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REVIEW ARTICLE

The Key to Strong Immunity: Lifestyle

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Abstract

The immune system works in coordination with other structures in the body to prevent infections from occurring and to fight existing infections. The immune system plays a role in the formation and regulation of almost every disease and therefore has a very important place for human health. Researches show that the regulation of internal and external factors that can affect immunity can be effective in protecting against diseases and in the healing process. In this review, nutrition, exercise-sports, regular life, sleep, environmental factors, addictive substances, psychological state, previous illnesses, and genetic predispositions, affecting immunity are discussed. A diet composed by adequate and balanced intake of macro and micro nutrients ensures that the immune system works at the desired level. In addition to nutrition, moderate intensity regular exercise, regular life and quality sleep contribute to immunity by affecting various physiological mechanisms. On the other hand, external factors such as previous diseases, air pollution, radiation, various synthetic compounds and harmful habits such as stress, alcohol, cigarettes and drugs can disrupt the immune system by disrupting the cytokine balance. Although genetic factors are important in immunity, it seems that lifestyle which includes factors such as diet, daily activities, sleep patterns, habits, and moods is much more determinant for strong immunity.

Keywords: Immunity, nutrition, exercise, sleep, immune system, inflammation

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1. Introduction

The immune system performs an important function by working as an orchestra with its cells, tissues, and molecules, preventing infections from occurring and fighting infections that settle. The host defense system, which contains many biological structures and processes that act simultaneously and regularly against pathogens and damaged tissues within the organism, consists of innate immunity that creates the first protective barrier and then (in connection to the innate immunity) acquired immunity that develops more specifically and more effectively (Abbas, 2018).

These immunological functions among individuals show heterogeneity in terms of some factors such as genetics, environment, lifestyle, and nutrition (MacGillivray, 2014). The correct functioning of the immune system has an important place in the protection of the body against harmful organisms, therefore, in the prevention of diseases and the course of treatment. This review aims to understand and collectively evaluate the factors that will protect the immune system.

2. Nutrition

The interchangeable effects of nutrition on immune functions have been studied as an important factor for the past decade, and research in this area has become an outstanding study topic called nutritional immunology. As with other body systems, the immune system requires sufficient nutrients for proper functioning (MacGillivray, 2014).

Nutrition is generally accepted as a determining factor of the immune response, and epidemiological and clinical data show that nutritional deficiencies can alter the immune response and increase the risk of infection. Previous studies have confirmed that impaired immunity is a critical factor in infection associated with malnutrition (Kubena, 1996).

Nutrition plays a very important role in the development, management, and treatment of non-communicable diseases such as allergic diseases, cancer, diabetes, and cardiovascular diseases. Such non-communicable diseases have well-defined immunopathological processes and nutrition is thought to affect disease risk and management as an immunomodulator (Venter, 2020).

In Western countries, where the incidence of immune-related diseases is high, it is noted that diseases typically result from high-calorie intake, fat, sugars, and low fibrous food consumption. Information on the development of less chronic inflammatory diseases and allergic diseases has been provided with specific nutrients and dietary models (Schwingshackl, 2015; Schulze, 2018).

In the data on nutrition models, especially the Mediterranean diet attracts attention. It has been suggested that wheezing or eczema is less common in babies of mothers who adapt to this nutrition model during pregnancy (Venter, 2020).

The European Academy of Allergy and Clinical Immunology (EAACI) emphasized that the inadequacy of the nutritional variety defined as the numerical and ideal consumption frequency of food groups consisting of different foods in infancy results in allergies seen in childhood (Ruel, 2003; Venter, 2020). In studies related to the prevention of childhood allergies, it has been understood that the effect of dietary diversity on the microbiome and immune system may affect allergy outcomes and it has been found that this change in the immune system is associated with several immune antigen tolerance mechanisms, including regulatory T and B cells, immune regulatory cytokines and suppressed IgE antibodies, as shown in other allergen tolerance models (Venter, 2020; Rivas, 2016; Palomares, 2017). The immune system develops an appropriate tolerance to prevent unwanted responses to harmless foreign substances or healthy tissues (Nicholson, 2016).

Nutritional deficiencies are particularly common in underdeveloped regions and contribute to the high incidence of morbidity and mortality from infectious diseases. Nutritional deficiencies should be corrected for the immune system to perform its functions. If some foods are taken in the recommended amount; It has been found to contribute to the optimization of immune functions, including resistance to infection (Black, 2014; Bailey, 2015).

2.1. Nutritional Components

Vitamin A.

Vitamin A plays a role in the innate and acquired immune functions. Vitamin A deficiency can impair barrier function, alter the immune response, and increase susceptibility to many infections (Calder, 2013). Intestinal barrier and mucus secretion, which may facilitate the entry of pathogens, have been shown to be impaired in mice with vitamin A deficiency (Ahmed, 1990). Vitamin A has an important place in the regulation of cells that control negative immune reactions. In vitamin A deficiency, the activity of natural killer cells may decrease and disrupt the response to the vaccine (Ross, 1996). Vitamin A deficiency is associated with increased morbidity and mortality for children. These rates have been reported to be associated with respiratory infections, diarrhea, and measles. In children with vitamin A deficiency, when supplements were given, an increase in the treatment of infectious diseases and a decrease in the morbidity rate was observed (Bailey, 2015).

Vitamin A is found in animal tissues in the form of retinoids and in plant tissues in the form of carotenoid. Retinoic acid supports T cell movement to gut-associated lymphoid tissues (Iwata, 2004). Carotenoids are stored in tissues and multiply in plasma and can be converted to vitamin A. There are studies showing that it can increase immune function by preventing oxidative stress due to being an antioxidant (Maijo, 2014). High doses of vitamin A have a strong teratogenic effect. The synthetic derivative of vitamin A, isotretinoin, is responsible for craniofacial defects together with a syndrome involving malformations of the central nervous system, heart, and thymus. Therefore, synthetic forms and excessive consumption are not recommended during pregnancy (Guillonneau, 1998).

Vitamin D.

Vitamin D and its metabolites have many roles in the immune system, autoimmunity, and susceptibility to infections. Vitamin D is converted into its active form, 1,25-dihydroxy vitamin D3 in kidneys. Immune cells both respond to vitamin D and are involved in its production. For this reason, vitamin D can directly affect host defense by providing antimicrobial peptide synthesis from macrophages (Calder, 2013). People who are deficient in vitamin D have been found to be at increased risk of respiratory viral infections (Sabetta, 2010). In a study conducted in Japan, schoolchildren were given a vitamin D supplement for 4 months during the winter, and there was a 40% reduction in the risk of developing influenza (Urashima, 2010). These studies show that vitamin D may reduce susceptibility to infections, thereby increasing immune function. Although there is a lot of research on the immune-supportive effects of vitamin D, it has been stated in some studies that it may have an immunosuppressive effect by playing a role in the prevention of autoimmunity. Current evidence suggests that vitamin D is a regulator of immune function, but its effects will depend on the immunological condition (Black, 2014). According to a study conducted in 489 patients who had their vitamin D levels measured 1 year before the COVID-19 test, it was found that the rate of being positive in patients with insufficient vitamin D levels was 1.77 times higher. It is thought that vitamin D strengthens innate immunity, thus reducing transmission. Moreover, high vitamin D level is associated with a low interlockin 6 level, which is the main target in controlling the cytokine storm seen in COVID-19 (Meltzer, 2020).

Vitamin E.

Vitamin E is a fat-soluble antioxidant that can protect polyunsaturated fatty acids (PUFAs) in cell membranes from oxidation, reduce the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and modulate signal transduction (Lee, 2018). It is a fat-soluble antioxidant that strengthens immune functions. It is found in the membrane of all nuclear cells, especially in the membrane of immune cells. Vitamin E consists of biologically active tocopherols and tocotrienols. Especially, α-tocopherol is frequently used in researches. Vitamin E can increase T cell function by directly affecting membrane integrity, signal transduction, or indirectly by reducing the production of suppressive factors such as prostaglandin E2 (PGE2) by macrophages (Maijo, 2014).

Vitamin C.

Vitamin C is an essential vitamin (Carr, 2017). It is an important cofactor of many enzymes and regulates gene expression by interacting with transcription factors (Sorice, 2014). It contributes to immune defense by supporting various cellular functions of both-innate and acquired immune systems. It protects against oxidative stress with its antioxidant feature (Carr, 2017). Anti-inflammatory, antiviral, and antibacterial properties are well known in the literature (Sorice, 2014).

Plasma vitamin C concentrations decrease rapidly in cases of infection or stress. Vitamin C deficiency resulted in the impaired immune system and increased susceptibility to infections. At the same time, studies are reporting that vitamin C supplements can both prevent and treat systemic and respiratory infections (Carr, 2017).

Zinc.

Zinc is an essential mineral. Zinc deficiency can reduce immune cell proliferation, the activity of natural killer cells, cytokine production, and neutrophil function (Prasad, 2008; Wessel, 2017). Zinc is essential for hematopoiesis, cell maturation, cell differentiation, and progression of the cell cycle in the immune system. Cytokine production and production of reactive oxygen species also depend on zinc. Zinc deficiency also negatively affects the maturation and function of T and B cells. Insufficient zinc intake in dietary has also been associated with cancer. Therefore, zinc is vital for the correct functioning of the entire immune system (innate-acquired) (Baltacı, 2012; Wessel, 2017).

Iron.

Iron is a trace element that has an important place in cell differentiation and growth (Mohammed, 2017). Iron has multiple effects on the immune system. Oxidative burst, T cell proliferation, cytokine production, and bacterial killing are the effects of iron on the immune system. In iron deficiency, thymus atrophy may develop (Calder, 2013). Iron deficiency impairs cellular immunity, especially from helper T cells **(**Elmadfa, 2019). In a case-control study, the effect of iron supplementation for 3 months was investigated in 485 children aged 2-5 years. As a result of the study, it was observed that acute respiratory infections, urinary tract infections, and gastroenteritis recurrences decreased significantly (Jayaweera, 2017). However, some studies have reported that excessive iron overload in infectious conditions can cause harmful effects by disrupting immune function and inducing inflammation (Calder, 2013).

Selenium.

Selenium acts as a cofactor of a group of enzymes involved in antioxidant defenses. Therefore, it supports immune functions by protecting against the immunosuppressive effects of oxidative stress. Selenium deficiency has been shown to affect both innate immunity and acquired immunity in experimental animals and increase susceptibility to infections (Black, 2014). Low selenium concentrations in humans have been associated with increased virulence (Beck, 2000; Beck, 2004; Wang, 2009), decreased natural killer cell activity (Wang, 2009), and increased mycobacterial diseases (Shor-Posner, 2002). Selenium supplementation has been shown to improve immune functions in humans (Roy, 1994; Hawkes, 2001). In adults with low selenium levels, selenium supplementation increased the immune response to the poliovirus vaccine (Broome, 2004).

Probiotics.

The term probiotic is a relatively new word meaning "for life". This term is used for bacteria associated with beneficial effects for humans and animals (FAO, 2001). Probiotics are living microorganisms that can provide the host with health benefits. The most characterized probiotic microorganisms are members of the genus Lactobacillus, Bifidobacterium, and Streptococcus. Yoghurt, kephir, pickles, sourdough bread, tarhana, ayran, turnip, beer, wine, soy, olive and dried meat are examples of probiotic foods (Yardım, 2019).

Probiotics can regulate immune functions in the gastrointestinal tract and more distant tissues (Maijo, 2004). It activates regulatory T cells, strengthens the gut barrier by increasing mucin secretion, tight-binding proteins, and goblet, Paneth cells. It provides the regulation of intestinal microbiota by suppressing the growth of potential

pathogenic bacteria in the gut and maintaining the balance. It has also been shown that long-term probiotic use does not alter intestinal homeostasis. In malnutrition studies, probiotics have been shown to increase intestinal and systemic immune responses. In addition, probiotics have been shown to contribute to improving intestinal and thymus damage in some diseases (Maldona, 2019).

There is strong evidence that probiotic intake in healthy adults increases immune function especially in common upper respiratory tract infection and decreases incidence and symptoms (Khalesi, 2019). Since the gut microbiota is accepted as the first line of defense against pathogenic microorganisms in the gut, it is important to protect the immune system through regular consumption of probiotic foods (Khalesi, 2019).

Prebiotics.

Prebiotics are nutrient components in fiber structure that are resistant to digestive enzymes, selectively stimulate the growth or activity of a limited number of fermented microorganisms in the colon, and thereby positively affect the health of the individual (Garipağaoğlu, 2010). Prebiotics are selectively fermented by colonic bacteria, which can be classified into three main groups: These bacteria are Bifidobacterium and Lactobacillus, Clostridia, and Bacteroides bacteria. Oats, barley, wheat, beverages obtained from these grains and legumes are examples of prebiotics (Salmeron, 2017). As a functional nutritional composition, prebiotics are oligosaccharide group carbohydrates. Many studies showing that prebiotics regulate the immune system in both humans and animals (Vulevic, 2008; Badia, 2012; Klatt, 2013).

It indirectly showed an immune supportive effect by increasing the balance of the intestinal microbial population of prebiotics by increasing beneficial and protective bacteria (such as Bifidobacterium, lactobacillus) and reducing pathogenic bacteria. In addition, prebiotics can be absorbed directly from the gut cells and can have a direct regulatory effect on the immune system by altering the expression of genes (Roller, 2004; Ito, 2011; Shokryazdan, 2017).

Essential fatty acids.

Essential fatty acids are nutrients that cannot be synthesized in the body and should be taken with food for humans. These are linolenic (which is omega-3) and linoleic (which are omega-6) acids. Of these, eicosapentaenoic acid (EPA, omega-3), docosahexaenoic acid (DHA, omega-3), and arachidonic acid (AA, omega-6) are synthesized in our body. EPA and DHA can also be taken with some foods. Omega-3 and omega-6 fatty acids are structural and functional components of the cell membrane. They are the precursors of eiazonoids that carry out the hormonal and immunological activity (Schuchardt, 2010).

While saturated fatty acids and omega-6 fatty acids have little effect on lymphocyte proliferation, cytokine production, and natural killer cell activity, oleic acid and omega-3 fatty acids can inhibit lymphocytes and natural killer cells. EPA and DHA are the most important immune cell effects among all omega-3 fatty acids. Omega-3 polyunsaturated fatty acids inhibit the development of eicosanoids and have an anti-inflammatory effect (Maijo, 2014).

2.2. Dietary Styles

Obesity.

Increased incidence of obesity in children and adults is a common concern worldwide.

Obesity and overfeeding are strongly associated with chronic inflammation. This obesity-associated inflammation is called metaflamation and the western-style diet is reported to be a risk factor for metaflamation. Western-style diet; it is characterized by a diet rich in sugar, trans and saturated fats, whereas poor in complex carbohydrates, fiber, micronutrients, polyphenols and omega-3 unsaturated fatty acids. The mechanisms underlying metaflamation caused by the western-style diet are still under investigation. A related mechanism is the increased ingress of lipopolysaccharide from microorganisms into the intestine due to increased intestinal permeability. With some mechanisms activated by lipopolysaccharides, inflammatory responses develop by immune cells (Childs, 2019).

One of the diseases that obesity is sensitive to is influenza. Obesity is a risk factor in the development of influenza. It has been associated with long stay and high mortality rates in health care units. In addition to being sensitive to influenza, obese people are reported to be at higher risk for developing complications such as sepsis and pneumonia (Alwarawrah, 2018).

Unlike the western-style diet, the Mediterranean diet, which includes a diet rich in vegetables, fruits, nuts, legumes, and fish, is defined as a healthy diet. A number of bioactive compounds found in fruits and vegetables have been reported to protect against chronic inflammatory diseases (Childs, 2019).

Besides obesity, some studies have also reported that malnutrition triggers inflammation as well. In case of malnutrition, the immune system fails to protect. This deficiency is explained by the developmental defects associated with insufficient nutrient intake and the lack of nutritional signals that play a critical role in immune cell proliferation and function, such as leptin (Alwarawrah, 2018).

Fasting.

Fasting is a worship that Muslims do without eating and drinking water from the dawn of the fajr until the sunset. It is one of the forms of intermittent fasting. Fasting and calorie restriction whip up autophagy (Anton, 2018). With autophagy, toxins and infectious agents are removed from the body, which plays an important role in the immune system. In the study of Mindikoglu et al. investigating the effects of fasting on 14 healthy individuals for 30 days from sunrise to sunset, positive changes were observed in protein-coding genes such as ASGR2, CEP164, CFHR1, COLEC10, LATS1, NR1D1 and HOMER1 (Mindikoglu, 2020).

In the studies of Ajabnoor et al., as a result of the 1-month fasting of Ramadan, there was a significant decrease in mRNA expression of IL-1α, which is responsible for the immune response to inflammation (Ajabnoor, 2017). In the study of 50 healthy individuals who fast during Ramadan, it was found that the expression of inflammation-related cytokines and circulating leukocyte levels decreased after 30 days (Kacimi, 2017).

In these systematic reviews, it has been reported that fasting in Ramadan causes an increase in anti-inflammatory cytokines and a decrease in inflammatory cytokines leading to have a regulatory effect on oxidative stress and immunity (Adawi, 2017).

2.3. Some Foods and Plant Types which are Consumed Frequently

Adequate and balanced nutrition is one of the important factors for the immune system to be strong. In addition, the consumption of certain nutrients and herbs in appropriate forms and amounts can contribute to the immune system. However, rather than consuming this type of herbal products, it is adequate and balanced nutrition and regular and active life that will contribute to the immune system.

The products we will examine below can reduce the inflammation caused by the immune system with their anti-inflammatory effects and support the immune system with their antioxidant effects.

Antioxidants help remove free radicals from the body by some mechanisms. The reduction of free radicals is important because their overproduction plays an important role in the development of many chronic diseases. Theoretically, antioxidants are expected to be effective. But people's health status, individual differences, lifestyle, diet factors; factors such as dosage, solubility, and oral intake of antioxidants may affect the bioavailability of antioxidants.

Turmeric.

Turmeric is a bright yellow-colored spice also known as Indian saffron. It has been shown that the compounds in it, especially curcumin, show anti-inflammatory effects. The anti-inflammatory effect of curcumin is being investigated, as it may be useful in acute and chronic inflammation. The immune system regulating ability of curcumin is due to its interaction with various immunomodulators. There are also studies showing that curcumin can increase the effectiveness of antimicrobial drugs with its synergistic effect (Catanzaro, 2018).

The consumption of curcumin with black pepper has been suggested to prevent its low absorption and rapid excretion from the body. The alkaline piperine in black pepper slows down the rapid metabolism of curcumin. In a study conducted with healthy volunteers, 2 g/kg pure curcumin was given to one group and 2g/kg curcumin + 20 mg/kg black pepper to the other group. As a result of the experiment, it was observed that the serum curcumin level was significantly higher in the group given black pepper and curcumin (Dei Cas, 2019).

Although results related to the immunomodulatory effects of turmeric have been published, there are inconsistencies between publications due to the lack of tests on standardization and effectiveness in the preparation of active compounds (Catanzaro, 2018).

Echinacea.

There are many studies on the immunostimulant effect of the echinacea plant. Echinacea may also have anti-inflammatory, antiviral, and antimicrobial effects. This broad effect is based on echinacea leaves, flowers, roots, different active compounds, and differences in its preparation. The use of echinacea for 6 months did not cause any toxic effects. There is not enough research for its long-term use (Catanzaro, 2018).

The phytochemical profiles of echinacea products vary depending on the harvested plant material, the type used, and the extraction protocols. Due to the lack of standardization and testing, its effects have not been clearly established. Due to its immune system stimulating effect, it can lead to the development or exacerbation of autoimmune diseases (Catanzaro, 2018).

Ginger.

Ginger is a spice rich in active compounds such as phenolic acid and terpene compounds. Many studies have shown that ginger has high antioxidant activities. It is reported that ginger can be effective in protecting against oxidative stress. Dry ginger contains more antioxidants than fresh ginger, and when dried ginger is roasted, its antioxidant level decreases (Li, 2016).

It is reported that ginger and its active compounds have antibacterial, antifungal, antiviral, and anti-inflammatory effects. In addition, ginger can relax the muscles in the airways and have a protective effect against respiratory diseases by reducing airway resistance and inflammation (Li, 2016).

Black Pepper.

Many studies are showing that black pepper and its bioactive compounds have antioxidant and anti-inflammatory properties (Butt, 2013). Due to its antimicrobial activity, it promotes defense mechanisms against many microorganisms, from preventing diseases to preserving food (Takooree, 2019).

Vinegar.

Vinegar is formed by a two-step fermentation, first of which is ethyl alcohol and then acetic acid is obtained from raw materials containing sugar or starch. Bioactive compounds such as polyphenols and vitamins in vinegar can protect against oxidative stress due to their antioxidant activities (Budak, 2014).

Garlic.

Garlic (allium sativum) is a vegetable in allium plant class which also include bulp-shaped plants containing chives, onions, leeks and spring onions. It is suggested that the high concentration of sulfuric compounds and thiosulfinates (including allicin) in garlic are active ingredients in garlic. Aliin turns into allicin by damaging, chopping or crushing the texture of garlic cloves (Halk Sağlığı Genel Müdürlüğü, 2020).

Allicin promotes host immune response (Feng, 2012). Garlic extracts have been shown to strengthen immune cell function and, accordingly, reduce cold and flu symptoms (Nantz, 2012). In addition, garlic regulates the inflammatory response and shows antioxidant properties (Rodrigues, 2019).

Garlic may increase the risk of bleeding due to its anticoagulant properties. For this reason, pregnant women and those who use blood thinners should avoid using garlic. To get more of its active compounds from garlic, it should be consumed raw.

According to the recommendations of the World Health Organization (WHO), the amounts that can be used as supplements in adults are as follows (Halk Sağlığı Genel Müdürlüğü, 2020):

- 2-5 g fresh garlic (one clove of garlic) / day
- 0.4-1.2 g / day dried garlic powder
- 2-5 mg / day garlic oil
- 300-1000 mg / day garlic extract
- 2-5 mg/day other formulations containing allicin

Sumac.

Sumac, which is a red plant, is widely used as a spice in our country. Sumac has antibacterial, antifungal, anti-inflammatory, antioxidant, antiviral effects with its bioactive components (Sakhr, 2020).

Carob.

Carob (Ceratonia siliqua L.) is a fruit with high sugar content that grows in regions where the Mediterranean climate is seen. In addition to being naturally energizing due to its rich sugar content, it has an important place in nutrition with its feature of being rich in mineral and phenolic substances (Pazir, 2018). Gallic acid, catechin and other catechin derivatives are the main polyphenolic components of carob. It has an antioxidant effect with its polyphenols (Stavrau, 2018).

Honey.

Honey, a popular foodstuff, consists of ~ 80% carbohydrates and ~ 19% water and contains organic acids, proteins, amino acids, minerals, polyphenols, vitamins, flavor compounds, and about 500 different kinds of enzymes (Hills, 2019). Honey contains components that are antioxidant, anti-inflammatory, and antibacterial, as well as cough-reducing and wound-healing properties (Meo, 2017).

In addition to these positive properties, Clostridium botulinum toxin, which is likely to be found in honey, can cause infantile botulism. Symptoms of infant botulism are usually constipation, followed by lethargy, weakness, poor nutrition, ptosis, dysphagia and loss of head control, hypotonia, vision problems, and dry mouth. Against the risk of infant botulism, which also causes sudden infant death, honey consumption is not recommended for children younger than 1-year-old and especially for non-Caucasian children (Abdulla, 2012).

Tea.

Tea is the most consumed beverage in the world after water. It was obtained from the leaves of the *Camellia sinensis* plant about fifty centuries ago. 78% of tea production in the world is black, 20% is green and 2% is oolong tea (Hayat, 2015). Black and green teas show their antioxidant properties with different ingredients. Polyphenols from the flavonoid group are high in green tea. Catechins from the polyphenol group and epigallocatechin gallate from catechins are particularly abundant. The most important catechins of black tea are theaflavins and thearubigins (Fisunoğlu, 2008). In addition to its antioxidant effects, teas have ~~an~~ anti-inflammatory and antimicrobial properties, supporting the immune system (Hayat, 2015).

2.4. Food Additives and Immunity

Food additives are ingredients added to foods to change or preserve the physical or chemical properties. Some food additives have been shown to cause an IgE-mediated immune response by acting as an allergen, or a non-IgE-

mediated immune response by acting as a pseudo-allergen. It has been reported that the resulting immune response may exacerbate diseases such as eosinophilic esophagitis, bronchial asthma, dermatitis, or anaphylaxis, but may also lead to different clinical outcomes (Velázquez-Sámano, 2019).

Tertiary-butylhydroquinone used to prevent oxidation in foods, has been shown to inhibit the production of IL-2 and IFNγ, leading to the suppression of the immune system (Turley, 2015). In another study, sodium benzoate, which is used as a preservative in foods, has been shown to decrease the T and B cell expression and cause the immune system suppression (Yadav, 2016). A study by Maier et al. found that sodium benzoate used as a preservative and curcumin used as a colorant with propionic acid, suppresses the synthesis of interferon-gamma (IFN-γ) mediated neopterin. It has been suggested that the suppressive effect of these food additives in Th1 immune response may be harmful in defending against tumors and pathogens while causing benefits against infections and may also cause allergic diseases (Maier, 2010).

It has been reported that synthetic food dyes, the use of which has increased rapidly in recent years, lead to an increase in many allergic diseases and immune system disorders (Vojdani, 2015). Synthetic food dyes have been found to increase histamine and leukotriene production, leading to allergic and inflammatory diseases in both IgE-mediated and non-IgE-mediated immune responses. In a study, it was observed that plasma histamine levels increased after consumption of Tartrazine, a synthetic colorant used for obtaining yellow color (Feketea, 2017).

3. Exercise and Sport

It is known that exercise affects the immune system by causing changes in blood circulation, leukocytes, cytokines, red blood cells, and similar parameters. The immune response varies according to the duration and severity of the exercise and adaptation of an individual (Şenışık, 2015). Light and moderate regular exercise for up to 45 minutes have been found to reduce the risk of cardiovascular and metabolic disease by increasing the activity of natural killer cells, which act as protective agents in the body, dendritic cells, neutrophils and other leukocytes (Simson, 2020; Simspson, 2020). Long-term intense exercise has been shown to suppress immunity by increasing the levels of cytokines. It has been reported that individuals with intense physical activity above the recommended time and intenseness, such as high-performance athletes and military personnel, are more susceptible to infections (Simspson, 2020).

7 different studies were evaluated in the review in which Sitlinger et al. investigated the effects of exercise on immune functions in hematological malignancies. Studies have shown that exercise improves immune function and leads to a decrease in tumor growth (Stlinger, 2020). In the study where the effect of endurance and resistance training has been investigated twice a week for 12 weeks in breast cancer patients undergoing adjuvant chemotherapy treatment, it was observed that chemotherapy caused a decrease in immune cells in the experimental and control groups, but physical activity did not suppress cellular immunity by endurance and resistance training (Schmidt, 2018).

With aging, decreased muscle strength, limited joint movements and slowed movements cause decreased physical activity (Torlak, 2018). Skeletal muscle is involved in immune regulation by ensuring that cytokines called myokines, which have anti-inflammatory and immunoprotective effects during physical activity, are released into the circulation (Duggal, 2019). The effect of skeletal muscle on immunity is weakened by decreasing physical activity in older individuals. For this reason, various diseases associated with aging are mostly associated with a sedentary lifestyle (Torlak, 2018). There is evidence in the current literature that exercise reduces mortality in older individuals and has positive effects on quality of life (Kırdı, 2019).

As a result of the Covid-19 pandemic, which started in China in December 2019 and spread all over the world, Turkey and many other countries had restrictions in order to avoid the spread of the virus. In addition to the closure of parks and gyms, the implementation of curfews led to a significant reduction in individuals' physical activities. Although there is no scientific data on how physical activity prevents contamination against coronaviruses or how it affects immunity, it is known that exercise at the recommended time and intensity suppresses inflammation and increases the immune response to diseases (Simpson, 2020).

4. Regular Life and Sleep

Sleep is an essential process for the individual to maintain body homeostasis. The immune system and sleep are indirectly related. Sleep has been found to positively affect the function of the immune system by causing changes on the hypothalamus-pituitary-adrenal axis and sympathetic nervous system. In addition, it has been reported that the amount of hormones such as cortisol and adrenaline decreases at night to support the immune system (Rico-Rosillo, 2018).

Sleep patterns, duration, and intensity of sleep have an effect on the body's defense system. As a result of impaired sleep patterns, it has been suggested that increased release of harmful cytokines such as C-reactive protein, IL-6, and tumor necrosis factor (TNF) may increase the risk of metabolic diseases (Nicholson, 2016). It has been reported that changes in sleep quality and time lead to disruption of circadian rhythms (Onur, 2020). It has been found that disruption of circadian rhythms, defined as physiological changes within the body within 24 hours, causes the immune response to be disrupted by changing the function of cells responsible for the release of cytokines (Labrecque, 2015). In a study by McAlpine et al., mice exposed to sleep interruption showed an increase in inflammatory Ly6Chi monocytes and a decrease in the production of hypothalamic hypocretin, a larger atherosclerotic lesion and stimulating neuropeptide. Reduced plasma hypocretin is associated with a risk of myocardial infarction, heart failure, and obesity. In the other group of mice taking hypocretin supplements, a decrease in circulating monocytes and smaller atherosclerotic lesions were observed. (McAlpine, 2019). In his study on mice, an effective glymphatic system was discovered in the removal of metabolic wastes of harmful proteins. The glymphatic system has been expressed as a drainage system formed by aquaporin-4 (AQP4) water-channel proteins in the central nervous system, which also controls the immune system (Xie, 2013). The glymphatic system, whose activity appears to increase by 60% during sleep, has been associated with short and long-term harmful effects as a result of insufficient sleep (Mestre, 2020) As a result, sleep quality has been found to indirectly affect the immune system by causing changes in the nervous system

5. Environmental Factors

It is known that the immune system is affected by various external factors. Research has shown that air pollution affects autoimmunity. It has been reported that the risk of morbidity and mortality is higher in diabetic patients exposed to air pollution (Schraufnagel, 2019).

Another external factor, endocrine disruptor pesticides, has been found to interact with various receptors, alter the intestinal microbiome, or induce oxidative stress through circadian disruption, leading to impairments in the immune system. In a study, it has been shown that exposure to bisphenol A (BPA) increases the release of proinflammatory cytokines and insulin resistance by activating the janus kinase (JNK) and nuclear factor kappa beta (NFκB) pathways (Bansal, 2018). Soil and 6 kinds of vegetable samples collected from various regions in Pakistan were examined. As a result of the research, contamination with endocrine-disrupting pesticides such as γ-HCH, α-HCH, heptachlor epoxide, p,p′-DDT, heptachlor, α Chlordane, p,p′-DDE, γ-Chlordane, p,p′-DDD, and δ-HCH which are possible carcinogenic (C Class) β-HCH pesticides and probable carcinogen (B2 Class) have been detected in lettuce> radish> spinach> onion> turnip> and garlic respectively (Ali, 2019).

In a study conducted on radiology workers, those who were exposed to ionizing radiation for a long time showed a significant reduction in immune regulation CD4+ T lymphocytes and total immunoglobulin levels (Yüce, 2015).

6. Smoking, Alcohol and Addictive Drugs

Harmful habits such as consuming alcohol, smoking, and drugs have been found to increase the susceptibility to infections by suppressing immune response and phagocytosis (Karavitis, 2011). In animal studies, it has been reported that the use of heroin, cocaine, or nicotine causes immune cell deficiency and activation of the

hypothalamus-pituitary-adrenal axis (HPA) leading to disruption of the function of the immune system (Friedman, 2004).

It is known that alcohol consumption alters both innate and acquired immunity in humans and animal models. While moderate alcohol consumption is associated with a decrease in inflammation and a better response to vaccination, the effect of excessive alcohol consumption decreasing the lymphocyte count has been shown to increase the risk of bacterial and viral infections (Barr, 2016). In the study in which the effects of alcohol consumption on the alteration of maternal immunity that may cause neurodevelopmental delay in children were investigated, blood samples were taken for cytokine and chemokine measurement in the second and third trimesters of pregnancy. Especially in the second trimester, interferon-gamma (IFN-ɣ), IL-10, TNF-β, TNF-α, and CRP levels, which are associated with a neurodevelopmental delay in children, were found higher. Alcohol-induced mothers of children with neurodevelopmental delay were found to have higher IL-15, IL-10, macrophage-induced chemokine (MDC), and vascular endothelial growth factor (VEGF) cytokine levels (Bodnarr, 2018).

In vitro study examining the changes in macrophage functions as a result of exposure to cigarette smoke extract of the third-trimester placenta macrophages revealed that cigarette smoke extract disrupts the immune balance required for a healthy pregnancy period by decreasing the release of IL-10 while increasing TNF and IL-33 release (Belhareth, 2018).

Smoking is a serious risk factor for COVID-19 disease, for which strong immunity is essential. It is known that cigarette smoke contributes to the transmission of the virus and harms almost all organs. Toxins in cigarette smoke damage many tissues, including the upper respiratory tract and lung alveoli, after they enter the body through the mouth and nose. As a result of tissue destruction, it is easier for the COVID-19 virus to settle in the lung tissues. In addition, inflammation in the lungs causes a decrease in lung and immune system functions (Haddad, 2021).

7. Psychological State

Stress is indirectly effective in suppressing immunity. Corticosteroid hormones, which increase in stress, lead to a decrease in antigens and increase susceptibility to infections (Nocilaides, 2015).

Stress is one of the environmental factors that cause neuron degeneration. Leukocytes have receptors for most of the neurotransmitters released by nerve endings. This situation explains the relationship between the impaired immune system and the nervous and endocrine systems. In a study where changes in the immune parameters caused by psychological stress were observed in female rats, restrictive stress was applied to pregnant rats for 1 hour in 4 days a week before 5 weeks of the pregnancy. As a result of the study, changes on immunity effected by stress factors were observed by evaluating the immunoglobulin (IgG) concentration that can cross the placenta and the Morris water maze test. As a result, a significant increase in serum IgG concentration was found in rats exposed to stress, and a decrease in learning and memory was found as a result of the Morris test (Haloui, 2016). In the study of Padgett et al., it was observed that serum corticosterone levels increased in mice that were put under social stress by changing their cages. The rising corticosterone level activated the HPA axis, leading to the re-emergence of the herpes virus. The study showed that the nervous, endocrine and immune systems are interrelated. (Padgett, 1998). In the study of Zou et al., it was found that IL-1β, IL-10, and TNF-α cytokine levels were higher in patients with major depression compared to the healthy group, while IL-8, which was involved in the immune response in acute inflammation, was lower. As a result, it has been reported that depression causes disorders in immune regulation and immune system activation (Zou, 2018).

8. Previous Diseases

The immune system can be disrupted as a result of certain previous diseases. Suppression of the immune system after various infections, malignancies, malnutrition, metabolic diseases, collagen vascular diseases, lymphocyte or

antibody loss, and etc. are defined as secondary immune deficiency (Turul, 2013). IgG level below normal or immunoglobulin function disruption causes these individuals to become more susceptible to infections (Savaş, 2015).

As well as being asymptomatic and leading to serious infections and malignancy, it has been found that damage to CD4+ T lymphocytes in HIV infection immunopathogenesis and imbalance in CD4+ T cell homeostasis lead to severe impairment of immunity (Vidya Vijayan, 2017).

In a study conducted on with nine patients diagnosed with Acute Myeloid Leukemia, it was found that NKP30 expression, which provides natural killer cells and activation of these cells, was higher than the control group. According to these results, it was observed that immune function differs in patients with Acute Myeloid Leukemia compared to healthy individuals (Aydın, 2013).

9. Genetic Predisposition

Helper T cells (Th) play an important role in the acquired immune response. For example, Th1 cells are effective in intracellular pathogens by triggering type 1 response, while Th2 cells are important in the immune response to extracellular parasites by triggering type 2 response (Bülbül, 2013). In addition, the immune system response differs by gender. While estrogen enhances the immune system in women, testosterone in men acts as an immunosuppressant. In the study of Roved et al., it has been reported that estrogen and progesterone suppress the type 1 response while supporting the type 2 response in women; whereas testosterone in men suppresses the type 2 response and shows inconsistency in type 1 response (Roved, 2017).

Due to the defects in the functions of the immune system in individuals depending on the gene defect, the increased risk of infection susceptibility, disease, and malignancy is defined as primary immunodeficiency. In a study of 78 children with primary immunodeficiency, patients had antibody deficiency and frequently recurrent lower and upper respiratory tract infections (Kılıç, 2015).

Nguyen et al. suggested that variations in human leukocyte antigen (HLA) in individuals may alter the course of the new coronavirus disease (COVID-19). In their study, they showed that the severity of the disease increased in individuals with the HLA-B*46:01 genotype, while the HLA-B*15:03 genotype increased the immune response by increasing the involvement of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) peptides. It has been stated that testing HLA variations may be important in providing vaccination priority to patients with severe COVID-19 and in the treatment process (Nguyen, 2020).

10. Conclusion

The immune system is affected by many factors. Taking adequate macro and micronutrients with an adequate and balanced diet ensures that the immune system functions properly. As a result of researches, it has been shown that malnutrition and obesity caused by overnutrition suppress the immune system. In addition, it has been shown that some plants' leaves and seeds can support the immune system with the phytochemicals they contain. As a result of fasting in Ramadan, changes occur in the state of hunger and sleep patterns. These changes emerging with fasting have been shown to be effective in reorganizing the circadian rhythm associated with immunity and reducing inflammation-related cytokine levels. It has been demonstrated that moderate-intensive regular exercise, regular life, and good quality of sleep indirectly support immunity by affecting various physiological mechanisms. On the other hand, it has been proven that past diseases, air pollution, radiation, various synthetic compounds, and similar external factors, stress, harmful habits such as alcohol consumption, smoking, and drug usage disrupt the immune system by compromising the cytokine balance. As a result of the studies, an important relationship has been found between genetic differences and immunity. Genetic variations and gender differences in individuals can lead to positive or negative changes in the immune response.

When all the factors regulating the immune system are considered, improvement of internal and external factors, especially lifestyle, can ensure the proper functioning of the immune system and play an effective role in protection and treatment against diseases.

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