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A Perspective

Current Status and Prevention of COVID-19—What Do We Know?

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Abstract:

COVID-19 spread across the world, like a wildfire during the first half of the year 2020. It coincided with the flu season in countries located in northern and southern latitudes, during their respective winter periods. Whereas in the middle east, during its summertime people develop hypovitaminosis D, when people completely avoid the sun due to extreme heat. Consequently, people stay away from the hot sun and consequently, vitamin D concertation and the innate immunity reduce, increaseing the risks of acquiring respiratory viral infections. Thus, it is not necessary the low temperature and high humidity but the lack of exposure to ultraviolet (UV) B rays from the sunlight that reduces the population vitamin D concentration, which weakens the immunity, thereby increasing the risk of contracting COVID-19, and to develop associated complications and deaths. The effective public health modes for prevention of COVID-19 includes, wearing face masks properly covering nose and mouth, avoid crowd gatherings, especially in enclosed spaces, washing hands each time returned to office or home, and having a balance diet with adequate micronutrients, and these use of UVC lamps. At present there is no specific antiviral, or safe, effective, and affordable vaccine against COVID-19; it is unlikely such would materialize during the year 2020 or even beyond. At present, the only proven intervention that prevent COVID-19 and reduces its complications and deaths is vitamin D.

Keywords: Angiotensin; cardiovascular; coronavirus; endocrine; infection; inflammation; innate immunity; vitamin D; pandemic; renin; SARS-CoV-2

Abbreviations

angiotensin-converting enzyme 2 (ACE-2)

acute respiratory distress syndrome (ARDS)

25-hydroxy vitamin D [25(OH)D]

1,25 dihydroxyvitamin D [1,25$(OH)_2$D]

COVID-19 (SARS-CoV-2)

renin–angiotensin hormonal system (RAS)

randomized controlled trials (RCTs)

ultravioletB (UVB) rays

vitamin D receptor (VDR)

posttraumatic stress disease (PTSD)

Introduction

The pattern of worldwide spread and the clinical features of COVID-19 syndrome are well documented in recent publications. Over 75 to 82% of persons infected have none or only mild flulike symptoms[1, 2]. Whereas most people who experienced complications are known to have severe vitamin D deficiency and thus have poor innate immune systems. Vitamin D deficiency is highly prevalent among the elderly, institutionalized persons, those with dark skin living in temperate climatic countries, and persons with multiple comorbidities such as metabolic disorders, diabetes and obesity, hypertension, cardiovascular and pulmonary diseases. Incidentally, the same group of people have the lowest concentrations of angiotensin converting enzyme-2 that increases the vulnerability to contract and die from COVID-19.

The two common denominators present in the mentioned vulnerable groups are vitamin D deficiency and low concentrations of membrane bound angiotensin converting enzyme-2 (ACE-2), also known as ACE-2 receptors. The combination makes increased these groups of said people highly susceptible to contract COVID-19, develop complications and die from it. Deaths occur primarily in the elderly and institutionalized persons with comorbidities, such as hypertension, diabetes, and chronic pulmonary and cardiac diseases [3, 4].

The spread of COVID-19

On average, a cough produces in excess of 2,000 large respiratory droplets, most of which are larger than 5 microns. Whereas a sneeze can produce more than 30,000 small, infectious droplets, most of can which become aerosolized. Such droplets are responsible for the airborne spread of COVID-19 as well as tuberculosis [3]. Irrespective of the differences in the number of viruses in each droplets, these can infect others, contaminate surfaces, and food items in supermarkets. Therefore, regardless of the location, those who have symptoms, and are coughing or sneezing must use effective face masks to protect others. Similarly, others must take precautions themselves by wearing face masks when they are leaving home.

It is highly recommended that individuals wear face masks in public to minimize viral transmission. If a person at home is not well, it is necessary for everyone else to ware face masks to protect themselves, including at home. As discussed later, there are additional precautions that can be taken, including the installation of effective ultraviolet C ray lamps that are capable of destroying most viruses including coronaviruses, and natural substances that could boost the immune system, such as vitamin D supplements and safe exposure to sunlight. COVID-19will not survive outside humans for more than few hours or within a person with a strong immune system for a longer period.

Dissemination of Misleading Information

While facts and right guidance are important in epidemics and COVID-19 pandemic. However, these were hampered by misleading information and false propaganda by the mainstream news media and circulating in the social media platforms, and contradictory information provided by key organizations like, the World Health Organization. Examples of such statements includes, discouraging wearing face masks, non-infectiousness of asymptomatic carriers, lack of infectivity by children to adults, etc., are particularly ambiguous and worrisome with reference to misleading the public, derailing disease prevention measures and advices for COVID-19. Consequently, people lost the trust that led to reduction of adherence with disease prevention measures that might have initiated the second wave of COVID-19.

In this regards, obtaining information and authentic advice from trustworthy sources is important. In addition, some administrations failed to explain to the public, of their policies but rushed to implement lockdowns and curfews that had little effect on disease control and reduced the adherence to guidance by the public. These examples highlight the need for straightforward,

truthful, and inclusive approaches to communication.

Wearing Face Masks and Reducing the Entry of Viral Load

Non-pharmaceutical means of interventions strategies for COVID-19 includes, wearing face masks in public, social distancing, adhering to proper sanitary procedures, avoiding shaking hands, and other health guidelines. Another tragedy during the pandemic was that authoritarian governments opted to enforce inhumane, gunpoint quarantine measures mentally and physically harmed thousands of people and apparently, a significant proportion got infected while their stay in these centres; such enforcements had little effect on preventing the spread of COVID-19[5]. This is not the public perception portrayed played by the mainstream media and reinforced by such policies and ill thought actions.

Wearing face masks properly would significantly reduce the entry of viral load into individuals, allowing them to develop immunity and antibodies against the COVID-19. In addition, this would allow them to have minimal or asymptomatic infection and prevent complications and deaths and reduce the viral spread. Yet allowing them to develop antibodies against COVID-19. Moreover, consequently, acquiring asymptomatic or mild infection can facilitate the development of herd immunity, quicker than otherwise would. On the other hand, when the community serum 25(OH)D concentrations are maintained higher than 30 ng/mL forced, harmful lockdown and curfews become unnecessary.

The Mode of Entry of COVID-19 into Human Cells

COVID-19 uses the ACE2 surface receptors on human epithelia as the entry point into the body. The process of attachment to ACE-2 receptor and internalization are facilitated by cell-membrane bound heparin sulphate proteoglycans (HSPG) molecules [6]. The latter process is inhibited by lactoferrin, a nutrient present in mammalian milk. While the ACE-2 receptor is necessary for the COVID-entry into cells, ironically, less concentration of these molecules, as in those with multiple comorbidities and advanced age, enhance its entry. Whereas the combination of excess ACE-2 and lactoferrin interfere the entry of COVID-19 into epithelial cells in human [6, 7].

Following internalization of viruses, through a presumed cytokine mediated mechanism, virus indirectly sustain the activity of the RAS, leading to increase generation of angiotensin-II (Ang-II) hormone while down regulate the expression and production of ACE-2 and the proteolytic vasodilatory peptide Ang $_{(1-7)}$ [8, 9]. In addition to inactivating excess Ang-II, ACE-2 dampens the production of inflammatory cytokines [10, 11]. Moreover, COVID-19 causes diffuse endothelial cell damage and pulmonary micro-thromboembolism, worsening the clinical outcome[12].The combination, aggravate the COVID-19 syndrome with an unopposed escalation of systemic inflammation, pulmonary hypertension, cytokine storm, and acute respiratory distress syndrome (ARDS)[13, 14].

There are no specific drugs or vaccines capable of controlling COVID-19. The best, practical, and most economical way to protect from this virus is by strengthening the immune system[15]. Having a strong immune system expedite the process of neutralizing and destroying COVID-19 and other infections. The key component that enhances the immune response is vitamin D[16], which also counters the pro-inflammatory cytokines and upregulates ACE-2 receptors. These actions initiate following binding of calcitriol to intracellular vitamin D receptors (VDRs) that promote the transcription of the ACE-2 gene, antimicrobial peptides, etc.[17, 18], and supressing excessive oxidation and inflammation [19]. Hypovitaminosis D impairs every step in the inflammatory cycle [20, 21].

Why Respiratory Viral Infections are Common during Winter Periods

Because serum 25(OH)D concentrations are lowest during the winter

months in those who live in northern latitudes, the risks of getting respiratory viral illnesses are highest during this period [22, 23]. This can be counteract by supplementing vulnerable populations, such as residents in developmental disability centres and nursing homes, the elderly, night workers, healthcare workers, and first responders with adequate doses of vitamin D[24, 25]. In addition, multivariate regression analyses reports that those with darker skin are at a much greater risk than are whites not only for hypovitaminosis D but also for developing complications and dying ofCOVID-19 [26, 27].

Empirical Therapies

There are suggestions that increases in intracellular pH dampen the multiplication of the COVID-19 virus, in part through modifying the activity of ACE-2. Considering this, it has been suggested that alkalizationa gents, such as amiloride, which increases the cytosolic pH can be used as an adjunct therapy for COVID-19 [28, 29]. In this regard, the ACE-2 agonist diminazene aceturate was reported to improve the RAAS- homeostasis and reduce damage induced by ischemia-reperfusion injury in a mouse model regulating ACE2-Ang system (1-7) [30].

Among empirical agents, chloroquine or hydroxychloroquine (600 mg/day) is one of the cheapest interventions available to prevent coronaviral entry into human cells [14, 31]. Hydroxychloroquine alone or in combination with azithromycin (a stat dose of 500 mg/day and then 250 mg/day) administration for 10 days [32, 33] has been tried in pilot clinical trials with mixed clinical outcomes [31, 34]. Currently, there is no tangible evidence to suggest that this combination is necessary or better in comparison with hydroxychloroquine alone. Importantly, hydroxychloroquine use should be discontinued if the patient experiences prolonged QT syndrome, which is a rare event, especially those without glucose-6-phosphate deficiency. It is arare adverse effect that has been exaggerated by the mainstream media and those with conflict of interest, pharmaceutical and vaccine companies, and others for political reasons.

Other combinations, including hydroxychloroquine [14] in combination with zinc or curcumin, with or without a currently available antiviral agent such as remdesivir, lopinavir/ritonavir[35], or favipiravir, are being studied in randomized controlled clinical trials. In addition, emerging data strongly support vitamin D being used in high doses in all persons with COVID-19 infection as an adjunct therapy [3, 15, 36]. Oral lactoferrin and vitamin D are known to stimulate the immune system and should be examined in randomized clinical trials to assess their efficacies in stimulating the immune system to subdue COVID-19 [37, 38].

Animal studies have reported that in the presence of curcumin, intravenous infusion of Ang-II in rats failed to increase mean arterial blood pressure [39]. Using the same regimen, studies reported that curcumin reduced the Ang-II type 1 (AT1) receptor concentration but upregulated the Ang-II type 2 (AT2) receptor and ACE-2[39]. Also reported was a significant reduction inthe expression of transforming growth factor beta-1, phosphorylated-Smad2/3, and synthesis of collagen I, markers of tissue fibrosis [39]. Other key micronutrients should be investigated in clinical studies.

Ongoing COVID-19 Related Clinical Trials

In response to the global COVID-19 emergency, controlled clinical trials are being conducted in several countries to assess the safety and efficacy of different medical and nutritional interventions to combat this syndrome. As described, others are investigating the efficacy of empirical agents such as hydroxychloroquine [31, 34], azithromycin [32, 33], and vitamin D as an adjunct therapy.

Other therapies under investigation include interleukin-6 inhibitors, such as tocilizumab and sarilumab; remdesivir; convalescent plasma therapy; stem-cell transfusion these are in phase I and II and very few in phase III studies and a variety of vaccines. Whether pharmaceutical industry and scientific groups could bring up safe, effective, and an affordable agent is yet to

be see. In general, these must be compared to standard and the best supportive care as a comparator, with or without a placebo. In addition, agents such as lactoferrin [37, 38] and vitamin D, which are known to stimulate the immune system, should be examined as an adjunct therapy, in statistically adequate, randomized controlled clinical trials for controlling the activities of COVID-19 and prevention of complications and deaths.

Conclusions

A common feature of the winter months and the inhabitants of countries north of the 42nd parallel is the higher repellence of hypovitaminosis D, occurring increased frequency during this period. In addition, during cold temperature the virus will be more easily transmitted and thus the spread of the disease is higher. The fundamental issue of those getting severally affected and dying is the existence of severe vitamin D deficiency. Those who are at a higher risks have common features of hypovitaminosis D and low expression of ACE-2 receptors. These two entities are most commonly present in the elderly, especially with comorbid conditions, such as hypertension, diabetes, obesity, chronic cardiovascular and pulmonary diseases, which causes higher complication and death rates from COVID-19.

During the process of entering and replication within host cells, COVID-19 uses an immune evasion mechanisms and stimulating the RAS. In less than 5% of infected people, this syndrome can lead to immune hyperreaction and subsequent cytokine storm (1). The latter is a shared pathogenic pathway that can cause acute respiratory disease syndrome (ARDS), coagulopathy, and systemic inflammatory response syndrome (SIRS), pulmonary hypertensions and oedema and death. Vitamin D deficiency is strongly associate with negative clinical outcomes, such as serious complications, sepsis, hospital length of stay and duration of mechanical ventilation, and mortality.

Conflicts of Interest

The author declares no conflicts of interest. He received no funding for this work or received professional assistance in writing this article.

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