acids decrease systemic inflammation and ameliorate clinical manifestations and laboratory parameters in some autoimmune diseases. Evidence is still inadequate on whether Omega-3 fatty acids can lower the risk of developing autoimmune diseases, such as in the VITAL trial[8] where Vitamin D supplementation for five years, with or without Omega-3 fatty acids, reduced autoimmune disease risk by 22%, while the supplementation with Omega-3 fatty acid alone reduced the autoimmune disease rate by 15%, which was not statistically significant compared to the reference arm.

The VITAL study[8] revealed that taking Omega-3 in combination with vitamin D can lead to a decrease in autoimmune diseases, as the two nutrients can work synergistically to reduce inflammation; however, when the Omega-3 was taken alone at the dosage studied, the incidence of autoimmune diseases was not significantly decreased, as reported by participants, and confirmed by review of medical records. Nonetheless, the supplementation with Omega-3 PUFA did reduce the rate of autoimmune diseases compared to placebo when participants with "probable" autoimmune disease were included, and a significant interaction was observed with time, pointing to an increased effect after a longer duration of supplementation. A sub-study of VITAL study[9] participants assessed the levels changes of systemic inflammation biomarkers like IL-6, TNF receptor 2, and high sensitivity C reactive protein and found no evidence of reductions by Omega-3 alone over the first 2 years. Other studies in animals and *in vitro*, though, indicate that increased dietary intake of eicosapentaenoic acid and docosahexaenoic acid inhibits the production of C reactive protein (CRP) and inflammatory cytokines such as TNF-α, IL-1β, and IL-6, on top of decreasing T cell proliferation and activation and functioning as substrate for specialized pro-resolving lipid mediators, including resolvins, protectins, and maresins, which promote inflammation's resolution. It is probable, we believe, that the timing (the study was done in older adults >55 years of age), length of treatment, and the dose of the Omega-3 in the VITAL study were not sufficient to show the full advantage[10], especially if patients had a background diet rich in Omega-6.

Omega-3 fatty acids have been shown, in fact, as described previously, to have anti-inflammatory effects by decreasing the production of pro-inflammatory cytokines and eicosanoids, such as prostaglandins and leukotrienes. This is partly due to their ability to compete with Omega-6 fatty acids for enzymes involved in eicosanoid synthesis, resulting in a decreased production of pro-inflammatory eicosanoids. In addition, Omega-3 fatty acids can also modulate the activation of immune cells, such as macrophages and T cells, resulting in a decreased inflammatory response.

Several studies have demonstrated the anti-inflammatory effects of Omega-3 fatty acids in various diseases. In a study[11] of patients with rheumatoid arthritis, supplementation with Omega-3 fatty acids resulted in a decrease in the production of pro-inflammatory cytokines and a decrease in disease activity. Similarly, supplementation with Omega-3 fatty acids was found to decrease inflammation and improve clinical outcomes in individuals with inflammatory bowel disease[12]. Omega-3 fatty acids have also been shown[13] to be beneficial in asthma, where they decrease airway inflammation and improve lung function.

Prevention of Age-Related Disease Progression and Omega-3 Fatty Acids

Aging is thought to be linked with persistent activation of the inflammatory response, often referred to as inflammaging, in both men and women. As individuals age, there is an increase in

blood levels of inflammatory markers, regardless of other health conditions, which contributes to the development of anabolic resistance, appetite loss, muscle wasting, and frailty in elderly individuals. Omega-3 PUFA have been consistently demonstrated in a majority of clinical and translational research[14] to exert anti-inflammatory properties in the elderly population.

Lipids and CV

Cardiovascular disease remains the leading cause of death worldwide. Supplementation with EPA and DHA appears to be an effective lifestyle strategy for cardiovascular disease (CVD) prevention, and the protective effect probably increases with dosage[15].

The well-known fact that increased intake of polyunsaturated fatty acids, particularly Omega-3 types like EPA and DHA, leads to reduced levels of plasma cholesterol[16] and triglycerides (TG) level and reduction of coronary heart disease (CHD) and heart failure[17] has been widely acknowledged. Omega-3 PUFA have been shown to decrease cardiovascular disease in several clinical trials in the last 20 years, starting with the Japanese JELIS[18] study on Omega-3.

Trials like JELIS, REDUCE-IT[19] and RESPECT-EPA[20] indeed demonstrated significant reduction in cardiovascular events with high dose of EPA. In contrast, other studies, including the most recent VITAL, utilizing other formulations of Omega-3 EPA+DPA combinations, failed to demonstrate such clear benefits.

The VITAL study[8] mentioned in the introduction is a completed randomized, double-blind, placebo-controlled trial for the primary prevention of cancer and cardiovascular (CV) disease in adults, that had negative results because the treatment was not demonstrated to be effective. Ancillary studies, in subsets of VITAL participants, investigated the role of Omega-3 PUFA in the prevention of other diseases like diabetes and autoimmune diseases[8]. Participants received a daily dosage of 1 g marine Omega-3 PUFAs (comprised of 460 mg EPA and 380 mg DHA in a fish oil capsule), either with or without vitamin D, for a period of 5 years. Using a two-by-two factorial design, patients were randomly assigned to one of four groups: (i) 2,000 IU active vitamin D and 1 g active Omega-3, (ii) active vitamin D and Omega-3 placebo, (iii) vitamin D placebo and 1 g active Omega-3, or (iv) vitamin D and Omega-3 placebos. This dose of Omega-3 is very small, for example, compared to the dose used in the REDUCE-IT study[19], possibly not high enough to reduce CV risk[10] but also not powerful enough to counteract the underlying inflammation[21] of autoimmunity, and especially in the contest of unknown Omega-6 content in the diet of the population studied.

Omega-3 fatty acids can lower the likelihood of developing cardiovascular disease by lowering blood pressure, on top of decreasing triglycerides and reducing inflammation. A meta-analysis[22] was conducted on ten trials involving 77,917 individuals to explore the relationship between the use of Omega-3 fatty acid supplementation and the risks of cardiovascular diseases. The findings indicated that, while the use of Omega-3 supplements was not significantly associated with a reduced risk of major cardiovascular events, such as heart attacks and strokes, it was associated with a slightly lower risk of coronary heart disease. The study suggests that the evidence supporting the use of Omega-3 supplements to prevent cardiovascular diseases remains inconclusive. An additional study[23] showed that consumption of fish, which is an abundant source of Omega-3 fatty acids, was associated with a lower risk of heart failure in older adult subjects.

The Genome-wide association study (GWAS) investigated the impact of fish oil supplementation on lipid parameters in a large population sample of 81,246 individuals and confirmed that fish oil supplementation was associated with a significant decrease in triglycerides and an increase in high-density lipoprotein (HDL) cholesterol levels. They also identified several genetic loci, that could be modified by fish oil supplementation, which can modulate lipid levels[24].

Metabolic Diseases

High levels and dietary consumption of Omega-3 have favorable effects in patients with obesity[25,26], hypertriglyceridemia and metabolic syndrome[27], T2D, nonalcoholic fatty liver disease (NAFLD); all these metabolic diseases have in common a background of underlying chronic inflammation[28].

Aging and Mortality

In 2017, low intake of Omega-3 was among the nutritional risk factors that contributed to 11 million deaths and 255 million disability-adjusted life years[29]. High Omega-3 PUFA intake reduces mortality from major causes at 16 years follow-up[30] and is associated with longer telomeres, which is inversely correlated with cell senescence, and

less oxidative stress[31,32]. Also, Omega-3 seems to alleviate the harmful influence of chronic mental stress on the immune system, which can contribute to susceptibility to infective diseases, inflammation, and cellular aging[33-35]. Omega-3 also reduces cardiovascular response to stress[36]. Individuals with higher levels of circulating long-chain Omega-3 fatty acid, mainly derived from seafood, have a significantly lower all-cause mortality risk, by at least 15-18%, compared to individuals in the lower quintiles[37].

Neurodegenerative Diseases

Polyunsaturated fatty acids are a major component of brain lipids; they have critical functions such as increasing fluidity of cell membranes, functioning as precursors for molecules like endocannabinoids which regulate synaptic neurotransmission, oxidative stress, neurons excitotoxicity, and inflammation, and generating pain-inducing molecules such as prostaglandin E2. Omega-3 PUFA have been shown to have positive effects on cognitive impairment[38,39], as well as potential neuroprotective benefits for degenerative diseases and ischemic stroke. Lipo-modulators derived from Omega-3, like resolvins and maresins, have been shown to downregulate inflammation initiated by β-amyloid within the human microglia, suggesting a possible favorable effect on the neurological tissue and Alzheimer's disease even if, the evidence on Alzheimer's disease is still inconclusive[40]. DHA and its downstream metabolite neuroprotectin D1 (NPD1) are neuroprotective in the retina, Central Nervous System (CNS), and brain, and protectin D1 (PD1)/NPD1, together with resolvins, at the right levels, may protect the nervous system in early-stage Alzheimer's due to their neurotropic, anti-apoptotic and anti-inflammatory effect on the brain. Despite some prospective studies and meta-analyses suggesting that marine Omega-3 PUFA, especially DHA, intake is associated with a reduction in development and progression of mild cognitive decline, the benefits in Alzheimer's disease are still less in agreement. DHA is an essential component of neuronal cell membranes, and vasoactive molecules, derived from Omega-3 EPA and DHA, increase brain vascular perfusion. Additionally, Omega-3 PUFAs have been shown[41] to decrease the frequency and severity of headaches in patients with migraines. Omega-3 fatty acid levels were associated with advanced cognitive processes in children two to six years of age. A study[42] revealed that higher levels of Omega-3 fatty acids in children's blood were associated with improved executive function, particularly in the areas of inhibitory control and working memory. Children with ADHD have been found to have an elevated Omega-6/Omega-3 ratio which correlates with their symptoms[43]. Traumatic brain injuries, very common in athletes and soldiers, have dramatic consequences: preliminary studies[44]in animals indicate that the consumption of Omega-3 FA may have a beneficial functional effect on these disabling injuries[45].

Studies have explored the potential impact of Omega-3 fatty acids on neurodegenerative disorders like Alzheimer's and Parkinson's disease[40]. A meta-analysis[46] of 12 studies suggested that Omega-3 fatty acid supplementation can improve cognitive function in older adults with mild cognitive impairment. Omega-3 fatty acids have been shown[47] to reduce inflammation and oxidative stress, which are major contributors to the pathogenesis of neurodegenerative diseases. Omega-3 PUFA intake may be a useful nutritional strategy to correct impairments of cerebral glucose metabolism during aging[48]. In a healthy aging population, Omega-3 fatty acid levels correlate with the integrity of the blood-brain barrier measured by magnetic resonance imaging (MRI)[49].

A correlation between the levels of EPA and DHA in the bloodstream and a decrease in the frequency of ischemic strokes, dementia, major depression, and some brain damage has been observed[1]. Intervention studies have also shown that higher blood levels of EPA and DHA are linked to enhanced brain function and cognitive performance, as well as a reduced risk of neurodegenerative diseases such as Alzheimer's disease. There is proof that EPA and DHA play important roles in brain structure and function by regulating neurotransmitter synthesis, cell signaling, and inflammation[50]. A proposed strategy to increase plasma levels of DHA-lysoPC is through the consumption of dietary sources rich in DHA in phospholipid forms, such as fish roe or krill oil. This method may circumvent the impaired transport of free DHA and effectively transport DHA-lysoPC into the brains of subjects at risk of AD[51].

A research study performed on the cohort of subjects aged 65 years and older who were free from dementia, as part of the Framingham Heart Study, found that those with a baseline DHA proportion in the red blood cells (RBC) above 6.1% had a significantly lower risk of developing Alzheimer's disease (AD) and all-cause dementia. In comparison to participants with lower RBC DHA levels (below 3.8), subjects with higher levels of

RBC DHA had an estimated additional 4.7 years of life free of AD[52].

Eye Health

Omega-3 fatty acids are essential nutrients that are critical for maintaining the optimal functioning of several organs of the human body. One of the many benefits of Omega-3 fatty acids is their potential role in improving eye health. The Mediterranean diet, which is considered healthy and beneficial to reduce inflammation, and the consumption of Omega-3, and even topical use of Omega-3, offer promising protection from chronic and age-related degenerative ocular diseases like cataract, dry eye disorder, glaucoma, retinopathy[53]; Omega-3-PUFAs have been found to offer protection to the retina against the effects of ischemic conditions[54]. Omega-3 PUFA are associated with a decreased occurrence of microaneurysms, which may be part of diabetic retinopathy[55]. Even myopia, the leading cause of visual impairment in the world without a known preventive treatment available, was attenuated by DHA and EPA in animal and human studies[56].

Several studies have explored the effects of Omega-3 PUFA on eye health, particularly in relation to age-related macular degeneration (AMD), a major cause of vision loss in older adults. SanGiovanni et al[57] published a study in the Journal of the American Medical Association, that demonstrated an association between higher consumption of Omega-3 fatty acids and a decreased risk of advanced age-related macular degeneration (AMD). Analyzing data from the Age-Related Eye Disease Study (AREDS), it was found that subjects who consumed higher amounts of Omega-3 fatty acids had a 30% lower risk of developing advanced AMD compared to those with lower consumption[57]. According to a study published in the Journal Investigative Ophthalmology & Visual Science, Omega-3 fatty acids could potentially help prevent and slow the progression of AMD. The study, which utilized data from the Blue Mountains Eye Study, indicated that participants who consumed higher amounts of Omega-3 fatty acids had a lower likelihood of developing early-stage AMD, and suggested that supplementing with Omega-3 fatty acids could be beneficial in preventing the advancement to late-stage AMD[58]. Furthermore, Omega-3 fatty acids may also play a part in improving other aspects of eye health. Bhargava and Kumar[59] found that Omega-3 fatty acid supplementation may improve dry eye syndrome symptoms. The study described that the participants who received Omega-3 fatty acid supplements had significant improvements in symptoms such as eye discomfort, dryness, and redness[59]. Overall, the evidence suggests that Omega-3 fatty acids may have a role in improving eye health, particularly in relation to AMD and dry eye syndrome. Further research is needed to fully understand the mechanisms behind these effects and to determine the optimal intake levels of Omega-3 fatty acids for eye health.

Actions on Inflammation and Immunity by Omega-3 Fatty Acids

The influence of dietary polyunsaturated fatty acids on the immune system has been investigated for a long time, with special attention on the Omega-3 PUFAs α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Both Omega-3 and Omega-6-derived bioactive metabolites have important immune-regulatory functions. Omega-6 arachidonic acid (AA) is the precursor of proinflammatory eicosanoids like leukotrienes (LT), prostaglandins (PG) and thromboxane (TX), which play an important role in the acute inflammatory process of endothelial permeability, neutrophil chemotaxis, and platelet aggregation. Omega-3 are the precursors of anti-inflammatory metabolites produced by neutrophils (PMN) and macrophages called specialized pro-resolving lipomediators or specialized pro-resolving mediators (SPMs), which modulate neutrophil infiltration and reduce inflammatory cytokines and oxidative stress, promoting resolution of inflammation and return to homeostasis. According to their structure and function, the metabolites are divided into families, which include lipoxins, resolvins, protectins, maresins. The most studied anti-inflammation metabolites are resolvins which have two main classes. EPA is the precursor of the E-series of resolving (RvE1, RvE2, RvE3), all of which are synthesized from EPA by enzymes such as cytochrome P450, cyclocygenase-2 (COX-2), and 15-lipoxygenase. The D series resolvins (RvD1-RvD6) are derived from DHA by such enzymes as COX-2, 12/15 LOX, and 5-LOX. DHA leads to the generation of three distinct families of SPMs, namely D-series resolvins, protectins (protectin D1), and maresins. The D series resolvins (RvD1-RvD6) are derived from DHA by such enzymes as COX-2, 12/15 LOX, and 5-LOX. All the metabolites synthesis is orchestrated by cyclooxygenase, lipoxygenase, or

cytochrome P450 enzymes, Omega-3 and Omega-6 substrates compete for these desaturation and elongation enzymes. Therefore, in the presence of Omega-3 fatty acids, the competition for enzymes reduces the synthesis of Omega-6-derived metabolites, which also have effects on immune cells. This competition constitutes an additional level of immune regulation by Omega-3 fatty acids. Overall, ALA, DHA, and EPA exert an inhibitory effect on the activation of immune cells from both the innate and adaptive branches. Omega-3 fatty acids have shown to affect three main properties of macrophage biology: that have been identified to be altered by Omega-3 fatty acids: the production and secretion of cytokines and chemokines, the capacity of phagocytosis, and the polarization into classically activated or alternatively activated macrophages.

Omega-3 PUFA Effects on Macrophages

One of the main anti-inflammatory properties of Omega-3 is the action on innate immune cells like macrophages; in fact, Omega-3 inhibits macrophages pro-inflammatory cytokines production, blunt inflammatory (M1) macrophages polarization while stimulating anti-inflammatory M2 macrophages and increase macrophage phagocytic capacity. On PMN, the most abundant leukocytes of the body, by being incorporated in their phospholipidic membrane, Omega-3 PUFA and their metabolites reduce cell migration and cytokine production, while enhancing their phagocytic capacity. Unlike the innate immune response, the adaptive immune response is antigen-dependent, clonally antigen-specific, and possesses long-lasting immunological memory. Due to its exquisite antigen specificity and durability, the adaptive immune defenses, particularly upon initial exposure, require several days to two weeks to mount a response. However, because of immunological memory, subsequent exposure to the same antigen allows for a much faster and stronger immune response, that can usually eliminate an infection prior to the onset of the disease. The adaptive immune response can be further divided into two categories: antibody and cellular responses mediated by B- and T-lymphocytes. On T cells, Omega-3 PUFA regulate the native immune response of T lymphocytes and their cytokines: decrease IL2, TNF-α, INF-γ by CD8, and control differentiation of naïve CD4+ T-cells into effectors Th1 and Th17 cells. Additionally, Omega-3 induces regulatory T cells in the liver[60] and other organs. On B lymphocytes: although there are some reports of decreased B cells activation by Omega-3, the effect is still controversial. On natural killer (NK) cells: the effect of Omega-3 supplementation on the reduction of NK may be age-dependent since an effect has been seen in humans>55 years old[61,62].

Action on Cellular Immune Response in Autoimmunity

Omega-3 polyunsaturated fatty acids have the potential to exhibit anti-inflammatory properties by activating the toll-like receptor 4 pathway and the G-protein coupled receptor 120 pathway, which ultimately leads to the inhibition of the cytokine NF-κB and subsequent inflammatory reactions. Many favorable effects of Omega-3 are believed to occur through their anti-inflammatory properties, but additionally, EPA and DHA have inhibitory effects on the mammalian target of rapamycin (mTOR) on immune cells, contributing to the differentiation of naïve CD4+ T cells into T regulatory cells instead of Th1 and Th17 cell; this effect is opposite with Omega-6 AA. Also, the lipomodulators resolvins and maresins, derived from Omega-3 FA, reduce proinflammatory cytokines released by activated CD8 cells. All these mechanisms can be beneficial in autoimmunity. Epigenetic modifications can also occur in the immune cells and can be passed on with each cell division to daughter cells. Consequently, epigenetic modifications can potentially influence immunological phenotypes and impact disease outcomes.

Autoimmune Diseases

Autoimmune disorders are a large family of chronic diseases in which the immune system mounts an inflammatory response against the body's own tissues, resulting in tissue and organ damage. These diseases, the incidence of which is steadily increasing, are highly debilitating and currently represent the third leading cause of morbidity in industrialized countries. The financial consequences of uncontrolled inflammation in the United States alone are estimated in hundreds of millions of dollars for each disease, with a substantial projected rise in the next decade. Currently, autoimmune diseases affect about 20% of the population, mostly, but not only, women. Their etiopathogenesis involves some genetic predisposition plus the triggering of environmental factors, which may be in crescendo in the Western population, like for example, the consumption of a proinflammatory Omega-6 rich diet, not bal-

anced by enough Omega-3. There are no effective preventions or definite cures for autoimmune diseases, whose pathophysiology remains ill defined. There is currently a lack of effective treatments to decrease the incidence of autoimmune disorders, but it is possible to reduce their progression. The life-long pharmacological treatment of these diseases is often accompanied by side effects, thus, the exploration of nutritional approaches to decrease the severity and progression of these diseases is warranted. Omega-3 PUFA, like vitamin D, is quite harmless even at the right doses, but significant in improving cellular inflammation. Circulating values of the Omega-6/Omega-3 ratio (AA/EPA ratio) have been proposed as a biomarker of systemic inflammation. The optimal AA/EPA ratio value to reduce cellular and systemic inflammation should be ideally between 1.5 and 3. Nutritional interventions aimed at maintaining this ratio should be implemented on a large scale for metabolic reasons, but also to prevent the consequences of autoimmune diseases.

A review and meta-analysis of randomized controlled trials[63] to assess the impact of Omega-3 fatty acid supplementation on disease activity in patients with autoimmune diseases found that Omega-3 fatty acid supplementation was associated with a significant reduction in disease activity, as measured by disease-specific activity scores. The authors suggested that Omega-3 fatty acids could be considered as adjunctive therapy in the management of autoimmune diseases.

Type 1 diabetes (T1D) is a serious and common organ-specific autoimmune disease affecting the youth, in which a subclass of T lymphocytes executes an autoimmune attack that leads to the destruction of the pancreatic b cells. The incidence of this disease is increasing, even with variations in different countries[64], and predicting the real rate of new cases in certain low-income parts of the world is even more complicated. Norway has one of the highest incidences of new cases, and several risk factors have been studied in this population[65]. A study showed that fish oil consumption in the first year of life was associated with a lower incidence of T1D, but fish (cod liver) oil is a dietary supplement of both Omega-3 fatty acids and vitamin D, so it is hard to dissociate their possible benefits, as food is a source of dietary patterns more than a source of one single nutrient. The Search Nutrition ancillary study has shown us many risk changes related to diet in patients with T1D, including the benefits of blood glucose control and c-peptide levels of Omega-3 levels and intake[66,67]. The beneficial effects may be related to metabolic benefits on the islets, like reduced lipo and glucotoxicity[68], or reduced glycemia[69]. But the main contribution of Omega-3 intake seems to be on autoimmunity[70,71].

An early longitudinal study, DAISY (Diabetes Autoimmunity Study in the Young), conducted in Colorado, revealed that prolonged dietary intake of a small dose of 150-mg of EPA/DHA Omega-3 in infants could have a strong preventive effect in children, starting at the age of 1 year , and may reduce the risk of islet autoimmunity in children with familial T1D[72], and even supplementation in utero and in the first months of life, in high-risk infants, decreases the levels of inflammation[73].

The EPIC-interact study[74], which was conducted in eight European countries, examined the adjusted hazard ratios (HRs) for incident diabetes in relation to glutamic acid decarboxylase-65 (GAD65) antibody status and terciles of plasma phospholipid Omega-3 PUFA. The study found that individuals who were positive for GAD65 antibodies and had a low intake of total and fatty fish had a significantly higher risk of diabetes. Furthermore, subjects with high GAD65 antibody levels and low total plasma phospholipid Omega-3 PUFA had a more than fourfold higher risk of diabetes compared to antibody-negative individuals with high Omega-3 PUFAs.

In the Norwegian study that suggested that daily supplementation of 1.0 g DHA/EPA could reduce the risk of developing T1D[65], the EPA/DHA levels were much lower than those reached in a model of Type 1 diabetes (NOD) mice study. Intervention with dietary Omega-3 PUFAs reduces the incidence of T1D in NOD mice as demonstrated in the fundamental dietary intervention study[75], in which NOD mice were fed a diet enriched with EPA/DHA for 35 weeks, starting at 5 weeks of age, and compared to a control group fed a regular diet, and a separate group supplied with a diet containing omega 6 arachidonic acid (AA). The diet rich in Omega-3 resulted in significant changes in fatty acid composition in mice serum and tissues accompanied by a significant decrease in Omega-6 PUFAs, leading to sharply reduced ratios of Omega-6/Omega-3 PUFAs relative to ratios in AA diet-fed mice. Omega-3 PUFAs blocked the progression of immune infiltration in the pancreas of NOD mice and the progression of peri-insulitis and insulitis. EPA/DHA-enriched diet increased the levels of cytokines with immunosuppressive properties, like IL-4 and IL-10. By contrast, the AA-enriched

diet promoted the secretion of pro-inflammatory IFN-γ, IL-17, IL-6, and TNF-α, while having no effect on IL-4 and IL-10. Treatment with Omega-3 EPA/DHA reduced the population of Th1 cells and increased the Th2 and Treg. Human peripheral blood mononuclear cells (PBMCs) were then collected and isolated from T1D patients, treated with DHA, EPA, and AA, separately, for 24 hours, and CD4+ T cell differentiation was analyzed by flow cytometry, *vs.* nondiabetic controls. Consistent with the findings in NOD mice, it was detected that EPA and DHA rebalanced the Th1/Th2 ratio from approximately 12 to 1 by both increasing Th2 cell populations and decreasing Th1 cells in the samples from T1D patients. At the same time, a significant reduction of Th17 cells and an elevation of Tregs was observed. In contrast, AA Omega-6 did the opposite, significantly reducing Tregs while considerably increasing Th17 cells. Also, EPA/DHA strongly inhibited the activation of mechanistic target of rapamycin complex 1 (mTORC1) by AA. These effects were observed in PBMC from subjects with and without type 1 diabetes, suggesting that an imbalance between Tregs and Th17 could represent a diet-induced risk factor that could impair the ability to modulate immunity and inflammation in response to an autoimmunity-triggering event, such as a viral infection. This could also explain why low levels of Omega-3 have been associated with a higher risk of severe viral infections, such as COVID-19. The AA/EPA ratio was tested in children with T1D. When the ratio was <22.1 the patients required less insulin, and also, children with diabetic ketoacidosis (DKA) showed a lower intake of Omega-3 and vitamin D, compared to patients without DKA. These findings confirm that nutritional deficiency could impair blood glucose control, and possibly influence the immune function, suggesting that T1D could be mitigated in its severity by maintaining a healthy anti-inflammatory supplementation and diet[76]. Possibly also, Omega-3 PUFAs improve insulin resistance in T1D during pregnancy[77] and improve vascular health associated with insulin resistance in T1D[78], suggesting that EPA and DHA consumption may reduce the severity and delay the progression of T1D complications due to their anti-inflammatory actions.

In autoimmunity prevention studies, the timing of intervention is essential, as it has been demonstrated in the Teplizumab phase 2 prevention trial for Type 1 diabetes[79], where a single course of the anti-CD3 teplizumab significantly slowed progression to clinical diabetes in high-risk, nondiabetic relatives of patients with diabetes, who had at least two autoantibodies and abnormal results of an oral glucose tolerance test. The median delay in the diagnosis of diabetes was 2 years; the findings suggest that immunomodulation before the development of clinical T1D disease can be the most beneficial in delaying the progression. It is possible that the nutritional intervention with Omega-3 supplementation should be implemented very early before the immunological abnormalities have manifested and continued for a long time.

In a pilot study at T1D onset, supplementation of Omega-3 fatty acids for 1 year decreased prandial insulin demands in children with T1D on a Mediterranean diet[80]. Following this study, a larger Phase I/II study (Poseidon) is currently being conducted at our institution to explore the possible function of high dose Omega-3 and vitamin D on the preservation of beta-cells[81], in a population that includes children and adults with new-onset T1D. Some anecdotal case reports have shown that high doses of Omega-3 and vitamin D3 administered to these patients resulted, by 12 months, in increased peak and area under the curve (AUC) C-peptide from baseline, which points to a beneficial effect on beta-cell function. Therefore, randomized controlled trials[82,83] are now necessary to confirm whether this therapy may assist in preserving beta-cell function in patients with new onset T1D. A field study approach with Omega-3 and Vitamin D supplementation[84], like the T1D Prevention Field Study, in 15 countries, aims to find a definite link between the AA/EPA ratio, other markers of inflammation like CRP, and progression to T1 Diabetes in patients with only positivity of autoantibodies at enrollment. Also, maintaining an anti-inflammatory ratio of Omega-6/3 may be advantageous post-islet transplantation[85], an effective cell replacement treatment for T1D.

The gut microbiota seems to be involved in the development of T1D by affecting intestinal permeability, short chain fatty acids (SCFA) production, and by modulating the immune system and promoting gut homeostasis, with the contribution of tryptophan metabolites and Omega-3 fatty acids. Individuals with T1D may experience improved metabolic control with a higher intake of polyunsaturated Omega-3 FA. The Mediterranean diet, which is rich not only in dietary fibers but also in Omega-3 fatty acids, has been proposed[86] as a potential therapeutic approach for preventing or delaying the progression of T1D and its compli-

cations by improving gut microbiota composition and function.

Omega-3 and Rheumatic Diseases

Several clinical trials have demonstrated improvements in symptoms and delayed disease progression in these systemic autoimmune diseases. The positive influence of unsaturated fatty acids on treatment outcomes induced some authors[87] to suggest that a diet rich in long-chain PUFA should be the standard of care, in addition to pharmacotherapy, in treating patients with diseases such as rheumatoid arthritis (RA). The mechanism at the basis of the beneficial effects of this nutritional intervention is believed to be the decrease in inflammatory cytokines like IL-1 and IL-6, TNF-α, INF-γ, and IL17, as well as the T cells proliferation and differentiation that can be regulated by Omega-3 PUFA. RA is a chronic inflammatory autoimmune disease of the joints and bones, that ultimately advances into tissue damage and painful loss of function, with a disease progression that evolves even after the inflammation has stopped. In RA studies, the amount of Omega-3 PUFAs, EPA, and DHA consumed ranged up to 4.6 g EPA daily and to 2.1 g DHA daily. As stated[88], the purpose of supplementing with Omega-3 PUFA should be to intervene early in the inflammatory process, before joint damage sets in. Eicosanoids derived from the arachidonic acid (AA) play a role in RA and marine Omega-3 PUFAs have been proven to provide anti-inflammatory activities by reducing T cell reactivity, moderating inflammatory cytokine production, and decreasing reactive oxygen species, when used at proper dose above the anti-inflammatory threshold[89]. A Danish study on the prevention of rheumatoid arthritis showed that an increase in the intake of (30 g) fatty fish per day was associated with a 49% reduction in the risk of RA many years later[90]. Fish oil may provide an additional advantage in reducing cardiovascular risk among patients with RA, besides lowering the use of non-steroidal anti-inflammatory drugs (NSAID), which are also associated with cardiovascular risk. The use of fish oil in RA may indeed promote a reduced CV risk through direct mechanisms[91]. The effect of Omega-3 fatty acid supplementation on the expression of pro-inflammatory cytokines in patients with rheumatoid arthritis (RA) was assessed in a study[92] that found that Omega-3 fatty acid supplementation significantly reduced the expression of pro-inflammatory cytokines, including TNF-α and IL-1β, in patients with RA. The authors suggested that Omega-3 fatty acids could be a potential therapeutic option for managing inflammation in RA.

Systemic Lupus Erythematosus (SLE)

Lupus is a common autoimmune disorder characterized by the formation of immunocomplexes and connective tissue inflammation, and vessel involvement. It has been observed[93,94] that 6 months of supplementation with Omega-3 relieves Lupus symptoms. Probably prolonged use is necessary to observe an advantage on vascular and endothelial function in this disease, which carries a high risk of atherosclerotic complications[95].

Systemic Scleroderma

In systemic scleroderma, an autoimmune disorder, the Omega-3 metabolites resolvins contribute to the resolution of the inflammation, promoting the efferocytosis of macrophages and the differentiation of proinflammatory macrophages M1 into anti-inflammatory macrophages M2, limiting the acute inflammatory process and modulating ischemia-reperfusion (during Raynaud's phenomenon for example) induced inflammation, preventing chronic inflammation and fibrosis so Omega-3 PUFA supplementation would be the perfect treatment to delay the progression of this autoimmune disease[96].

Thyroiditis

It has emerged that the intake of Omega-3-rich oily fish was inversely correlated to serum thyroid antibodies throughout pregnancy and early postpartum[97], and Omega-3 supplementation reduces post-partum thyroiditis[98]. Thyroid autoimmune diseases, such as Hashimoto thyroiditis, are very common, and they have been linked to low resolvin D1 levels[99]. Some authors believe that it would be very advantageous and very low risk to treat with an Omega-3 supplementation[100] initial autoimmune thyroiditis because it is often associated with other autoimmune diseases and can lead to thyroid and cardiometabolic complications in the long term.

Psoriasis

Psoriasis is a common inflammatory autoimmune disease of the skin. It has been identified that a high intake of Omega-3 helps to reduce the severity and frequency of psoriatic plaques[101].

Multiple Sclerosis (MS)

MS is an autoimmune disease of the nervous system that can evolve in impaired functional capacity and difficulty walking. Resolvins are reduced in patients with MS, and this reduction correlates with disease progression. Prolonged use of Omega-3 at high doses with other antioxidant vitamins, like Vitamin A and E, showed improvement in gait in patients with MS[102]. Parks et al found that Omega-3 fatty acid supplementation was not associated with a significant reduction in the risk of developing MS and in the rate of disease progression[103]. However, in all clinical trials, the possible efficacy of the selected dose of Omega-3 should be evaluated in combination with the target ratio of Omega-6/Omega-3, to assess if an immunomodulatory, anti-inflammatory effect could be achieved[10].

Omega-3 and Infective diseases

Both influenza and COVID-19 wide outbreaks of infections, despite the availability of vaccines, have been a major concern for vulnerable, frail, and senior patients, due to the possible hyperimmune and hyperinflammatory reaction observed following the infection. In addition to the risk of complications like acute respiratory distress syndrome (ARDS), there is also a possible link to the increase in autoimmune diseases, including T1D[104], after these respiratory infections, which is troublesome in people of all ages. Omega-3 PUFAs have shown anti-inflammatory properties in many tissues and organs, even in the lungs[105,106], and indeed clinical studies are ongoing to verify the protection of the use of Omega-3 FA in subjects at risk for COVID-19 complications. Elevated serum pro-inflammatory cytokine levels have been strongly associated with mortality in COVID-19 patients, which has led to further exploration of the use of Omega-3 in these patients[107], since Omega-3 has already shown benefits in other critically ill patients[108]. Studies[109] on COVID-19, even if not statistically significant, already showed a trend in mortality reduction with Omega-3 supplementation[107]. A randomized controlled trial[110] was conducted in Tehran to investigate the effects of Omega-3 fatty acids supplementation on hospitalized patients with COVID-19 disease. Thirty adults were allocated to either a control group receiving Hydroxychloroquine or an intervention group receiving Hydroxychloroquine plus 2 grams of DHA and EPA for 2 weeks. The subjects that received Omega-3 demonstrated beneficial improvements in symptoms like body pain, fatigue, and appetite. Furthermore, Omega-3 supplementation was associated with a decrease in ESR and CRP levels, which suggests that a moderate dose of Omega-3 fatty acids may have a favorable effect in the management of inflammation-mediated clinical symptoms in patients with COVID-19. A double-blind RCT[111] in critically ill patients with COVID-19 enterally fed with an Omega-3 fortified formula showed a higher survival rate at 1 month and improved renal function. Parenteral nutrition supplementation with Omega-3 FA improves the recovery prognosis and the probability of survival in critically ill patients[112]. In other viral infections, high levels of Omega-3 seem to have a value as well, in fact, for example, higher PUFA levels at birth were associated with reduced risk of coxsackievirus infection and respiratory syncytial virus infection[113] in children. In certain bacterial illnesses, the anti-inflammatory properties of Omega-3 fatty acids have demonstrated beneficial outcomes. However, in the case of intracellular bacterial infections like *salmonella* or tuberculosis, these compounds might have adverse consequences because of their impact on immune cells[114].

Polyunsaturated Omega-3 fatty acids have been reported to have potential protective effects against SARS-CoV-2 infection by inhibiting the binding and entry of the virus into the cells. A study[115] published in 2021 investigated the effects of PUFAs on the expression and activity of angiotensin-converting enzyme-2 (ACE2), a cellular receptor that facilitates the entry of SARS-CoV-2 into the cells. The *in vitro* study on RBC found that Omega-3 fatty acids can inhibit the binding and entry of SARS-CoV-2 into the cells. Omega-3 fatty acids may provide an extra therapeutic benefit by reducing virus entry into cells, stabilizing the spike glycoprotein's closed conformation, and preventing the interaction of ACE2 with the receptor binding domain[116]. Other potential benefits of Omega-3 fatty acids in COVID-19 may be mediated by reduction of inflammation, improvement of the immune function, and reduction of the severity of COVID-19 symptoms[106].

A recent review by Calder et al[117] explored the effects of Omega-3 fatty acids in the context of viral infections. The authors reported that Omega-3 fatty acids have been shown to have antiviral effects in animal models and *in vitro* studies. Furthermore, they have been found to improve immune function and reduce inflammation, both of which are crucial in viral infections. However, the authors noted that more research is needed to

determine the optimal dose and duration of Omega-3 supplementation in the context of viral infections. Another study[118] investigated the effects of Omega-3 supplementation on the immune response to influenza vaccination in healthy adults. Omega-3 PUFA supplementation was associated with enhanced production of certain immune cells and antibody response to the vaccine.

According to a study involving patients diagnosed with Hepatitis C virus (HCV) infection[119], the administration of Omega-3 fatty acids resulted in an enhancement of liver function and a decrease in the viral load. The study's authors suggest that Omega-3 fatty acids could be a beneficial additional treatment for HCV infection. Moreover, supplementation with Omega-3 fatty acids resulted in reduced hospitalization time and increased survival rates among patients with sepsis[120].

Omega-3 Effects on the Gut Microbiome

The gut microbiota may initiate inflammation by releasing compounds like lipopolysaccharides (LPS); certain nutrients like probiotics and Omega-3 fatty acids can increase microbiota variety, decrease inflammation, and promote short-chain fatty acid production. Omega-3 fatty acids also increase bacteria that suppress LPS and decrease bacteria that produce LPS, which helps to prevent gut permeability and chronic low-grade inflammation[121].

A study conducted on a murine model revealed that various doses of Omega-3 PUFA have distinct therapeutic effects on gut microbiota and immunity. The study found that doses of 60 mg and 90 mg had better recovery effects than a 30 mg dose. These higher doses were linked to an increase of beneficial bacteria such as *Lactobacillus*, *Helicobacter*, and *Ruminococcus*, and a reduction of the levels of harmful bacteria like *Bacteroides*, *Clostridium*, and *Prevotella*. Moreover, elevated doses were linked to increased mucus Secretory immunoglobulin A (SIgA) and serum IL-10 levels, and decreased serum levels of LPS, IL-1β, and TNF-α[122].

A clinical study was conducted to investigate the impact of enriched seafood sticks that contained postbiotic and bioactive compounds, including Omega-3, on cardiometabolic disease (CMD) risk factors and gut microbiota in individuals with abdominal obesity. This randomized study[123] found that enriched seafood sticks can be used as a supplemental approach to managing CMD risk factors in this population, and the study further suggests that this strategy could potentially offer protection against Type 2 Diabetes and cardiovascular disease, accompanied by modifications in the gut microbiota composition.

A diet rich in Omega-3 fatty acids has been found to modify the composition of the gut microbiome. The cardiovascular benefits associated with Omega-3 may be partially attributed to their effect on gut microbial fermentation products, suggesting they may function as a prebiotic nutrient[124].

Effect on Other Age-Related Diseases

NAFLD

Liver disease is common in obesity and metabolic syndrome. Studies[125] have demonstrated that subjects with NAFL supplemented with fatty acids have beneficial effects on biomarkers of hepatocellular damage, and show additional benefits on insulin levels and inflammation, especially if fatty acids supplementation is paired with vitamin D. Treatment using Omega-3 polyunsaturated fatty acids enhances the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and hepatic fat content in individuals diagnosed with non-alcoholic fatty liver disease[126]. In mice, dietary Omega-3 PUFA stimulated Tregs generation through up-regulation of peroxisome proliferator-activated receptor (PPAR)-γ and Transforming growth factor beta (TGF-β) expression and protected the animals from liver injury[127].

Cancer

There are data[128] suggesting that Omega-3 PUFA may have therapeutic effects on cancer, including lymphoproliferative diseases and breast cancer. There is evidence[129,130] that Omega-3 may have epigenetic functions, like modification of histone acetylation in cancer cells, and regulation of pathways important to cancer, including promoting immunogenic apoptosis. Fish dietary consumption is significantly inversely correlated with the risk of colorectal cancer[131]. In terms of symptoms, cancer-related fatigue improves with a greater increase in serum Omega-3 after supplementation[132]. Initially, it was believed that Omega-3 fatty acids could interfere with the coagulation process, however, research[133,134] has shown that doses up to 10 gr/day of EPA and DHA, or consumption of 1.5 gr/day for 52 weeks by cancer patients and ICU patients, are safe and do not lead to adverse bleeding. In humans, anticancer prop-

erties of Omega-3 fatty acids have been shown, particularly in breast, prostate, and colorectal cancer. According to a meta-analysis of 38 studies[135], the intake of Omega-3 fatty acids was found to be linked with a decreased likelihood of developing breast cancer. Despite one report of a link between Omega-3 consumption and prostate cancer, in a study that showed some limitations like lack of randomization[136], a comprehensive analysis of the pertinent literature indicates that elevated Omega-3 fatty acid intake does not increase the risk of prostate cancer and actually decreases prostate cancer mortality and decreases risk for sudden death and CV events in these patients[137]. A study[138] conducted on mice has found that long-chain Omega-3 fatty acids and their oxidized metabolites may help to slow the growth of prostate tumors.

Chronic Kidney Disease (CKD)

The occurrence of CKD among adults is nearly 1 out of 10 individuals in developed nations, making it a significant public health issue. In fact, CKD is strongly correlated to early death, especially from CV causes. The NHANES study[139] observed that there is an inverse relation between dietary Omega-3 PUFA intake and all-cause mortality in patients with CKD. There is evidence[140] of the clinical benefits of Omega-3 FAs intake in improving cardiometabolic parameters in CKD patients. A pooled analysis of data[141] from a consortium in 19 countries has found that higher levels of total marine Omega-3 PUFAs, EPA, and DHA, were associated with a lower incident CKD risk. The anti-inflammatory effect in CKD may be mediated by monocyte chemoattractant protein 1 and fibroblast growth factor 23[142]. Omega-3 supplementation in patients with end-stage renal disease on hemodialysis has been studied[143] and it has been demonstrated to be a beneficial nutrition-based intervention on several parameters in this population.

Musculoskeletal System and Frailty

Omega-3 PUFAs have anabolic properties on muscle proteins in healthy adults, as well as improving sarcopenia of aging and CKD, and cancer cachexia. Systemic low-grade inflammation, which characterizes disease- and age-related muscle decline, induces muscle wasting, as seen in multiple sclerosis (MS).

Dietary Omega-3 PUFA mitochondrial antioxidant effects result in the normalization of catabolic derangements and protection from muscle wasting. In human and animal studies, Omega-3 fatty acids suppress muscle protein degradation, enhance the rate of muscle protein synthesis in response to anabolic stimuli (feeding or physical exercise), reduce systemic oxidative stress and inflammation, and improve insulin sensitivity and lipid profile. A recent study[144] showed that supplementing older individuals with Omega-3 PUFAs derived from fish oil for six months positively influenced their body composition, muscle strength, and physical performance, suggesting it is an effective approach for the primary prevention of sarcopenia.

The Western diet, specifically its Omega-6 content, has been linked to the development of persistent neuropathic pain[145], which is one of the leading causes of invalidity, but that can be reversed by Omega-3 fatty acids. Omega-3 FA also improves the pain of degenerative spine disease[146] and spinal cord injury[147]. Omega-3 and its metabolites reduce pain from chronic inflammation[148], like in arthritis or inflammatory bowel disease, for example, treatment for which is desperately needed to avoid lifelong use of NSAID[149]. A group of individuals in their mid-60s free of cardiovascular disease, known as the Framingham offspring cohort, showed that their red blood cell fatty acid measurements were just as effective as standard risk factors in predicting their risk of death within the next 11 years. To verify this fatty acid profile as a reliable predictor of overall mortality, further studies are necessary using different populations[150].

Conclusions

The evidence of the beneficial effect of Omega-3 on metabolic diseases associated with aging is compelling[151]. Various studies have demonstrated that Omega-3 consumption improves lipids, fatty liver disease, obesity, cognitive function, and cardiovascular complications. The importance of addressing chronic inflammation cannot be overstated, as it has a primary role in the pathogenesis and persistence of many degenerative, autoimmune, and infectious diseases. In response to environmental triggers, those predisposed to dysfunctional hyperinflammatory and hyperimmune disease can become susceptible to complications and the onset and progression of autoimmune diseases.

Endogenous lipid mediators with positive effects on the resolution of inflammation, like the Omega-3 metabolites resolvins, are currently the focus of intensive investigation.

A healthy Omega-6/3 ratio should be targeted, through diet and supplementation, to achieve modulation of low-grade inflammation and prevent immune dysregulation. The modern Western diet increases the risk of complications of uncontrolled inflammation triggered by insults of any nature, like infections, and the consequence of oxidative stress due to aging.

Immunonutrition is not known to reverse tissue damage, which is a long-term complication of inflammatory disease but has demonstrated repeatedly to have favorable effects on low-grade inflammation with a high dosage of Omega-3. Combining Omega-3 with Vitamin D may enhance the singular anti-inflammatory and immunomodulatory effect of both. No supplementation is effective alone as a primary preventive intervention without, at the same time, reducing the consumption of high pro-inflammatory Omega-6-rich foods.

Like physical exercise, keeping a strict anti-inflammatory diet is the most cost-effective immunomodulatory defense against the loss of homeostasis that leads to vulnerability to illnesses and early disability, so we believe that Omega-3 consumption should be promoted, combined with healthy nutrition, to prolong a healthy lifespan.

There is a need for large randomized clinical studies to validate current evidence supporting supplementation with a correct dose of Omega-3 PUFA, to maintain a correct target range of the ratio between Omega-6 and Omega-3 PUFA.

Conflict of Interest

No conflicts of interest relevant to this article are reported by RP, KH, and VGJ; CR is a member of the Scientific Advisory Board of the Inflammation Research Foundation and is the author of *The Healthspan Code*, English edition of the Oscar Bestseller Mondadori, *Il Codice Della Longevita' Sana*.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

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Authors' Contributions

RP wrote the manuscript, HK and VGJ contributed, reviewed and edited the manuscript, CR contributed to the content, discussion, review and editing of the manuscript.

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