The Importance of Maintaining a Low Omega-6/Omega-3 Ratio for Reducing the Risk of Inflammatory Cytokine Storms

by James J. DiNicolantonio, PharmD & James O'Keefe, MD

A higher omega-6/3 ratio is associated with lower immune cell function, which may result in lower immunity.

James J. DiNicolantonio, PharmD, (left), and James H. O'Keefe, MD, (right), MSMA member since 2003, are at Saint Luke's Mid America Heart Institute, Kansas City, Missouri.

Abstract

Inflammatory cytokine storms in the lungs are a potential consequence of RNA viruses. One issue that may increase the risk of developing inflammatory cytokine storms in the lungs during viral infections is an imbalance in the dietary omega-6/3 ratio. Indeed, over the past 100 years the omega-6/3 ratio in the Western world has increased from approximately 4:1 to 20:1. This has increased the production of pro-inflammatory metabolites from omega-6 and reduced the anti-inflammatory metabolites from omega-3s. A high dietary omega-6/3 ratio may promote excessive inflammation, which may be contributing to inflammatory cytokine storms in the lungs during viral infections.

Introduction: The Omega-6/3 Ratio and Inflammation

Inflammation is important in treating infections and wounds as it promotes tissue healing and the killing of pathogens. The omega-6 fat linoleic acid, and arachidonic acid (AA) formed from it, are important in responses such as redness, swelling, heat, and pain.[1] However, acute inflammatory responses are meant to be quickly suppressed by resolvins formed from the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Thus, a balance in the dietary omega-6/3 ratio may be important for ensuring that an excessive and prolonged inflammatory response does not occur, which could lead to tissue damage and potentially to autoimmune disease.

Up until about 100 years ago, the omega-6/3 ratio had been around 4:1 or less.[2] However, the typical Western diet now provides an omega-6/3 ratio approximately 20-fold higher in favor of omega-6.[2] While foods such as nuts, seeds, and eggs are high in omega-6, the increase in the omega-6/3 ratio is primarily due to an increase in the intake of industrial seed oils (soybean, corn, safflower, cottonseed, and canola). Additionally, there has been a reduction in the intake of long-chain omega-3s, which can primarily be found in fatty fish and shellfish. A high omega-6/3 ratio predisposes

to supraphysiologic inflammatory responses and perpetuates chronic low-grade inflammation.[3] The overconsumption of linoleic acid, mainly from industrial omega-6 seed oils, and the lack of EPA and DHA, has been proposed to put the population in a pro-inflammatory and pro-thrombotic state.[3, 4]

The Immune System

One of the functions of our immune system is to fight against pathogenic viruses, fungi, bacteria, and parasites.[5] The immune system does this by releasing inflammatory cytokines during infections to defend against these pathogens. If our immune system, and especially our gastrointestinal system is healthy, then there is a lower risk of autoimmunity.[5]

There are two main types of immunity: Innate (natural immunity) and acquired (adaptive immunity).[5] Immune cells concentrate in lymphoid organs (lymph nodes, thymus, spleen and gastrointestinal lymphoid tissue) and in the circulation as well as other parts of the body. The innate immune system is a first line of defense against infection. It functions to prevent and eliminate infectious pathogens. Examples of the innate immune system include complement, skin, phagocytic cells (neutrophils, eosinophils, basophils), monocytes, and macrophages.

The acquired immune system has "memory" (unlike the innate immune system), whereby prior exposure to pathogens improves its response. Although the acquired immune system is slower to respond than our innate immune system, once it becomes effective it has a lasting effect. Acquired immunity involves antibodies, which help bind to and neutralize pathogens as well as activate complement proteins, which promotes phagocyte activation and pathogen elimination. Once an invading pathogen is inside a host cell it has escaped antibody defense, otherwise known as humoral immunity. However, T lymphocytes can eliminate these pathogens in conjunction with helper T lymphocytes (indicated by the presence of CD4 protein on their surface). Type 1 helper T cells activate macrophages, cytotoxic T lymphocytes (CD8+) and natural killer cells, whereas Type 2 helper T cells activate mast cells and basophils. Regulatory T cells are involved with suppression of inflammation and cell-mediated immunity via production of IL-10.[5]

The Importance of Omega-3s for Suppressing an Overactive Immune System and Reducing the Risk of Inflammatory Cytokine Storms

There is a need for an effective immune system to prevent and eliminate infectious agents. However, the immune system can become over activated leading to self-attack. This can start by the immune system mounting a response to dietary or environmental allergens. Arachidonic acid is the main fatty acid in immune cell membrane phospholipids and mainly forms the inflammatory 2,4-series eicosanoids, whereas incorporation of EPA/DHA will decrease AA-derived eicosanoids and increase the anti-inflammatory 3/5-series eicosanoids, docosanoids and resolvins/protectins, leading to an overall anti-inflammatory state.[5] Consuming a typical Western diet leads to immune cells (neutrophils, lymphocytes and monocytes) that contain ~20% of fatty acids as arachidonic acid with just 1% EPA and 2.0-2.5% DHA.[5] However, supplementing the diet with 3.2 grams of EPA/DHA for 12 weeks has been shown to increase phospholipid long-chain omega-3 fatty acids to around 3.5% EPA and 3.5% DHA.[5] Thus, a dietary increase in omega-3 PUFAs will lower the omega-6/3 ratio in immune cells.

Animal models have demonstrated that omega-3 polyunsaturated fatty acids (PUFAs) have immunomodulatory effects and are useful in inflammatory disorders.[6] Infections can also increase arachidonic acid and decrease the anti-inflammatory omega-3 PUFA DHA.[7] Dietary, or supplemental omega-3 PUFAs, can incorporate into the cellular membranes of all immune cells investigated to date.[8] Numerous clinical studies in humans have found that supplementing with EPA/DHA (reducing the omega-6/3 ratio) lowers inflammation in humans, whereas oxidized linoleic acid metabolites (OXLAMs) activate nuclear factor kappa-beta (NF-kB), which increases proinflammatory cytokines.[3] Importantly, cytokine storms and lung injury in persons infected with coronaviruses, such as severe acute respiratory syndrome (SARS-CoV) or middle east respiratory syndrome (MERS), are usually the result of NF-kB activation.[9, 10] Studies show that inhibiting NF-kB-mediated inflammation increases survival in animal models of SARS-CoV.[11] Considering that SARS-

Table 1. **Potential mechanisms of omega-3s for reducing cytokine storm in the lungs**

Decrease AA-derived eicosanoids and increase the anti-inflammatory 3/5-series eicosanoids, docosanoids and resolvins/protectins/maresins/lipoxins.[5]
Lower omega-6/3 ratio in immune cells.[5]
Inhibiting NF-kB activation.[3]
Resolving inflammation and potentially improving survival in sepsis.[12-14]
Suppression of arachidonic acid-derived eicosanoids and leukotrienes produced from immune cells as well as inflammatory interleukins and cytokines.[15-21]
Increase in neutrophil and monocyte phagocytic activity.[25]

CoV and SARS-CoV2 are both coronaviruses, and that the latter can lead to COVID-19, inhibiting NF-kB activation by increasing omega-3 intake and reducing processed omega-6 seed oil intake,[3] may be an important strategy in combating inflammatory cytokine storms in the lungs and acute respiratory distress in patients infected with RNA viruses such as influenza and coronaviruses. Moreover, considering that the dietary intake of omega-6/3 is now ~ 20:1 or higher, compared to an ancestral intake of ~ 4:1 or less, this may predispose to inflammatory cytokine storms and chronic inflammatory conditions.[2, 3] Omega-3 PUFAs are important for resolving inflammation and may improve survival in sepsis and acute respiratory distress syndrome (ARDS).[12-14]

EPA/DHA not only reduces AA-metabolites by competition in the cellular membrane phospholipids, but they also inhibit AA metabolism via inhibition of cyclooxygenase and lipoxygenase. Inhibiting the metabolism of arachidonic acid to proinflammatory metabolites is likely more consequential in preventing a supraphysiological inflammatory response than reducing the phospholipid content of arachidonic acid. Many studies have shown that fish oil (between 2.4 and 14.4 grams of EPA/DHA/day) suppresses the arachidonic acid-derived eicosanoids and leukotrienes produced from immune cells as well as inflammatory interleukins and cytokines.[15-21] Moreover, the metabolites from EPA/DHA are considered less inflammatory compared to those from arachidonic acid.[5, 22, 23]

A higher omega-6/3 ratio is also associated with lower immune cell function, which may result in lower immunity.[24] DHA-rich fish oil (3 grams per day, 26% EPA, 54% DHA) has been shown to increase neutrophil and monocyte phagocytic activity by 62% and 145%, respectively,[25] whereas changes in neutrophil and monocyte phagocytic activity was not found with EPA-rich fish oil.[26] In other words, DHA may strengthen the immune system while at the same time suppressing its overactivation.

Long-chain omega-3s can also inhibit inflammatory cytokine production from monocytes, macrophages, and endothelial cells. Many of the benefits of long-chain omega-3s are due to their ability to reduce gene expression for producing inflammatory cytokines partly by reducing the activation of NF-kB.[1] Thus, supplementing with long-chain omega-3s not only reduces inflammatory eicosanoids derived from arachidonic acid but also increases the anti-inflammatory eicosanoids and resolvins/protectins/maresins/lipoxins derived from EPA/DHA, thereby reducing inflammatory cytokine production from NF-kB. Table 1 summarizes the potential mechanisms of omega-3s for reducing cytokine storm in the lungs.

References

1. Calder PC. Polyunsaturated fatty acids and inflammatory processes: New twists in an old tale. Biochimie 2009;91:791-5.
2. Simopoulos AP, DiNicolantonio JJ. The importance of a balanced omega-6 to omega-3 ratio in the prevention and management of obesity. Open Heart 2016;3:e000385.
3. DiNicolantonio JJ, O'Keefe JH. Importance of maintaining a low omega-6/omega-3 ratio for reducing inflammation. Open Heart 2018;5:e000946.
4. DiNicolantonio JJ, J OK. Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis. Open Heart 2019;6:e001011.
5. Calder PC. Immunomodulation by omega-3 fatty acids. Prostaglandins, leukotrienes, and essential fatty acids 2007;77:327-35.
6. Sierra S, Lara-Villoslada F, Comalada M, et al. Dietary fish oil n-3 fatty acids increase regulatory cytokine production and exert anti-inflammatory effects in two murine models of inflammation. Lipids 2006;41:1115-25.
7. Lachance C, Segura M, Dominguez-Punaro MC, et al. Deregulated balance of omega-6 and omega-3 polyunsaturated fatty acids following infection by the zoonotic pathogen Streptococcus suis. Infection and immunity 2014;82:1778-85.
8. Gutierrez S, Svahn SL, Johansson ME. Effects of Omega-3 Fatty Acids on Immune Cells. International journal of molecular sciences 2019;20.
9. Yang CW, Lee YZ, Hsu HY, et al. Targeting Coronaviral Replication and Cellular JAK2 Mediated Dominant NF-kappaB Activation for Comprehensive and Ultimate Inhibition of Coronaviral Activity. Sci Rep 2017;7:4105.
10. Lucas R, Czikora I, Sridhar S, et al. Arginase 1: an unexpected mediator of pulmonary capillary barrier dysfunction in models of acute lung injury. Frontiers in immunology 2013;4:228.
11. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, et al. Inhibition of NF-kappaB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. Journal of virology 2014;88:913-24.
12. Korner A, Schlegel M, Theurer J, et al. Resolution of inflammation and sepsis survival are improved by dietary Omega-3 fatty acids. Cell death and differentiation 2018;25:421-31.
13. Chen H, Wang S, Zhao Y, et al. Correlation analysis of omega-3 fatty acids and mortality of sepsis and sepsis-induced ARDS in adults: data from previous randomized controlled trials. Nutrition journal 2018;17:57.
14. Buechler C, Pohl R, Aslanidis C. Pro-Resolving Molecules-New Approaches to Treat Sepsis? International journal of molecular sciences 2017;18.
15. Lee TH, Hoover RL, Williams JD, et al. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. The New England journal of medicine 1985;312:1217-24.
16. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. The New England journal of medicine 1989;320:265-71.
17. Sperling RI, Benincaso AI, Knoell CT, et al. Dietary omega-3 polyunsaturated fatty acids inhibit phosphoinositide formation and chemotaxis in neutrophils. The Journal of clinical investigation 1993;91:651-60.
18. Caughey GE, Mantzioris E, Gibson RA, et al. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. The American journal of clinical nutrition 1996;63:116-22.
19. Rees D, Miles EA, Banerjee T, et al. Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. The American journal of clinical nutrition 2006;83:331-42.
20. Meydani SN, Endres S, Woods MM, et al. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. The Journal of nutrition 1991;121:547-55.
21. von Schacky C, Kiefl R, Jendraschak E, et al. n-3 fatty acids and cysteinyl-leukotriene formation in humans in vitro, ex vivo, and in vivo. The Journal of laboratory and clinical medicine 1993;121:302-9.
22. Goldman DW, Pickett WC, Goetzl EJ. Human neutrophil chemotactic and degranulating activities of leukotriene B5 (LTB5) derived from eicosapentaenoic acid. Biochemical and biophysical research communications 1983;117:282-8.
23. Bagga D, Wang L, Farias-Eisner R, et al. Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. Proceedings of the National Academy of Sciences of the United States of America 2003;100:1751-6.
24. Kew S, Banerjee T, Minihane AM, et al. Relation between the fatty acid composition of peripheral blood mononuclear cells and measures of immune cell function in healthy, free-living subjects aged 25-72 y. The American journal of clinical nutrition 2003;77:1278-86.
25. Gorjao R, Verlengia R, Lima TM, et al. Effect of docosahexaenoic acid-rich fish oil supplementation on human leukocyte function. Clinical nutrition (Edinburgh, Scotland) 2006;25:923-38.
26. Miles EA, Banerjee T, Dooper MM, et al. The influence of different combinations of gamma-linolenic acid, stearidonic acid and EPA on immune function in healthy young male subjects. The British journal of nutrition 2004;91:893-903.

Disclosure

JD is Director of Scientific Affairs for Advanced Ingredients for Dietary Products (AIDP). JOK is an owner of a nutraceutical company.

MM