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NUTRITIONAL APPROACH TO IMMUNITY

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Review:

Nutritional approach to immunity

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Introduction

It has been known since the time of Hippocrates that poorly nourished people are more susceptible to infectious diseases. Under-nutrition impairs the immune system, suppressing immune functions that are fundamental to protect the host efficiently from bacterial and viral infections.

In addition, under-nutrition may potentiate the effects of both viral and bacterial infections. For example, some viruses cause only mild illness in well-nourished but can be fatal in those with malnutrition. Immune system plays a critical role in the relationship between malnutrition and infection. This interrelationship applies not only to nutritionally deprived in developing countries but also to people of all ages throughout the world. Those especially susceptible include the children, elderly, and individuals with eating disorders, alcoholics and patients with debilitating diseases, all of whom may suffer from nutrition-related impairments in immune function. [(1)]

This review discusses intricate relationship between immunity and nutrition. It tries to provide some basic information as to how Immunity works, and emphasize how nutritionals can boost up immunity especially during viral catastrophes.

SECTION 1. Principles of immunological process.

1.1 The Immune System

The immune system is a complex defence network that protects body against potentially harmful agents and has the capacity to respond to millions of antigens. The body is protected from infectious agents and other harmful substances by a variety of cells and molecules that make up the immune system. Immunity is the ability of the human body to tolerate the presence of material indigenous to the body (self), and to eliminate foreign (non-self) material. Foreign substances such as viruses, bacteria, toxins, and parasites are surrounded by *antigens* that, when introduced into the body, are capable of inducing a response by the immune system. This discriminatory ability provides protection from infectious disease, since most agents or associated toxins are identified as foreign by the immune system. [(2)]

Through reactions, the immune system can recognize and remove pathogens. It serves to distinguish "non-self" from "self" and acts to ensure tolerance of "self", food and other environment components and commensal bacteria inherent in the body. However, any mistake or alteration in tolerance pathways may lead to an immunological disordered process. Although there are plenty of factors involved in the aetiology of disease, most conditions are related to the immune system, frequently being infectious, inflammatory, or autoimmune processes. [(3)]

Nutritional approach to immunity

All living things can act as hosts for infectious organisms and thus have evolved mechanisms to defend themselves against infection. Infection can be by other living things, non-living things (viruses) and possibly even molecules. Since it is so crucial to survival, much of understanding of immunity has come from scientific studies. Defence against infection is divided into two main forms termed innate immunity and adaptive immunity. Innate defence mechanisms are present in different forms in all multi-cellular organisms, including plants. Adaptive defense mechanisms have evolved more recently in vertebrates. In vertebrates, the interaction of innate and adaptive immune mechanisms is essential for the generation of effective immunity to infection. [(4)]

1.2 Host Defence against Infection

Immune responses are needed to defend against infection. Many different kinds of organism have the potential to infect and, if they do so, can cause harm in many ways. Potentially infectious agents include the following: (Table 1)

Viruses, which are non-living entities. -

Common examples are influenza virus, corona virus, human immunodeficiency virus (HIV), herpes simplex virus (HSV), , which can cause cold sores or genital ulcers.

Bacteria, are single-celled prokaryotic organisms. Examples include Staphylococcus and Streptococcus that cause acute infections such as abscesses and sore throats, and Mycobacteria that cause chronic infections such as tuberculosis and leprosy.

Fungi, which are unicellular, such as Candida that causes thrush or systemic fungal infection..

Parasites, are eukaryotic organisms. Some are single- celled protozoa that cause diseases such as malaria; others are large, multicellular organisms (metazoa) such as tapeworms. [5]

Table1. The major types of pathogens confronting the immune system and some of the diseases they cause

Type of Pathogen	Examples	Disease
Extra cellular Bacteria, Fungi, Parasites	Streptococcus pneumonia Clostridium tetani	Pneumonia Tetany
Intracellular bacteria, parasite	Mycobacterium tuberculi Plasmodium	Tuberculosis Malaria
Viruses	Influenza Corona	Flu Acute respiratory syndrome

1.3 Specific immune mechanisms

At the heart of the immune system is a sophisticated specific system of defences with three extraordinary capabilities: Nutritional approach to immunity

• The ability to distinguish the body's own components from those of foreign invaders (often referred to as the ability to distinguish "self" from "non-self")

• The ability to recognize and respond, in specific ways, to an essentially unlimited number of different molecules

• The unique capacity to respond with an accelerated and enhanced response on re - exposure to foreign agent (that is, the system has "memory").

The recognition of self is accomplished by means of an elaborate system of specific molecules present on the surfaces of all cells in the body. In normal circumstances the cells of the immune system do not attack those cells which carry these distinctive marker molecules which denote self. However, any encounter with certain foreign marker molecules (called *antigens,* from *Antibody gen*erator) activates cells of the immune system, causing them to mount a defensive response. During this response, immature immune cells are stimulated to differentiate into specialized cells capable of responding to the specific antigen. These cells are equipped with special receptor structures that allow them to recognize and interact with their individual targets. A few of these specialized cells, called *memory cells*, remain functional even after the response to a foreign agent is completed. Thus, the next time the immune system meets up with the same antigen, it can respond to it quickly and effectively. [6]

The principal defensive "soldiers" of the immune system are a class of mobile white blood cells called lymphocytes. There are two distinct types of lymphocytes with the special characteristics of specificity and memory: B cells and T cells . B cells originate from the bone marrow. Upon stimulation by antigens, B lymphocytes develop into cells which produce antibodies. Antibodies are complex proteins called immunoglobulins. Each B cell produces one type of antibody which reacts specifically to a single variety of antigen. B-cell-stimulating antigens are usually protein molecules. They originate from specific parts of the human body. (Fig.1.)

Some of the activities of the B cells are under the control of T cells. Like B cells, T cells originate in the bone marrow but they undergo important stages of development in an organ called the thymus. Specific signals drive the undifferentiated T cell to develop into functionally different T cell types. "Helper" T cells regulate the immune response by secreting signaling molecules called *cytokines*. Cytokines bind to target cells and mobilize other cells and substances, producing a complex variety of defensive responses. "Suppressor" T cells can reduce the activity of other functional cells. Phagocytes are large white blood cells engulf and destroy microbes or other particles. Phagocytes include macrophages and neutrophils. Macrophages mature continuously from circulating monocytes and leave the circulation to migrate into tissues throughout the body. Macrophages and neutrophils express surface receptors that help them recognize constituents common to many pathogens. Bacterial molecules binding to these receptors trigger the cells to engulf and kill the bacterium and to induce the secretion of chemical mediators by these phagocytes. (Fig. 2)

1.4 Types of immunity

Passive immunity

It is called passive because the individual does not create the antibodies, but instead receives pre-formed antibodies. Here protection is effective, but duration is short lived and no memory is created. Examples of passive immunity are maternal antibodies (transplacental and breast milk) and injected antibodies (e.g., rabies, varicella, and tetanus immune globulins). [7]

Active Immunity:

When the body is exposed to a foreign substance the cells of the immune system "actively" respond. Active immunity is further divided into categories: Innate Immunity - protective

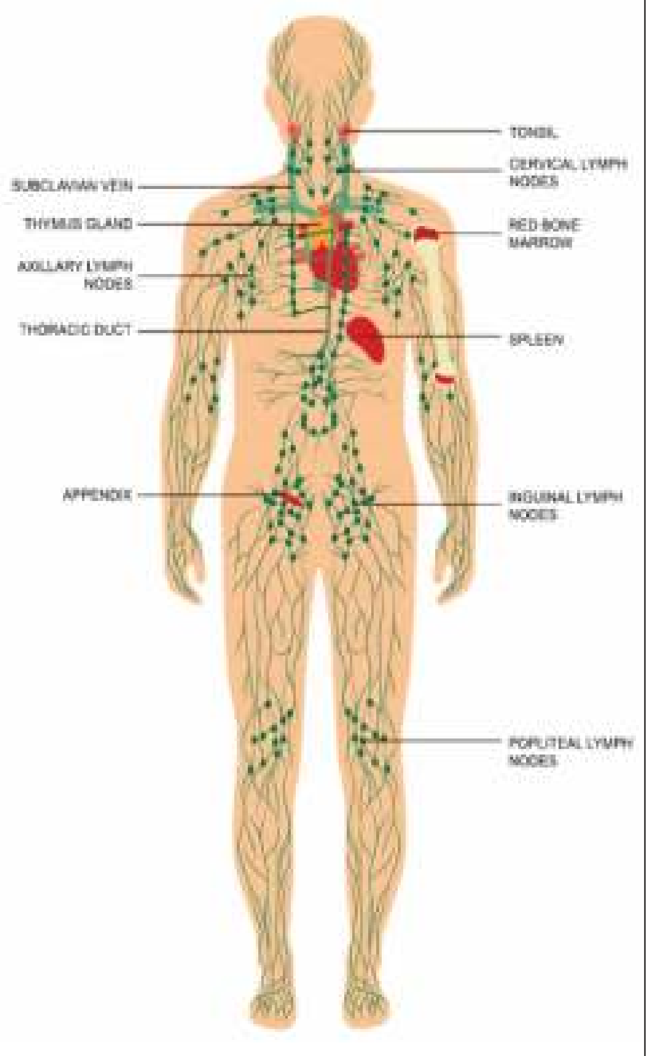


Figure 1 - Lymphatic System

mechanisms we are born with and Adaptive Immunity-cell mediated immunity and humoral immunity. Innate cells (macrophages, dendritic cells) respond by recognizing viruses and bacteria as foreign and specialize in engulfing these invaders (phagocytosis).

These innate cells and protective barriers are part of innate immunity because they "innately" respond to foreign substances. In the lymph nodes the dendritic cells present the antigen to the T cells. The T cells then activate the B cells to make antibodies. The T cells and B cells are part of the adaptive immunity because they are "adapting" to the foreign substance and creating memory against future infections. [6]

1.5 Innate immunity-"first" immune defence

Innate immunity consists of protective

mechanisms we are born with, and are the first line of defence against anything recognized as non-self. (Fig. 2)

The produced immune response is not specific to the antigen and no memory of the antigen persists. However, innate immunity is the crucial first step in most adaptive immune responses.[7]

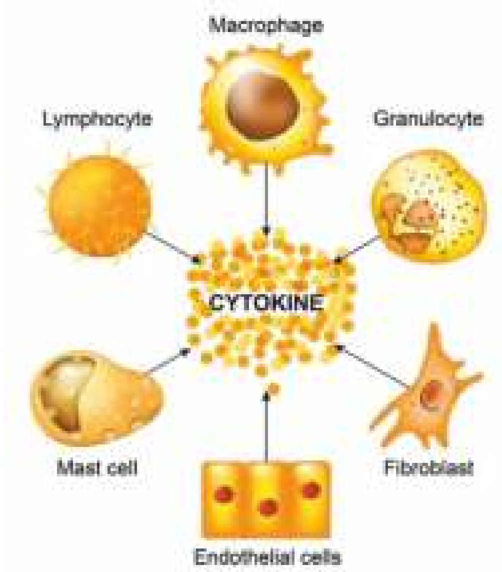


FIG. 2. Cytokines and immune cells.

1.6 Adaptive immunity -"second" immune defence

Adaptive immunity is the second line of defence against anything recognized as non-self and it provides protection against re-exposure to the same pathogen.

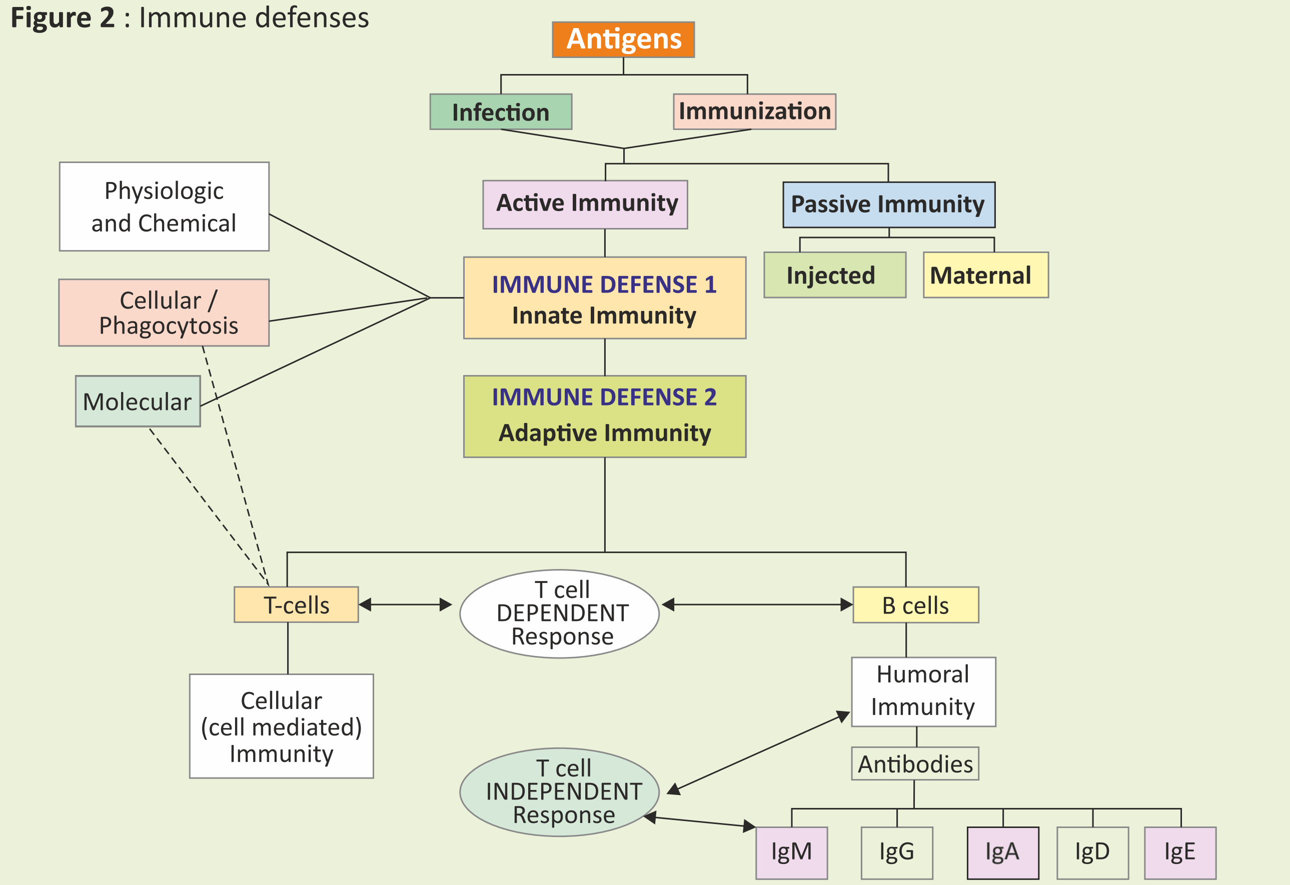
Characteristics of adaptive immunity: Specificity: the immune response is specific to the antigen that produced it (e.g. antibody for measles antigen has no effect on rubella antigen)

Tolerance: the immune response is able to differentiate between self and non-self so that body tissues are not destroyed. This can be cell mediated or humoral immunity.

Cell mediated immunity describes any immune response where T cells have the main role.

B cells are not activated by most antigens without "help" from helper T cells. The activation of T cells is an essential first stage in virtually all adaptive immune responses. This is called the "T cell-dependent immune response".[1,2]

Figure 2 : Immune defenses



1.7 Antibodies

There are five classes of antibodies: IgM, IgG, IgA, IgD and IgE. Each class performs particular functions. The immune response to injected vaccines involves IgG and IgM. Antibodies as a class are known as immunoglobulins. (IgM) A valuable diagnostic marker for infectious disease because it is usually the first immunoglobulin made following Ag exposure and is relatively short-lived. (IgG) The most abundant class of antibody, constituting approximately 80% of all antibodies in serum and produced slowly upon primary exposure to an antigen. (IgA) represents approximately 10% to 20% of the immunoglobulins in serum, most abundant immunoglobulin in tissues and Prevents or interferes with the attachment of viruses and bacteria to mucosa of respiratory and digestive systems. It also protects against enterotoxins released by certain bacteria. (IgE) minute concentration in serum and involved in mediating allergic reactions. (Fig. 3)

Antibodies have main function of neutralization of antigen. [3]

Table 2. Immunity Players

	Innate immunity	Adaptive immunity
Cellular components	Granulocytes, neutrophils, basophils, eosinophils Mast cells, NK Cells	B lymphocytes T lymphocytes T helper cells
Soluble components	Complement factors Acute phase proteins	Antibodies Cytokines

Origination of Immune Cells

Immune cells (Table 2) originate through Hemopoietic and Lymphopoietic systems.

Hematopoiesis takes place primarily in the bone marrow (also a primary lymphoid tissue). The earliest cells in hematopoiesis are the multi-potential stem cells, which can give rise to all blood cells. When cells divide, each of the progeny cells is usually of the same type. Stem cells are unusual in that the one of the progeny cells is another stem cell, thus maintaining this population, while the other can start to differentiate into a different cell type, ultimately producing all the cells of different lineages.

Precursors can ultimately produce monocytes and macrophages, different types of granulocytes, and other cells including erythrocytes (RBCs), megakaryocytes (the precursor of blood platelets). The development of cells in each pathway is regulated by growth factors that are more or less restricted in their activities. Thus, interleukin (IL)-3 and stem cell factor (SCF) stimulate stem cells which can develop into many different lineages, granulocyte macrophage colony-stimulating factor (GM-CSF) preferentially stimulates development of monocytes, granulocytes and some DCs, and erythropoietin stimulates red cell development.

The term lymphopoiesis refers to the generation of lymphocytes. Lymphocytes are the primary cells involved in adaptive immune responses. Lymphoid precursors are present in the bone marrow. Bone marrow cells start to differentiate in the bone marrow and are released as partially mature (transitional) B cells into the blood. T cell precursors, however, migrate directly to the thymus and T cells complete their development in this organ.. They have highly discriminatory antigen receptors and are divided into two main groups: B cells and Tcells. B cells are the precursors of plasma cells that secrete antibodies.

T cells are themselves divided further into two main groups: CD4 T cells that function principally as regulator and coordinator cells in adaptive immune responses, and CD8 T cells that can develop into cytotoxic cells with the capacity to kill cells infected with viruses or other microbes. Macrophages are one of the two main types of specialized phagocyte that can engulf and internalize (phagocytosis), and subsequently kill microbes such as bacteria.[2,3]

1.8 Primary humoral response

This starts with the entry of antigen. Antibodies recognize epitopes on the surface of antigens.

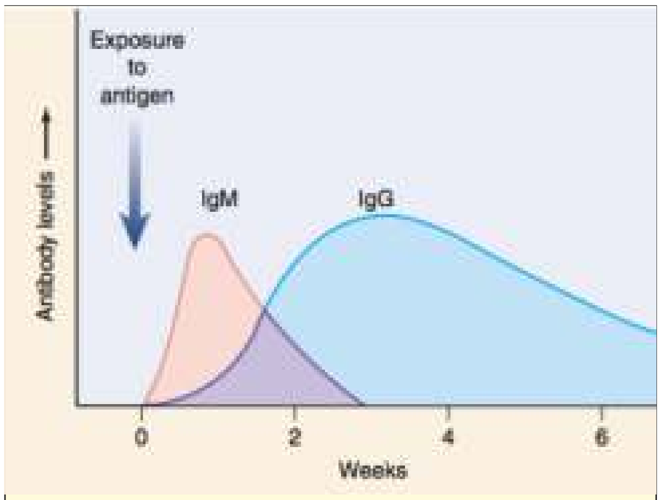


Fig. 4. The first antibodies produced in the humoral immune response are IgM antibodies. IgM is very effective at activating the complement system. IgM production peaks after about one week and is followed by a more extended production of IgG antibodies.

The type of innate or adaptive response that occurs after infection is tailored to the type of infectious agent that initiated it. Thus, the immune system generates an immune response that is most appropriate for eliminating the infectious agent. For example, phagocytes are involved in direct killing of bacteria, cytotoxic cells can kill cells that have been infected by viruses, and eosinophils and basophils may help in resistance to worm infestations. Each of these cell types uses very different mechanisms to perform its functions.

Cells that are involved in any immune response do not act independently, they are regulated by, and can regulate the functions of, other cells. The production of innate cells from the bone marrow may be increased or decreased during both innate and adaptive responses, their accumulation at sites of infection is regulated by inflammation and, importantly, their functions can be modulated. In this way each cell can help to fine tune the type of immune response that needs to be induced at different times after infection.[7]

1.9 Immunity and corona viral infection

Since the emergence of SARS-CoV in 2019 and its spread throughout, the world has experienced the outbreak of 2019-nCoV. All these viruses belong to the subfamily Coronavirinae in the family Coronaviridae. Since CoVs emerge periodically and unpredictably, spread rapidly, and induce serious infectious diseases, they become a continuous threat to human health. This is especially true when there are no approved vaccines.

In recent years, profound understandings of the innate immune response to viruses have been made. This type of immune response inhibits virus replication, promotes virus clearance, induces tissue repair, and triggers a prolonged adaptive immune response against the viruses. In most cases, pulmonary and systemic inflammatory responses associated with CoVs are triggered by the innate immune system when it recognizes the viruses.[8,9]

Although a broadly protective, universal vaccine is considered the ultimate protection against the virus spread, vaccine development can be time- consuming. To fulfill the pressing need, we should propose effective therapeutic protective measures using the accumulated knowledge of the innate immune response system. Can nutrition provide protection against this deadly virus?

Section 2. Role of nutrition in immunity

2.1 Relationship between nutrition and immunity.

Nutrient availability has the potential to affect all aspects of the immune system. In general, deficiency of several nutrients will lead to impaired immune responses, and replenishment of those specific components will typically restore the affected responses. It is well accepted that diet constitutes a critical determinant of immune status, and malnutrition is the most common cause of immunodeficiency worldwide. Deficiency of single nutrients could result in altered immune responses. Such response has been clearly identified in case of zinc, selenium, iron, copper, magnesium, manganese, vitamins A, C, E, B-6 and folic acid .This is in addition to other nutrients called Macronutrients.[10]

New branch of medicine called Immuno-nutrition is coming up. It comprises several aspects related to Nutrition, namely Immunity, Infection, Inflammation, and Injury or tissue damage. (Aptly called 4 "Is").

Fig. 5. Nutritional Ingredients.

The role of specific macro- and micronutrients in immune function has been extensively discussed in the literature. Immune cells may be particularly sensitive compared to other types of cells to the status of certain nutrients and food components. Nutritional status, as a modifiable factor, is a key element in the functioning and maintaining of our immune system integrity and remains closely associated with immunity and host resistance against any infectious agent. [10]

To function correctly, the immune system is depending on adequate amounts of nutrients (carbohydrates fats and proteins, as well as water and micronutrients such as vitamins and minerals). It is well stated that deficiency or insufficiency in nutrients, caused by inadequate intake, reduced absorption or bioavailability require corrections to properly maintain the immune system function.

The immune system consists of an intricate array of defence mechanisms which protect the body against potentially harmful foreign agents. Nutritional factors may influence immune functioning in many ways and at many levels. This will be answer to ways of boosting immunity.

Concerning certain nutrients, increased intake above nutritional recommendation can optimize immune defense mechanisms. Declines in both specific and non-specific immunity have been reported in association with under-nutrition and protein deficiency. Furthermore, some polyunsaturated fatty acids (PUFA), as well as their metabolic derivates, contribute to regulating cell functions, especially omega-3 fatty acids (EPA and DHA) that influence immune cell functions. Scientists have understood since that the immune system plays a critical role in the relationship between malnutrition and infection. Another major focus of current research is the possibility of stimulating the immune system of healthy people by nutritional means in the hope of improving health. For example, some scientists are investigating the possibility that supplementation with certain nutrients, such as vitamin E, at levels above the Recommended Dietary Allowances (RDA) may improve immune function in vulnerable segments of the population, such as the elderly.

2.2 Macronutrients intake and immunity

It is well known that severe malnutrition, especially wasting malnutrition in children, leads to impairments in immune function. Such malnutrition, which is primarily a problem in developing countries, substantially increases the risk of childhood mortality from infection. Most host defence mechanisms are impaired in protein-energy malnutrition, even if the nutritional deficiency is only moderate in severity. T cells are especially affected, resulting in a decrease in their numbers.[11]

Malnutrition is a condition that occurs when a person's diet does not contain the right amount of nutrients and can refer to both undernutritions. Protein-energy malnutrition is associated with a significant impairment of cell-mediated immunity, phagocyte function, complement system, secretory immunoglobulin A antibody concentrations, and cytokine production. Deficiency of single nutrients also results in altered immune responses: this is observed even when the deficiency state is relatively mild. ***World Health Organization*** monograph on "Interactions between Nutrition and Infection" presented the mechanisms linking infection and poor nutritional status.[11,12,13] Following the development of immunology as a science, increasing evidence was obtained as well to show how undernutrition may impair resistance to infections and the immune response. The understanding that protein-energy malnutrition (PEM) is not only protein and energy but also involves insufficiencies in the cellular supply of multiple micronutrients, serves to highlight the importance of specific micronutrients (vitamin A, Fe, Zn, and Cu) and their respective carrier proteins on specific and non-specific components of the immune response.[12]

Protein-energy malnutrition

It is well known that protein calorie malnutrition adversely affects various components of the immune system. In particular, with regard to the humoral immune response, clonal expansion and antibody production require rapid protein synthesis, so that amino acid restriction will inevitably interfere with these functions.

Lymphoid atrophy is a dramatic feature of protein-energy malnutrition (PEM). The size and weight of the thymus are reduced. Histologically, there is a loss of corticomedullary differentiation. In PEM there is also a loss of lymphoid cells around small blood vessels in the spleen and in lymph nodes the thymus dependent paracortical areas show depletion of lymphocytes. Most host-defense mechanisms are impaired. Delayed-hypersensitivity cutaneous responses both to recall and new antigens are markedly depressed.

There is also a reduction in mature fully differentiated T lymphocytes due in part to a reduction in thymic activity. There is also a moderate reduction in the number of suppressor cytotoxic CD8+ cells. The ratio of CD4+ to CD8+ cells is significantly lower than that in well- nourished control subjects. Phagocytosis is also affected in PEM. Lysosome concentrations are decreased, largely as the result of reduced production by monocytes and neutrophils and increased excretion in urine. Adherence of bacteria to epithelial cells is an essential first step before invasion and infection can occur. The number of bacteria adhering to respiratory epithelial cells is increased in PEM.

2.3 Milk proteins and Immunity

Epidemiological evidence shows that growing up on a farm is a protective factor, which is partly explained by the consumption of raw cow's milk. Indeed, recent studies show inverse associations between raw cow's milk consumption in early life and asthma, hay fever, and rhinitis. A similar association of raw cow's milk consumption with respiratory tract infections is recently found.

In milk, the main categories of compounds related to antiviral activity through immune stimulation and suppression of host immune inflammation are the casein proteins, whey proteins and their derived peptides. The casein family accounts for approximately 80% of the protein mass and includes several types of casein, e.g. αs1, αs2, β and κ, which form micelle complexes in the water phase of milk. [13]

In line with these findings, controlled studies in infants with milk components such as lactoferrin, milk fat globule membrane, and colostrum IgG have shown to reduce respiratory infections. (frontier immune)

Fig 6. Simple view of Immunity and infections

2.4 Casein and immune activity

Among the biologically active peptides derived from milk proteins, one of the most studied is casein phosphopeptides the major proteins in milk, have been considered principally as a source of amino acids . In recent years, some of the peptides liberated from caseins by the action of mammalian intestinal proteinases have been found to retain in vitro immunoenhancing properties .Casein phosphopeptide-added diet for approximately 2 months exhibited sustained enhancements of IgA responses in experiments. Casein proteins, as well as casein fragments, function as antiviral and immune regulatory factors by regulating the innate immune response both through up-regulation to enhance killing of viruses, and down-regulation to reduce detrimental conditions such as sepsis . Additionally, caseins link the innate immune system to the adaptive immune system by activating and/or enhancing B- and T-cell mediated functions.

Casein proteins, as well as casein fragments, function as **antiviral and immune regulatory** factors

- Up regulating the innate immune response both through up-regulation to enhance **killing of viruses,**
- and down-regulation to reduce detrimental conditions such as sepsis .
- Additionally, caseins link the innate immune system to the adaptive immune system by activating and enhancing B- and T-cell mediated functions.

Immune enhancing effect of casein is because of one its amino acid called **Arginine**.

A large body of evidence from animal studies indicates that adequate provision of arginine is required for lymphocyte development and that dietary arginine supplementation enhances immune function in various models of immunological challenges . Arginine has a number of pharmacological actions, crucial one is its effect on Immunity. Researches including clinical studies have indicated a number of findings in this regard. For many years, dietary arginine supplementation, often combined with other substances, has been used as a mechanism to boost the immune system. Emerging knowledge promises to clear allow for arginine's safe use.

It increases release of transmitters like interleukins. The use of dietary arginine supplementation along with n-3 fatty acids has been extensively tested in over 40 clinical studies in high-risk surgical patients, leading to a consistent and significant reduction in postoperative infections. Based on these studies, the European Society of Parenteral and Enteral Nutrition has recently published its guidelines recommending the routine use of arginine-containing diets in surgical patients.[14-21]

- **T lymphocytes depend on arginine for proliferation, z-chain peptide and T-cell receptor complex expression, and the development of memory cells. T-cells exhibit the molecular and functional effects associated with arginine deficiency**
- **The use of dietary arginine supplementation has been extensively tested in over 40 studies in high-risk surgical patients, leading to a consistent and significant reduction in post-operative infections.**

To date 40 trials using arginine have been performed in a wide variety of patient populations . These trials demonstrate a consistent benefit by reducing infections in patients undergoing high-risk surgery such as colon or pancreatic resection. Trauma patients also appear to benefit from these diets, but they must be started soon (ideally within 24 h) after injury.

Arginine, amino acid, also improves the immune parameters during physiological stresses. Dietary arginine has also been reported to be important for the maintenance of NK cell activity. Some evidence suggests that arginine is associated with reduced length of hospital stay after cancer surgery. Immune enhancing diets that have arginine were beneficial in moderate to severely malnourished patients undergoing gastrointestinal procedures. The benefits of Arginine are indicated by enhanced T-cell function, increased antibody production, accelerated wound healing mediated by immune cells or a reduction in infection, ventilator days, intensive care unit stay and hospital stay.

A large body of evidence from animal studies indicates that adequate provision of arginine is required for lymphocyte development and that dietary arginine supplementation enhances immune function in various models of immunological challenges

Clinical studies have shown that enteral or parenteral provision of arginine (e.g. 8–20 g/d; corresponding to 1·5–3·6 times the arginine intake by an average adult) improves immune functions and clinical outcomes in patients with burn injury, cancer, HIV infection, major traumas and gastrointestinal surgical operations.The benefits are indicated by enhanced T-cell function, increased antibody production, accelerated wound healing mediated by immune cells or a reduction in infection, ventilator days, intensive care unit stay and hospital stay.

Whey protein

The whey proteins account for the 20%, and include β-lactoglobulin (not present in human milk), α-lactalbumin, serum albumin, immunoglobulins, and many minor proteins. Most of the whey proteins have been demonstrated to effectively prevent viral infection. For example, milk derived proteins including α-lactalbumin, β-lactoglobulin, apo-lactoferrin (iron free), and homo-lactoferrin (Fe^{3+} carrying), were able to inhibit rotavirus attachment to cellular receptors by binding to the viral particle.[22]

Whey proteins appear to modulate immune function by boosting glutathione production in various tissues and preserving the muscle glutamine reservoir. GSH is the centerpiece of the body's antioxidant defense system that regulates many aspects of immune function. Muscle glutamine is the essential fuel of the immune system. The incorporation of whey proteins into the diet may help promote strong immunity and protect the health of active people of all ages as well as those with a compromised immune system.

The glutathione (GSH) antioxidant system is the principal mechanism that protects cells against oxidative stress caused by pollution, toxins, exercise and UV exposure. An integral role of the immune system is to reduce oxidative stress. Therefore, an adequate supply of GSH is a crucial factor in the maintenance of an effective immune system.Among the potential uses, whey proteins have recently been highlighted for their utilization as functional food ingredients. The immune system, in particular, has been shown to be modulated by dietary whey protein concentrate (WPC) consumption in both animal models and human studies.

Studies have provided additional evidence that dietary Whey can enhance antibody responses to systemically-administered antigen in mice, possibly via a mechanism of enhanced lymphocyte activation and cellular function. Thus, the common paradigm appears to be that some WPCs can potentiate immune activity, in particular B cell production of antibodies in response to systemic immunization.

Studies have shown that WPCs can enhance immunity and consequently increase protection against tumour development/ progression, in both clinical studies and animal and can promote enhanced resistance to infectious pathogen challenge. Supplementation with dietary WPC may therefore be beneficial in a dietary formulation to optimize/enhance immuno-competence and health. Moreover dietary whey protein concentrate can enhance intestinal mucosal antibody responses against orally administered cholera toxins.

Whey-It modulate immune function by boosting glutathione (GSH) production in various tissues and preserving the muscle glutamine reservoir. GSH is the centerpiece of the body's antioxidant defense system that regulates many aspects of immune function. Muscle glutamine is the essential fuel of the immune system.

Fig. 7. Whey Milk Proteins

Whey protein and its components have protective pharmacological activity in terms of immune boosting.

2.5 α-lactalbumin and immunity in infants

α-Lactalbumin is a dominant protein present within the Golgi apparatus of the mammary gland. It is capable of modifying the enzyme β-1,4-galactosyltransferase to allow the formation of lactose and facilitates mineral uptake . In addition, α-lactalbumin accounts for almost 60% of essential amino acids, including tryptophan, an amino acid that is higher in human breast milk than bovine milk. To compensate for this difference between human breast milk and bovine milk, protein content is adjusted to a higher percentage in infant formula to make amino acid composition similar to that in human breast milk. In a study by Fleddermann et al. the inclusion of α-lactalbumin in an infant formula increased energy efficiency substantially.

α-lactalbumin, demonstrates enhanced antiviral activity against human influenza virus A subtype H3N2 , subtype H1N1 and lethal avian influenza A. α-lactalbumin was also found to be bactericidal against an antibiotic resistant strain of Streptococcus pneumonia .

α-Lactalbumin could prevent rotavirus infection through the binding to structural viral protein .

Lots of scientific information is available on effect of alpha lactalbumin on immunity. Alfa-lactalbumin, α-lactalbumin hydrolysate and whole whey protein concentrate have each been shown to enhance antibody production to foreign antigen Human rotavirus (HRV) is a major etiologic agent of severe infantile gastroenteritis. κ-Casein (κ-CN) from both human and bovine mature milk has been reported to have anti-HRV activity.[23-25]

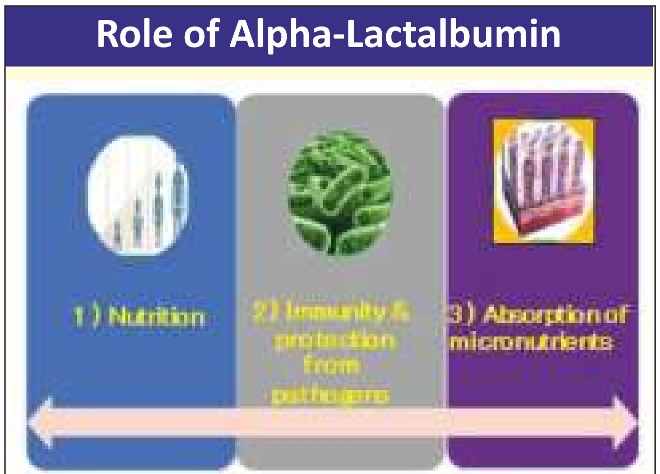


Fig. 8. Alpha lactalbumin functions

Lactalbumin is a protein that is present in the milk of all mammals. In the mammary gland, it participates in lactose synthesis, Lactalbumin -major protein in breast milk (20 –25% of total protein), balanced supply of essential amino acids to the growing infant. (2 to 3 g/L), One of the recent approaches is to add more bovine α-lactalbumin to the infant formula to increase the protein quality.

- **protein fractions enriched with -lactalbumin may now need to be added to infant formula to provide some of the benefits of human -lactalbumin.**
- **have antibacterial and immuno stimulatory properties, thereby possibly aiding in the protection against infection.**

2.6 Fats and fatty acids

Fatty acids can be divided into distinct families that differ in structure and dietary origin. Fatty acids which contain double bonds are termed unsaturated, and are further classified by the position of the double bonds, that is, n-3 or n-6 (see Box 4). Saturated fatty acids do not contain double bonds in their structure. The principal roles of fatty acids are as energy sources and as membrane constituents. In addition, certain fatty acids have specific roles, and are therefore regarded as essential nutrients.

A particular family of unsaturated fatty acids known as polyunsaturated fatty acids (PUFA) can potently alter the functioning of immune cells. There are two classes of PUFA: the n-6 series (found primarily in vegetable oils) and the n-3 series (found in fish oils and also in certain vegetable oils such as canola, soy, and linseed).[17]

These fatty acids can be converted by immune cells into tissue hormones, for example, prostaglandins . Depending on the type of PUFA in the diet, immune cells produce different quantities and kinds of prostaglandins with very diff e rent effects on the immune response. In addition to their effects on tissue hormone levels, PUFAmay exert some of their effects by other mechanisms.

Functional roles of FA are largely and selectively attributable to the long-chain polyunsaturated fatty acids (LC PUFA) of the n–6 and n–3 series. Most of these activities can be attributed to the PUFAs, with some opposing effects at the cellular levels of the n–6, especially AA, which are partly derived as such from the dietary intake but mainly derived from the conversion of LA, and of the n–3 FA, especially of the LC compounds EPA and DHA.

Most of the attention of researchers has therefore been devoted to the roles of these FA and to their effects on processes taking place in immune and inflammatory cells, on the basis of the established understanding and knowledge of the underlying mechanisms (cell signalling and lipid mediators, expression of pro- and anti-inflammatory compounds, etc.), emerging from basic research and animal experiments.[28]

α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) can increase the phagocytic capacity of macrophages. This omega-3 fatty acid-mediated increase in the phagocytic capacity has been demonstrated for the engulfment of zymosan particles and *P.aeruginosa E.coli* .

2.7 Micronutrients

These are crucial substances necessary for maintenance of health in human beings, they are required in smaller quantities, hence called micronutrients. They include Vitamins and Minerals. Vitamins are essential constituents of our diet that have long been known to influence the immune system (Mora *et al.*, 2008). There are nine water soluble vitamins including the eight in the vitamin B complex and vitamin C. The B complex Vitamins include thiamin, riboflavin, niacin, B6 (pyridoxine), B12, folic acid, biotin and pantothenic acid. Adequate vitamin and mineral intakes are essential for the maintenance of health and disease prevention.

Dietary intake is the most important source for micronutrients. Vitamins and minerals boost immunity. Micronutrient deficiency suppresses immune function by affecting the innate T-cell mediated immune response and adoptive antibody response.

It has since been established that the complex, integrated immune system needs multiple specific micronutrients, including vitamins A, D, C, E, B6, and B12, folate, zinc, iron, copper, and selenium, which play vital, often synergistic roles at every stage of the immune response. Adequate amounts are essential to ensure the proper function of physical barriers and immune cells; however, daily micronutrient intakes necessary to support immune function may be higher than current recommended dietary allowances.[18]

Nucleotides-8 mg /100ml

- Increase Bifidobactirium
- Lymphocyte proliferation,
- Activation of lymphocytes

(Nutrition in clinical practice 2014)

Vitamin A

Physicians and scientists have recognized for hundreds of years that xerophthalmia (the "dry eye" disorder caused by vitamin A deficiency) is linked to high morbidity and mortality from infectious diseases. More recently, clinical trials in developing countries where vitamin A deficiency is prevalent have shown that supplementation with this vitamin reduces child mortality by 20–30%. Vitamin A capsule distribution is recognized as one of the most cost-effective interventions to improve public health in developing countries. Vitamin A appears to play a particularly important role in the body's defences against the measles virus. Recent studies suggest that high-dose vitamin A supplementation is of significant value in preventing complications of severe measles and reducing mortality from this Disease. Networks of cytokines which influence immune responses may also be altered during vitamin A deficiency, and antibody responses to antigens may be modified.[19]

Vitamin C

The effects of vitamin C in reducing the risk of common cold have long been debated. One analysis of mostly high-quality studies determined that there was no reduction in incidence in the general population, but that vitamin C supplementation (≥0.2 g/day) in those who regularly undergo severe physical exercise reduced the incidence of common cold by more than half.

Vitamin C or Ascorbic acid is a hydrophilic molecule, composed of six carbons, similar to glucose. In the organisms, Vit C can be found in its reduced form (ascorbic acid orascorbate) or in its oxidized form called dehydroascorbic acid (DHA), which is a product of two-electron oxidation of ascorbic acid.[2] It has essential physiological and metabolic activities in humans, but is only obtained through diet .

Vit. C is essential for the synthesis of immunoglobulins, for the production of interferon, and for the suppression of the production of interleukin-18, a regulating factor in malignant tumors. Therefore, Vit. C supplementation is recommended during infection and stress.[5] Systemically, Vit. C acts in epigenetics such as in the synthesis of immunoglobulins, in the production of interferon. Vitamin C deficiencies are found to be associated with decreases in the bactericidal activity and locomotion of neutrophils and macrophages and decreases in resistance to microbial infection. Some have noted significant increases in serum IgG and IgM levels in elderly woman receiving 400 mg ascorbic acid /day.[25]

2.8 Vitamin D

Observational studies report consistent independent associations between low serum concentrations of 25-hydroxyvitamin D (the major circulating vitamin D metabolite) and susceptibility to acute respiratory tract infection. 25-hydroxyvitamin D supports induction of antimicrobial peptides in response to both viral and bacterial stimuli, suggesting a potential mechanism by which vitamin D inducible protection against respiratory pathogens might be mediated.

Numerous randomized controlled trials to determine whether vitamin D supplementation can decrease the risk of acute respiratory tract infection have been carried out. A total of five aggregate data meta-analyses incorporating data from up to 15 primary trials have been conducted to date, of which two report statistically significant protective effect.

In an individual participant data (IPD) meta-analysis of randomised controlled trials, vitamin D supplementation reduced the risk of experiencing at least one acute respiratory tract infection. Subgroup analysis revealed that daily or weekly vitamin D supplementation without additional bolus doses protected against acute respiratory tract infection, whereas regimens containing large bolus doses did not.

Among those receiving daily or weekly vitamin D, protective effects were strongest in those with profound vitamin D deficiency at baseline, although those with higher baseline 25-hydroxyvitamin D concentrations also experienced benefit. Also, vitamin D plays an important role in pulmonary resistance and its deficiency has been linked to various respiratory infections. It affects both cytokine and immunoglobulin production.

Five meta-analyses of mostly high-quality studies demonstrated that vitamin D (300–3653 IU/day) in adults and children can reduce the risk of RTI . Better results were achieved in those with a low vitamin D status at the start of the trial , with a lower odds ratio for risk reduction with low (0.30) versus high (0.75) vitamin D status. Low-to-moderate quality evidence supports the potential benefits of vitamin D supplementation in reducing the risk of upper RTI, tuberculosis, and influenza in adults and children, although other analyses found no such effect against RTI , pneumonia , tuberculosis or diarrhea .[26]

Probiotics are beneficial microbes that confer a realistic health benefit on the host (Hardy *et al*., 2013). Probiotics have beneficial effects on intestinal immunity, prevention of infection, elimination of toxins and eradication of microbial pathogens (Corthésy *et al*., 2007; Duncan and Flint, 2013). Probiotic bacteria have been reported to exert immune modulatory effects by increasing macrophage phagocytosis and increasing natural killer cell activity and numbers.Excessive production of proinflammatory cytokines may lead to chronic inflammation which increase the risk of cancer. Probiotics have the ability to modulate the immune response and counter the inflammatory process (Philpott and Ferguson, 2004).

Many elderly subjects are at increased risk of infectious and noninfectious diseases due to an age related decline in lymphoid cell activity. Dietary supplementation with probiotic lactic acid bacteria (LAB) enhances natural killer cell activity and thus improves the immune system

Prebiotics are non digestable food stuffs such as fiber and oligosaccharides which enter the colon and are metabolized by probiotics (Fric, 2002). Vulevic *et al.* (2008) observed that administration of galactooligosaccharides to healthy elderly persons results in an increase in the numbers of beneficial bacteria, especially bifidobacteria, increases in phagocytosis, NK cell activity, the production of anti-inflammatory cytokine interleukin-10 (IL-10) and reduction in the production of proinflammatory cytokines.[27]

2.9 Minerals and immunity

Zinc

Zinc is present in all body tissues and fluids. The total body zinc content has been estimated to be2g. Skeletal muscle accounts for approximately 60% of the total body content and bone mass with a zinc concentration of 100-200mg/g, for approximately30%.

Zinc is an essential component of a large number (>200) of enzymes participating in the synthesis and degradation of carbohydrates, lipids, proteins and nucleic acids as well as in the metabolism of other micronutrients. Results from zinc supplementation studies suggest that a low zinc status in children not only affects growth but is also associated with an increased risk of severe infectious diseases. Malnutrition, especially insufficiency of micronutrients such as zinc, is identified consistently as one of the most important host factors that determine the risk and severity of diarrhea.

Zinc supplementation reduced the duration of diarrhea in almost all studies. In fact, zinc-supplemented children had a 15% lower probability of continuing diarrhea on a given day and a 24% lower probability of continuing diarrhea than those children in the placebo group.[21] In some studies, growth retarded children or those with initial low serum zinc values experienced the most pronounced reductions in diarrhea duration.

Second, almost all studies reported reductions in the severity of diarrheal illnesses after zinc supplementation. Zinc supplementation enhances immune system activity and protects against a range of infections including colds and upper respiratory infections (such as bronchitis). Several important studies have revealed that zinc lozenges may reduce the intensity of the symptoms associated with a cold, particularly cough, and the length of time that a cold lingers.

Few clinical trials are available to evaluate the effects of zinc supplementation on acute lower respiratory infection (ALRI) rates. Effect of weekly zinc supplements on incidence of pneumonia and diarrhea in children younger than 2 years in an urban, low-income population in Bangladesh was studied in a recent randomized controlled trial.[27] Authors found that among young children zinc has a substantial protective effect against pneumonia, severe pneumonia, suppurative otitis media, and most importantly, mortality secondary to pneumonia. Mostly high-quality evidence indicates that supplementation with zinc (5–50 mg/day) can reduce the incidence of otitis media in younger or undernourished children . A reduction in the incidence of lower RTI after zinc supplementation (20–140 mg/week) in children is supported by low-to-moderate evidence, but this outcome depends on the criteria used to define lower RTI; a greater reduction was observed using specific clinical criteria, compared with those based on caregiver reports or "non-severe pneumonia" from the World Health Organization.

An analysis of mostly high-quality studies has demonstrated that the risk of RTI or pneumonia and diarrhea or dysentery may be reduced in children after zinc administration.[28]

ZINC- protective effect against respiratory infections, severe pneumonia, Otitis media, and most importantly, mortality secondary to pneumonia.

Selenium (Se) via its incorporation into cytosolic glutathione peroxidase (GSHPx) and biomembranes has been associated with the expression of specific, non specific and cell mediated immune response (Spallholz, 1990; Teixeira *et al*., 2014). Selenium supplements augmented the cellular immune response through an increased production of IFγ and other cytokines, T cell proliferation, and increase in T helper cells. Humoral immune responses were not affected by Se. Selenium supplemented subjects showed more rapid clearance of the poliovirus (Broome *et al*., 2004). Se protects the cardiac muscle from invasion by pathogens. Se deficient mice were more susceptible to infections by coxsackievirus as well as influenza virus . Moreover Se decreases the possibilities of AIDS virus infection

Iron salts have been reported to enhance the immunity (Chandra, 2004). Iron in metalloenzymes or proteins participates directly in immunity such as iron catalase and lactoferrin (Ha and Zemel, 2003). Iron supplementation in population with high incidence of iron deficiency anemia has been shown to decrease the morbidity from infections and diarrheal diseases (Scrimshaw *et al.*, 1990). The action of iron occurs via influencing the innate immune responses.[24]

The Role of Nutrition in Enhancing Immunity in Aging

Nutritional intervention has been recognized as a practical, cost-effective approach to attenuating age-associated decline in immune function, vaccination efficiency, and resistance to infectious and neoplastic diseases.

Aging is associated with declined immune function, particularly T cell-mediated activity, which contributes to increased morbidity and mortality from infectious disease and cancer in the elderly. Studies have shown that nutritional intervention may be a promising approach to reversing impaired immune function and diminished resistance to infection with aging. evidence indicates that increased intake of some nutrients above the recommended levels is needed to maintain proper function of the immune system and to reduce the incidence of infection in the elderly.

Intake of Casein and Vitamin E above recommended levels can enhance T cell function in aged humans. This effect is believed to contribute toward increased resistance to influenza infection in animals and reduced incidence of upper respiratory infection in the elderly. Zinc supplementation has also been tested for its potential enhancement of low vaccination efficacy observed in the elderly.[31]

2.10 Conclusion

Every stage of the immune response depends on the presence of certain macro and micronutrients, which have synergistic roles based on their complementary modes of action. Clearly, nutrients are an integral part of the immune system, and the body needs optimal levels for effective immune function. It is well established that overt nutrient deficiencies can adversely affect the immune system and predispose individuals to infections. It is likely that marginal deficiencies are also associated with in.[25]

Recently an expert panel concluded that there is huge need of awareness to parents or guardians for role of nutrition in first 1000 days of an infant. This role of nutrition does not pertain only to the growth & development of an infant but also to the immune system programming.

Any nutritional inadequacy or nutritional insult during this period may have long term consequences like impaired immune system, cognition etc. resulting in increased susceptibility to infections or even reduced 5-10 IQ points later increased risk of infections, although the effect may be less seen.[28-29]

Effective nutritional interventions in the immune system may find value not only in therapeutic applications, but also in the prophylactic treatment of subjects at risk of immune incompetence because of illness or prior to immunosuppressive drugs and surgical regimens. thus dietitians should encourage the intake of a variety of nutrients to promote proper balance among all nutrients. For consumers who are not deficient in one or more nutrients but nevertheless are intent on using supplements, products that provide multiple nutrients without supplying excess amounts should be encouraged.

Some neutraceuticals are beneficial for the immune system. Far more research into nutrient-nutrient interactions and immune function particularly in human subjects is needed. At this time, the best dietary advice to enhance immune function in healthy people is to ensure variety, balance and moderation of the nutrients. Casein, Alpha lactalbumin, Zinc , minerals , Vitamin D are playing very crucial role to prevent the chances of viral infections, specially like Corona .[30]

There are many factors that affect immune system functions, one of those is nutrition. There is a significant correlation between immune system and nutrition, furthermore malnutrition shouldn't be considered as energy and a protein deficiency alone.[31-34] Due to these reasons, the main aim of nourishment is not merely to gain energy and protein, but to enhance resistance against ailments with some specific nutriment and to turn the inflammatory response in someone.

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Dear Doctor,

Nutrition is one of the important factor that affect our immune system function. This interrelationship applies not only to nutritionally deprived in developing countries but also to people of all ages throughout the world. Every stage of the immune response depends on the presence of certain macro and micronutrients, which have synergistic roles based on their complementary modes of action. Clearly, nutrients are an integral part of the immune system, and the body needs optimal levels for effective immune function. It is well established that overt nutrient deficiencies can adversely affect the immune system and predispose individuals to infections. Thus, main aim of nourishment is not merely to gain energy but also to enhance immunity.

It is indeed a pleasure to present to you this QMR issue by **Dr. Swaroop Hegde,** renowned physician. In this issue he is enlightening us on "Nutritional approach to immunity."

I signoff by once again reminding you to continue sending your comments and suggestion regarding the QMR. Do write to me at rahul.badwaik@raptakos.com with your write ups, notes or tidbits on various topics of interest that can make for informative and interesting reading.

Dr. Rahul Badwaik

Vice President - Medical

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Nutritional approach to immunity

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