Nutrition metabolism and infections

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Editor: Fudi Wang

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Funding: This work was supported by NSFC Grants (82072250 and 31670879 to GZ), Guangdong Science and Technology Project Grant (2018A05056032 to GZ), National Science and Technology Major Project “Construction of Demonstration Zone for Integrated Prevention and Control of Infectious Diseases” (2018ZX10715004-002-012 to FY).

Conflicts of interest: The authors reported no conflicts of interest.

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Abstract

Infection and nutrition are intricately interacted and further influence human health. Infections are a worldwide health problem and malnutrition plays a significant role in the emergence of infection. Growing evidence suggests that the optimization of dietary nutrients intake is crucial in maintaining systemic immunity and may help improve resistance to infections. In this review, we explore a wide range of topics including interactions between nutrients and various infectious diseases. We also discuss the role of diet-induced gut microbiota in the infection-nutrition cycle and review how dietary-microbiome crosstalk may affect disease development and progression, which may provide an attractive option to the design of a diet leading to favorable outcomes in the future. We will also present evidence and propose mechanisms of nutrients that may specifically modulate host immunity and metabolism to infectious pathogens and also cover its influence on nutrition, focusing on immuno-nutrients. We provide representative nutrients in the present review based on their intensive studies and wide acceptance of their immuno-modulating properties. Moreover, the efficacy and translational cost of their plausible utility to be anti-infective nutrients are also reviewed. Finally, we highlight the current progress and challenges to gain a better understanding of the research into microbiota, infectious diseases, and nutrition with an emphasis on future research directions.

Key words: nutrition; infection; metabolism

Introduction

Diet nutrition, an essential aspect of body homeostasis, is usually associated with a variety of components, systems, and processes, including the occurrence of infectious diseases. For this reason, nutritional status has crucial importance on the persistence, remission and incidence of a wide range of infectious diseases and global survival. Nutrition is defined by the World Health Organization (WHO) as the ingestion of food in relation to the dietary needs of the body. Malnutrition is still prevalent in less developed regions and is a major cause of high infectious disease morbidity and mortality. However, even in developed countries, nutritional problems such as specific nutritional deficiencies, suboptimal diets and excessive calorie consumption remain a challenging reality. It has been reported that approximately 792 million people in developing countries and 34 million in developed countries are undernourished. Previous analysis showed that malnutrition was associated with 3.1 million child deaths annually or 45% of all child deaths in 2011 and increased the risk of death from infectious diseases in childhood. It has been reported that 32% of the worldwide
infections could be eliminated by increasing nutritional status; however, others have reasoned that even this figure is an underestimation of the real burden, particularly with the emergence of HIV/AIDS.\cite{3}

Ample evidence confirms that nutritional status is closely related to immunity and host resistance to infection. Undernutrition is viewed as a significant reason for immunodeficiency around the world, inclining the malnourished to various kinds of infections. All types of immunodeficiency are prone to undernutrition, especially opportunistic immunodeficiency, which is associated with altered immune status. Undernutrition increases the risk of the host's sicknesses, and associated diseases have a negative impact on host metabolism, exacerbating the nutritional state.\cite{4} The complex of malnutrition and infection is associated with significant morbidity and mortality around the world. However, comparative studies on human body composition patterns in developing countries showed that there was a double burden of nutrition. The population of undernourished countries persists, while a growing population is over-nourished.

Balanced nutrition is assumed to be important in keeping the health of an individual. The body utilizes supplements from food to generate energy, keep up or fix the structures of the body and direct or regulate host metabolism.\cite{5} Nutrition metabolism, which begins from the ingestion of diet, is a combination of physical and chemical processes that occur in the body to acquire energy and utilize it to synthesize, process, transform and eliminate substances for the optimal maintenance of life.\cite{6} Thus, defenselessness against the establishment and development of the infectious disease is characteristically identified by the immune capacity of the host, whose reliance on appropriate nourishment has been broadly illustrated.\cite{7,8}

This article describes the relationship between nutrition metabolism, infection and immunity, with a focus on current knowledge of nutrition and metabolism in the context of infectious diseases.

The cycle between nutrition and infection

*Interactions of Nutrition and Infection*, which was published in 1968 by WHO, suggested that there was a synergistic relationship between infection and malnutrition.\cite{5} An insufficient dietary intake causes weight reduction, lowered immune capacity, mucosal damage, pathogen invasion, and impeded growth in kids. It is accepted that diseases can adversely impact the subjects' nutritional status that results in a decrease of the body's capacity to battle infections. Thus, nutrition and infection are interacting with each other.\cite{8} The intricate interaction between infections and
undernutrition makes a threatening situation that sustains an endless loop that prompts these two profiting from one another. Nutrition deficiency leads to increased susceptibility to disease, and infections likewise affect the nutritional status and further contributes to malnutrition, which causes an endless loop (Figure 1).

*Abnormal nutritional status increases the risks of infection*

The relationship between malnutrition and a higher risk of infections has been reported in various age groups in different nations, and generally in clinical settings. Tuberculosis is a disease that is especially affected by malnutrition, and it is a major cause of morbidity and mortality in developing countries. Roughly 33% of the population of the world is infected with *Mycobacterium tuberculosis*, usually in a subclinical form. Malnutrition likely influences the outcome of tuberculosis and may lead to the prevalence of drug-resistant *M. tuberculosis* strains.

Another example of infectious diseases related to undernutrition is measles. Although there is an existing effective vaccine for measles, it still causes severe disease and death in children worldwide. Among different nutrients, lack of vitamin A increases the mortality rate. Experimental data suggest that vitamin A supplementation in children is related to a decrease in both disease severity and mortality rate. The unpredictability of the relationship between diseases and undernutrition has been investigated by another study in Angola, where analysis of demographic and health survey information pointed out that nutrient deficiency and anemia are linked to malaria.

Strikingly, excessive caloric nutrition has also been found to have an adverse effect on disease resistance. During the 2009 H1N1 epidemics, obesity was identified to be a risk that increases susceptibility to the infection, indicating that abnormal nutritional status is linked to infections. In addition to the observations on obesity in H1N1 infections, several studies have detailed the relationship between high body mass index and defenselessness to respiratory diseases in general.

*Effects of infection on nutritional status*

Infections may lead to decreased nutritional status. For example, cross-sectional studies reported lower plasma concentrations of nutrients, such as vitamin E, in patients with infectious diseases compared with healthy controls. In animal models of influenza virus infection, reduced concentrations of nutrients, such as glutathione and vitamins, were observed in the lung. Hypermetabolism and hypercatabolism are characteristics of various diseases, particularly infectious diseases such as
tuberculosis\textsuperscript{19} and malaria.\textsuperscript{20} These high pressure conditions require an expanded need for supplements of nutrients, known as hypermetabolism—an abnormal increase in the basal metabolic rate that will cause a consistent energy or protein deficiency to meet the metabolic needs of the body. Carbohydrates, lipids and proteins are required for offering energy and structure while vitamins and minerals, which regulate various metabolic processes including hormone homeostasis,\textsuperscript{21} are required for increased metabolism. Immunosuppression caused by HIV, \textit{Plasmodium} or \textit{Leishmania} infection results in increased host susceptibility to other infections and imbalanced or degenerated metabolism, and deepening of nutritional deficiency in a vicious circle. Indeed, there are several examples showing that malnutrition, AIDS, tuberculosis, leishmaniasis and helminthic diseases have poor clinical development and poor response to drug treatment.\textsuperscript{7,8,11,22}

Nutritional status alternations are common complications of HIV infection and exert a critical impact on morbidity and mortality.\textsuperscript{23} Studies on HIV have expanded our knowledge on nourishing perspectives in the field of hypermetabolism and hypercatabolism.\textsuperscript{7,24,25} Since such studies have deeply investigated various events and systems, they can be applied to other debilitating infectious and inflammatory diseases. A lot of researches have explored how co-infection (co-infection between HIV and a variety of other pathogens) occurs frequently and interacted with malnutrition, leading to cachexia and poor clinical outcomes.\textsuperscript{26,27}

Intracellular parasites not only utilize the existing nutrients and cellular energy production systems in the cell, but also further induce the cell to actively provide its nutrition.\textsuperscript{28,29} In fact, proof of a connection between undernutrition, leishmaniasis and immunosuppression has been illustrated. A poor nutritional status is related to a weak sodium gluconate chemotherapy response and decreased serum levels of metal matrix metalloproteinase 9 (MMP9), a cytokine that is negatively correlated with disease progression.\textsuperscript{30,31}

According to historical reports and recent experimental animal studies, malnutrition is usually considered to be a major cause for the development of active tuberculosis. Tuberculosis is one of the well-documented examples of major global disease burdens in which malnutrition leads to worse disease outcomes.\textsuperscript{11} In vitro and animal experiments have shown the detrimental consequences of chronic protein and energy malnutrition on the immunity against \textit{M. tuberculosis}.\textsuperscript{32} Studies on tuberculosis patients also showed that the body composition may change due to altered protein, fat and micronutrient metabolism.\textsuperscript{33} Immune dysfunction is also believed to account for the strong link between diabetes and tuberculosis. These interactions have significant
ramifications in individuals with a high incidence of malnutrition, diabetes mellitus, and latent tuberculosis infection.\textsuperscript{19}

**Nutrient metabolism and infections**

During the mobilization of the immune system against pathogens, protecting cells from oxidative stress is a key function of vitamins.\textsuperscript{34,35} Vitamin D is firstly hydroxylated to 25-hydroxyvitamin D, primarily in the liver, and further hydroxylated by the activity of a 1-\(\alpha\)-hydroxylase to the dynamic structure of 1,25-hydroxyvitamin D, primarily in the kidneys. Vitamin D is engaged with a wide scope of immunomodulatory functions, including affecting monocyte, macrophage, and dendritic cell (DC) capacities, producing inflammatory cytokines and activating subsequent responses of adaptive immune cells.\textsuperscript{36} A recent meta-analysis reported a link between adequate vitamin D levels and a decreased risk of respiratory infections. Previous studies have also shown that the supplementation of vitamin D can reduce the risk of COVID-19 infection in people with vitamin D deficiency.\textsuperscript{37} As such, vitamin D supplementation may be a potential prevention strategy for infectious diseases, including tuberculosis, upper respiratory tract infections, hepatitis C, and HIV.\textsuperscript{38}

Vitamin E also plays some roles in the immune system, such as regulating T cell function, producing immunoglobulins and pro-inflammatory cytokines and chemokines as well as controlling oxidative stress.\textsuperscript{17,39,40} Accumulated researches reported that vitamin E can enhance immunity against some bacterial pathogens (ie, *Streptococcus pneumoniae*),\textsuperscript{40} significantly improve resistance to influenza virus infection, reduce helminth parasites infection\textsuperscript{11} and help to treat hepatitis B.\textsuperscript{17}

Metabolism and decomposition of caloric balance play a crucial role in host's gluconeogenesis in response to excessive metabolic demands. In the process of synthesizing glucose from lipid reserves, a large number of free radicals are generated, leading to cell membrane oxidation and ketone formation, thereby increasing organic acidification.\textsuperscript{42} In addition, if the proportion of adipose tissue exceeds the optimal state before the onset of infection and disease, the host is more prone to higher levels of inflammation, more oxidative stress, and more acidification.\textsuperscript{8,43} A number of studies have found that the quality, not quantity of dietary fat, is the key to providing essential fatty acids involved in multiple metabolic functions.\textsuperscript{44,45} Diet-related metabolic functions are critical to disease outcomes, including infection and inflammatory processes, regardless of health status.

Protein involvement in caloric balance also reflects hypermetabolic and catabolic
processes, as during the process of gluconeogenesis, muscle collagen, actin, and myosin are mobilized and metabolized to produce glucose, thereby producing energy. Since muscle tissue plays the role of the storage of amino acids and glycogen, it is released immediately when the metabolic demand increases. Therefore, during the catabolism period, the loss in muscle tissue occurs first to retain important functions. When protein loss exceeds 20% of the body's total protein, the physiological system begins to show functional defects, especially in terms of immunity, as well as in the cardiopulmonary and musculoskeletal systems. Glycogen and lipid reserves will be used and catabolized when protein loss exceeds 30%, and the survival rate is reduced by 20%. Thus, protein balance re-establishment should be considered for adaptation to metabolic conditions related to the response to infections and body recovery.

Excessive calorie nutrition also has negative effects on immunity to infections. Accumulated evidence has shown that the metabolic pathways of glucose, which is the main energy source of the human body, are involved in many processes related to immunity and the response to infections, as well as the pathophysiology of infectious diseases. Muscle is the main source of glucose during acute or immediate physical demand, which explains why body mass is lost at the expense of muscle in the course of severe diseases, while protein loss is involved in the process of hypercatabolism.

Dietary sugar and glucose in human reserves in combinations with peptides form glycoproteins. These glycoproteins are the molecular basis of various functional components of the immune response. Exogenous signal transduction, such as the participation of the major histocompatibility complex-T cell receptor, is a stimulating factor that regulates the glucose absorption and metabolic activity of lymphocytes. Similarly, the glycolytic pathway plays a fundamental role in the differentiation of macrophages into type 2 (M2)-regulated phenotype or into inflammatory type 1 (M1). In fact, inhibiting glycolysis can lead to a loss of regulatory phenotypes, including the production of IL-10. Key aspects of glucose pathways are involved in host-pathogen interactions and infection outcomes. For example, the glucose metabolic machinery of host T cells and phagocytes was regulated by viruses. The imbalance of glucose metabolism is not only a consequence but also participates in the process of tissue damage, catabolism and dysfunction during infection and inflammation. During sepsis, the activation of pro-inflammatory factors and the release of regulatory components results in hyperglycemia and hypoglycemia, leading to liver gluconeogenesis and peripheral insulin resistance. Moreover, T lymphocytes are reported to be continuously activated during HIV infection, which is characterized by up-regulated
expressed of glucose transporter 1 (GLUT-1) and high glycolytic activity, leading to metabolic failure and cell death.\textsuperscript{53}

**Immunomodulatory role of nutrients and clinical relevance during infections**

The synergistic interaction between infection and nutrition was first discovered in the 1960s and now there is large evidence supporting that insufficient intake of dietary nutrients adversely affects the immune system and predisposes the malnourished to infectious diseases.\textsuperscript{55,56} The immune response is the major cause of increased calorie requirements during infectious diseases.\textsuperscript{55,57} The immune system is prepared to respond strongly to antigen stimulation and inflammatory signals, which requires the acceleration of cell metabolism, thereby increasing energy requirements.\textsuperscript{53}

Immuno-nutrition is a therapeutic application that exploits the beneficial effects of certain nutrients on the immune response, since specific nutrients regulate various activities of the immune system.\textsuperscript{58} The most regularly utilized supplements for immuno-nutrition include amino acids, nucleotides, polyunsaturated fatty acids (PUFA), vitamins and minerals.\textsuperscript{39} It is known that these nutritional supplements may valuably influence immune function, regulate chronic inflammatory and autoimmune conditions and reduce the risk of infection.

Nutrition-sensitive hormones regulate the activity of white blood cells during hormone receptor binding. Enhanced neuroendocrine activity to ensure tissue repair and homeostasis is a hallmark of hormone-induced increased glucose production, increased use of nitrogen products, and increased enzyme activity, resulting in increased catabolism and reserve combustion.\textsuperscript{42,59} Although such processes are not well explored and described in infectious diseases that are not considered to be hypermetabolic, due to the activated immune response to a given infection, a higher calorie expenditure should be expected at a proportional level.

Carbohydrates and lipids are the main sources of cellular energy. Not only do they make up an important proportion of the diet, but the quality of carbohydrates and lipids in the diet related to metabolic and immune function is also of concern during diseases.\textsuperscript{6} Omega-3 fatty acids help reduce inflammation, while certain omega-6 fatty acids tend to promote inflammation.\textsuperscript{60} The overall caloric balance will affect the progress and outcome of the infection process.\textsuperscript{54,57} During an immune response, the lipids are very important since their functions as components of cell membranes, constituents of hormones and maintainers of body temperature are all crucial.\textsuperscript{61} In healthy individuals, carbohydrates and lipids in the diet form adipose tissue, which is responsible for fat storage. During infections, in the course of infection and immune
response, the increase in metabolic demand results in lipid mobilization, which is converted into easy-to-use glucose for energy.\textsuperscript{53,62} Furthermore, liposoluble vitamins will also migrate from the host’s adipose tissue under conditions of hypermetabolism and hypercatabolism during infections or inflammation.

Severe protein-energy malnutrition (PEM) in newborns and young children results in thymus atrophy and subsequent dysplasia of peripheral lymphocyte organs, such as lymph nodes and spleen. This causal relationship leads to persistent immunodeficiency characterized by leukopenia, a decreased ratio of CD4 to CD8, increased numbers of CD4/CD8 double-negative T cells as well as appearance of immature T cells in the periphery. Malnourished children have a higher proportion of respiratory infections, infectious diarrhea, measles and malaria, which are characterized by prolonged disease course and worsening of the disease. These malnourished children show decreased functional T cell counts, increased numbers of undifferentiated lymphocytes, and repressed serum complement activity. Compared with healthy donors, expression of the peripheral blood T lymphocyte activation marker CD69 in malnourished children is lower, and the expression is mainly intermediate (CD45RAlow/CD45ROlow) rather than memory phenotype (CD45ROhigh).\textsuperscript{63,64} These T cells are biased towards type 2 T helper cells. The IFN-γ response is suppressed, IL-10 and Th2-related antibody IgE are elevated, while IL-4 production remains normal in weaned mice with experimental malnutrition.\textsuperscript{64} However, these findings should not be interpreted that PEM generally favors Th2 responses. On the contrary, PEM seems to alter the immune response, thereby preventing any type of protective immunity.

Vitamins, trace elements and minerals comprise a group of nutrients that support virus-host immune responses. They can regulate and function on innate immune cells, including neutrophils, natural killer cells, monocytes, and macrophages.\textsuperscript{58} They also contribute to the production of pro-, and anti-inflammatory cytokines, responses to inflammation, reductive-oxidative hemodynamics of adaptive immunity responses,\textsuperscript{7} as well as the interaction with the presenting viral antigens. For example, pathogens are the common pathophysiological cause of certain infectious diseases, such as viral hepatitis. DCs rely on retinoic acid to perform their antigen presentation function and induce naive T cells to differentiate into T regulatory cells.\textsuperscript{65} During the infection process, Vitamin A produced by DCs is involved in the metabolic pathway that facilitates the differentiation to Th1 T cells and induction of pro-inflammatory cytokines. In T cells, vitamin D inhibits T cell proliferation and effector functions of both CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells by inhibiting the production of IL-2 and IFN-γ. Vitamin K also is vital in preventing oxidative stress and inflammation-induced host damage.\textsuperscript{66}
Vitamin K has been shown to have anti-inflammatory properties by down-regulating the pro-inflammatory cytokines TNF-α, IL-1β and NF-κB mediated by Gla-rich proteins. Derivatives of vitamin K can inhibit the proliferation response of activated T cells and induce apoptosis. However, there remains concerns about the standards used to provide vitamins and other micronutrients to vulnerable patients and populations.

For minerals, calcium is involved in events related to the recognition of pathogens by antigen presenting cells, and it plays a role in the intracellular signal transduction of immune cells such as macrophages and lymphocytes. Magnesium has a regulatory function in immune-inflammatory response and antagonizes the effect of calcium. Moreover, magnesium can change the direction of metabolism as its concentrations are strictly regulated. It has been proven that calcium receptor blockers can prevent lipopolysaccharide-induced transcription and the release of IL-1β, IL-6 and TNF-α, while extracellular magnesium shows a regulatory effect. Phosphorus plays a basic role in immune responses, during which phosphorylation and dephosphorylation reactions occur in the process of intracellular signal transduction, which is essential for achieving all immune functions. A number of studies in different species have shown that dietary phosphorus plays a vital role in the proper immune response during infection (especially for the adaptive immune system) and the maintenance of a stable gut microbial ecosystem to resist potential pathogens. Sulfur is a component of the sulfur amino acid glutathione (GSH), homocysteine and taurine, which are the main end-products of the sulfur amino acid metabolism and play an important role in various mechanisms of the immune response.

It has been evidenced that trace elements are significant in the immune response to infectious diseases. Selenoprotein is involved in macrophage activation and immune regulation, therefore selenium supplementation may be related to the enhancement of human and animal immunity and leukocyte function. Insufficient iron supply is the most common trace element deficiency in the world, affecting approximately 50% of the world’s population, mainly infants, children and women of childbearing age. Iron is essential for both hosts and their pathogens. For example M. tuberculosis, an intracellular bacterial pathogen, has the ability to obtain iron from the host, while the host attempts to inhibit the growth of bacteria by withholding iron. Iron deficiency is related to impaired cell-mediated immune function, reduced interaction with neutrophils and decreased bacteria and myeloperoxidase activity, thus, iron supplementation in infectious diseases is a matter of concern.

Zinc deficiency has been shown to have an effect on B cell lymphogenesis and can
induce effective thymic atrophy, which subsequently leads to reduced peripheral blood T lymphocyte numbers in mice and humans.\textsuperscript{79} Inadequate zinc supplies prevent the liver from properly releasing vitamin A, which has been linked to growth retardation, malabsorption syndrome, fetal loss, neonatal death and congenital malformations, resulting in a higher susceptibility to severe forms of disease.\textsuperscript{80} It has been found that zinc concentrations in the blood of patients with tuberculosis, Crohn's disease, diarrheal disease, and pneumonia are critically low.\textsuperscript{81} Thus, zinc supplementation may serve as a protective component in diseases related to multiple pathogens.\textsuperscript{82}

Some nutrients, such as essential amino acids and various phytochemicals that include flavonoids, carotenoids, lycopene, and dietary fibers, are classified as conditionally essential nutrients because they are critical to various functions during diseases or defined metabolic conditions. Glutamine has been widely studied as an amino acid because it is an immuno-nutrient and is considered an essential amino acid for patients suffering from hypercatabolism.\textsuperscript{83} Glutamine has shown to be a preferred source of energy for intestinal cells; therefore, it can facilitate the digestion, utilization and absorption of other nutrients and maintain the activity of intestinal cells during infectious diseases, including bacterial,\textsuperscript{84,85} viral\textsuperscript{86} and protozoal infections,\textsuperscript{87} and their treatment.

**New paradigms on the research horizon**

Nutrition research has evolved from epidemiological and physiological research to the identification of molecular mechanisms of nutritional effects and responses. In previous studies, macronutrients and micronutrients were usually regarded as energy or cofactor fuel, while nowadays they are considered to be effective signaling molecules that can affect gene expressions, production of proteins and metabolites. Knowledge on the molecular effects of nutrients has been greatly promoted by high-throughput technologies, including transcriptomics, proteomics and metabolomics. Therefore, research paradigms in basic and applied research in the field of infection and nutrition are constantly changing.

**Systems biology and nutrition**

Systems biology is a comprehensive methodology in which all the cell reactions can be identified by high-throughput technologies, such as proteomics, metabolomics, transcriptomics, or different techniques that are incorporated to comprehend the wide image of homeostasis in the entire organism. The nutritional methods of systems biology can help us study the complex interplay of diet, genes, and epigenetic factors
on the homeostasis of the entire human organism. The development of systems biology methods has been greatly facilitated by high-throughput "omics" techniques. The identification of biomarkers helps us further understand the nutritional processes, which in turn can lead to the development of new intervention strategies for the entire organism. This will prompt a superior comprehension how disease and dietary reactions affect our lives and health.

Nutrigenomics and nutrigenetics

Nutrigenomics is a method to help us understand the mechanisms by which nutrients or diet regulate the expression of genes or proteins, while nutritional genetics studies the mechanism by which genetic background modulates the nutrients or dietary response. Zinc, copper, iron and other trace elements play important roles in modulating the immune system and antioxidant properties. These micronutrients can regulate the expression of many genes, and genetic variability between individuals can also affect the absorption of micronutrients. Therefore, it is possible to directly target the activation and regulation of immune pathways by identifying the specific mechanisms by which individual nutrients affect the immune system.

Nutrigenetics is a study of the effect of genetic variations on nutrient-gene interactions. Due to genetic variation, the needs of nutrition and nutritional responses vary from person to person, and single nucleotide polymorphisms (SNPs) are among the most commonly studied variations. Some genetic polymorphisms can affect an individual’s nutritional and metabolic status, such as folate metabolism, iron homeostasis, bone, lipid metabolism and immune function. Although genotype may affect the interaction between nutrients and genes, in most cases, there is little evidence that nutritional intervention can change the interaction between nutrients and genes to benefit health.

Pathogen virulence and the nutritional status of the host

Beck et al. studied a murine respiratory infection model using benign Coxsackie virus, which produces a self-limiting mild respiratory infection in nutrient-rich mice. However, when infecting selenium-deficient mice, the same virus becomes virulent. Subsequently, mutant viruses isolated from selenium-restricted hosts became also lethal when passed to selenium-rich animals. The findings suggested a new trend in nutrition: infection-micronutrient axis of the individual can determine the virulence of pathogens in the entire society.
Dietary pattern for infectious disease resistance

The extent to which dietary patterns themselves influence the risk of disease was first discussed in the *Diet and Health* journal of the National Research Council in the 1980s. Since then, dietary guidelines for long-term health and prevention of chronic diseases have been continuously developed. The paradigm of interactions between food, diet and acute illness are not well studied. However, in the case of infant feeding, it has been documented that there is a strong link between total or major consumption of breast milk and the protection of infants and toddlers from infection. In addition, the central role of dietary changes in shaping the microbiome has been identified. For example, decreased abundance of *Bacteroides* and related *Escherichia coli*, and increased levels of *Prevotella* were observed in people who switched from a western diet to a vegetarian lifestyle. As a result, these subjects were less exposed to endotoxins that cause inflammation.

Coronavirus disease 2019 (COVID-19) is a global public health problem caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which poses a major threat to global healthcare. Currently, there is no approved treatment for COVID-19, but preventive strategies such as preventing social interactions, staying away from public places and wearing masks are the most effective ways to resist COVID-19. Recent evidence suggests that nutritional supplementation can play a supporting role in patients with COVID-19. The administration of nutrients higher than the recommended daily dose may have beneficial effects, which may reduce viral loads of SARS-CoV-2 and hospital stay. Therefore, during COVID-19, adequate vitamin C, D, and E levels are essential to reduce the burden of symptoms and shorten the duration of respiratory infections. Studies also support the role of minerals such as zinc, because of their antiviral properties that can boost the immune response and inhibit viral replication. Therefore, to ensure the proper functioning of the immune system, it is necessary to get enough vitamins and minerals from the diet.

Gut microbiome, probiotics and infections

The gut microbiota is a metabolic powerhouse influencing many physiological processes. It may play key roles in the occurrence and development of major diseases such as cancer, metabolic diseases and infectious diseases. Microbes in the gastrointestinal tract also exert a significant impact on innate and adaptive immunity, metabolism, intestinal growth and nutrition. Given their diverse roles, it is highly likely that gut microbes also play a key role in nutrition-infection interactions in humans.
It is widely believed that gut microbes influence metabolic activities, such as digestion and the production of bioactive substances. The colon microbiome uses butyrate as its sole source of energy and acetate as a substrate for cholesterol synthesis. Gut microbes are also involved in the synthesis of amino acids, the biotransformation of bile, and the production of various vitamins.

The intake of probiotics in the diet allows them to interact closely with the intestinal mucosa and mucosal immune system and regulate the immune and inflammatory response of the intestine. The effect of probiotics on the mucosal system is not limited to the intestinal tract, but also has a positive effect on the systemic immune system. Some studies have shown that probiotics can induce pro-inflammatory cytokines to promote anti-infective immune responses, and they can also induce anti-inflammatory cytokines to suppress inflammatory hyperactivity and maintain homeostasis. It is worth noting that based on mixed results and that the consumption of probiotics can induce IFN-α and reduce TNF-α and IL-2, the effect of probiotics on cytokine production may be strain-dependent. Furthermore, probiotics have been shown in clinical applications to enhance the host's resistance to infections.

Conclusions

Undernutrition synergistically interacts with infections, while infections exert a major negative impact on dietary patterns and nutritional status. In addition to single nutrient deficiency, global malnutrition is also a major contributor to more serious and even fatal infections. Interaction between infections and undernutrition is diverse, and there is a great potential in preventing and controlling infections by optimizing nutritional status.

How to cite this article: Yang F, Yang Y, Zeng L, Chen Y, Zeng G. Nutrition Metabolism and Infections. Infect Microb Dis 2021;00:00-00. doi:10.1097/IM9.0000000000000061
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Figure Legends

Figure 1. The cycle between nutrition and infection. Undernutrition and overnutrition affect the immune system and make individuals susceptible to infectious diseases. Infections adversely influence nutritional status.