Review Article

IMMUNE COMPETENCY IN A CORONAVIRUS ENVIRONMENT

ABSTRACT

Coronavirus disease 2019 [COVID-19] belongs to the class of coronaviruses - one of a group of RNA[ribonucleic acid] viruses that infect animals and humans, primarily the upper respiratory and gastrointestinal tract and these are zoonotic, meaning that they can be transmitted between animals and people. The elderly and immunocompromised persons were considered more vulnerable to severe infections of such respiratory tract diseases but the spread of this recent pandemic raises fear that immunodeficiency is not quite the main factor. Vaccines and treatment options are currently being investigated and deployed but there is no definitive evidence that certain medications are effective with regard to preventing illness or transmission of the COVID-19. As is wont in a pandemic of this nature, claims are being made that nutritional regime which is of value in boosting the immune system will either prevent such infections as COVID-19 or enhance recovery. There are also claims that some people are more genetically predisposed to the infection than others. This review brings to the fore information that will clear speculations and make sense of confusing and often conflicting scientific data about the role of immune competence in the prevention, transmission of and recovery from COVID-19 and other similar infections. This involved a Google search for keywords like immunecompetence, influenza, coronaviruses, COVID-19, Nutrient value, Vitamin C and Vitamin D, in all available publications in the public domain without regard to the age of publication. This broad search spectrum is intended to capture all the historical effort to understand the role of immune function in the treatment and recovery to the influenza virus which seems to be the primogenitor of COVID-19.

Keywords: Immune competence, COVID-19, Nutrient value, Vitamin D

INTRODUCTION

Coronaviruses are zoonotic pathogens that gain the ability to cross the species barrier especially from animal to human [1]. They are positive-stranded RNA viruses. The first human coronavirus appeared in reports in the mid-1960s and was isolated from persons with common cold [2, 3]. The risk of initial infection is higher in settings where persons have close and prolonged contact with infected animals [4, 5]. Their widespread prevalence, extensive host range, various disease manifestations and increased frequency of recombination events all underline their potential for inter-species transmission [4]. In humans, Coronaviruses are associated with common cold symptoms [6]. Younger children and the elderly were considered more vulnerable to lower respiratory tract infections [7]. But the signs and symptoms of COVID-19 in children are similar to adults with more positive outcomes [8, 9]. Severe lower respiratory tract infection had much earlier been described in immunocompromised patients [10,11], but a case of acute respiratory distress syndrome was first reported developed in a healthy adult with no comorbidities and a strain of coronavirus identified as the only causative agent [12]. This present coronavirus disease outbreak, caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], was first reported from China in December, 2019 [13]. It presents with illness ranging from the common cold to more severe diseases [14]. Atypical presentations have been described, and older adults and persons with medical comorbidities may have delayed presentation of fever and respiratory symptoms [15, 16]. The cluster was initially reported on 31 December 2019, when the World Health Organization [WHO] China Country Office was informed about the disease outbreak. The evidence is highly suggestive that the outbreak is associated with exposures in one seafood market in Wuhan. Infection is thought to be transmitted via respiratory droplets, which can remain active and contagious, either airborne or on any inanimate object [as a towel, money, clothing, dishes, books or toys etc.] that can transmit infectious agents from one person to another, for several hours [17]. Initial infection and viral replication occur locally in tracheal and bronchial epithelial cells [18]. Common signs of infection include respiratory symptoms, fever and cough, shortness of breath and breathing difficulties. In more severe cases, infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death [19]. Since the outbreak, this new virus has shown to be very contagious as it has quickly spread globally [20-22]. WHO had earlier declared this outbreak a Public Health Emergency of International

Concern [23] and though scientists are working round the clock, no safe and definitive treatment or vaccine has been determined with 100% efficacy. Though some vaccines have been deployed and other vaccine candidates still at the trial phase, major efforts at eradication are still targeted to the prevention of person-to-person transmission. Standard recommendations to forestall infection spread include regular hand washing, wearing face masks, covering mouth and nose when coughing or sneezing and shunning of close contact with people especially those exhibiting symptoms of respiratory illness such as coughing and sneezing [23].

The human immune system has the function to defend against different types of pathogen. Host immune responses play a major role in clearance of viral infections from the body, and may limit long-term expression and clinical efficacy of viral vectors [24].The ability of a human host to produce a normal immune response following exposure to an antigen is determined by nutrient intake value and genetic environment among other factors [25, 26]. All organisms have developed complex immune systems that protect against infectious diseases. To function properly, the body's immune system must be able to recognize foreign intruders [i.e. pathogens such as bacteria, viruses, and parasites] and send protectors to fight the incursive pathogen. Immunity in the mammalian host has developed as a structured network of interacting cells and cell products that coordinately recognize and respond to foreign antigenic stimuli [27]. The quality of this response is dictated by the nature of this antigen, as well as by the diverse biologic, immunologic, and genetic constitution of the immunized host. The word "Corona", in Latin, meaning crown, is taken from the fact that the virus is adorned with an outer layer of protein covered in spikes, like a crown. These spikes help the virus attach to target cells. This tiny piece of genetic material wearing a lipid coat and a protein crown is thought to evolve to bypass and evade the defense systems; the immune systems, in turn, learn to discern and deter them. Though the research community is fast learning about immunity to COVID-19, knowledge of similar respiratory viruses is being applied to predict and manage transmission and outcomes from this infection [13].

The role of Immune competence

Immune competence, Immune competency, immunecompetence or immunocompetence is the ability of the immune system to produce an appropriate immune response following exposure to an antigen. Immunecompetence is the opposite of immunodeficiency or immuno-incompetent or

immuno-compromised [where the immune system is not working as it should be]. Immunecompetence is a word used to describe the overall level of function of the immune system and is based on a complex genetic trait [25] and nutritional status [26] among other factors. The immune system of an organism provides protection against parasites, parasitoids and pathogens, thereby strongly influencing its fitness [28]. To adapt to novel threats, the immune defense of the host evolves continuously, causing counter adaptations in the intruder's virulence. Both the innate and acquired immunity may be affected in these processes. As a consequence, even comparatively simple immune systems show considerable variation in the usage of effector mechanisms. The strength of the immune system and the intruder's virulence will affect the strength of species interactions [28].

Innate versus adaptive immune competence

The immune system has many different defense mechanisms and responses to recognize and neutralize pathogens, and can respond to pathogens in two different ways: innate and adaptive immunity [29]. Innate immunity functions in conjunction with adaptive immunity and is characterized by rapid reaction to hostility, irrespective of previous stimulus, being the organism's first line of defense. Its mechanisms include physical, chemical and biological barriers, cellular components, as well as soluble molecules [30]. The adaptative immune response includes both cell-mediated [mediated by T cells and natural killer: NK cells] and humoral immunity -mediated by B cells [29]. This biologic system provides a defense from foreign, invading organisms; promoting protective immunity while maintaining tolerance to its own self.

The immune system consists of thousands of different components, and the application of systems biology [29, 30] leads a better understanding of the interactions between these during immune health and disease. For so many years the study of twin pairs has provided a powerful means for separating heritable from non-heritable influences on measured traits [31]. These studies have been used to understand autoimmune diseases, vaccine responses [32], serum cytokines [33], or the frequencies of major immune cell populations [34, 35]. The conclusion from most of these studies is that both heritable and non-heritable factors impart to the ensuing phenotype.

Recovery and deaths from COVID-19 have shown that some people seem to handle the infection better than others. This has promoted the belief that innate immunity has a major role to play but a previous analysis of immune function on blood samples from 105 sets of healthy twins seems to have concluded to the contrary [36]. The investigators measured immune cell populations and their chemical messengers before and after participants received the seasonal influenza vaccination. They discovered that differences in three out of four of the measured parameters depended less on genetics than on environmental factors. Evaluated by antibodies developed against the injected material they conclude that genetics had almost no effect on how well individuals reacted to the influenza vaccine [36]. Also among identical twin sibs, immune system features differed more within older twin pairs than in younger sets. This study spotlights that innate immunity has a lesser role to play than environmental influence on so many components of immunity in infection and transmission of a coronavirus strain. A recent study indicated that the primary SARS-CoV-2 infection could protect from subsequent exposures [37], which have the reference of prognosis of the disease and vital imports for vaccine design. Among 176 patients who had had severe acute respiratory syndrome [SARS], SARS-specific antibodies were maintained for an average of 2 years, and a significant reduction of immunoglobulin G–positive percentage and titers occurred in the third year. Thus, SARS patients might be susceptible to reinfection >3 years after initial exposure [38].

The role of innate and adaptive immunity in COVID-19 infections

For COVID-19 to gain access to the human body it has to first pass through the biological barriers of immunity. On getting inside the cytosol, it uses proteins, lipids and nucleotides to replicate its own copies. Having attached to the target cell's membrane the virus fuses with the cell and releases the virus genome to invade target cells, remove its coat and deploy its RNA. The virus initially uses the materials of the cell to replicate quickly [39]. Once immune cells detect the presence of the viruses, counteracting antibody proteins are released to stick to the virus-spike proteins, and forestall attachment to the target cells. This subsequently lead to signaling of the cytotoxic T-cells which detects peptide fragments of virus displayed on the infected cell surface and kills the infected cells thus reducing the viral load [40]. Antiviral T-cells often take several days to expand and antibodies to be generated and memory cells ensure the

detection and elimination of the same virus on reinfection [41]. Consequent to the novelty of the Sars-Cov-2 there exist no proven protective immunological memory in the new infections.

Person-to-person transmission of COVID-19 occurs from persons with no presentation of evident symptoms through droplets that can be coughed or sneezed to a distance of up to two meters **[**42-45]. These droplets can survive on surfaces for several hours which then serve as fomite that enables pick-up by a new host. Based on these, a healthy immune system is supposed to be able to control infection from COVID-19 in a couple of weeks while immunocompromised persons are thought to be more vulnerable especially those with comorbidities [46, 47], but the mechanisms behind these are not conclusive as it appears. Antiviral antibodies emerge as early as three to four days after virus detection, which is supposed to be protective against future reinfection [27]. Serological tests for antibodies in the blood are helping to identify people who are immune to infection for a period of time [48]. Antibodies to other coronaviruses have been seen to last from one to three years but this is yet to be determined for COVID-19 [38]. Vaccines have been discovered to eradicate infections of some previous viral diseases like smallpox and this is hoped for the COVID-19 strain of coronavirus based on the numerous and ongoing research in that direction.

Nutrient value and immune competence

The immune system is deprived of the components needed to generate an effective immune response when there is inadequate nutrition [26]. Vitamins, minerals, trace elements and other crucial components in the diets are used in maintenance of immunocompetence. These include vitamin A, beta-carotene, folic acid, vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, riboflavin, iron, zinc, and selenium [49, 50]. Lipids for instance exert profound effects in the modulation of the immune system as the fatty acid composition of lymphocytes, and other immune cells, are altered according to the fatty acid composition of the diet. Thus, an immunomodulatory role, which could be used in the management of some diseases involving inflammation processes, has been suggested for dietary lipids [51]. Deficient nutrients can be added to diet for the restoration of immune function and resistance to infection, but excessive amounts of some nutrients can also impair immune function [52]. Though all existing vitamins have roles to play in the maintenance of the integrity of the physiological system, two of them have been more taunted over the years

and will be mentioned further about their roles in immune function and the treatment of coronaviruses; these are vitamins C and D.

Role of Vitamin C in immunity

Vitamin C has been long promoted by many a scientist since it was isolated in the 1930s but others consider its promotion a hoax based on available scientific data. Nobel laureate Linus Pauling in 1970s strongly promoted vitamin C which he concluded from placebo-controlled trials that it would prevent and alleviate the common influenza infections [53, 54]. He went on to recommend unprecedented high doses of vitamin C for the prevention and treatment of diseases [53]. A review of placebo-controlled trials testing 0.2 g/day or more of vitamin C reveals that regular ingestion of vitamin C had no effect on common cold incidence in the ordinary population, based on 29 trial comparisons involving 11,306 participants [54]. It was found out that regular supplementation with vitamin C had a modest but consistent effect in reducing the duration of common cold symptoms based on 31 study comparisons with 9745 common cold episodes [54]. In five trials with 598 participants exposed to short periods of extreme physical stress vitamin C halved the common cold risk [55]. Therapeutic trials of high doses of vitamin C, starting after the onset of symptoms, showed no consistent effect on the duration or severity of the common cold infections [55]. Low levels of vitamin C have been found in patients with Covid-19 associated acute respiratory distress syndrome [56]. Recent research indicate that patients with pneumonia and sepsis have low vitamin C status and elevated oxidative stress and that administration of vitamin C to patients with pneumonia can decrease the severity and duration of the disease [57]. Critically ill patients with sepsis have been found to require intravenous administration of great amounts of vitamin C to normalize plasma levels, which is thought to reduce mortality [58]. Based on existing knowledge, routine vitamin C supplementation is often recommended, though not yet completely justified in the prevention and treatment of coronavirus infections; but intravenous administration of great amounts of vitamin C to Covid-19 infected patients is thought to reduce mortality to the disease [53-58].

Understanding Vitamin D as a dominant player

Sufficient amounts of Vitamin D are synthesized by the body in response to sunlight when the sun’s UVB rays hit the skin and are associated with numerous health benefits. It is essential to

bone health throughout life and studies have linked adequate levels of vitamin D with a lower risk of cardiovascular, inflammatory and autoimmune diseases, certain cancers and death [59-61]. Another study found that vitamin D also affects key cells of the immune system [62]. One study focused on how vitamin D affects dendritic cells' ability to activate T cells. These T cells play a crucial role in helping to fight infections in healthy persons; but in people with autoimmune diseases, they can start to attack the body's own tissues. This study found that vitamin D caused dendritic cells to produce more of a molecule called CD31 on their surface and that this hindered the activation of T cells. They observed how CD31 prevented the two cell types from making a stable contact - an essential part of the activation process- and the resulting immune reaction was far reduced. This finding sheds light on how vitamin D deficiency may regulate the immune system and influence susceptibility to autoimmune diseases [63].

A randomized controlled trial suggests a role for vitamin D in innate immunity, including the prevention of respiratory tract infections [RTIs]. The study hypothesizes that serum 25-hydroxyvitamin D [25[OH] D] levels are inversely associated with self-reported recent upper Respiratory Tract Infections and that this association may be stronger in those with respiratory tract diseases [64**].**

Certain genetic variations increase the risk of having a lower level of vitamin D. A study of the relationship between 25 different genetic variations in seven different genes and the level of vitamin D show that some genes influence the level of vitamin D in a person's blood [62]. This study shows that some persons are genetically predisposed to lower levels of vitamin D [62]. Differences in the concentrations of circulating 25-hydroxyvitamin D are associated with a wide range of disease conditions [64-66].

Vitamin D, immunecompetence and the gene composition

The immune system has been discovered to be highly active in some people but much less effective in others indicating differences in protection against pathogens. Several factors that affect our response to viral and bacterial infections have been investigated so that we can understand why some people are predisposed to certain diseases. One study observed that the amplitude of the immune response in Africans and Europeans differed, especially in the case of genes involved in inflammatory and antiviral responses [67]. They concluded that these differences can largely be attributed to genetic variants, distributed differently among Africans

and Europeans, which modulate the expression of immunity genes. Vitamin D synthesis has also been implicated [67].

Vitamin D levels are dependent on skin pigmentation and have been shown to affect immune function. During the summer months the majority of persons in Europe and America get sufficient amounts of vitamin D from sunlight irrespective of their skin pigmentation. But during the winter months the sun's UVB rays may not be strong enough for this process to take place in some people especially those with darker skin. Consequently, Africans in Diaspora are more susceptible to vitamin D deficiency because their darker skin tone limits the penetration of ultraviolet light. This in turn reduces the cutaneous synthesis of vitamin D and as such blacks have to rely on their diet and dietary supplements to meet their need for vitamin D in these climes. Ethnic differences in the prevalence of common genetic polymorphisms are another likely explanation for the low vitamin D levels found in such Africans [68-70]. Some genetic studies associated vitamin D deficiency with several candidate genes, including the cytochrome P450, family 2, R [CYP2R1] gene; the group-specific component [GC] gene, and the 7-dehydrocholesterol reductase/NAD synthetase 1 [DHCR7/NADSYN1] gene. These genes are involved in hydroxylation, vitamin D transport, and cholesterol synthesis, respectively. One main indicator of vitamin D levels in humans is the serum concentration of the circulating metabolite, 25-hydroxyvitamin D [25[OH] D]. The association between polymorphisms in these genes and 25[OH] D levels has been previously studied in African Americans and it was found to exhibit a strong signal of association [71].

Role of Vitamin D in treatment of infections

Vitamin D had inadvertently been used to treat infections such as tuberculosis before the era of effective antibiotics. Then tuberculosis patients were sent to sanatoriums where treatment included exposure to sunlight which was thought to directly kill the tuberculosis [72, 73]. Cod liver oil, a rich source of vitamin D has also been employed as a treatment for tuberculosis as well as for generally increased protection from infections [74, 75]. Vitamin D deficiency has been recognized as a major public health issue worldwide. This condition has been linked to bone disorders such as rickets and osteoporosis [76, 77] as well as extra skeletal diseases that include cancer [60], cardiovascular disease [59] and diabetes [61]. Vitamin D deficiency is

rampant especially among the elderly in America, Europe and Asia [78-81]. Low levels of vitamin D have been associated with worsening autoimmune diseases [82] and the incidence of frequent infections especially with colds and influenza [83]. Vitamin D deficiency is not limited to bone-related diseases but is also implicated in cardiovascular disease, type 1 diabetes mellitus, several cancers, inflammatory bowel disease, and multiple sclerosis [84].
A 2017 analyses of prospective clinical trials showed that taking vitamin D reduces the odds of developing a respiratory infection by approximately 42% in people with low baseline levels of 25-hydroxyvitamin D [85]. This analysis suggests that taking vitamin D daily or weekly was more effective than larger doses taken in single or monthly boluses.
A more recent study found that monthly high-dose vitamin D supplementation does not prevent acute respiratory infections in older adults with low levels of vitamin D [86].
Presently vitamin D levels appear to play a role in COVID-19 mortality rates**.** After studying global data from the COVID-19 pandemic, some researchers have discovered that a strong correlation exists between severe vitamin D deficiency and mortality rates [87]. From this study, it was noted that patients from countries with high COVID-19 mortality rates, such as Italy, Spain and the UK, had lower levels of vitamin D compared to patients in countries that were not as severely affected. Also discovered was a strong correlation between vitamin D levels and cytokine storm -- a hyper inflammatory condition caused by an overactive immune system -- as well as a significant correlation between vitamin D deficiency and mortality [87]. Vitamin D deficiency can make people susceptible to mortality from COVID-19.

Thus, appropriate supplementation should be provided to protect vulnerable populations, such as African-American and elderly patients, who have a prevalence of vitamin D deficiency. There are three sources of vitamin D: ultra violet [UV] B radiation-dependent endogenous production, dietary supplements, and nutritional sources. The most significant source of vitamin D seems to be UVB exposure. The conversion of 7-dehydrocholesterol to vitamin D_3 occurs in the epidermal layer of skin. 7-Dehydrocholesterol maximally absorbs UVB radiation from the sun at wavelengths of ~300–325 nm, the presence of which is influenced by latitude, altitude, season, and cloud cover. For approximately six months of each year, at sea-level locations at latitudes of 45°, the UVB intensity is inadequate for vitamin D synthesis. This low intensity extends at distances further away from the equator [88].

Many other essential nutrients may aid cellular defense and repair mechanisms that would promote recovery and/or control of symptoms of disease in covid-19 infected persons [26, 49, 50, 51, and 89] but a detailed analysis of these is out of the scope of this paper.

CONCLUSION

Though recovery from the novel coronavirus infections has been correlated with the detection of immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies which signal the development of immunity no conclusive data is available to show the limit of immunecompetence in this disease infection, transmission and recovery. Nutrient value has been established as a factor in COVID-19 mortality as it concerns vitamin D deficiency which is mainly obtained from sunlight and nutritional supplements. The classical actions of vitamin D are to promote calcium homeostasis and bone health but its role in immune modulation is well established. Considering the low intensity of sunlight in Europe, America and Asia within the outbreak of COVID-19, mortality rate is explicably high due to immune incompetence and susceptibility to comorbidities occasioned by low levels of vitamin D. People of African origin have also been seen to be disadvantaged in mortality rate and this can be explained by genetic factors and skin pigmentation which comparatively reduces their absorption of UV light within the season of scarcity. This review of the current knowledge of the interplay between coronavirus infection and the host immune system suggests that the COVID-19 is likely to follow infection patterns of the previous coronaviruses. A future point of consideration that will contribute greatly to the understanding of the role of immune competence and the development of severe outcomes from COVID-19 in humans include a better elucidation of the molecular mechanisms governing coronavirus pathogenesis and virulence, and time seems to be the major factor standing in the way. Also determining the quality of antibodies to COVID 19 over a period of time will be important to understanding long-term protection from reinfection.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication.

Not applicable.

Availability of data and materials

Not applicable.

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