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The importance of balanced nutrition to fortify the immune system during the COVID-19 outbreak

La importancia de una nutrición equilibrada para aumentar el sistema inmunológico durante el brote de COVID-19

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ABSTRACT

COVID-19, first reported in December 2019 in Wuhan, China, quickly spread worldwide and was announced as a pandemic in March 2020. As symptoms and outcomes are varied, the elderly and those who have at least one comorbidity (diabetes, cardiovascular disorders or other chronic diseases) are considered to be at high risk and are generally have lower immunity. An optimal immune system is critical for survival, as it protects the body against infectious agents. Nutrition is an essential factor in the immune system, contributing to components in physical barriers, biochemical, innate and adaptive immunity. Research advances show that nutritional deficiencies, namely the inadequacy of energy, macronutrients and micronutrients, affect the immune system and increase infection risk. The following discussion explains the comprehensive role of nutrition in the immune system, nutrition recommendations that can be used as precautions and the need for supplementation during this outbreak.
Keywords: COVID-19; Immune; Nutrition; Pandemic; Supplementation.

RESUMEN

COVID-19, informado por primera vez en diciembre de 2019 en Wuhan, China, se extendió rápidamente por todo el mundo y se anunció como una pandemia en marzo de 2020. Como los síntomas y los resultados son variados, los ancianos y los que tienen al menos una comorbilidad (diabetes, trastornos cardiovasculares u otras enfermedades crónicas) se consideran

de alto riesgo y generalmente se asocian con una inmunidad más baja. Un sistema inmunológico óptimo es fundamental para la supervivencia, ya que protege al cuerpo contra agentes infecciosos. La nutrición es un factor esencial en el sistema inmunológico, contribuyendo a componentes en las barreras físicas, innata y adaptativa. Los avances de la investigación muestran que las deficiencias nutricionales, a saber, la insuficiencia de energía, macronutrientes y micronutrientes, afectan el sistema inmunológico y aumentan el riesgo de infección. La siguiente discusión explica el papel integral de la nutrición en el sistema inmunológico, las recomendaciones nutricionales que se pueden tomar como precauciones y la necesidad de suplementación durante este brote.
Palabras clave: COVID-19; Inmune; Nutrición; Pandemia; Suplementación.

INTRODUCTION

COVID-19 infection, as a global concern, is still ongoing and has not been able to be resolved. To date, it has a mortality rate of 3.1% in 215 infected countries[1]. The main symptoms that arise are in the respiratory system with varying severity, where a person may only produce mild symptoms, and even be asymptomatic. However, in some cases, persons experience severe symptoms with rapid onset pneumonia and massive alveolar damage that result in death. The population considered to be at high risk includes the elderly and those who have at least one comorbidity (diabetes, cardiovascular disorders, and other chronic diseases) generally associated with lower immunity[2].

The immune system protects the body against external particles, infectious agents, cell transformation changes, and has an essential role in metabolic homeostasis and tissue inflammation. Nutritional status along with other factors such as exercise, hormonal activity, smoking, sleep requirements, and even psychological stress can affect various aspects of immunity[3,4,5,6]. Nutrition plays an essential role in many aspects of the immune system, whether innate or adaptive[3,7]. During the activation of immune cells, energy is needed, so it is closely related to various metabolic pathways. Besides producing energy, optimal nutrition also protects against prolonged activation of the immune system to avoid any chronic inflammation[3]. Nutritional imbalances in various aspects, both insufficient energy, macronutrients, and micronutrients, have been shown to affect the immune system and increase infection risk[8,9,10,11].

The exact evidence for balanced nutrition to prevent COVID-19 infection remain lacking. Yet, with the plausible mechanisms available, maintaining a balanced diet to strengthen our immune system is one practical precaution highlighted in WHO advice[12]. The following discussion outlines the nutrition recommendations that can be undertaken as precautions during this outbreak based on the current understanding of the role of nutrition in the immune system.

Overview: The Immune System

The human body has two types of immune systems, innate and adaptive/acquired. When there is an infectious agent or external factors that tries to enter the body, the agent will be confronted with the innate immune system. This first-line immunity is not specific (broad-acting); it does not have the ability of immunological memory, but can react quickly (in minutes)[13]. The first defense is physical and chemical barriers consisting of skin, mucous layers, certain structures (e.g. hair, cilia) or certain chemicals (mucus, gastric acid, bile acid) that coat the epidermal layer of various organ systems, such as respiratory, digestion, reproduction and integument systems[14].

Innate immune cells are able to recognize foreign agents through various receptors, for instance toll-like receptors (TLRs), or recognition of other molecules such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)[13]. The mechanism of killing external agents can also be done indirectly through cytokines or elements of the complement systems that facilitate foreign particles to specific molecules present on phagocytes (opsonisation). The main players in innate immune responses are phagocytic cells and natural killer (NK) cells that bind to type 1 major histocompatibility complex (MHC) proteins to induce cell apoptosis. Some of the innate immune systems, such as dendritic cells (DC), macrophages and monocytes, are antigen-presenting cells (APCs), which are responsible for carrying infective antigens to the final defense system, the adaptive/acquired immune system[14]. More specifically, DCs express pattern recognition receptors (PRRs) as responses to pathogens. DCs can then promote the activation of naive T cells in the lymph nodes[15].

Adaptive immunity kills specific infectious agents based on antigen exposure and has immunologic memory. Yet, it takes time for B cells and T cells to differentiate, mature and become effector T cells or B cells that have memory or capable of secreting antibodies[16]. It is known that microRNAs (miRNAs) are key controllers of T - cell differentiation and function, which are also influenced by costimulation and cytokines[17]. The main subsets of T lymphocyte cells are CD4+ and CD8+. The effector CD4+ T cells involve co-stimulation between MHC type-II complexes found in APCs and T cell receptors on naive CD4+ cells. Depending on the microenvironment cytokines and transcription factors, CD4+ T cells can differentiate into a subset of effector T cells, namely Th1, Th2, Th17 or

Treg. Each subset secretes certain cytokines that affect the immune system. Meanwhile, CD8+ requires MHC type I to mature into cytotoxic effector T cells (releasing perforin and granzymes to kill infectious agents). Thus, each type of immune system has advantages and disadvantages and work synergistically to achieve optimal immunity for an individual[14]. B cell receptor (BCR) can recognize the antigen presented by T cells that binds to either soluble or membrane bound antigen and form microclusters, resulting downstream signalling cascades. It facilitates the immune humoral response via opsonization, complement fixation, and pathogen neutralization[18].

Immune system and COVID-19

As the first line of defense, mucosal surfaces (respiratory tract, oral mucosa, and conjunctival epithelium) are protected against the virus via mucosa-associated lymphoid tissues (MALT) by producing IgA. Studies showed that specific IgA response is detectable in 75% of the patients within the first week of infection and appears to be stronger and more persistent than IgM response[19].

Briefly, COVID-19 triggers two stages in the innate immune system. The initial stage is a general immune response in any pathogen, which occurs when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enter the cells via the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane serine protease 2 (TMPRSS2)[20]. The immune system recognizes viral nucleic acids, PAMPs, by the specific pathogen recognition receptors (PRRs) in the cytosol. The second stage, which is said to be the beginning of the problem in COVID-19, is the existence of inflammation characterized by the development of a pro-inflammatory feedback loop induced by pro-inflammatory chemokines and cytokines (including IL-6, IP-10, macrophage inflammatory protein 1α (MIP1α), MIP1β, and MCP1). Studies show hyperactivation of immune cells such as macrophages, monocytes, neutrophils (characterized by an increased neutrophil: lymphocyte ratio), and IL-6 production from macrophages in COVID-19 patients[21,22,23].

In the adaptive immune system, it is presumed that COVID-19 induces a similar Th1 type immune response as other viral infections[24]. This is accompanied by decreased CD8 + T cells, and memory CD4 + T cells and T regulatory in severe cases. Moreover, spleen and lymph nodes in COVID-19 patients were found as atrophic[25].

In a healthy immune response host, virus-specific T cells come to the infection site and kill infected cells; thus limiting the virus spread. Neutralizing antibodies in these individuals can also block viral infection, then alveolar macrophages clear neutralized viruses and apoptotic cells by phagocytosis[26]. All of these responses cannot adequately reach an inadequate immune host, resulting in an accumulation of immune cells in the lungs, which eventually damages the lung infrastructure and produce a situation called “cytokine storm,” leading to multi-organ damage and death[27]. In severe cases of COVID19, immune dysregulation is characterized either by the presence of components of macrophage activation syndrome (MAS) or decreased levels of human leucocyte antigen D-related (HLA-DR) expression, and followed by profound depletion of CD4 and CD19 lymphocytes, as well as NK cells[28].

The role of nutrition in the immune system

A balanced diet provides adequate amounts of energy, proteins, vitamins, minerals, essential fats, micro and macronutrients, which are required for all cells, include immune cells, to function optimally[3]. In the following section, we will elaborate on nutritional recommendations for achieving optimal immune balance.

Nutritional status and immune system

Adequate energy is needed to meet the body’s metabolism and synthesis of various non-essential proteins and immune cells. Adipose tissue, aside from being a major nutrient reserve, is also an immune organ that can secrete various hormones and cytokines (called “adipokines”) that control cellular metabolism and immune activity. Two of the most studied adipokines are leptin and adiponectin. Leptin increases in obesity and promotes inflammation. Leptin is recognized by leptin receptor (LepR) presented on the surface of immune cells. Leptin regulates immune cells by stimulating monocytes differentiation to macrophage, modulating NK cells, and inducing proinflammatory cytokines release. Leptin increases the glucose transporter expression, Glut 1, thus promoting glucose uptake and glycolysis of T cell, leading to inflammation. Conversely, adiponectin, which is also an anti-inflammatory hormone-sensitive and hormone insulin, has anti-inflammatory effects through decreased phagocytic activity, low production of TNFα in macrophages and monocyte precursor differentiation. Adiponectin levels are inversely related to the amount of fat mass[11,29]. It is also known that adiponectin level can be modulated by diet intervention, low-fat diet, carbohydrate-restriction diet (20-25% energy), fish and fish oil, and fiber consumption[30].

Malnutrition results in hypoleptinemia thus affecting the immune response in an opposite manner[7,11,31]. This explains why poorly nourished individuals are at a greater risk of various infections. Obesity is associated with hyperleptinemia, yet this does not translate into a better immune response as this also accompanied by reduction of adiponectin level. Hyperlectinemia and hypoadiponectinemia increases inflammation and decreases the inflammatory response, known as the state of chronic low-grade inflammation[11,31]. Diet-induced obesity shows an early activation of TLR-mediated inflammatory signalling cascades by CD antigen genes and leads to increased expression of pro-inflammatory cytokines and chemokines[32]. Therefore, ideally, the immune system is in the normal range, not deficient or excess, thus ensuring an accurate and optimal immune system in confronting the stimulus (as seen in Figure 1).

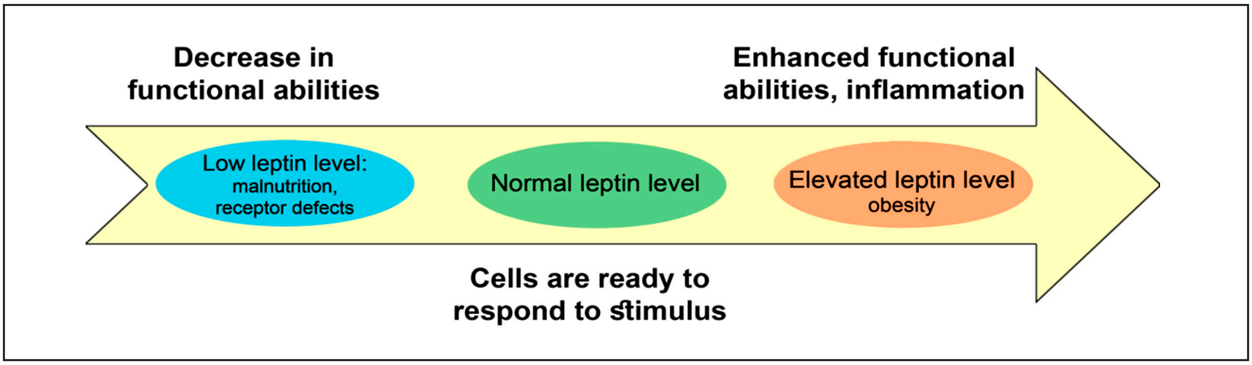

Figure 1: Leptin level associated with nutritional status and immune balance. Adapted from "Leptin regulation of immune responses" by Naylor and Petri[30] with modification.

Macronutrients

A balanced diet is composed of five food groups: staple foods, meat and alternatives, vegetables, fruits and drinks. Alternatively, it can be classified according to macronutrient type with a proportion of 45-60% carbohydrates, 15-25% protein, 20-30% fat, and adequate liquid according to age. One easy way to obtain a balanced nutrition in adults is to follow the practical guidelines from the Indonesian Ministry of Health, named "Isi Piringku" as shown in Figure 2[33].

Carbohydrates, as the primary energy source, take up the most significant proportion of food composition. Simple and refined carbohydrates are associated with increased inflammation, so it is preferred to consume complex carbohydrates and those rich in fiber[34]. The recommended fiber consumption is 14 grams/1.000 kcal of energy[35]. One of the advantages of fiber in the immune system is that colon bacteria will ferment non-digestible fiber into short-chain fatty acids (SCFA), including acetate, propionate and butyrate, which are the primary nutrients for enterocytes, the main barrier in the gut mucosal permeability. The gut is part of the immune system in which its metabolites not only act locally, but can also enter the circulation a phenomenon called "luminal conversion"[36]. SCFA as a "good" metabolite, modulates immune responses by promoting Treg cell differentiation and maintaining intestinal B cell homeostasis[37].

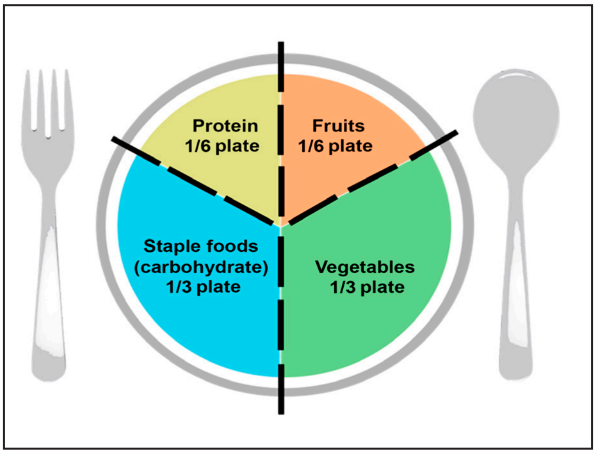

Figure 2: Practical recommendations in meeting balanced nutritional needs as suggested by the Ministry of Health of the Republic of Indonesia. Adapted from "Isi Piringku Sekali Makan", with modification[31].

In animal protein, the amino acid content is generally more complete and easier for the body to digest, but tends to have higher levels of fat and cholesterol[34]. In 2015, the International Agency for Research on Cancer (IARC) classified processed meat as a Group 1 carcinogen (a carcinogen to humans), and red meat as a Group 2A agent (possibly carcinogenic to humans)[38]. Therefore, the consumption of processed meats should be avoided, while the consumption of red meat should be limited to 1-2 times per week. This can be balanced with the consumption of meat other than red meat, such as poultry and fish, a minimum of 2 times per week[12].

Fats are the main component of the cell membrane which act as a molecular signal and participate directly in the inflammatory response. Unsaturated fats, mono-or-polyunsaturated, as found in fish, avocado, olive oil, are "good fats" compared to saturated and trans fats. The recommended saturated fats consumption is less than 10 percent of calories per day[35]. One of the polyunsaturated fats, omega 3 (n-3), inhibits inflammatory signaling, as well as regulates food intake and substrates for the synthesis of pro-resolving lipid mediators. On the contrary, saturated fatty acid (SFA) increases LDL, endotoxemia, and induces cellular stress[37]. As inflammation is a key component of the immune response, the anti-inflammatory effect of omega-3 might be beneficial or cause unintended health consequences to the current conditions, although this is an area of further research. Studies show that omega-3s (ALA, DHA, EPA) have inhibitory effects on innate and adaptive immune system activation. However, some specific immune functions are promoted in specific immune cell types, i.e., phagocytosis by macrophages and neutrophils or Treg differentiation, suggesting that omega-3 fatty acids do not act as specific immune-repressors[39].

A Cochrane meta-analysis study concluded that the use of an immuno-nutrition enteral formula or additional supplementations of omega-3 fatty acids, γ-linolenic acid and antioxidants result in no difference in all-cause mortality in people with acute respiratory distress syndrome (ARDS). Due to the very low quality of evidence, it is uncertain whether immuno-nutrition with omega-3 fatty acids and antioxidants improves ICU length of stay, ventilator days and oxygenation, or increases harm[40]. However, other studies show that instead of the amount, the ratio of omega 6: omega 3 controls metabolic homeostasis. Although epigenetic and genetic variations also influence this, various prospective cohort studies and randomized controlled trials support the idea that populations that consume a ratio of n−6 to n−3 fatty acids (FAs) closer to 1:1 have fewer chronic diseases than those in areas that consume mostly n−6 FAs with Western diets (having a ratio of n−6 to n−3 FAs at 15/1 to 16.7/1)[41].

Another practical approach is to limit sugar consumption to no more than 50 g (4 tablespoons), sodium no more than 2.000 mg (1 teaspoon), and oil no more than 67 g (5 tablespoons)[34]. Free sugars consist of all sugars naturally present in foods (honey, syrups, fruit juices and fruit juice concentrates), as well as sugars added to foods[42].

Water comprises 75% to 55% of body weight in infants to the elderly[43]. It is essential for cellular homeostasis as it carries nutrients and compounds to the blood, controls body temperature, flushes bacteria and waste and lubricates joints. The actual fluid requirements depend on body composition, organ function and additional energy requirements such as physical activity level, pregnancy and lactation. Meeting fluid needs is obtained through food and drinks. Only 1/3 of the portion is usually obtained from food. Therefore, it is recommended to drink 8-10 cups, approximately 2 liters, of water every day in healthy adults[12,34]. The amount of liquid consumed can be obtained from drinking water, fruit juice, tea or coffee, but attention is needed to limit the consumption of sugar per day. In the elderly population, the regulation of thirst is impaired when compared with younger people and thus requires special attention[44].

Micronutrients

More than two billion people suffer from micronutrient deficiencies globally, either in malnutrition or in overweight and obese (also known as "hidden hunger"). Micronutrients (vitamins and minerals) have a specific role in the development and maintenance of the immune system, as shown in figure 3. Generally, the needs of micronutrients are met based on the recommended dietary allowance (RDA), which can be achieved by eating a variety of foods. It is recommended to consume 2 cups of fruit (4 servings) and 2.5 cups of vegetables (5 servings) daily. It is also essential to take notes on food processing, as overcooked vegetables and fruit can lead to loss of important vitamins[12].

Micronutrients and dietary components have very specific roles in the development and maintenance of an effective immune system. For example, Vitamins A, C, D, E, B_6, B_{12}, folate, iron and zinc maintain the integrity of the physical barrier system through various physiological effects, such as differentiation and growth of the epithelial tissue[3], promoting collagen synthesis[45], increasing keratinocyte differentiation and fibroblast migration[46] and maintaining intestinal microbiota composition[5]. Furthermore, the active form of Vitamin D (calcitriol) stimulates expression of cathelicidin and defensins which directly kill pathogens and stimulates expression of E-cadherin and connexin in the gastrointestinal tract[47].

In the innate and adaptive immune system, Vitamins A, C, D, E, B_6, B_{12}, folate, zinc, selenium, iron, copper and magnesium enhance the immune system mostly by maintaining or enhancing NK cells and cytotoxic activity. These nutrients stimulate monocytes differentiation into macrophages that are essential for immune protection. Macrophages and neutrophils generate free radicals to combat invading microbes and have specific roles in production, differentiation, and proliferation of T cells[48].

Nevertheless, Vitamins A, C, E, selenium, copper, zinc and manganese play an essential role in maintaining pro-oxidant and antioxidant balance[48]. An imbalance between pro-oxidants and antioxidants accompanied by a failure of the body's antioxidant mechanisms results in a buildup of oxidative stress that is closely related to the inflammatory reaction and hyperactivation of the immune system leading to immune dysfunction[49]. Vitamins A, C and E have endogenous antioxidant abilities through electron donation. Selenium, copper, zinc and manganese are cofactors in the synthesis of the antioxidant enzyme superoxide dismutase, catalase and glutathione peroxidase. Vitamin C can help regenerate vitamin E and glutathione in the glutathione peroxidase system, which is an endogenous antioxidant that is very important in stopping the lipid peroxidation chain[50].

Supplementation: Is It Needed?

Satisfaction of nutritional needs is expected to be achieved through the consumption of natural food sources. However, data shows that most people consume diets that do not acquire sufficient nutritional needs according to national guidelines[35]. This is exacerbated by the increased risk of food scarcity and economic shocks during this pandemic. Therefore, the use of multi-micronutrients (MMN) supplementation may be an alternative to obtain nutritional needs and is relatively inexpensive. MMN supplementation is considered safer compared to specific single supplementation because single supplementation generally has a higher dose, and this can affect the absorption of other nutrients and increase side effects[51]. Nonetheless, studies have shown results that are not yet conclusive of infection risk[8,52].

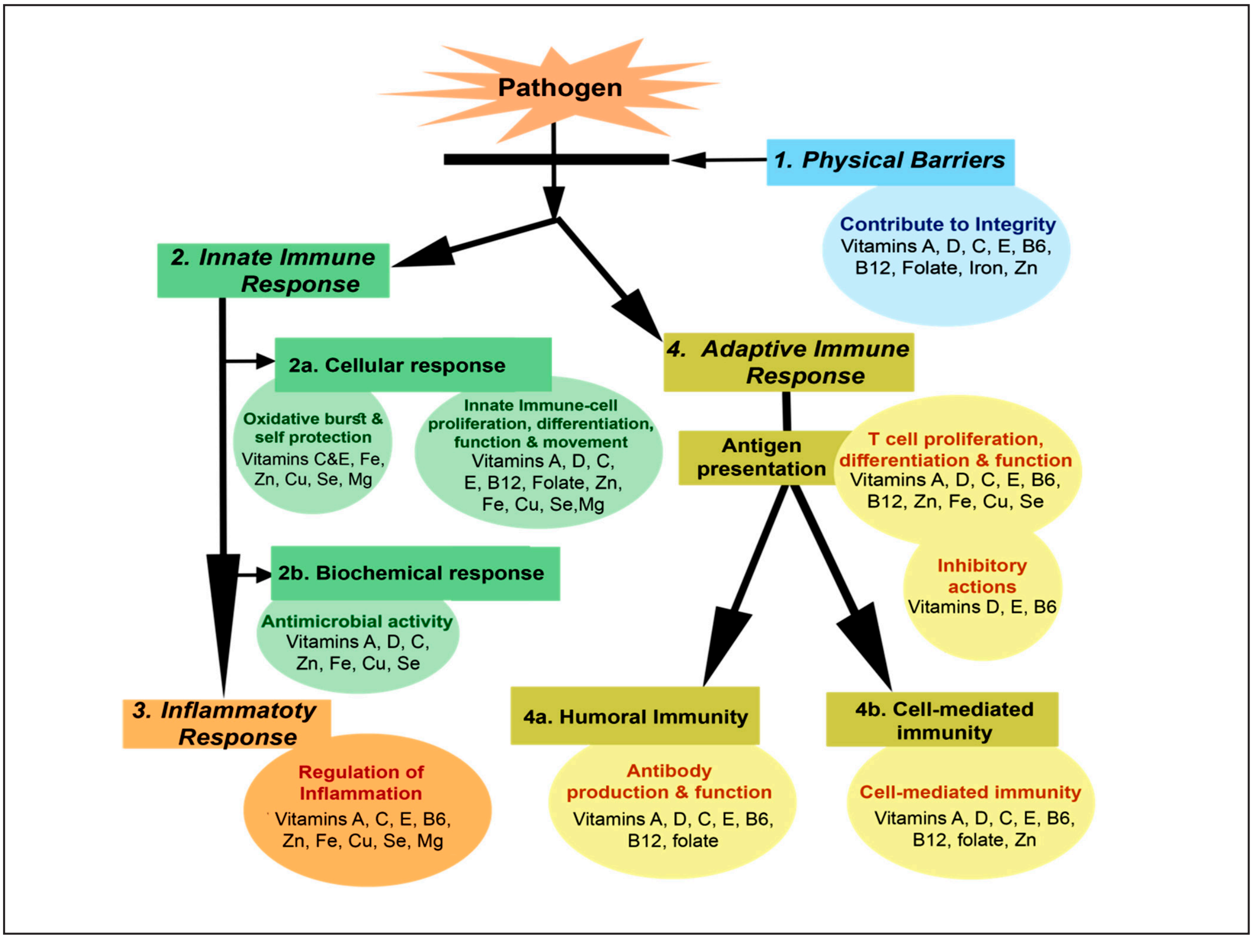

Figure 3: Micronutrient involvement in the immune system. Adapted from "A review of micronutrients and the immune system-working in harmony to reduce the risk of infection", with modification[45].

The effect of vitamin A in preventing infection has been evaluated with contradictory results. A recent systematic review states that supplementation of 50,000-200,000 IU every 4-6 months can reduce the incidence of diarrhea and measles, but not respiratory infections or pneumonia[48].

Studies on vitamin E supplementation as prophylaxis have a controversial effect[53]. A study shows that vitamin E supplementation of elderly smokers can reduce the incidence of pneumonia by 69%, but these results cannot be extrapolated to the general population[54]. Interestingly, one meta-analysis study shows that high doses of supplementation of vitamin E (>400 mg/day) increase all-cause mortality[55]. One possible explanation is that the anticoagulant property of vitamin E (interfering with vitamin K-dependent clotting mechanisms) increases the risk of hemorrhagic stroke. In the elderly, physiological changes indicate a higher vitamin E requirement; 200 IU / day to obtain optimal immune function[56].

Vitamin C is one of the most frequent supplementations given, as it is relatively low cost and safe, yet the recommended dose for disease prevention is also still controversial. A meta-analysis at the age of 3 months to 18 years showed no difference between vitamin C administration and placebo (odds ratio= 0.75, 95% CI [0.54-1.03], p= 0.07, I2 = 74%) for frequency of upper respiratory tract infections. However, it significantly decreased the duration of URTI by 1.6 days with no serious adverse events. This shows that supplementation in children may be justified, especially in children under six years old, as they have greater statistical power than a 6-18 years old[9]. To date, there were two Cochrane meta-analyses analyzing vitamin C supplementation in reducing the risk of respiratory diseases. First, vitamin C supplementation for reducing the incidence of community-acquired pneumonia was significant (80% or greater), but these studies were carried out in special groups, namely soldiers during World War II and in groups of children from low-income families[57].

Another study indicated that 200 mg or more vitamin C supplementation daily was effective in ameliorating the duration and severity of the common cold, also the incidence of the common cold for those who exposed to severe physical stress only[58]. Compared with the RDA, the administration of 200 mg vitamin C is 2-3 three times greater. Although studies show that high doses do not show serious side effects, administration above the upper level (2000 mg for adults and 400 mg for kids 1-3 years old) can cause diarrhea, nausea, fatigue, gastritis, heartburn and insomnia. In the case of COVID-19, a small scale trial suggests that administering 12 g of vitamin C/50 ml intravenously every 12 hours for 7 days can significantly lower pro-inflammatory cytokine IL-6 level[59]. Of note, patients with a history of calcium-oxalate kidney stones, liver or kidney disorders and gout should not consume high doses because, as a water-soluble vitamin, excess vitamin C will be excreted in the urine. Excretion rates will increase with increasing doses of vitamin C, suggesting that high doses of supplementation do not indicate more absorption[60]. In participants who had inadequate vitamin C status (<50 µmol/L), supplementation with a dietary source (kiwifruit) of approximately 250 mg/day vitamin C resulted in an enhanced immune function, marked by 20% increase in neutrophil chemotaxis and a comparable increase in oxidation generation[61].

Vitamin D is a fat-soluble vitamin that has long been associated with the immune system. However, the therapeutic effect of vitamin D supplementation for COVID-19 treatment is still debatable. A study performed by Jain et al.[62] showed that patients with severe COVID-19 had significantly lower levels of vitamin D compared to asymptomatic COVID-19 patients (mean vitamin D level (ng/mL) was 27.89±6.21 in the severe vs symptomatic group vs 14.35±5.79 in the asymptomatic group). A meta-analysis by Pereira et al.[63] showed that vitamin D deficiency was not associated with a higher likelihood of COVID-19 infection (OR= 1.35; 95% CI= 0.80-1.88), but vitamin D deficiency increased length of stay (OR= 1.81, 95% CI= 1.41-2.21) and risk of death from COVID-19 (OR= 1.82, 95% CI= 1.06-2.58). Furthermore, a meta-analysis by Martineau et al.[10] with almost 11,000 samples shows that vitamin D supplementation (with varying doses) is safe and reduces the risk of respiratory tract infections (adjusted odds ratio (aOR) 0.88, 95% confidence interval (CI) 0.81 to 0.96; heterogeneity p <0.001), results supported by other recent studies[64,65]. Conversely, in a subgroup analysis by Martineau et al.[10] it was found that this protective effect was only significant in routine daily or weekly consumption (not in those receiving bolus doses), in supplementation of doses <800 IU, but not those who received doses of 800-2000 IU or> 2,000 IU, and in children 1-16 years but not in those aged 16-65 know, or over 65 years. The recommended dosage of supplementation is controversial, but to date, doses up to 4,000 IU can be considered safe. Studies of large doses, especially bolus, show immune system suppression from peripheral blood monocytes, inflammatory reactions and an increased risk of respiratory tract infections[66,67,68].

Various factors can influence whether someone needs supplementation or not and what dose is needed, for example, age, body mass index, skin color, vitamin D levels before supplementation, geographical location and climate[10,69]. According to Holick's rule, exposure to sunlight at the face and both arms for 25 min, three times a week at 9 am, should maintain adequate vitamin D status. After exposure to sunlight at this specific time and duration for six weeks, mean 25 (OH) D levels of participants increased from 59 nmol/L at baseline to 84 nmol/L[70].

As previously described in the micronutrients section, it is well known that marginal zinc deficiency impacts immunity, notably increased diarrheal and respiratory morbidity in children[71]. This deficiency is also common in the elderly because of decreased intake and some age-related factors (mastication, intestinal absorption, psychosocial factors, drug interactions and subcellular processes)[72]. At the time of this writing, specific recommendations for zinc supplementation as prophylaxis have not been found in healthy people. However, studies show that the effect of zinc as an anti-viral is virus-specific. Excessive doses may interfere with copper absorption, which could conversely, increase infection risk[71].

Selenium is a cofactor for glutathione peroxidase, an endogenous antioxidant and plays a vital role in immune health. Studies in animals have shown that selenium supplementation increases immunity against influenza strains, but evidence in humans is lacking[49]. Selenium supplementation in healthy adult humans with marginal status produces beneficial and detrimental effects on cellular immunity against influenza. Thus, the evidence does not support the simple assumption that Selenium benefit for one immune parameter will benefit all[73]. A Cochrane study shows that the use of selenium supplementation in the prevention of cardiovascular disease has no beneficial or detrimental effects; therefore, it is not necessary, especially for those who are already well-nourished and who get selenium intake from natural foods. Quite surprisingly, high selenium exposure links to an increased risk of type 2 diabetes[74].

With the development of knowledge about intestinal symbiosis, the intestinal microbiota is known to be able to interact with intestinal epithelial cells in maintaining intestinal defense functions and communicating with specific immune cells. A Cochrane review concluded that probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTI, the mean duration of an episode of acute URTI, antibiotic use, yet the quality of evidence was low or very low[75]. We admonish that the benefits of probiotics are strain-specific, thus evidence cannot be simply generalized.

CONCLUSIONS

Nutritional status, energy adequacy and balanced composition of macronutrients and micronutrients have a pivotal role in maintaining and optimizing the immune system during COVID-19 outbreak. MMN supplementation can be an alternative in efforts to meet nutritional needs, especially for trace elements and antioxidant vitamins, only if the needs cannot be met through natural source food ingredients.

Balanced nutrition cannot stand alone in achieving an optimal immune system; it must be supported by other factors: regular moderate-intensity exercise, quitting smoking, a healthy mental state and adequate sleep. Public health practices, such as vaccinations and hygiene measures, also have an important role in limiting the spread and impact of infections. Lastly, all health workers, whether as the frontline or not, are expected to take part in educating the public. Hopefully, with a healthy lifestyle and balanced nutrition, the performance of the immune system will be fortified to minimize infections during the COVID-19 outbreak.

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REFERENCES

1. Infeksiemerging. COVID-19: Coronavirus Disease. 2020. https://covid19.kemkes.go.id/
2. Kluge, H. Older people are at highest risk from COVID-19, but all must act to prevent community spread. World Health Organization 2020. http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/statements/statement-older-people-are-at-highest-risk-from-covid-19,-but-all-must-act-to-prevent-community-spread
3. Childs CE, Calder PC, Miles EA. Diet and immune function. Nutrients. 2019; 11: 1933.
4. Irwin MR. Why sleep is important for health: A psychoneuroimmunology perspective. Annu Rev Psychol. 2015; 66: 143-172.
5. Biesalski HK. Nutrition meets the microbiome: Micronutrients and the microbiota. Ann N Y Acad Sci. 2016; 1372: 53-64.
6. Batatinha HAP, Biondo LA, Lira FS, Castell LM, Rosa-Neto JC. Nutrients, immune system, and exercise: Where will it take us? Nutrition. 2019; 61: 151-156.
7. Alwarawrah Y, Kiernan K, MacIver NJ. Changes in nutritional status impact immune cell metabolism and function. Front Immunol. 2018; 9: 1055.
8. Stephen AI, Avenell A. A systematic review of multivitamin and multimineral supplementation for infection. J Hum Nutr Dietet. 2006; 19: 179-190.
9. Vorilhon P, Arpajou B, Roussel HV, Merlin É, Pereira B, Cabaillot A. Efficacy of vitamin C for the prevention and treatment of upper respiratory tract infection: A meta-analysis in children. Eur J Clin Pharmacol. 2019; 75: 303-311.
10. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. Br Med J. 2017; 356: i6583.
11. Francisco V, Pino J, Campos-Cabaleiro V, Ruiz-Fernández C, Mera A, Gonzalez-Gay MA, Gomez R, et al. Obesity, fat mass and immune system: Role for leptin. Front Physiol. 2018; 9: 640.
12. World Health Organization. Nutrition advice for adults during the COVID-19 outbreak. WHO, 2020. http://www.emro.who.int/nutrition/news/nutrition-advice-for-adults-during-the-covid-19-outbreak.html
13. Kumar H, Kawai T, Akira S. Pathogen recognition by the innate immune system. Int Rev Immunol. 2011; 30: 16-34.
14. Kresno S, Kadir A, Sutandyo N, Harianto S, Setiawan L. Immuno-oncology. Sagung Seto, Jakarta, 2018.
15. Lemos MP, Fan L, Lo D, Laufer TM. CD8α + and CD11b + dendritic cell-restricted MHC class II controls Th1 CD4 + T cell immunity. J Immunol. 2003; 171: 5077-5084.
16. McHeyzer-Williams M, Okitsu S, Wang N, McHeyzer-Williams L. Molecular programming of B cell memory. Nat Rev Immunol. 2012; 12: 24-34.
17. Jeker LT, Bluestone JA. MicroRNA regulation of T-cell differentiation and function. Immunol Rev. 2013; 253: 65-81.
18. Nothelfer K, Sansonetti P, Phalipon A. Pathogen manipulation of B cells: The best defense is a good offence. Nat Rev Microbiol 2015; 13, 173-184.
19. Padoan A, Sciacovelli L, Basso D, Negrini D, Zuin S, Cosma C, et al. IgA-Ab response to spike glycoprotein of SARS-CoV-2 in patients with COVID-19: A longitudinal study. Clin Chim Acta. 2020; 507: 164-166.
20. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020; 12: 1-5.
21. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Chinese J Pathol. 2020; 49: E009.
22. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMed. 2020; 55: 102763.
23. Park MD. Macrophages: A Trojan horse in COVID-19? Nat Rev Immunol. 2020; 20: 351.
24. Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S. Associations between immune-suppressive and stimulating drugs and novel COVID-19-A systematic review of current evidence. Ecancermedicalscience. 2020; 14: 1022.
25. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. Clin Immunol. 2020; 214: 108393.
26. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020; 20: 363-374.
27. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.
28. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in covid-19 patients with severe respiratory failure. Cell Host Microbe. 2020; 27: 992-1000.e3.
29. Cohen S, Danzaki K, MacIver NJ. Nutritional effects on T-cell immunometabolism. Eur J Immunol. 2017; 47: 225-235.
30. Silva FM, de Almeida JC, Feoli AM. Effect of diet on adiponectin levels in blood. Nutr Rev. 2011; 69: 599-612.
31. Naylor C, Petri WA. Leptin regulation of immune responses. Trend Mol Med. 2016; 22: 88-98.
32. Kwon, EY, Shin, SK, Cho YY, Jung UJ, Kim E, Park T, et al.

Time-course microarrays reveal early activation of the immune transcriptome and adipokine dysregulation leads to fibrosis in visceral adipose depots during diet-induced obesity. BMC Genom. 2012; 13: 450.
33. p2ptm.kemkes.go.id. Fill my plate at one time. http://www.p2ptm.kemkes.go.id/infographic-p2ptm/obesitas/page/14/isi-piringku-sekali-makan
34. Ministry of Health of the Republic of Indonesia. Guidelines for balanced nutrition. Ministry of Health of the Republic of Indonesia, Jakarta, 2014. http://hukor.kemkes.go.id/uploads/produk_hukum/PMK%20No.%2041%20ttg%20Pedoman%20Gizi%20Seimbang.pdf
35. U.S. Department of Health and Human Services and U.S. Department of Agriculture. Dietary Guidelines for Americans 2015-2020, 8th edition. USDA, US, 2020.
36. Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nat Med. 2016; 22: p. 1079-1089.
37. Christ A, Lauterbach M, Latz E. Western diet and the immune system: An inflammatory connection. Immunity. 2019; 51: 794-811.
38. International Agency for Research on Cancer. Q&A on the carcinogenicity of the consumption of red meat and processed meat. 2015. https://www.iarc.who.int/wp-content/uploads/2018/07/Monographs-QA_Vol114.pdf
39. Gutiérrez S, Svahn SL, Johansson ME. Effects of omega-3 fatty acids on immune cells. Int J Mol Sci. 2019; 20: 5028.
40. Dushianthan A, Cusack R, Burgess VA, Grocott MPW, Calder P. Immunonutrition for adults with ARDS: Results from a Cochrane systematic review and meta-analysis. Respir Care. 2020; 65: 99-110.
41. Saini RK, Keum YS. Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance- A review. Life Sci. 2018; 203: 255-267.
42. World Health Organization. Reducing free sugars intake in children and adults. 2018. https://www.who.int/elena/titles/guidance_summaries/sugars_intake/en/.
43. Popkin BM, D'Anci KE, Rosenberg IH. Water, hydration, and health. Nutr Rev. 2010; 68: 439-458.
44. Indonesian Hydration Working Group. Things to know about drinking water. 2018. http://ihwg.or.id/hal-yang-harus-diketahui-tentang-minum-air/
45. Pullar JM, Carr AC, Vissers MCM. The roles of vitamin C in skin health. Nutritients. 2017; 9: 866.
46. Carr A, Maggini S. Vitamin C and immune function. Nutrients 2017; 9: 1211.
47. Linus Pauling Institute. Immunity in depth. 2020. https://lpi.oregonstate.edu/mic/health-disease/immunity
48. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. Nutrients. 2020; 12: e236.
49. Zuo L, Prather ER, Stetskiv M, Garrison DE, Meade JR, Peace TI. Inflammaging and oxidative stress in human diseases: From molecular mechanisms to novel treatments. Int J Mol Sci. 2019; 20: 4472.
50. Bello A, Dandare A, Danmaliki GI. Effects of cigarette smoking on lipid peroxidation and serum antioxidant vitamins. IOSR J Pharm Biol Sci. 2017; 12: 40-44.
51. Sandström, B. Micronutrient interactions: Effects on absorption and bioavailability. Br J Nutr. 2001; 85: S181-S185.
52. Tam E, Keats EC, Rind F, Das JK, Bhutta ZA. Micronutrient supplementation and fortification interventions on health and development outcomes among children under-five in low-and middleincome countries: A systematic review and meta-analysis. Nutrients. 2020; 12: 289.
53. Lee GY, Han SN. The role of vitamin E in immunity. Nutrients. 2018; 10: 1614.
54. Hemilä, H. Vitamin E administration may decrease the incidence of pneumonia in elderly males. Clin Interv Aging. 2016; 11: 1379-1385.
55. Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005; 142: 37-46.
56. Meydani SN, Lewis ED, Wu D. Perspective: Should vitamin E recommendations for older adults be increased? Adv Nutr. 2018; 9: 533-543.
57. Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. Cochrane Database Syst Rev. 2013; 8: CD005532.
58. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database of Syst Rev. 2013; 1: CD000980.
59. Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care. 2021; 11: 5.
60. Shibata K, Hirose J, Fukuwatari T. Relationship between urinary concentrations of nine water-soluble vitamins and their vitamin intakes in Japanese adult males. Nutr Metab Insights. 2014; 7: 61-75.
61. Bozonet SM, Carr AC, Pullar JM, Vissers MCM. Enhanced human neutrophil vitamin C status, chemotaxis and oxidant generation following dietary supplementation with vitamin C-rich SunGold kiwifruit. Nutrients. 2015; 7: 2574-2588.
62. Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Sci Rep. 2020; 10, 20191.
63. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: Systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2020:1-9.
64. Rejnmark L, Bislev LS, Cashman KD, Eiríksdottir G, Gaksch M, Grübler M. Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data. PLoS One. 2017; 12: e0180512.
65. Kimball S, Vieth R, Dosch HM, Bar-Or A, Cheung R, Gagne D, et al. Cholecalciferol plus calcium suppresses abnormal PBMC reactivity in patients with multiple sclerosis. J Clin Endocrinol Metab. 2011; 96: 2826-2834.
66. Coussens AK, Wilkinson RJ, Hanifa Y, Nikolayevskyy V, Elkington PT, Islam K, et al. Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. Proc Natl Acad Sci USA. 2012; 109: 15449-15454.
67. Manaseki-Holland S, Maroof Z, Bruce J, Mughal MZ, Masher MI, Bhutta ZA et al. Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: A randomised controlled superiority trial. Lancet. 2012; 379: 1419-1427.
68. Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, Van Eldere J et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: A randomized trial. Annal Intern Med. 2012; 156: 105-120.
69. Nimitphong H, Holick MF. Vitamin D status and sun exposure in Southeast Asia. Dermatoendocrinol. 2013; 5: 34-37.
70. Setiati S, Sutrisna B, Oemardi M. The role of ultraviolet-B from

sun exposure on vitamin D3 and parathyroid hormone level in elderly women in Indonesia. Asian J Gerontol Geriatric. 2007; 2: 126-132.
71. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The role of zinc in antiviral immunity. Advan Nutr, 2019; 10: 696-710.
72. Mocchegiani E, Romeo J, Malavolta M, Costarelli L, Giacconi R, Diaz LE, et al. Zinc: Dietary intake and impact of supplementation on immune function in elderly. Age (Dordrecht, Netherlands). 2013; 35: 839-860.
73. Ivory K, Prieto E, Spinks C, Armah CN, Goldson AJ, Dainty JR, Nicoletti C. Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults. Clin Nutr (Edinburgh, Scotland). 2017; 36: 407-415.
74. Rees K, Hartley L, Day C, Flowers N, Clarke A, Stranges S. Selenium supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013; 1: CD009671.
75. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev. 2015; 2: CD006895.