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Importance of Supplementation of Vitamin C and Vitamin D in Prevention and Treatment of COVID-19

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ABSTRACT

The globe presently has been under the torment of the Corona virus disease which was publicly announced as a health emergency in January 2020 and declared a pandemic on 11th March 2020, which now has become a subject of widespread havoc by mutating at a rapid speed and rendering it as a complete nuisance for the healthcare fraternity. Symptoms include dry cough, weakness and fatigue, fever, severe pneumonia, loss of taste or smell, severe respiratory distress syndrome and may even result in death. This virus creates immune feedback systemically, or creates a cytokine storm by producing inflating levels of chemokine's and pro-inflammatory cytokines. With new variants being discovered such as omicron which are known to have shown resistance to the presently used vaccines, nutrition is, undoubtedly a key facet of maintaining a strong and sustainable immunity against the Corona virus ailment. Challenges are arising concerning the ways to support the immunity of infected persons, optimally, in the general population. Crucial components of diet such as vitamin C and vitamin D have confirmed and established effects which are in relation to immunomodulation, increased immunity and attenuation of heavy and unrestrained immune response activation, thus resulting in a decrease in viral yield and increase in survival rates of Corona virus infected individuals. By means of the following review, the function and purpose of vitamin C and vitamin D in relation to prevention and treatment of the infection, has been highlighted and discussed. Challenges are arising concerning the ways to support the immunity of infected persons optimally, in the general population.

Key words: Corona virus, Vitamin C, Vitamin D, Nutrition, Immunomodulation, Chemokine's, Inflammatory molecules

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INTRODUCTION

The recent pandemic of 2019 is caused due to severe acute respiratory syndrome corona virus variant 2 which is also called SARS-CoV-2. Corona viruses (CoVs-2) are single stranded (positive sense) RNA viruses, and possess the capacity to mutate, recombine [1] and have a hand in infecting and causing a spectrum of diseases in birds and mammals. These belong to the group of pleomorphic enveloped viruses consisting of a small, envelope of protein integrated in the membrane that is responsible for various characteristics of the its wheel of life, together with its congregation, budding in order to multiply and further pathogenesis [2] and which renders them endangered to antimicrobial peptide chains [3]. In human beings, CoVs-2 give rise to mild infections of the respiratory expanse which are customarily manageable and make up for just about 15% of the total epidemic common colds during the winter season. Furthermore, Corona viruses have mastery in contaminating a massive plurality of animals, cross species and inter species hurdles, which sequel in grievous and sometimes very baleful RTIs like the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) due to presence of ACE-2 in many mammals [4]. After the virus undergoes an incubation period of two to fourteen days (approximately five days taken as median), it ends up eventually resulting in an RTI with signs and symptoms spanning from mild or asymptomatic to a form that is on a very lethal extremity of the disease. Nonetheless, our comprehension, knowledge and understanding with regard to this disease are in its infancy up to this time and expeditiously evolving. The sickness has swiftly unrolled all over the globe, with a figure of 232,075,351 of confirmed cases and 4,752,988 deaths which have been reported to World Health Organization [5]. Studies have shown that severity of COVID-19 can be guided by several elements like sex, genetic makeup, age and underlying comorbidities [6-9]. Despite of significant amount of quality research, no specific treatment is approved for the treatment of Corona virus infection.

It has been suggested in a study performed by the world renewed ESPEN or European society for clinical nutrition and metabolism, those sufficient amounts of vitamin and mineral supplementation is pivotal in preventing a viral infection [10].

LITEARURE REVIEW

A latest review article by Zhang and Liu [11] showed that, in addition to Vitamin A, Vitamin D, vitamin C, vitamin B, omega 3 PUFA and nutrients such as Selenium (Se), Zinc (Zn), Iron (Fe), should be measured in patients of COVID-19.

Vitamin C, widely accepted as having antiviral properties shows a favourable effect when given in high dose [12,13].

This review talks through the importance of vitamin D and vitamin C in immunity, prevention and treatment of Corona virus infection.

Importance of vitamin C

Ascorbic acid is an essential and natural water soluble vitamin along with vitamin B. Ascorbic acid is the proper name for it and form found naturally in foods. In plants, it is synthesized from fructose and, from glucose, in just about all the animals. However, some animals like most varieties of bats, primates, small number of birds, guinea pigs and fish are unable to synthesize ascorbic acid as these species do no possess a final enzyme called glucono lactone oxidase known as GULO most likely due to mutations in their genes which took place antecedent to the evolution of homo sapiens [14]. Because there is no possibility of synthesizing their own ascorbic acid, these living beings depend upon external intake of ascorbic acid through food. Among these, primates have an ample reservoir which is furnished by intake of herbage and fruits ranging approximately from four and half gram per day for gorillas [15] to six hundred milligrams per day for lesser sized monkeys (seven and half kilograms $1/10^{th}$ of the size of humans) [16].

In the chronic absence of proper and adequate intake, the person is likely to suffer from scurvy, especially when it is under continuous physiological stress and is under the exposure of the virus. According to the EU, to sustain a standard typical plasma level of fifty micro mol per litre [17,18], it is important to have an average daily intake of ninety milligrams per day for males and eighty milligrams per day in case of females. This amount of intake is ample to avert scurvy but may not suffice when an individual is under the torment of viral attack and therefore, is under physiological stress.

Pharmacokinetic studies were done in healthy subjects which support daily dose of two hundred milligrams to generate seventy to ninety micro mol per litre of plasma level of circa [19,20]. When one gram daily is taken and three gram is taken four hourly, which is the maximum permissible oral dose, complete plasma saturation occurs, resulting in a predicted peak plasma concentration of 220 micro mol per litre [21]. If the same dose is given *via* intravenous route, it results in an approximately ten fold rise in vitamin C levels of plasma. During viral infections, the body requires to have loft intakes of vitamin C (about two to three grams per day) which is necessary to maintain the plasma levels between sixty to eight micro mol per litre [22,23]. As of now, that fact higher level in plasma have additional advantage or not is still to be confirmed, but anticipated to be congruous with the clinical trials discussed in the article.

Whenever conditions arrive involving physiological stress, such as, trauma, surgery and infection, the plasma levels of vitamin c in humans start falling rapidly, which very commonly results in overt deficiency of vitamin D (less than eleven micro mol per litre) in hospitalized infected individuals [24-28].

Scurvy, which is a disease caused due to the deficiency of ascorbic acid has been associated with pneumonia since a very long time which has steered to the perspective of vitamin C determining vulnerability to respiratory infections [29]. To rephrase it, subjects lacking in vitamin C levels in body may be more vulnerable to pneumonia and related grievous respiratory infections. A prospective study involving nineteen thousand three hundred and fifty seven males and females followed over twenty years established that individuals belonging to the upper quartiles of baseline plasma concentrations of vitamin C possessed a 30% lesser peril of suffering from pneumonia [30]. By the same token, a decline in the peril of pneumonia has been indicated by a meta-analysis, supplementation of vitamin C orally, especially in persons who have low dietary intakes [31].

Vitamin C is believed to possess prime, important and principal, immunomodulation, anti-inflammatory, antiviral, antithrombotic and antioxidant attributes [32-34]. It displays unswerving virucidal effects that play a major role in both the adaptive as well as innate immune systems by having various effector mechanisms [35-38]. Vitamin C has many effects on immunity during the time of infection which also include chemo taxis and phagocytosis of leucocytes and the maturation and development of T-lymphocytes [39]. Apart from that, it owns a title role as an antioxidant through which scavenger cells are able to thrust in ascorbic acid's oxidized form called Dehydroascorbic Acid (DHAA) and reproduce it to reduced form of ascorbate [40,41].

With the proviso that vitamin C shows a prospective welfare, in bringing down severity, extent and time span of sepsis, pneumonia, common cold and ARDS when given in doses of two to eight grams per day intravenously and orally, this rationales investigation to find out whether prior oral augmentation and supplementation with vitamin C could be advantageous in averting transformation from mild infection to a very condemnatory state, if given *via* iv route to patients with progressive or advanced COVID-19 signs and symptoms. It has been shown to contribute towards decreasing death rates and ultimately, a shortened stay in Intensive Care Units (ICUs), thus accelerating recuperation.

Intriguingly, many of the risk factors for vitamin C deficiency imbricate over those for COVID-19 [42]. Certain individuals suffering from co-morbidities like chronic obstructive pulmonary disease, hypertension, diabetes, asthma and some sub-groups like older people, males, African American, having a sky high danger of dire and severe and grave Corona virus infection, has also exhibited to have diminished levels of vitamin C in serum [43].

Evidently, and with mention specifically to the critical juncture of COVID-19, ascorbate gives an important contribution in shielding of endothelium from oxidation injury, down regulation of cytokines and in tissue repair [44,45]. The activation of NF-κB mediates the synergy betwixt oxidative strain and trigger of genes fundamental to the inflammatory reactivity, including tumour necrosis factor alpha, interleukin-1, interleukin-8, and intercellular adhesion molecule-1 [46]. Vitamin C has a job in minimizing inflammation and ROS (Reactive Oxidative Species) by attenuating the activation of NF-κB [47]. Vitamin C crucially decreases serum tumour necrosis factor alpha and interleukin-1β levels and increases SOD (Superoxide Dismutase), glutathione and catalase in a rat model [48]. These properties of ascorbate may be due to its epigenetic role *i.e.*, down regulation of proinflammatory cytokines up regulation of antioxidant proteins, in lieu of its direct scavenging of oxidants.

An administration of high dose vitamin C, intravenously, to a patient suffering from sepsis and septic shock caused by COVID-19, has revealed advantageous effects. In a study, the treatment group has remarkably reduced hospital mortality and no organ failure which was progressive and related to sepsis when given I/V vitamin C, hydrocortisone and thiamine for seven months [49].

Therapy with vitamin C possesses demonstrated antiviral actions in clinical trials including beneficial and favourable effects against common cold after vitamin C therapy, of high dose. [50,51].

Some studies have concluded that the anti-viral activity of vitamin C may be *via* a number of mechanisms. These include vitamin C adhering to the viral surface or interacting with integral molecular components during replication process of the virus. The production of various cytokines such as interferon beta or interferon alpha or even the free radical production may be responsible for the same.

Vitamin C potentially diminishes imprudent immune reactivity in Corona virus patients. In comparison to healthy individuals, COVID-19 patients have significantly elevated levels of inflammatory levels of inflammatory molecules like lactate dehydrogenase, C Reactive Protein (CRP), NO_2- and NO_3- in blood. In a study, the blood measures of met haemoglobin, CRP, LDH and NO_3- were significantly decreased in four out of five patients, after they were administered vitamin C intravenously with methylene blue and N-acetyl cysteine [52].

Vitamin C inhibits glyceraldehyde 3-phosphate dehydrogenase which is a glycolytic enzyme and may save immune cells from being hyper activated [53].

Till date, the evidences, corroborations and proofs to indicate that oral vitamin C may lower the time scale and incidence of respiratory infections. In addition to that, intravenous vitamin C has shown to decrease death rates, stays in hospitals and ICUs and time on mechanical ventilators. Additional trials are beseechingly called for. In view of approving safety silhouette and lesser price of vitamin C, treatment of vitamin C deficiency may be valuable and in COVID-19 affected individuals admitted in hospitals for advanced care.

Importance of vitamin D

For several years earlier, vitamin D or Cholecalciferol was contemplated as a component of food and has crucial business in osteo metabolism. So far, widely known as a steroid hormone, it has major regulatory actions in the immune system and many other processes and physiological systems in the human body. It has been illustrated from several evidences from around the world which are quite a variety of infectious diseases, mainly arising from viruses, chaperoned with a bad response to typical banner treatments [54-58]. Vitamin D negatively regulates renin angiotensin signalling pathway by several different mechanisms which has been highlighted through various experimental studies in laboratory which have also supported many clinical trials demonstrating an interrelation between increased risk of pulmonary infection and vitamin D shortage. The production of vitamin D occurs in the skin from 7-Dehydroxy Cholesterol (7-DHC) which is a zoosterol, by Ultraviolet (UV) radiation. Vitamin D binds to the vitamin D binding protein known as go globulin to get carried to the liver to undergo hydroxylation to form major circulating form of vitamin D known as calcifediol or calcidiol or hydroxycholecalciferol (25(OH)D), which is the paramount circulatory embodiment of vitamin D. It then gets transported to the renal organs, after which the hormonally active configuration of vitamin D known as calcitriol or $1,25(OH)_2D$ or 1,25-dihydroxycholecalciferol is synthesized [59,60].

Despite of the fact that reaching the adequate levels of vitamin D is not radical, vitamin D deficiency has been an intercontinental health issue. It is generally estimated that more than a billion people all over the map suffer from sub-normal levels of vitamin D among which nearly 50% are suffering from clinical vitamin D deficiency [61].

Vitamin C is known as pleiotropic stress hormone for a reason that, it plays a critical role in sepsis mediation of adrenocortical stress response [62]. Vitamin C concentrations are found in the highest amount in adrenal glands (3 to 10 times higher as compared to other organs) [63]. It is generally released from the cortex region of adrenal glands during physiological conditions of stress (by adrenocorticotropic hormone stimulation), during exposure to virus, raising plasma levels fivefold [64]. Ascorbate magnifies cyto protective

and anti-inflammatory properties of glucocorticoids by enhancing production of cortisol from cortex of adrenal glands [65,66].

DISCUSSION

Sufficient levels of vitamin D in the body can be attained through adequate consumption of vitamin D and proper exposure to sun. According to National Health and Nutrition Survey (NHANES) 2001-2006, acute respiratory infection was inversely correlated with 25-hydroxy vitamin D levels [67]. ACE II which is the receptor for the bonding of the virus particle, counterbalances the activity of renin angiotensin system, and therefore, serves a defensive purpose antagonistic towards the expansion of complications of the viral ailment. Vitamin D serves the role of inducing the expression of angiotensin converting enzyme 2 and regulation of the immune system *via* various mechanisms. In a study conducted in Indonesia, out of 10 COVID patients, 9 suffered from deficiency of vitamin D and 1 was be devilled by insufficient levels of vitamin D [67]. This stipulates that inadequacy of vitamin D can conceivably be a risk factor for COVID-19 ailment. A number of studies have also shown association between vitamin D insufficiency and COVID-19 [69,70]. The death prevalence rate due to COVID-19 were crucially more in states with high latitudes (>37 degrees) than those with low altitude (<37 degrees) in the United States [69], vitamin D is synthesizing through subjection to sunlight on skin.

In another meta-analysis of eleven studies, 37.7% COVID-19 patients had deficiency of vitamin D whereas 32.2% suffered from vitamin D insufficiency.

According to an additional meta-analysis which sheltered one thousand three hundred and sixty eight patients of Corona virus, conveyed that, lesser amount of vitamin D had been notably analogous with worse prognoses in those infected individuals [71]. Vitamin D deficiency conveyed a positive correlation with ICU admission and hospitalization with 24 hours [72].

The introductory studies advocate that poor prognosis in Corona virus patients could have occurred due to deficiency of vitamin D. Hence, vitamin D decreases risk of viral infection by regulating production of tight junction proteins [73], adheres junctions [74] and gap junctions [75]. It prevents cytokine storms be decreasing production of, IL-6, TNF-α, IL-13 [76], INF-Ɣ and IL-12 [77].

Vitamin D can demonstrate antimicrobial effects in the body by producing antimicrobial peptides like cathelicidin and defencing [78].

CONCLUSION

COVID-19 presented a unique challenge to healthcare professionals as well as researchers around the world. Ever since its genesis in late 2019, right up till today, we continue to explore the plethora of characteristic properties that make it unique, as well as the properties that fall within our pre-established notions of viral replication and virulence mechanisms along with the widely accepted genial principles of virulence and disease theory. Even though many novel prophylactic measures have been implicated to be beneficial in the COVID-19 epidemic, many studies have shown that the very basic evidence based prophylaxis and treatment measures are still relevant in fighting against infections. The role of vitamin C and vitamin D, both as adjuncts and mainstay immuno complementary therapies, is one such paradigm. As demonstrated in this article, it is beyond the shadow of a doubt that vitamin C and vitamin D levels as well as vitamin C and vitamin D therapies play an essential role against SARS-CoV-2 infection and also have a significant role in controlling its severity as well as a reasonably available and accessible prophylactic measure. This not only demonstrates that the basics of medicine still apply to a pandemic level threat like COVID-19 but also implies the need to further research the scope of adjunct nutritional therapies in controlling the infection. Along the same lines, the author also places emphasis on not merely the importance of but also the dire need for nation vitamin C and vitamin D prophylaxis programs as well as nutritional surveillance and security measures. Ultimately, it is concluded that adjunct therapies such as nutritional fortification are a powerful weapon against the present and quite possibly, future variants of SARS-CoV-2.

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