CURRENT CONCEPTS REVIEW

How to Boost Your Immune System Against Coronavirus Infection?

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Abstract

New emerging viruses like coronavirus 2019 (COVID-19) infections are always frightening. We know little about their transmission, behaviors, clinical manifestations, and outcomes. There is no vaccine or therapeutic strategies to deal with these infections yet. In this situation, preventive measures may be promising. Hand hygiene is a very important issue in preventing viral infection; however, there are other entities that can enhance the immune response and help in infection prevention. Herein we review some measures for boosting the immune system.

Level of evidence: Moderate

Keywords: COVID-19, Immune system, Viral infection

Introduction

Our immune system protects us against foreign invaders including different microbial infections, malignant cells, and anything other than us. The coronavirus 2019 disease (COVID-19) is a new emerging viral infection that caused approximately 3000 deaths worldwide between Januarys to March 3, 2020. In a study on 7736 admitted patients with COVID-19 in China, the median age of patients was 47 years old and only 0.9% of the patients were under 15 years old. The most common symptoms were fever (43.8% on admission -with median temperature of 37.3 degree Celsius- and 88.7% during hospitalization), cough (67.8%), fatigue (38.1%), sputum production (33.7%), shortness of breath (18.7%), sore throat (13.9%), nausea or vomiting (5.0%) and diarrhea (3.8%). Laboratory finding on admission were lymphocytopenia in 83.2%, thrombocytopenia in 36.2% and leukopenia in 33.7% of patients. This novel virus can cause severe respiratory compromise. About 6.1% of the patients in the above-mentioned study required mechanical ventilation during admission (1). The emergence of covid-19 depends on the interaction between the virus and the host immune system. Viral factors include virus type, mutation, viral load, viral titer, and viability of the virus in vitro. Host immune system factors are genetics (such as HLA genes), age, gender, nutritional status, neuroendocrine-immune regulation, and physical status (2). Viral transmission can occur via different ways most known are droplet and contact routs. Hand hygiene, Hygienic education about social distancing and appropriate use of mask are the best ways to interrupt transmission cycle of respiratory viruses (3). We know little about the protective measures against this virus (1). Nowadays there are some questions about how to boost our immune system against this new onset virus.

How COVID-19 interacts with host cells?

During the past 20 years, several corona viruses have caused several outbreaks of severe respiratory diseases in humans. Different coronaviruses need receptors on host cell surface that mediate virus cell entry. The known

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host cell receptors for beta coronaviruses are dipeptidyl peptidase 4 (DPP-4) for the Middle-East respiratory syndrome related to coronavirus (MERS-Cov) and angiotensin converting enzyme 2 (ACE2) for severe acute respiratory syndrome related coronavirus (SARS-Cov) and even the recently emerging virus in China in January 2020. ACE2 is an ecto-enzyme that converts angiotensin 2 to angiotensin. The ACE 2 function in lungs is unknown (4, 5).

ACE2 is expressed on airway epithelium, lung parenchyma and intestine. The expression of this receptor is correlated with the differentiation state of cells. Undifferentiated cells have lower ACE2expression. SARS-Cov preferentially infects well differentiated ciliated epithelial cells that express ACE2 (5).

Dendritic cell specific intracellular adhesion molecule 3(ICAM-3)-grabbing non integrin (DC-SIGN) (CD209) and DC-SIGNR (CD209 L) can aggravate SARS-Cov infection in ACE2 expressing cells. DC-SIGNs are one of the innate pattern recognition receptors (PRRs) in human that are primarily expressed on immature dendritic cells. These receptors recognize fucose and mannose of a wide range of microbes. They may have immune regulatory roles and induce IL-10 based response and suppress the production of pro inflammatory cytokines (5-8).

In productive infection in epithelial cells of conducting airways, SARS-Cov released from apical pulmonary epithelium can reach gastrointestinal tract by mucociliary clearance. Gastrointestinal epithelial cell infection may induce diarrhea, a remarkable and important clinical manifestation in SARS patients (5).

There is a limited number of naïve T cells specially CD8+ cytotoxic T cells in the elderly. This population have age associated attrition of naïve B and T cells, more memory cells and aged and end stage CD8+ cytotoxic T cells. In children before puberty there are large repositories of progenitors of naïve B and T cells, that are released into the blood stream and naïve T cells reach the thymus and undergo processing there. After thymus degeneration, the number of these cells would increasingly diminish. Therefore, elderly is more prone to severe acute infections (9).

Vitamin D

Antimicrobial peptides (AMPs) are secreting pattern recognition receptors with microbicidal properties. AMPs are fast acting and, when expressed on epithelial cell surface, can create a microbicidal shield against connection and invading of microbes. AMPs have anti-microbial properties against a wide range of bacteria, fungi, chlamydia, and encapsulated viruses. Two of the important AMP categories in human include defensins and cathelicidin LL-37. Epithelial cells and neutrophils secret cathelicidin LL-37. Cathelicidin LL-37production is induced by vitamin D. Therefore, this vitamin can influence microbicidal protection in skin and circulating phagocytic cells. It can explain why some certain human infections like mycobacterium tuberculosis are more prevalent in population with insufficient vitamin D (6, 10-14).

There is strong clinical correlation between vitamin D status and the incidence or severity of some immune regulated disorders including infectious diseases, cancers, and autoimmune disorders. Some analyses have revealed that administration of vitamin D supplement (specially daily or weekly rather than large single or monthly bolus dose) can decrease respiratory infection risk in population with vitamin D level below 25 ng per ml (15-18).

In many countries staying at home is advised as a preventive measure against COVID-19 which causes lower sun exposure and increased vitamin D deficiency especially in winter when there is a tendency towards reduced serum vitamin D due to limited sun exposure (19). Therefore, vitamin D supplement could be effective against the new emerging virus.

Exercise

To date there is no known vaccine for prevention of novel coronavirus COVID 19. No effective treatment has yet been found for the respiratory distress syndrome caused by this virus. Therefore, governments in many countries recommend some preventive measures including staying at home and limiting contacts with other people. They close schools and recommend people to minimize out of home activity. These can reduce physical activity in a large population and sometimes worsen the underlying conditions like preexisting cardiopulmonary disorders (20-22).

On the other hand, Exercise with medium intensity can promote immune system against different infections and cancers. It can increase lymphoproliferative responses; increase the number and function of natural killer (NK) cells; and decrease CD4 + T cells to CD8+ T cells ratio (23). We can conclude that sedentary lifestyle can predispose people to various diseases including viral infections.

Therefore, there is strong recommendation for continuing physical activity at home. Moderate physical activity for about 20 to 30 minutes per day can have protective effects on overall health, decrease depression and anxiety, and improve immune system functions.

On the other hand, prolonged vigorous physical activity may also predispose people to some infectious diseases (20).

Diet

Malnutrition is one of most common etiologies of secondary immune deficiency. Appropriate diet is very important in immune system development and maintenance. Protein-energy malnutrition can induce abnormal thymus degeneration and drop in T cells count particularly CD4 + T cells. In addition to abnormal function of T cells, an impaired function in innate immunity including NK cells and complement function also occurs in malnutrition. Malnourished patients are more susceptible to mycobacterium tuberculosis, pneumocystis jiroveci pneumonia (PJP), and dermal bacterial infections. Diarrhea is more frequent and prolonged in malnourished patients compared to the normal population (23).

It has been proven that the complex, integrated immune system requires adequate amounts of multiple micronutrients including vitamins A, D, C, E, B6, and B12 as well as folate, zinc, iron, copper, and selenium, which play essential and synergistic roles at every stage of the immune response. While certain populations have insufficient dietary micronutrient intakes, conditions with increased requirements (e.g., infection, stress, and pollution) result in additional decrease in stores within the body. Supplementation with multiple micronutrients with immune-supporting roles may modify immune function and decrease the risk of infection. Micronutrients with the strongest evidence for immune support include vitamins C and D and zinc (24).

There is low-to-moderate evidence that vitamin A supplementation in children (50,000–200,000 IU every 4–6 months) can reduce the incidence of diarrhea and measles (25). However, other analyses in children did not show that vitamin A significantly decreases the incidence of pneumonia or lower respiratory tract infections, reduce mortality, the duration of illness, and hospital stay. It could have potential effect on novel coronavirus (25, 26). To the best of our knowledge, no study has yet assessed the relationship between coronavirus infection and symptom severity and vitamin A. in two animal studies low serum vitamin A was found to result in increased severity of bovine and chicken coronavirus infections (27, 28).

Vitamin C supplementation can significantly reduce the risk of pneumonia, the severity of disease and the risk of death in adults and children, particularly when dietary intake was low (low-to-moderate quality studies) (29). In three human trials, vitamin C administration was found to be useful in reducing the symptoms and duration of common cold (18). Based on the immune modulatory effects of vitamin C and its effects on critically ill patients, a course of high dose vitamin C has been hypothesized to be effective in patients with severe acute respiratory syndrome due to COVID-19 but no documentation has yet been published in this regard (30).

Similar to vitamin C, vitamin A can also act as a scavenger for free radicals and act as an antioxidant. It was previously shown that vitamin A deficiency can increase the severity of coxsackievirus B3 and increase the severity of bovine coronavirus infection in calves. Selenium is also responsible for antioxidant activities besides vitamin A. It can be hypothesized that antioxidants will be needed by the body at least after controlling the severe symptoms but there is a need for further studies to support these hypotheses (18).

The incidence of lower respiratory tract infection (RTI) reduction after zinc supplementation in children (20–140 mg/week) is supported by low-to-moderate evidence, but this outcome depends on the criteria used to define lower RTI; more reduction was detected using definite clinical criteria, compared with those based on caregiver reports or "non-severe pneumonia" from the World Health Organization (18, 31). It was previously shown that zinc ion alone or its conjugates inhibit the activity of papain-like protease 2 (PLP2) in the SARS-COV virus. The PLP2 enzyme is responsible for the production of a nonstructural polypeptide that is believed to affect virulence and pathogenesis of SARS-COV. It was also suggested that high dose zinc administration might reduce SARS-COV infection in vivo (32, 33).

Studies in children have demonstrated that multiple multivitamin and multi mineral (MMN) supplementation may reduce the risk of infection and reinfection from helminths (34). Low-to-moderate evidence studies have shown that MMN supplementation significantly reduced the number of infection episodes in younger adults (35). There are some clinical trials that representing flavonoids in citrus or buds of Rosa damascene as potentially suppressors of angiotensin converting enzyme (ACE) activity. Rosa damascene may be used to flavor foods or as herbal tea and so on. Beside cough relief effects, citrus fruits contain flavonoids that may bind to ACE 2 and also prevent cytokine storm. However further researches are needed (36, 37).

Probiotic/prebiotic

Probiotics are live microbial dietary supplements that can help balance intestinal microbial population and consequently improve health. In 2016, FDA stated that "To date, the U.S. Food and Drug Administration has not approved health claims for any probiotic" (35, 38, 39).

Probiotics can enhance IgA –secreting cells in respiratory and gastrointestinal mucosa. This secreted antibody provides immunity against some pathogens. They have immunomodulatory effects on dendritic cells and T lymphocytes. These food supplements increase short chain fatty acids (SCFAS) with anti-cancer, anti-oxidant, and anti-inflammatory effects (40).

In a recently performed meta-analysis, limited data on strain specific preventive effects have been proposed for probiotics, however some strains including Lactobacillus rhamnosus GG could modestly reduce the duration of respiratory infection symptoms (41, 42). Another Cochrane review in 2015 on 13 randomized clinical trials revealed that probiotic was better than placebo in reducing acute upper airway infection episodes and even the mean duration of each episode, however this observation had low to very low quality of evidence (42).

Due to strain specific effects of probiotics, different studies were reviewed in [Table1].

In fact, to date there is paucity of strong evidence for the efficacy of probiotics in prevention of acute respiratory infection (43).

Stress

Psychologic stress can induce immune suppression in healthy people. Researches have revealed that psychologic stress can shift Th1 cytokines toward Th2 cytokine and decrease the activity of natural killer (NK) cells. Furthermore, decreased CD4+ to CD8+ T ratio and impaired response to vaccines and low antibodies titer occur in stress (44). As a result, stress can increase the risk for upper respiratory tract infections and relapses of mucosal herpes (23). In a cohort study published in 2018, psychological distress and infectious diseases mortality were assessed in a large population. Results showed that the risk of infectious diseases, especially viral infections,

Table 1. Some of most recent studies about probiotic strains that have been used in respiratory infections

study	population	Probiotic strain have used	Route/ dose/ duration	conclusion
Li KL et al.(43)	One hundred twenty children with RTI/ thirty healthy control	Bifidobaeterium tetravaccine tablets (Live)	Oral/2 months	Reduction of RTI
Chong HX et al(44)	109 adult	Lactobacillus plantarum DR7	12 weeks	DR7 alleviated the symptoms of URTI
Campanella et al. (45)	Frothy subjects with a recent clinical history of RTI	Streptococcus salivarius K12, Streptococcus salivarius M18, Lactobacillus reuteri, Lactobacillus sakei, and Lactobacillus paracasei	PO/ tds in first month and then qd for two month	positive effects in prevention and reduction of respiratory tracts infections incidence
Murata et al.(46)	241 healthy young adults	*Lactobacillus paracasei* MCC1849	once daily for 12 weeks	potential to improve resistance to common cold infections in susceptible subjects
Wang et al.(47)	One hundred ninety-six nursing home residents aged 65 and older	Lactobacillus rhamnosus GG	2 capsules daily for 6 months	larger trial is warranted to determine whether probiotics reduce influenza and other respiratory virus infections in residents
Jespersen et al. (48)	1104 healthy subjects aged 18-60 y	≥10(9) colony-forming units of L. casei 431	Milk drink for 42 days	Reduced the duration of upper respiratory symptoms.
Turner et al.(49)	One hundred fifty two healthy volunteer how challenged by RV-A39	Bifidobacterium animalis subspecies lactis Bl-04	28 days oral	Did not influence lower respiratory inflammation following rhinovirus infection, subjective symptom scores, or infection rate.

were higher in psychological stress (45).

Discussion

While the most important preventive issue against microbial agents is hand hygiene, it is also likely that some other measures can boost immune system. These days, because of the new emerging coronavirus that can cause severe respiratory distress syndrome, there are concerns about different methods that can help immune system deal with this virus. We concluded that some dietary supplements including vitamin D, vitamin C and zinc as well as balance in macro/micro nutrients can improve immune functions especially if there is preexisting deficiency. Psychological stress, poor sleep, and sedentary life style can attenuate the immune system. There is no strong evidence to recommend probiotic/ prebiotic for prevention of viral infections.

Conflict of interests: None.

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