Effects of Dietary Fats on Immune System Response in Covid-19

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Coronavirus disease 2019 (COVID-19), which is affecting people around the globe, is a respiratory disease that is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and that has reached the pandemic state. It is known that people who are vulnerable but who are not immunocompromised can still suffer from serious complications of COVID-19. The general nutritional status and food consumption patterns of each individual affect the functioning of his or her immune system. The effects of these patterns can occur at the level of physical barriers, the microbiome, the innate immune system, and the adaptive immune system. Immune system cells and mediators, which are essential to the inflammatory response, are in the structures of proteins, fats, and carbohydrates and act through vitamins and minerals. The combination of chronic infection and malnutrition disrupts the immune response, affects the amount of immune cells, and increases inflammatory mediators. Dietary fat (in terms of both amount and type) affects cytokine biology, making the former a key player in inflammatory disease; also having an important role as macronutrients, because of how they affect immune cells and function. This review explores the role of dietary fat in the immune response, highlighting the role in protecting the individual from COVID-19 and mitigating the cytokine storm in the infection phase.

Key words: COVID-19, Pandemic, Immune system, Fatty acids, Fats, Infection

The system that recognizes pathogens and foreign substances, distinguishes them from its own cells and tissues, and protects our body against diseases is called the immune system (1). The immune system consists of both natural, fast, non-antigen-specific responses and adaptive, slower, antigen-specific, and specific responses (2). The innate immune system recognizes threats with the inflammatory process, reacts quickly to destroy any that might arise, resolves inflammation, and repairs damage. However, innate immunity does not increase its efficacy or the speed of its response when repeatedly exposed to a pathogen (3). While the adaptive system responds more slowly than the innate system does, it is responsible for creating immunological memory. Thus, it will create a strong, quick, and antigen-specific response against repeated infection with the same pathogen (4).

Coronavirus disease 2019 (COVID-19) is a respiratory disease that is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and that has reached the pandemic state. Since it is a pathogen the body is encountering for the first time, it has a more severe course in people who do not have a strong immune response (5). Clinically, it can be said that immune responses caused by SARS-CoV-2 infection have 2 stages (6). During the incubation period, a specific adaptive immune response is required to stop the progression of the disease. The development of this immune response depends on the general health of the individual and on that individual's having an appropriate genetic background (e.g. HLA haplotype), one that provides antiviral immunity (6). Genetic differences cause individual differences in the immune response. In this process, methods to strengthen immunity can be applied. If the protective response cannot eliminate the virus in the infected individual, the virus will multiply and major problems will occur, especially in organs with high ACE2 expression, such as the intestines and kidneys (6). Damaged cells induce strong innate inflammation in the lungs, and the severe phase starts. Lung inflammation can cause life-threatening breathing disorders. Therefore, when severe lung damage occurs, efforts must be made to suppress inflammation and manage symptoms (7). In other words, the aim is to try to increase the immune response in the first stage and to restrain the out-of-control immune response in the second stage (8).

During infection, the activated immune system is accompanied by an increased metabolic rate (to support enhanced biosynthesis) that requires both substrates for energy and regulatory molecules (9). The required energy and metabolites are provided from the diet. In order to support the optimal

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functioning of the immune system, special attention should be paid to maintaining a healthy diet and lifestyle and getting regular exercise (10,11). Dietary fats which are macronutrients have an important role in supporting immune function (in terms of both type and amount), and affects cytokine biology, making the former critical to the course of inflammatory diseases. An imbalance in the ratio of saturated/unsaturated fatty acids and omega-6/omega-3 fatty acids can provoke the onset of any one or all of several immune system issues: a severe allergic reaction, an autoimmune disorder, or a metabolic disorder (12). When the proportion of daily fat intake from energy decreases from 36% to 25%, the lymphocyte response and the activity capacity of natural killer cells increase (13).

Regarding the immune system's ability to fight disease effectively, having an adequate and a balanced nutrition before and during the disease, including the consumption of the right amount and type of fat, is one of the most important factors. This article explores the effects of the consumption of fat on the immune system and how such consumption affects this system's ability prevent or fight against COVID-19 and non-communicable diseases.

Fats and the Immune response

Fatty acids are the building blocks of cellular lipids. These fatty acids significantly affect the immune response by interacting with nuclear receptors (14). It has been proven in studies that fatty acids affect the function of immune cells such as epithelial cells, macrophages, dendritic cells, neutrophils, and T and B cells (12). High levels of high-sensitivity C-reactive protein (hs-CRP), an acute-phase protein, have been associated with the consumption of saturated fatty acids, while low levels of this protein have been associated with polyunsaturated fatty acids. Trans fats, especially those in processed foods, have been described as pro-inflammatory in that they increase tumor necrosis factor alpha (TNF-α), interleukin (IL) 6, and hs-CRP levels (15). The increased consumption of polyunsaturated fatty acids may cause lipid peroxidation if those acids cannot be balanced with antioxidant nutrients. Oxidized low-density lipoproteins stimulate cytokines such as TNF-α, IL-1α, IL-1, and IL-6, which are involved in the inflammatory response and may cause oxidative stress (14). Fatty acids in the cell membrane change the membrane fluidity. This change affects receptor expression, nutrient transport, and signal transmission. Therefore, saturated/unsaturated fatty acid and omega-6/omega-3 ratios in the diet are very important for immune system homeostasis (16).

Saturated fatty acids

Saturated fatty acids can affect the immune system in a destructive way by increasing the conversion of prostaglandin E2. Pro-inflammatory prostaglandin E2 increases the amount of IL-17 and activates macrophages in different ways (17). Two major risk factors for severe COVID-19 are obesity and type 2 diabetes. The high levels of these risk factors, worldwide, especially in the USA and other developed countries, are caused by the consumption of a diet rich in saturated fat (18). The high consumption of saturated fat causes an increase in oxidative stress and inhibits T and B lymphocyte function in the adaptive immune system. Oxidative stress disrupts T and B cell proliferation and induces B cell apoptosis. In addition, by disrupting adaptive (acquired) immunity, oxidative stress leads to an impaired host defense against chronic inflammation and viruses (18). Previously, mice fed with a high amount of saturated fat showed increased lung pathology due to influenza infection and due to a disrupted adaptive immune response; in addition, they exhibited impaired virus clearance (18). In another study in mice, the high consumption of saturated fat increased macrophage infiltration into lung tissue, and especially into the alveoli. This situation shows the importance of the issue in terms of COVID-19 pathology, in particular when lung tissue inflammation and alveolar damage are taken into consideration (19).

Fats also play an important role in modulating the gut microbiota. Saturated fat reduces beneficial microbes such as *Bifidobacterium* and *Faecalibacterium*. In contrast, unsaturated fats have been found to increase beneficial bacteria such as *Bifidobacteria* and *Akkermansia*, while reducing harmful microbes such as *Escherichia* and *Streptococcus* species (20). Avoiding foods high in saturated fat and sugar and consuming unsaturated fats, antioxidants, and grains with high fiber content strengthens the immune function and gives us an advantage against COVID-19 (20). The consumption of pre-packaged foods and of meat and other animal-based foods should be reduced to decrease saturated fat intake, and low-fat dairy products and healthy fats (e.g. olive oil and fish oil) should be included in the diet (21).

Omega 3 and Omega 6 fatty acids

The immune system must both respond to stimulus and analyze the situation. At the center of the indicated response are signaling molecules, including eicosanoids and docosanoids (22). Eicosanoids create the biological response to environmental stimuli such as diet, lifestyle, infection, and trauma. In eicosanoid synthesis, omega-6 and omega-3 polyunsaturated fatty acids act as substrates (23). The presence of fatty acid precursors in the cell membrane can be controlled by diet. The diet, in addition to providing essential fatty acids (linoleic acid and alpha linolenic acid), is a source of several important long-chain polyunsaturated fatty acids, which have more unsaturated sequences, including arachidonic acid (AA; 20, 4n-6), eicosapentaenoic acid (EPA; 20, 5; n-3), and docosahexaenoic acid (DHA; 22, 6; n-3) (23).

Omega-3 polyunsaturated fatty acids support the immune system by activating both the innate and adaptive immune system cells (21). AA, an omega-6 fatty acid, and EPA and DHA, the omega-3 fatty acids, affect inflammation and immune responses. Generally, eicosanoids derived from EPA and DHA are less inflammatory than those derived from AA. For example,

EPA-derived eicosanoid receptors typically have a lower affinity for EPA-derived mediators than do those derived from AA (24). Some eicosanoid derivatives, produced from AA and including prostaglandin E2 and 4-series leukotrienes, have been associated with increased sensitivity to allergens and increased disease severity. Prostaglandin E3 and 5-series leukotrienes, which are less inflammatory, are produced from EPA. Therefore, sufficient long-chain omega-3 fatty acid levels during immunological development may reduce the risk of disease (16). Wood et al. reported that omega-3 dietary supplementation may have a general beneficial effect against acute pneumonia by increasing the host's specific and non-specific immune defenses (25).

An imbalance in the ratios of saturated/unsaturated fatty acids and omega-6/omega-3 fatty acids has an important effect on immune system homeostasis and can stimulate the beginnings of allergic, autoimmune, and/or metabolic conditions (12). Because the same enzymes metabolize omega-3 and omega-6 fatty acids, a kind of competition takes place and can result in high concentrations of the omega-6 acids, which concentrations can block the metabolism of omega-3 acids; therefore, maintaining a healthy ratio (1:1 to 4:1) of these fatty acids is recommended (14). However, it has been reported that in those with so-called Western diets, the intake ratio of omega-6 to omega-3 fatty acids can be as high as 10:1, a dietary imbalance that might stimulate a pro-inflammatory response (14).

During the fight between the host immune system and coronaviruses, overstimulation of the inflammatory response can occur. It is characterized by an increase in inflammatory eicosanoids and inflammatory chemokines and cytokines such as TNF-a, IL-1β, and IL-6 (26). This pro-oxidative, pro-inflammatory state is called a "cytokine storm." This response of the innate immune system damages the host tissue causing harm to the lung and respiratory failure, a condition known as acute respiratory distress syndrome. (26). The mortality rate is high for acute respiratory distress syndrome. It has been reported that advanced COVID-19 patients have significantly high levels of inflammatory markers in the bloodstream (27). In addition to directly damaging the host tissue, the excessive inflammatory response (i.e. cytokine storm) suppresses the acquired immune response; the number of CD4+ and CD8+ T lymphocytes decreases, and the ability of CD4+ T lymphocytes to produce interferon gamma is impaired (28). A diet targeting oxidative stress and inflammation can be undertaken to support the treatment of acute respiratory distress syndrome brought on by the pro-oxidant, pro-inflammatory state. Another important issue to be considered while providing nutritional support in acute respiratory distress syndrome is the effect of major nutrients on the respiratory system. While O_2 is used in the transformation of these nutrients to energy, CO_2 is released as a result. The respiration quotient (RQ) is the ratio of CO_2 released to O_2 used; it is 1 for carbohydrates, 0.7 for fats, and 0.8 for proteins. An RQ greater than 1.0 indicates that there is increased O_2 consumption, which means that the respiratory system is overworked (29). When the infection gets into the lungs, the increased respiratory load causes the intensification of respiratory distress/disease and makes it difficult for COVID-19 patients to be weaned from mechanical ventilation.

To reduce the incidence of oxidative stress, acute respiratory distress syndrome, and sepsis, a mixture of fish oils—DHA combined with EPA—can be used. For patients receiving enteral and/or parenteral nutrition, the combination of EPA and DHA, 500 mg, can be added—from 0.1 to 0.2 g/kg/day (30). The general approach is to take approximately 500 mg of EPA and DHA every day and to consume 2 to 3 servings of fatty fish per week. This recommendation can be met by consuming at least 2 servings (90 grams each) of oily marine fish such as mackerel, salmon, sardines, herring, or smelt per week (21).

Clinical, animal, and epidemiological data show that nutritional supplementation can accelerate recovery and shorten hospital and intensive care stays. Omega-3 is natural and inexpensive; because of that and due to its anti-inflammatory, immunomodulatory, and other beneficial properties, it might be a healthy choice for a supplement during the ongoing pandemic (31). Omega-3 may play a central role in preventing the cytokine storm and reducing inflammation intensity and mortality risk (32), at least in COVID-19 patients.

Diets rich in saturated fatty acids and trans fatty acids have pro-inflammatory effects, and it is suspected that polyunsaturated fatty acids may have anti-inflammatory effects depending on the type (or types) of fatty acid consumed. The amount and type of fat consumed for individual needs are important. An intake of 7% or less of saturated fats and 1% or less of trans fats (or none at all of the latter) is beneficial for a healthy immune system and helps protect against such diseases as COVID-19. Clinical studies in COVID-19 patients are needed both to evaluate whether omega-3 dietary supplements can protect patients against severe forms of COVID-19 and to increase scientific awareness.

Resumen

La enfermedad del Coronavirus 2019 (COVID-19), que afecta a nivel mundial la vida de las personas, es una enfermedad respiratoria causada por el síndrome respiratorio agudo severo coronavirus-2 (SARS-CoV-2), que alcanza el estado pandémico. Se sabe que las personas vulnerables, pero no inmunocomprometidas, aún pueden sufrir complicaciones graves de la COVID-19. El estado nutricional general y los patrones de consumo de alimentos del individuo afectan el funcionamiento del sistema inmunológico. Este efecto puede ocurrir a nivel de barreras físicas, el microbioma, el sistema inmune innato y el sistema inmune adaptativo. Las células y mediadores del sistema inmunológico, que son esenciales en la respuesta inflamatoria, se encuentran en la estructura de las proteínas, las grasas y los carbohidratos y actúan a través de vitaminas y minerales. La combinación de infección crónica y desnutrición interrumpe la respuesta inmunitaria, afecta la cantidad de células inmunitarias y aumenta los mediadores

inflamatorios. Junto con el importante papel de los aceites de macronutrientes en las células inmunitarias, el tipo y la cantidad de grasa en la dieta son muy importantes en el curso de las enfermedades inflamatorias, ya que afectan la biología de las citocinas. En esta revisión, se aborda el papel de las grasas en el sistema inmunitario para luchar y protegerse de la COVID-19 o para aligerar la tormenta de citoquinas durante la fase de infección.

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