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REVIEW OF NUTRITIONAL AND PHARMACOLOGICAL STUDY OF PATIENTS INFECTED WITH COVID-19 VIRUS: CHALLENGE AND PERSPECTIVE

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Abstract

The emergence of new infectious diseases with new pathogenic properties is a serious health problem on a global scale and this is what is currently happening with the Covid 19 virus and its mutations. It is widely accepted that there is currently no effective way to stop the virus and its mutations other than certain precautions this implies strict preventive measures and a strategy to develop, throughout, good hygiene, healthy eating and balanced and compliance with containment rules. Although the vaccine remains the only effective solution against the virus. Numerous scientific studies have shown that there is a close relationship between nutrition and immunity, because all deficiencies in proteins, essential fatty acids, mineral enzymes, vitamin factors and antioxidant elements lead to imbalance of the immune system. This article aims to highlight the relationship between the immune system and nutrition and some alternative solutions are based on nutritional supplements intended for countries suffering from malnutrition.

Keywords: *Infectious diseases, Immunity, Nutrition, Healthy diet, Covid-19.*

Introduction

The immune response includes both simple and innate defense mechanisms as well as complex and adaptive responses, specific to antigens and involving many cells and molecules [1]. The immune system, like any other system in the body, depends on adequate food intake and is very sensitive to nutritional deficits and imbalances [2,3]. However, unlike other systems, the nutritional requirements of the immune system vary very rapidly depending on cell replication and synthesis, as well as other energy-demanding functions [4]. The immune system is therefore very responsive to the composition of the food, both short and long term [5]. Immune dysfunction is associated primarily with dietary micronutrient and protein deficiencies. Adequate intake of zinc, iron, and vitamins (Vit) B12, B6, E and A is primarily and particularly important for the maintenance of immune function [6-8]. Whereas, an excessive intake of certain micronutrients can have harmful effects on health, more specifically impair immune function. On the other hand, depression of the immune system has also been associated with excessive fat intake [9,10].

Immune system

The immune system helps maintain the integrity of the host organism by eliminating foreign constituents (viruses, bacteria, parasites and other microorganisms, grafts, allergens) and modified « self » constituents. It performs this function in close relation with other physiological systems, in particular the nervous and endocrine systems, with which it communicates through various mediators (neurotransmitters, hormones, cytokines) and specific receptors common to these systems. The immune system is made up of two types of defense mechanism: innate immunity and adaptive immunity [11,12]. (Figure 1).

Innate immunity

Innate immunity, also called natural or nonspecific, corresponds to a constitutive response of immediate action, it is the first line of defense against infections. Several types of mechanisms are involved, including physical barriers, such as the skin, the pH of gastric juice and innate immune cells, such as "Natural Killer NK" macrophages and neutrophils. The latter indiscriminately phagocytize foreign particles, as well as humoral mechanisms (complement, cytokines, proteins of the acute phase of inflammation, etc.) [13,14].

Innate immunity is responsible for the initial protection against infection. It quickly blocks and eliminates pathogens that enter the host's tissues. This defense is always present in healthy individuals and helps maintain good health. She understands :

- ✓ The mechanical barrier, formed by the epithelium and the mucus which trap and eliminate pathogenic elements by peristalsis. Mucus also contains secretory immunoglobulins A.
- ✓ The chemical barrier made up of anti-microbial molecules.
- ✓ Soluble constitutive factors such as complement proteins and defensins, but also soluble factors resulting from cell activation such as cytokines.
- ✓ NK lymphocytes are an integral part of the innate immune defense. They are able to rapidly secrete a large number of chemical effectors and induce cytotoxicity by cell lysis.
- ✓ Phagocytes.

The commensal bacterial flora also constitutes a barrier against pathogens since it allows the secretion of antimicrobial substances that prevent the growth of unwanted bacteria. In addition, this commensal microbiota competes with pathogenic invaders and thus prevents the latter from colonizing the host's intestinal tract. This innate immunity stimulates the adaptive immune response, there is a real cooperation between the two immunities.

Adaptive immunity

Adaptive or acquired immunity, of slower implementation, appears later. The cells of adaptive immunity are B and T lymphocytes. They participate in humoral and cellular immunity [15]. These include B lymphocytes which produce specific antibodies when they encounter a pathogen and T lymphocytes capable of destroying foreign particles.

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Some T and B cells retain the memory of certain pathogens, which allows them to respond more quickly in the future. The mechanism of vaccines is based on this property [16].

The immune system also produces mediators, called cytokines, such as interleukin-1β (IL-1β), Tumor Necrosis Factor-α (TNF-α) and IL-6, the latter of which are secreted by the cells present. in damaged or infected tissue and will trigger an inflammatory response [17]. They can also act, at a distance, in other organs, such as the liver, to stimulate the production of proteins of the acute phase of inflammation and of the central nervous system (CNS), to trigger, in particular, the increase of body temperature [18]. These cytokines, called pro-inflammatory, can also, in turn, regulate this inflammatory response, by inducing the production of neurotransmitters and hormones, such as glucocorticoids, which will have an immunosuppressive effect [19]. In addition, the production of interferons by infected cells plays an important role in resistance to infection and inhibition of viral replication. Impairment of cell-mediated immunity, phagocytic function, complement system, cytokines, antibody production and secretion are globally associated with protein-energy malnutrition.

Deficiency of micronutrients and vitamins, such as zinc, selenium, iron, copper, magnesium, manganese, vitamins A, C, E, B6 and folic acid could elicit altered immune responses by influencing immune responses [20].

Humoral-mediated immunity

It involves immunoglobulins which are secreted by B lymphocytes. Each cell secretes an antibody of unique specificity. We have already seen that there are several classes of immunoglobulins. A distinction must be made between transmembrane Ig (mainly IgM and IgD) and circulating Ig (IgM, IgG, IgA and IgE). IgA is the most important in the development of mucosal immunity. IgEs play an important role in allergic phenomena by binding to the constant fragment of their receptor present on the surface of mast cells and basophils. This fixation leads to degranulation of mast cells and basophils. The result of this degranulation is an inflammatory phenomenon. IgM and IgG are dominant in systemic immunity. The cleavage of an IgG by an enzyme, papain, separates two fragments: Fab which binds to the antigen (antigen binding) and blocks it and the Fc fragment which activates various effector mechanisms. Antibodies do not directly destroy the aggressor, but thanks to their Fc fragment, they will cause the attachment of various elements that will attach themselves to the aggressor and destroy it.

Cell mediated immunity

T lymphocytes are specialized in destroying infected cells or cancer cells. They recognize the antigen presented by antigen presenting cells (APC) coupled with MHC molecules. NK lymphocytes are specialized in destroying cancer cells that have lost the expression of MHC class I molecules. In fact, NK cells can either attach themselves to the Fc fragment of antibodies or recognize isolated tumor antigenic peptides. CD4 helper T cells activate both the humoral and cellular immune response. They secrete cytokines that recruit and activate other leukocytes to phagocytose and destroy pathogens. There is an increase in vascular permeability, attraction for polynuclear cells and activation for macrophages. Cytotoxic CD8 T lymphocytes recognize peptides from intracellular (cytosolic) protein Ag associated with MHC I and differentiate into effector T lymphocyte, having major cytotoxic activity against cells infected with pathogenic microorganisms or against cancer cells. During this immune response, a phenomenon of self-tolerance takes place. It is expected in the thymus during T lymphocyte education, where cells that respond to self-antigens are eliminated or differentiated. This self-tolerance is very important, as is tolerance towards certain foreign antigens, including those of our commensal bacterial flora. This in order to prevent any immune pathology. This is especially the role played by regulatory T lymphocytes (LTreg) which reduce the immune response generated by a stimulus that is not at risk.

Covid-19 infection

The emergence of new infectious diseases with pathogenic characteristics is a serious global health problem. The Covid-19 infection (Coronavirus Disease-2019) is a viral disease caused by the SARS-CoV2 coronavirus (Severe Acute respiratory syndrome Coronavirus-2), recognized as pandemic by the World Health Organization (WHO), which stipulates strict preventive measures and a strategy to develop, throughout their course, a healthy and balanced diet, good hygiene, and compliance with confinement requirements. The Covid-19 infection appeared in December 2019 in the Wuhan region of China, which has since affected more than 200 countries around the world and, in particular, Africa [21-23].

Coronaviruses belong to the Orthocoronavirinae subfamily, of the Coronaviridae family, of the order Nidovirales. This subfamily includes α coronavirus, β coronavirus, γ coronavirus and δ coronavirus, SARS - CoV2 is an RNA virus and belongs to the β coronavirus family [24,25]. Covid-19 infection can range from a simple asymptomatic infection to severe respiratory failure (Table 1). Its main symptoms are fever, fatigue and dry cough which can progress, in the most severe cases, to multisegment pneumonia, affecting both lungs and which results, clinically, by acute respiratory distress syndrome (ARDS), involving the patient's vital prognosis. This development is favored in the elderly and patients with co-morbidities, such as arterial hypertension, diabetes and cardiovascular diseases.

SARS-CoV-2 is characterized by the presence, on its surface, of an S protein capable of binding to the cellular receptor ACE2 (Angiotensin-converting enzyme 2), present on the apical pole of the pneumocytes. After the viral and plasma membranes merge, the virus passes inside the cell by endocytosis. In pneumocytes, viral RNA undergoes replication and transcription. The viral proteins and the new RNA genome are then assembled in the endoplasmic reticulum and Golgi apparatus, then packaged in exocytosis vesicles [26]. These will then ensure the release of viruses synthesized outside the cell (Figure 2).

Pulmonary involvement is dominated by bilateral diffuse alveolar lesions with exudates rich in lymphocyte-dominated inflammatory cells, with atypical hypertrophied pneumocytes, characterized by large nuclei and granular cytoplasm and prominent nucleoli have been identified in the intra spaces alveolar. The immune response during Covid-19 is characterized by an increase in the levels of B lymphocytes, follicular helper T lymphocytes, activated CD4 + T lymphocytes and CD8 + T with progressive increase of type M and G immunoglobulins. (IgM and IgG) from the 7th day of infection up to 20 days [27,28,29]. This immune response persists for at least 7 days after symptoms have completely resolved. We also note in Covid-19 patients a massive production of proinflammatory cytokines, in particular, IL-2 and IL-7 and TNF-α, following an overactivation of the immune system. This hypercytokinemia causes a massive influx of leukocytes into the lung tissue, causing fibrosis and ARDS [30].

Nutrition and immunity

Nutritional status is a key component in the functioning and maintenance of the integrity of our immune system [31]. To function properly, the immune system depends, closely, on the quality and quantity of nutrients consumed (carbohydrates, fats and proteins, water, micronutrients and minerals). It is well established that nutrient deficiency or insufficiency (insufficient food intake, absorption or reduced bioavailability) must be corrected to properly maintain the function of the immune system. On the other hand, an intake of certain micronutrients and vitamins above nutritional recommendations can optimize immune defense mechanisms.

Macronutrients

Carbohydrates are the main source of energy for the immune system, glucose is essential for monocytes, neutrophils and lymphocytes [32]. Following the activation of macrophages and neutrophils or the stimulation of lymphocyte proliferation, the oxidation of glucose, although partial, increases markedly and produces, mainly, lactate, even in the presence of oxygen, to produce the maximum ATP, necessary for the proliferation of different immune cells. Carbohydrate needs must, therefore, be covered during different infections, such as Covid-19 [33]. The level of lipids and the type of fatty acids in the diet can affect lymphocyte function. The fatty acid composition influences the function of lymphocytes and other immune cells, altering the ability of these cells to produce eicosanoids, such as prostaglandin E2, which is involved in immunoregulation. A diet high in fat can also affect lymphocyte function. Diets rich in eicosapentaenoic acid (omega-3 polyunsaturated fatty acid (PUFA)) and gamma-linolenic acid (omega-6 PUFA) inhibit arachidonic acid metabolism from phospholipids in immune cells. As a result, the synthesis of eicosanoids in macrophages is modulated during a significant inflammatory response, such as that observed during Covid-19 [34]. On the other hand, an imbalance of the omega-3 / omega-6 ratio of the order of 1/7 has also been observed in patients suffering from post-infectious respiratory distress. However, according to the authors of this study, the optimal ratio for controlling inflammation, following an infection, would be ½ [35]. Another study showed that the release of pro-inflammatory cytokines, at the alveolar level, depended on the proportion of omega-3 fatty acids and the omega-3 / omega-6 ratio [36]. Adequate protein intake is also necessary to maintain proper functioning of the immune system. Indeed, any protein deficiency is a major cause of cellular immunity deficit and leads to a predisposition to infectious diseases [31]. Glutamine, an important amino acid for certain cells of the immune system, is also the precursor of a powerful antioxidant: glutamate and an important modulator of the function of lymphocytes and macrophages [37]. In case of infection, the rate of glutamine consumption is similar or higher than that of glucose. During infections, glutamine supplementation is important because it stimulates phagocytosis by macrophages, helps maintain the circulating T cell population, and normalizes lymphocyte function. Meats, fish, eggs, seafood, legumes, spinach, parsley and oilseeds (walnuts, hazelnuts, almonds ...) are the foods richest in glutamine.

Micronutrients

Various micronutrients are essential for the proper functioning of the immune system, in particular, vitamins A, C, D, E, B1, B2, B6, folic acid, zinc, selenium, magnesium and copper [38,39,40]. Micronutrient deficiencies are a recognized global public health problem, poor nutritional status generally predisposes to different infections. Micronutrient supplementation can increase resistance to an infection such as Covid-19 [41,42].

Immune nutrients

Adequate micronutrient intakes are necessary for the immune system to function effectively. Micronutrient deficiency suppresses immune functions by affecting the innate T cell mediated immune response and adaptive antibody response, and leads to deregulation of the balanced host response. This increases susceptibility to infections, and in turn, infections worsen micronutrient deficiencies by reducing food intake, increasing losses, and interfering with metabolic pathways. Antioxidant vitamins and trace elements (vitamins C, E, selenium, copper and zinc) neutralize potential damage caused by reactive oxygen species to cellular tissues and modulate immune cell function by regulating sensitive transcription factors redox and affect the production of cytokines and prostaglandins. Adequate intake of vitamins B6, B9, B12, C, E and selenium, zinc, copper and iron supports an immune response mediated by Th1 cytokines, with sufficient production of pro-inflammatory cytokines, which maintains an efficient immune response and prevents the switch to a Th2 anti-inflammatory cell-mediated immune response and an increased risk of extracellular infections. Supplementation with these micronutrients reverses the Th2 cell-mediated immune response to a pro-inflammatory Th1 cytokine-regulated response with increased innate immunity. Vitamins A and D play important roles in both cell-mediated and humoral antibody response and support a Th2-mediated anti-inflammatory cytokine profile. Vitamin A deficiency impairs both innate immunity (epithelial regeneration of the mucosa) and the adaptive immune response to infection, resulting in a reduced ability to counteract extracellular pathogens. Vitamin D deficiency is correlated with increased susceptibility to infections due to impaired localized innate immunity and defects in the antigen-specific cellular immune response. Overall, inadequate intake and status of these vitamins and minerals can lead to weakened immunity, which predisposes to infections and worsens malnutrition. Biological markers such as immune markers are used to assess the nutritional status of a patient. Their use is based on the existence of an alteration in immune, cellular and humoral functions, induced by undernutrition and proportional to its severity. The blood lymphocyte assay is an easily accessible parameter in clinical routine. Undernutrition decreases lymphocyte maturation and can be the cause of true lymphopenia. An increased prevalence of infections is then observed in these patients. We will now detail these immune micronutrients a little more. And with regard to supplementation, the recommended doses are those suitable for healthy adults, for other categories of the population, details will be given in the event of risks or contraindications. The purpose of supplementation is to provide nutritional doses, outside the pathological context.

Vitamin A or retinol

Vitamin A (carotenoids) is a large family that includes more than 600 molecules, the most important and best known of the carotenoids is β-carotene, the latter has long been studied for its activity of provitamin A. However, all carotenoids cannot be converted into vitamin A. Their function in the body is unique to them and is independent of this conversion. There are three active forms of vitamin A in the body, retinoic acid, retinol, and the retina. The foods richest in retinol are liver and liver oil.

cod and, among the most consumed products, cheese, cream, butter and eggs. Vitamin A supplementation reduces morbidity and mortality in various infectious diseases, such as human immunodeficiency virus (HIV) infection, malaria and measles, pneumonia linked to B vitamins.

Vitamin A plays a role in the proper functioning of the immune system. It is one of the fat soluble vitamins essential for the body. It is provided by food of animal origin in the form of retinol ester and by fruits and vegetables in the form of pro-vitamin A carotenoids which can be transformed in the intestine into vitamin A: this is beta. carotene, alpha-carotene and beta-cryptoxanthin. Vitamin A and its retinoid derivatives have many functions, primarily in inflammation, cell development and growth, skin renewal, vision and immunity. It intervenes in the differentiation of immune cells, participates in the antigen-antibody response and intervenes in the mediation of cytokines. In addition, it plays a role in the formation of intercellular tight junctions and regulates the expression of the proteins that make up tight junctions (occludin and claudin). These tight junctions, located at the apical pole of the epithelial cell, play a fundamental role in maintaining the selective filter function of the epithelium, thus preventing food molecules from entering the body directly. It therefore helps prevent infections by strengthening physical barriers and increasing the production and efficiency of immune cells such as lymphocytes.

Vitamin B

B vitamins are water soluble vitamins that essentially act as coenzymes [48].

Vitamin B1 or thiamine modulates the activity of a nuclear factor called NF-KB (nuclear factor-kappa B), involved in the immune response and adaptation to oxidative stress. It also has anti-inflammatory properties. Vitamin B1 deficiency can induce T cell infiltration, activation of a chemo-attracting monocyte cytokine called the chemokine MCP-1 (monocyte chemoattractantprotein-1), overexpression of pro-inflammatory cytokines, such as IL -1, IL-6 and TNF-α. Almost all foods contain thiamine [49]. Meats, dried nuts (walnuts, pistachios, etc.), organ meats, garlic, whole grain foods (unlike refined grain products) are particularly rich.

Vitamin B2, also called riboflavin, is a vitamin that plays an essential role in the energy metabolism of cells.

Vitamin B2 is more abundant in foods of animal origin, such as dairy products, organ meats, eggs, fish and meats [50]. Among plants, green vegetables are relatively rich.

Vitamin B6 or pyridoxine

Vitamin B6 is a water soluble vitamin, it exists in three main forms: pyridoxal, pyridoxine and pyridoxamine [51]. It is a coenzyme recognized in various pathways of protein metabolism. It also plays an important role in immune function, through its action in the proliferation, differentiation and maturation of lymphocytes, as well as the production of cytokines and the activity of NK cells. Vitamin B6 is mainly found in fatty fish (mackerel, salmon, tuna), organ meats (livers), poultry, meats and potatoes [52].

Vitamin B6 plays a major role as a cofactor of many enzymes involved in multiple metabolic pathways. It is rather widespread in animal and plant food products, and the coverage of needs in France is satisfactory. After intestinal absorption, vitamin B6 is distributed throughout the body. At the cellular level, it is transformed into pyridoxal phosphate, its active form, a cofactor of a large number of enzymes involved in the metabolism of carbohydrates, in the reactions of amino acids (decarboxylation and transamination), in the synthesis of DNA, in the synthesis of hemoglobin, in the synthesis of neurotransmitters, in the protection of nerve cells and in the integrity of the immune system.

Vitamin B9 or folic acid

Vitamin B9 or folic acid is the metabolic precursor of a coenzyme, tetrahydrofolate, involved in the synthesis of nucleic acid bases, purines and pyrimidines, constituting the nucleic acids of genetic material [53]. Most vitamin B9 is found in organ meats, garlic, onions, legumes, and some green vegetables. During pregnancy, folic acid plays an important and essential role in preventing abnormal closure of the neural tube in the fetus. It also plays a key role in immune function [54]. A deficiency of folic acid induces a decrease in the antibody response to several antigens, associated with lower levels of proteins involved in the activation and regulation of immune function. All of this data suggests that supplementation with B vitamins may be a good option for treating viral infections like Covid-19 [55-57].

Vitamin B9 is the generic name given to a group of molecules comprising folic acid and its derivatives, folate. It is these which are mainly found in food and which, after digestion, provide the folic acid necessary for the body. It is involved in the metabolism of many molecules including nucleic acids. It is therefore very important for the immune response since it is involved in hematopoiesis.

Vitamin B12 or cobalamin

Vitamin B12 exists in the body in several forms referred to as cobalamins. There are four active isomers: hydroxocobalamin, cyanocobalamin, methylcobalamin, and adocobalamin. Synthesized in large part by the intestinal microbiota, cobalamins are necessary for the multiplication and proliferation of rapidly renewing cells. Indeed, vitamin B12 plays an important role in the formation and maturation of red blood cells.

Vitamin C or ascorbic acid

Vitamin C, also called ascorbic acid, is a water-soluble vitamin known for its powerful antioxidant power. It therefore strengthens the action of the immune system and protects against infections caused by the coronavirus. Vitamin C may also have an antihistamine effect, relieving symptoms associated with flu-like conditions, such as sneezing, runny nose, and sinusitis. Vitamin C is mainly found in citrus fruits, black currants, parsley, red and yellow peppers, Brussels sprouts and garlic [43].

- ✓ Vitamin C is involved in many mechanisms linked to physiological functions: Immune defenses: immune cells contain 100 times more ascorbic acid, in fact it is necessary for the mobility of polymorphonuclear cells.
- ✓ Antioxidant role: vitamin C is involved in redox reactions. It protects the body and helps destroy free radicals. It also allows the regeneration of vitamin E, which is also an antioxidant.
- ✓ Cofactor of synthesis: vitamin C is necessary for the synthesis of collagen, a protein that supports the skin and the skeleton. The synthesis of adrenaline and norepinephrine, important mediators of the nervous system, also requires vitamin C.
- ✓ Iron absorption role: Vitamin C makes it possible to better absorb iron in the intestine, by reducing the iron present in oxidized form into reduced form. But be careful not to administer it in too high doses and in the presence of an excess of iron because vitamin C then becomes pro-oxidant.

Vitamin D or calciferol

Vitamin D is a fat-soluble vitamin with a steroidal structure whose behavior more closely resembles that of a pro-hormone, it is provided by the diet (fish

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liver oil, sardines and dairy products). It is also synthesized in the human body, from a derivative of cholesterol or ergosterol, under the action of ultraviolet type B (UVB) radiation from the sun in the skin to give cholecalciferol or vitamin D3 inactive. The latter will then undergo a double hydroxylation, at the level of the liver and the kidney, to give the active form called calcitriol. Besides its well-established role in the regulation of phosphocalcic homeostasis, vitamin D has other physiological functions, such as immunomodulators, by controlling the differentiation of many cell types and by inhibiting their proliferation (dendritic cells, T lymphocytes and macrophages) [44].

There are two forms of vitamin D that are predominantly found in food, vitamin D2, ergocalciferol, produced by plants, and vitamin D3, cholecalciferol, of animal origin. It is also synthesized in the skin by the action of ultraviolet rays on cholesterol. Vitamin D is active after conversion into 25-dihydroxy-vitamin D by the liver and 1,25-dihydroxy-vitamin D by the kidney, the main active metabolite, also called calcitriol. Vitamin D mainly regulates bone metabolism. It has a hypercalcemic action and is used to maintain the homeostasis of calcium and phosphate via the kidneys, bones and intestine. In fact, it improves the intestinal absorption of calcium and phosphorus, which ensures optimal mineralization of bones, cartilage, teeth, and helps maintain plasma concentrations of calcium and phosphorus.

It is also involved in the differentiation, metabolism and activities of the immune system. It has an immunomodulatory effect and it also increases the production of antimicrobial substances.

Vitamin E

Vitamin E or α-tocopherol is a major fat soluble antioxidant. Free radicals increase the activity of membrane phospholipase A2 and the release by membrane lipids of arachidonic acid. This is at the origin of the production of prostaglandins and leukotrienes which are the major players in inflammatory reactions. By blocking this type of reaction, vitamin E would limit the runaway immune response and have effects. Vitamin E is mainly found in vegetable oils (sunflower, corn and grape seed oil) and oilseeds. To ensure a good daily intake of Vitamin E, it is strongly recommended to vary vegetable oils and consume them with each meal [45].

Copper

Trace elements, which belong to the class of micronutrients, are essential mineral elements, in very small quantities, for many functions of the body. They act in particular as enzymatic cofactors. It is present in many enzymes and proteins, including cytochrome C oxidase and certain superoxide dismutases (SOD), powerful antioxidant enzymes. It also plays a key role in the development and maintenance of immune system function [63]. A copper deficiency leads to neutropenia, which can increase the susceptibility to infections. Some are particularly involved in immunity such as copper, zinc, iron and selenium. Copper is only present in trace amounts in the body, yet its role is vital. First of all, it is an anti-oxidant, it protects cells by eliminating free radicals. It participates in the proper functioning of the nervous system by acting on communication between neurons. At the bone level, it also participates in the formation of cartilage. It also contributes to the proper functioning of the immune system. Copper is an essential element in anti-inflammatory and anti-infective processes. It fights against the proliferation of pathogens by stimulating the production of immune cells. It improves the absorption of iron in the intestine, and thus promotes the production of red blood cells in the blood, allowing better oxygenation of the tissues. And it has an anti-inflammatory action because it slows down the production of histamine, a compound resulting from the allergic reaction. All foods provide copper, but the richest are organ meats, seafood, nuts, and cocoa and measles. Vitamin A supplementation also plays a role in preventing complications from various infectious diseases [46,47].

Iron

Iron is the most abundant trace element in the body. It is essential for all living cells where it plays an active role in many metabolic pathways. It is never free, but it comes in two forms: 70% heme iron and 30% non-heme iron. Heme iron is involved in the constitution of hemoglobin (necessary for tissue oxygenation), myoglobin (muscle protein used to store oxygen) and enzymes playing a major role in many metabolic reactions necessary for synthesis of energy, DNA, metabolism of catecholamines, etc. Non-heme iron corresponds to the forms of transport and reserve.

It also contributes to the optimization of the immune system and it plays a fundamental role in the defense against pathogenic infections, by promoting the formation of reactive oxygen species (ROS) which are more toxic to the pathogen. Iron deficiency is associated with reduced phagocytic capacity and the activity of B and T lymphocytes. In contrast, excess iron promotes bacterial growth.

Selenium

Selenium (Se) is a trace element known for its antioxidant power. It is part of the building up of glutathione peroxidase (GPx), an enzyme that has antioxidant activity. This seleno-dependent enzyme participates in the recycling of glutathione and reduces lipid peroxidation, by catalyzing the reduction of oxidizing peroxides including H2O2 [60]. Other roles are attributed to this enzyme, it would be involved in the transduction of cellular signals and the regulation of gene expression (through its action at the level of transcription factors). Selenium would therefore play a key role during the cell cycle. In addition, selenium deficiency has an impact not only on immune function, but also on the pathogenicity of viruses, following the decline in antioxidant defenses [61]. Selenium deficiency induces an increase in the virulence of certain viral infections and an alteration, both in humoral and cell-mediated immunity.

Selenium involved in immune defense, through its powerful anti-oxidant effect. It acts in particular as a constituent of glutathioneperoxidase (GSH-Px), an antioxidant enzyme. This coenzyme activity of selenium with GSH-Px allows the regeneration of the reduced form of substances such as vitamin E, with which it acts in synergy. It helps cleanse ROS (reactive oxygen species), which reduces low-grade inflammation and protects phagocytic cells. But while it turns out to be an immunostimulant at low dose, it is on the other hand an immunosuppressant at high dose.

Zinc

Zinc (Zn) is a trace element essential for cell division and for the functioning of innate and acquired immunity [58]. Zinc deficiency can induce thymic atrophy, impaired humoral and cellular immune response, decreased plasma lymphocyte (especially T lymphocyte) and NK cell levels, increased oxidative stress and inflammation, by modifying the production of cytokines [59]. On the other hand, Zn supplementation could have antioxidant and anti-inflammatory effects, by decreasing C reactive protein (CRP), IL-6, macrophage chemo-attractive protein (MCP-1) and phospholipase. . secretory A2.

Zinc is one of the major and fundamental trace elements in nutrition and human health. Its most important role is linked to its involvement in the synthesis of nucleic acids and proteins. Today up to 2000 transcription factors are considered to be zinc-dependent. It contributes to multiple physiological functions and is involved in the activity of more than 300 enzymes. Indeed, it is also the cofactor of many enzymatic reactions involved in immune function. It acts as a regulator of humoral and cellular immunity: it optimizes the defense immune response, in particular through the synthesis of gamma interferon, and participates in the synthesis of thymulin necessary for the maturation of lymphocytes.

Magnesium

Magnesium is the most abundant mineral inside cells, it is the second most abundant intracellular cation after potassium. It performs several biological functions in the body. Magnesium is the cofactor of over 300 enzyme systems involved in nutrient metabolism. It is also involved in the synthesis of glutathione, a powerful antioxidant. It participates in the active transport of ions such as potassium and calcium across cell membranes. It exerts a protective and stabilizing effect on cell membranes. Magnesium deficiencies are common and impact our immune system. Studies have shown the mechanisms of these disturbances. Magnesium has very broad functions within the body, and with regard to the immune system, it is involved in the inflammatory response, in the synthesis of immunoglobulins (it is a cofactor), in the adhesion of immune cells T helper and B and in apoptosis. Magnesium deficiency impacts the immune system and induces increased production of pro-inflammatory cytokines (IL-1, IL-6, TNF-α), disrupted apoptosis, acceleration of thymus involution and immune cell dysfunction (macrophages, neutrophils, T lymphocytes, etc.). Several studies have shown that magnesium is responsible for the immune response and therefore plays a major role [62]. Nuts, legumes, whole grains, green leafy vegetables, wheat germ, and brewer's yeast are good sources of magnesium.

Glutamine

Glutamine is the most abundant amino acid in the body and plays a central role in nitrogen metabolism. It is essential and insufficient availability causes a reduction in immune defenses. It is a major amino acid in the various stages of the immune response, from the phagocytic activity of macrophages to the production of antibodies. It also exerts trophic effects on immune cells in the intestine, which is one of the body's main lymphoid tissues.

Arginine

Arginine is a nonessential amino acid because it can be synthesized by the body. It has multiple biological actions including stimulation of the immune system. Arginine is also known to be an essential precursor for the growth of rapidly renewing cells (enterocytes and immune cells). It is also the source of nitric oxide which plays a central role in many biological processes, including the modulation of the immune system. A clinical trial in children prone to respiratory infections indicates that arginine can stimulate the immune system and reduce the number of infections.

Omega 3 PUFAs

The term "omega-3" groups together a set of fatty acids that have several carbon-carbon double bonds, these are polyunsaturated fatty acids. In humans, there are three that have significant activity. It is :

- ✓ Alpha-linolenic acid or ALA (18: 3 ω-3).
- ✓ Eicosapentaenoic acid or EPA (20: 5 ω-3).
- ✓ Docosahexaenoic acid or DHA (22: 6 ω-3).

ALA is indispensable and essential. Indispensable because our body absolutely needs it to function and essential because it does not know how to manufacture it itself. ALA must therefore absolutely be provided by the diet. ALA is the precursor of the omega 3 family, it is from this compound that the body synthesizes long-chain polyunsaturated fatty acids including EPA and DHA. Fatty acids are the major constituents of triglycerides, phospholipids, sphingolipids and cholesterol esters. They are an integral part of biological membranes. They modulate their fluidity and the activity of the proteins inserted into them (enzymes, receptors, transporters). They thus act on functions as important as neurotransmission. Indeed, they are also essential for the nervous system. They facilitate neuronal connections, preserve cognitive functions and prevent the risk of neurodegenerative pathologies. By restoring membrane fluidity for the optimization of lymphocyte receptors and macrophage chemotaxis, omega-3s are also beneficial for the immune system. They help fight infections. This action is also explained by their ability to limit the overactivity of T lymphocytes, which increases the risk of inflammation.

Polyphenols

Polyphenols are among the antioxidant nutrients, such as vitamin C, vitamin E, zinc and selenium which are the main ones. Polyphenols are derived from the secondary metabolism of plants and can be subdivided into several classes. Recent research on phenolic compounds and flavonoids has shown their various physiological properties: they are endowed with antioxidant, antiallergic, anti-inflammatory, hepatoprotective, antimicrobial, antiviral, antibacterial, anticarcinogenic, anti-thrombotic, cardioprotective and vasodilatory activity. In addition, polyphenols are also believed to have prebiotic effects by beneficially modulating the composition of the intestinal flora, and thus have a beneficial action on the immune system.

Typical treatment of patients infected with covid-19

In various epidemiological studies the results obtained show that adequate nutrition effectively prevents viral infections, including the COVID-19 pandemic. Simply put, the increase in vitamin D in the body is considered to be a source that can reduce the risk of infection. But this information on prevention has not been highly appreciated by the medical device, especially in nutritional therapy for COVID-19 patients. Apparently, it seems to us that the root cause of the problem lies in clinical trials of nutritional protocols, which are very effective on patient cohorts, and therefore have not been funded for their implementation in large randomized controlled trials (ECR). Therefore, clinical trials of nutritional protocols for the reduction and prevention of Covid-19 have not been published. Evidence that adequate doses of micronutrients including vitamin D, vitamin C, zinc, magnesium and selenium are effective. However, these nutritional trials are very effective, safe, inexpensive, and widely available in all countries.

Discussions

Therapeutic protocols have been proposed during acute viral infections, based on megadoses of vitamin C, intravenously for five consecutive days. The results were very promising, following the reduction in free radical levels and inflammation, allowing faster healing [64,65]. This vitamin has also shown its effectiveness in pneumonia and lower respiratory tract infections, suggesting that vitamin C could be a molecule of choice for the treatment of Covid-19.

Clinically, a correlation has been observed between vitamin D deficiency and predisposition to respiratory tract infections in adults. During winter, vitamin D levels drop considerably, due to low sunlight [66]. This is also observed during the confinement applied in order to fight against the spread of Covid-19 [67, 68]. People confined to the house may have a vitamin D deficiency, which could weaken their immune system and predispose them to respiratory infections. Therefore, vitamin D supplementation is strongly recommended in such situations.

Magnesium supplementation can strengthen the immune system to fight against SARSCoV-2, thanks to its action on the metabolism of Vitamin D, by its role in renal and hepatic hydroxylation and, therefore, the activation of this vitamin. Different studies have reported that magnesium supplementation can correct vitamin D deficiency. Decreased serum Mg levels have been observed in patients with SARS [69, 70].

Zinc is also known to limit the replication of viruses, in particular that of influenza and RNA coronaviruses. Zinc deficiencies are very common in people most affected by Covid-19, especially the elderly [70]. Zinc supplements (20-50 mg / d) help the immune system fight viral infections, especially by inhibiting the replication of their genetic material [71].

Several studies also list that selenium plays an important role in regulating the production of cytokines and eicosanoids that orchestrate the immune response. Therefore, selenium supplementation could be an effective choice for the treatment of this new Covid-19 virus. This trace element is present in seafood in large quantities, in oilseeds, meat, and offal [72, 73].

Conclusion

We can conclude that malnutrition is the most common major cause of immunodeficiency in the world and that chronic malnutrition is a major contributor morbidity and mortality. Like any organ or system, the immune system needs proteins, energy, trace elements and vitamins to ensure, normally, its functions which are based on mechanisms of cell division and activation, protein synthesis and activities. Numerous enzymes. These needs are clearly demonstrated by the susceptibility to infections observed during different types of undernutrition and deficiency, which can impair both innate and adaptive immunity. Due to the increasing spread of the Covid-19 epidemic, it is essential to preserve a balanced food intake, while avoiding the consumption of industrial, refined, overcooked foods, which can cause micro-deficiencies in vitamins and in trace elements, which could have harmful consequences on the immune response. In the absence of treatment, supplementation with certain vitamins and trace elements may be indicated in the therapeutic management of viral infections, in particular, Covid-19, where several studies have been able to prove their role in maintaining immune function.

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Table 1. Different clinical forms of Covid-19 depending on the severity of symptoms.

Severity	Symptoms
Mild impairment	Aches ; conjunctivitis; diarrhea; sore throat ; loss of smell or taste ; headache.
Severe impairment	Fever ; dry cough ; tired; pulmonary involvement> 50% in 24 to 48 hours ; blood oxygen saturation Spo2≤ 93%; Dyspnea; respiratory rate ≥ 30 / min.
Critical state	Shortness of breath or difficulty in breathing; multiple organ failure feeling of tightness or pain in the chest and / or septic shock; loss of speech or motor skills ; respiratory failure.

Table 2. Typical treatment of patients infected with Covid-19.

Dietary supplement	Dose
Vitamin C	1g (or more) 3 x /D
Vitamin D	5000 UI/D
Magnesium	400 mg/D (as, citrate, malate, chloride chelate, or)
Zinc	20 mg/D
Selenium	100 µg/D

Figure 1. The Main Actors of Immunity.

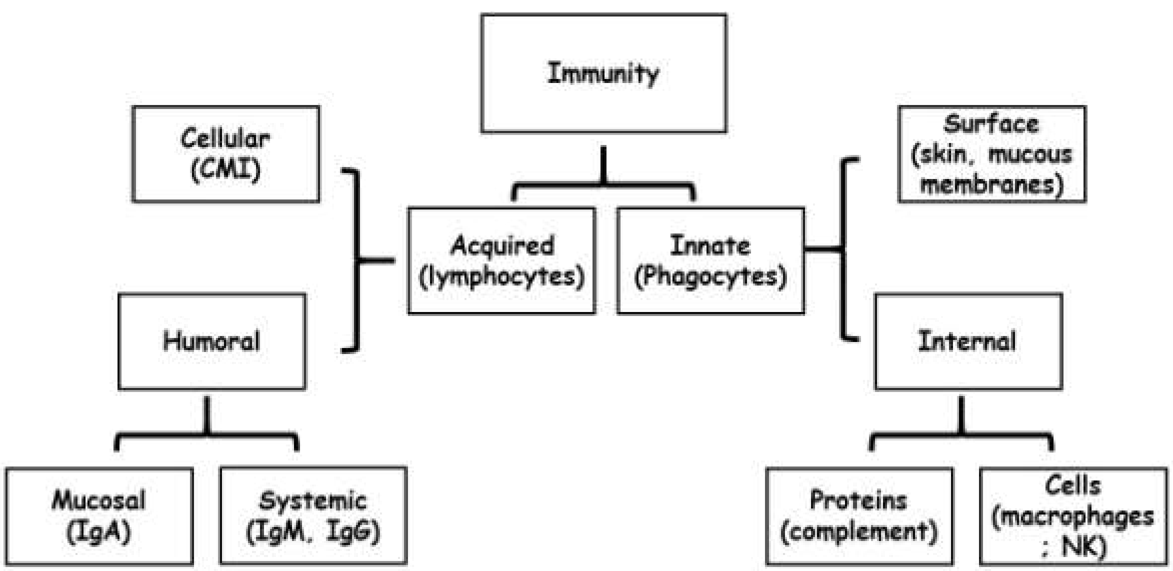
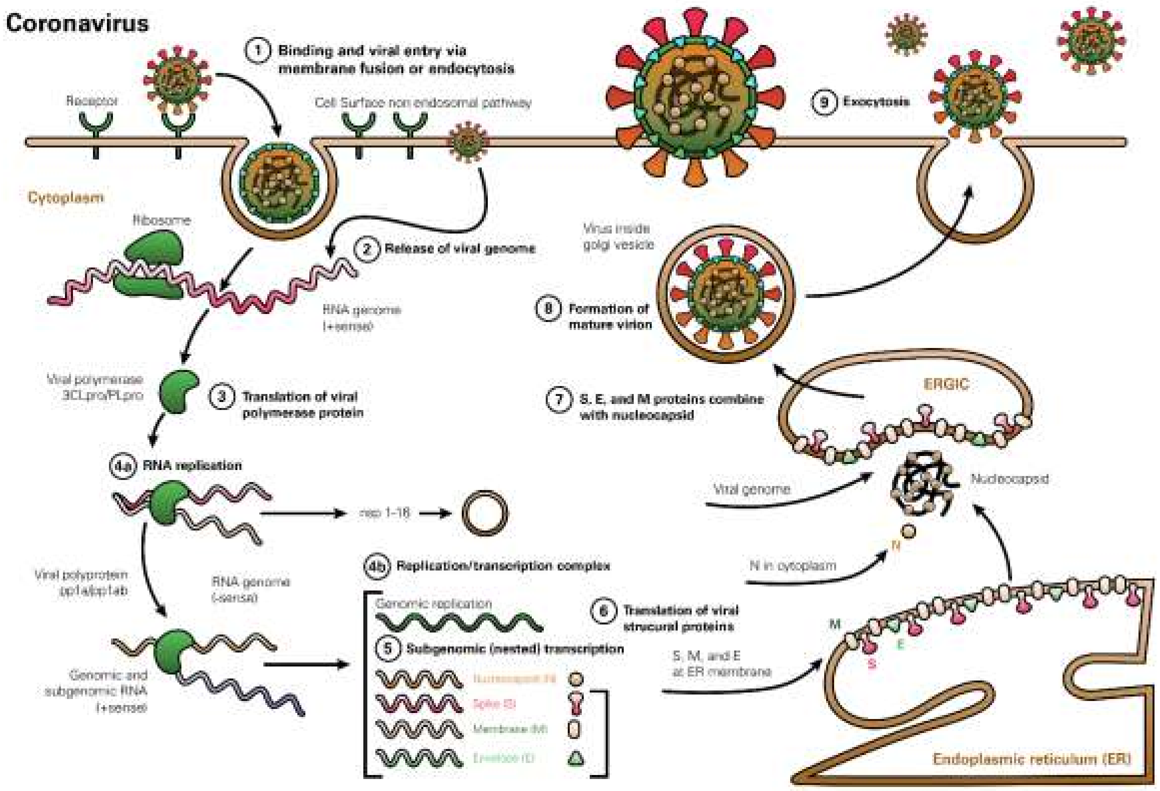


Figure 2. Coronavirus life cycle.


Coronavirus
1 Binding and viral entry via membrane fusion or endocytosis
Receptor
Cell Surface non endosomal pathway
9 Exocytosis
Cytoplasm
Ribosome
2 Release of viral genome
RNA genome (+sense)
Virus inside golgi vesicle
8 Formation of mature virion
Viral polymerase 3CLpro/PLpro
3 Translation of viral polymerase protein
7 S, E, and M proteins combine with nucleocapsid
ERGIC
4a RNA replication
rep 1-16
Viral genome
Nucleocapsid
N
Viral polyprotein pp1a/pp1ab
RNA genome (-sense)
4b Replication/transcription complex
N in cytoplasm
Genomic replication
6 Translation of viral strucural proteins
5 Subgenomic (nested) transcription
M
E
S
Spike (S)
Membrane (M)
Envelope (E)
Genomic and subgenomic RNA (+sense)
S, M, and E at ER membrane
Endoplasmic reticulum (ER)