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REVIEW

How anti-inflammatory and antioxidant dietary supplements are effective in undermining COVID-19 pathogenesis: the role of vitamin C and D

Cómo los suplementos dietéticos antiinflamatorios y antioxidantes son efectivos para socavar la patogénesis de COVID-19: el papel de la vitamina C y D

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Abstract

Due to lack of effective treatment for novel pandemic coronavirus disease (COVID-19) caused by severe acute respiratory syndrome corona-virus-2 (SARS-CoV-2), the prevention strategies are the best choices to significantly control increasing number of patients. Numerous studies suggest an association between vitamin D and C and the outcomes of SARS-CoV-2 infection. Therefore, supplementation of vitamins such as D and C has been recommended prevention and treatment of the COVID-19. Vitamin D as an immunomodulator hormone could affect various respiratory infections by maintaining the immune system and blocking hyper-inflammatory responses like cytokine storm through decreasing viral replication and regulating the levels of pro-inflammatory/anti-inflammatory cytokines. There are also some evidences that vitamin D could alter severity of COVID-19. The effectiveness of vitamin C in the prevention and treatment of coronavirus has also been undertaken by several studies. Due to the important role of vitamin C in the immune system, a deficiency of this vitamin may increase the incidence, severity and the risk of death of COVID-19 disease. This could explain by this fact that vitamin C deficiency increases the risk of infections, decreases the immune system response and increases the risk of pneumonia. People with chronic diseases as high-risk COVID-19 patients also showed deficiency of these vitamins which could explain the severity and the high rate of mortality among them. Thus, it seems that sufficient vitamin D and C level in serum may have positive impact on decreasing risk of COVID-19 infection. Considering all aspects, we try to overviewed on the potential role of supplementation of vitamin D and C in COVID-19 disease. We summarized suggested impacts of these vitamins on SARS-CoV-2 and its pathogenesis. We also discussed mechanisms in which these two vitamins involved that could alter the COVID-19 infection.

Key words: COVID-19, SARS-CoV-2, vitamin D, vitamin C, inflammation, treatment, supplementation.

Resumen

Debido a la falta de un tratamiento eficaz para el síndrome respiratorio agudo severo, la nueva enfermedad pandémica por coronavirus (COVID-19) causada por -2 (SARS-CoV-2), las estrategias de prevención son las mejores opciones para controlar de forma significativa el creciente número de pacientes. Numerosos estudios sugieren una asociación entre la vitamina D y C y los resultados de la infección por SARS-CoV-2. Por lo tanto, se ha recomendado la suplementación de vitaminas como la D y la C para la prevención y el tratamiento del COVID-19. La vitamina D, como hormona inmunomoduladora, podría afectar a varias infecciones respiratorias manteniendo el sistema inmunitario y bloqueando las respuestas hiperinflamatorias como la tormenta de citoquinas mediante la disminución de la replicación viral y la regulación de los niveles de citoquinas proinflamatorias/antiinflamatorias. También hay algunas evidencias de que la vitamina D podría alterar la gravedad de la COVID-19. La eficacia de la vitamina C en la prevención y el tratamiento del coronavirus también se ha llevado a cabo en varios estudios. Debido al importante papel de la vitamina C en el sistema inmunitario, una deficiencia de esta vitamina puede aumentar la incidencia, la gravedad y el riesgo de muerte de la enfermedad por COVID-19. Esto podría explicarse por el hecho de que la deficiencia de vitamina C aumenta el riesgo de infecciones, disminuye la respuesta del sistema inmunitario y aumenta el riesgo de neumonía. Las personas con enfermedades crónicas como los pacientes con COVID-19 de alto riesgo también mostraron deficiencia de estas vitaminas, lo que podría explicar la gravedad y la alta tasa de mortalidad entre ellos. Por lo tanto, parece que un nivel suficiente de vitamina D y C en el suero puede tener un impacto positivo en la disminución del riesgo de infección por COVID-19. Teniendo en cuenta todos los aspectos, tratamos de hacer un resumen sobre el papel potencial de la suplementación de vitamina D y C en la enfermedad de COVID-19. Hemos resumido los impactos sugeridos de estas vitaminas en el SARS-CoV-2 y su patogénesis. También discutimos los mecanismos en los que estas dos vitaminas están involucradas y que podrían alterar la infección por COVID-19.

Palabras clave: COVID-19, SARS-CoV-2, vitamina D, vitamina C, inflamación, tratamiento, suplementación.

Introduction

Nutrient is as important issue in maintenance of immune system. Immune dysfunction due nutrient deficiency could increase prevalence of various respiratory infections. Multi essential micro-nutrient such as vitamins supplementation could reduce the incidence and prevalence of respiratory infection[1].

Following the emergence of a novel coronavirus from Wuhan, China, in December 2019, the respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected the whole world and is declared a pandemic by World Health Organization (WHO) on March 26, 2020.1 According to World metrics, this novel virus has been responsible for approximately 461,650,510 infections, of which 6,051,400 patients have died worldwide up to March 16, 2022[2]. After months of medical communities' efforts, one of the hottest topics is still the role of vitamin D in the prevention or treatment of COVID-19. Several functions, such as modulating the adaptive immune system and cell-mediated immunity, as well as an increase of antioxidative-related genes expression, have been proven for vitamin D to prevent and treat of acute respiratory infections. According to available investigations, it seems that such functions lead to cytokine storm suppression and avoid acute respiratory distress syndrome (ARDS), which has been studied on other pandemics and infectious diseases in recent years. To the best of our knowledge, unfortunately, after several months, there is no adequate high-quality data on different treatment regimens, which raise questions about gaps in scientific works such as observational studies without a control group or non-randomized controlled studies with retrospective nature covering a small number of patients[3]. The same issue is debatable for ascorbic acid or vitamin C with antioxidation and anti-inflammatory properties which confirmed in infections and sepsis. SARS-CoV-2 could also cause sepsis and ARDS with severity and critical illnesses. Effect of this vitamin as a cofactor has been also confirmed on cellular immunity and vascular integrity[4].

COVID-19: The immune system response

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptor of type II alveolar cells of lungs and enters into the cells and spread its viral RNA to replicate. Through recognition of viral RNA by pattern recognition receptors (PRRs) in innate immune response[5], a series of downstream signaling activates Nuclear factor kappa B (NF-κB) and type I interferon to the produce pro-inflammatory cytokines and antiviral proteins respectively. SARS-CoV-2 also leads to endocytosis of ACE2 that maintain a proinflammatory cycle to promote accumulation of angiotensin II that resulted in acute lung damage. Furthermore, the studies confirmed association of enhanced inflammation and thrombosis in COVID-19 infection due to endothelial dysfunction and activation of coagulation. The angiotensin-converting enzyme 2 receptor (ACE2r) has been also overexpressed as the entry door for COVID-19 in endothelial cells leading to impaired endothelial homeostasis by IL-6[6,7].

Non-specific proteins (NSPs) of SARS-CoV are the key of inhibition the host innate immune response by inhibition of the expression of INF-β by binding to the host 40S ribosomal subunit and inhibition of translation and increasing translation efficiency of the viral mRNAs relative to human mRNAs[8].

SARS-CoV increases levels of interferon gamma (IFN-γ), IL-1, IL-6, IL-8, IL-12 induced protein 10 (IP-10), and Monocyte chemoattractant protein-1 (MCP-1) and also over activates of the T helper type 1 (Th1) cells-mediated immune response and subsequent increase in natural killer (NK) cells and polymorphonuclear neutrophils (PMN) which could cause lung damage. The severity of disease could increase by higher levels of IL2, IL6, IL7, IL10, Granulocyte colony-stimulating factor (GCSF), IP10, MCP1, Macrophage Inflammatory Protein (MIP)-IA, and Tumor necrosis factor (TNF) that heighten inflammatory responses and parenchymal damage which resulted in ARDS[9].

SARS-CoV-2 engages inflammasome and triggers pyroptosis in human monocytes, and cause infection. Pyroptosis could activate caspase-1, produce IL-1ß, cleavage gasdermin D, and enhance pro-inflammatory cytokine levels in human primary monocytes[10].

Level of IL-6 due to pleiotropic activity and having extensive effects on major biological systems of the body and the pathogenesis of diseases increases in the COVID-19 patients and is associated with the severity of the disease and mortality that make it potential predictor of COVID-19 severity in hospitalized patients. IL-6 promotes expression of the Tissue Factor (TF) gene and TF protein with procoagulant activity that have prothrombotic effects on human endothelial cells. IL-6 also increases expression of ACE2r protein that modulates the effects of COVID-19 on endothelial cells. The studies showed higher level of IL-6 was in COVID-19 patients with severe clinical complications than mild COVID-19 patients[11]. IL-6 also significantly increases levels of Caspase-1 protein as inflammatory mediator[10].

In cytokine storm as a consequence of severe COVID-19 infection, the level of IL-10 is increased earlier than IL-6. This feature is specifically seen in SARS-CoV-2 rather than SARS. Identified elevated levels of IL-6 and IL-10 are introduced as predicted covariates of severity of COVID-19 disease by clinical trials which represented pathological role of IL-10 in COVID-19 severity[12].

Hyperinflammation could be induced by SARS-CoV-2 N protein that promotes NLRP3 inflammasome through

mechanistically interaction, maturates proinflammatory cytokines that lead to aggravate lung injury and increase excessive inflammation[13].

Vitamin D responsibility in immune system response to COVID-19

The importance of the role of vitamin D in immune system is regulation of immune cells including dendritic cells (DCs), macrophages, natural killer cells and B-cells which involve in innate and adaptive immune system to regulate some immune responses with anti-inflammatory effects[14].

1,25-dihydroxyvitamin D (1,25 (OH)2D), the active form of vitamin D, synthesized from its precursor 25-hydroxyvitamin D (25-OHD) via the enzyme 1α-hydroxylase (CYP27B1) in immune cells (antigen-presenting cells: APCs) like macrophages and DCs in response of pathological invasions and also epithelia to activate dendritic cells and macrophages. This could represent importance of vitamin D as a regulator of the immune system response[15]. Vitamin D activates enzyme of 1-α hydroxylase to upregulate synthesis of calcitriol in antigen-presenting cells (APCs) to mediate antimicrobial action and anti-inflammatory effects. Vitamin D in innate immune system enhances increased chemotaxis, phagocytosis, phagolysosomal fusion, and barrier function in innate cells. Vitamin D3 upregulate cAMP in macrophages, monocytes, and epithelial cells and decrease anti-inflammatory cytokines. Moreover, vitamin D decreased cytokine secretion by effect on CD4+ T cells[16].

Production of cathelicidin antimicrobial peptide (CAMP) as antimicrobial peptides and interleukins including IL-4, IL-5, and IL-10 as type 2 anti-inflammatory cytokines is also induced by vitamin D in immune cells that increase immune system efficiency. ILs upregulate the NF-kB inhibitory protein IkBa to block NF-kB p65 activation. In addition, vitamin D could also stimulate conversion of proinflammatory M1 macrophage to the anti-inflammatory M2 phenotype[9].

Vitamin D also altered the mRNA expression of SARS-CoV-2 entry genes such as Tmprss2 and Ctsl genes that change activation of spike protein of SARS-CoV-2 for membrane fusion and viral control by the humoral immune response[17].

The renin-angiotensin system (RAS) is also involved in inflammation. Once RAS is activated by renin, angiotensin II levels increase, eliciting inflammation via NF-κB activation which in turns stimulates proinflammatory cytokines such as TNF, IL-6, and IL-12. ACE2 halts RAS activation. Vitamin D can decrease renin to revert the proinflammatory cycle[18].

Vitamin D could inhibit differentiation, maturation and antigen presentation of DCs which resulted in preventing autoimmunity and promoting self-tolerance by reducing expression of CD1a, CD40, CD80, & CD86, CCL4 & CCL19 and MHC class II, that decreasing activation of T cells. Adverse impact of this vitamin on DCs cells lead to decreased production of IL-12 and IL-23 that switches the immune axis from Th1 to Th2 phenotype. vitamin D also enhances development of regulatory T cells in viral infections. vitamin D could inhibit the inflammatory response to SARS-CoV-2 infection and also maintain the antiviral state of immune system by increasing the expression of IκBα protein and decreasing the expression of phosphorylated STAT-1 along that decline mRNA levels of IRF1, IRF7, IFN-β and CXCL8[19].

Vitamin D could reduce the cytokine storm by decreasing production of Th1 cells and suppressing the progress of inflammatory cascade by altering the proinflammatory cytokine signatures which has been implicated in severe COVID-19 infection. The active metabolite of vitamin D, Calcitriol (1,25(OH)2D3), prevents the production of proinflammatory cytokines, such as IFN-γ, TNF alpha, IL-2, IL-17, IL-21, NF-κB and toll-like receptors on monocytes and lead to upregulation of IL-4, IL-5 and IL-10[20].

Calcitriol also decreased the expression of adhesion molecules, as well as lipopolysaccharide-induced expression of receptor of the advanced glycation end product and IL-6 and upregulates a NF-κN inhibitor, IkB alpha and also upregulates the expression of ACE2. These implications may be uniquely applicable to the disease pathogenesis and severity of COVID-19[21].

Vitamin D significantly reduces effects of IL-6 on expression of TF and ACE2r genes that modulating effects of COVID-19 on endothelial cells via modulation of NF-κB and STAT3 activation[22].

Vitamin C responsibility in immune system response to COVID-19

Immune cells are highly enriched with vitamin C to modulate immunological functions including scavenging of oxidative species, trigger signaling pathways, activation of pro-inflammatory transcription factors and signaling cascade, regulation of inflammatory mediators, and phagocytosis and increasing neutrophil motility to the site of infection that require for the prevention of COVID-19 infection. During COVID-19 infection, dysfunctional immune system produced free radicals. Vitamin C as an emerge antioxidant enhances the immune system against oxidative stress that could cause severe lung injury in COVID-19 infection by neutralizing free radicals and creating balance between oxidants and antioxidants[23].

Vitamin C could influence replication mechanisms and life cycles of viruses by interaction with ACE2 by inhibiting the receptor binding domain (RBD) that disrupts binding SARS-CoV-2 to ACE2 receptor [24]. Vitamin

C can decrease cellular expression of ACE2 receptors in lung small airway epithelial cells (SAEC) and human microvascular endothelial cells (HMEC) at the protein and the RNA levels.

The Antioxidant properties of vitamin C can explain immunomodulating effects of it. Vitamin C could exhibit its impact on cellular and humoral immune response in lower concentrations and lymphoproliferative, chemotactic effects and enhanced natural killer cells activity in higher concentrations[25].

Antiviral effects of vitamin C is represented in its active form (L-dehydroascorbic acid (DHA) by inhibiting replication of viruses via upregulation several important pathways in antiviral responses include eIF2 signaling, autophagy, interferon response, and the JAK/STAT pathway[26].

NF-κB play a crucial role in immune system including regulation of cytokine and chemokines genes, inflammatory mediators, adhesion molecules, and apoptosis inhibitors as primary proinflammatory transcription factor. Vitamin C can inhibit the activation of NF-κB, production of TNF-α and IL-6[27].

Granulocyte-macrophage colony-stimulating factor (GMCSF) is a hemopoietic growth factor and cytokine that enhances survival, activation and differentiation myeloid cell populations such as monocytes, macrophages, neutrophils and eosinophils. This factor has beneficial effects in inflammatory disease. Vitamin C could reduce the GMCSF signaling responses that regulate cytokines redox-signal transduction in immune cells to control inflammatory responses. The other mentioned role for vitamin C is regulating the proliferation and function of T cells, B cells, NK cells to inhibit the progression of cytokine storms for improving immune system. Vitamin C also enhances lung epithelial barrier function, improving ARDS symptoms and respiratory function by control epigenetic and transcriptional factors of protein channels to regulate clearance of alveolar fluid.

Vitamin C could also directly inhibit of protease enzymes such as 3-chymotrypsin protease, which are responsible for SARS-CoV-2 entry production of interferon, and maturation of T-lymphocytes. Vitamin C also acts as a protection of these immune cells against oxidative damage[23].

Evaluation of administration of vitamin or in combination of other substances (such as vitamin D) in some clinical trials revealed benefit effects of that for treatment or prevent severe COVID-19. The effective dosing of vitamin C reported ranging from 250 to 500 mg orally to 10-24 g intravenous (IV) daily. The use of high-dose vitamin C is also reported for management and treatment of hospitalized COVID-19 patients by reduce cytokine storms in ARDS. According to these findings, for management the COVID-19 infections particularly sever one, many hospitals and health centers in China and USA have already started administrating IV vitamin C[4].

Concluding these findings, vitamin C possesses positive impacts on curing of infection and this may play a protective role in the current COVID-19 pandemic through boosting the immune system. Vitamin C could improve signaling cascades and signaling pathways and immune cells functions. These properties could be noteworthy for prevention and treatment of COVID-19 infection and improving immune system against COVID-19 infection.

Vitamin D deficiency

One of the proposed risk factors for numerous viral respiratory diseases is vitamin D deficiency.

Three factors have been identified as causing vitamin D deficiency including
(1) inadequate consumption by unhealthy diet with low D-rich foods such as cereals or Breastfeeding infants (low vitamin D in human milk)
(2) impaired absorption or metabolism of vitamin D because of skin type, pregnancy, smoking, obesity, age, may affect the related genes, diseases such as Crohn's disease and celiac diseases kidney and liver illness or taking medications like steroid drugs,
(3) limitation in sunlight (ultraviolet B (UVB)) exposure due to modern lifestyle, wearing full-cover clothes for jobs, cultural, religious and geographical reasons , air pollution that may cause less access to the UVB rays[28].

Vitamin D deficiency could cause impaired immune responses due to less available precursor of vitamin D (25-OHD) for synthesis of active form of vitamin (1,25 (OH) 2D)[15].

Although several attempts tried to confirm effects of this vitamin deficiency as immunomodulatory factor, on increased risk of COVID-19, higher severity and increased rate of hospitalization of patients, most of them represented conflicting results[29]. Moreover, some studies have ruled out an effective link between vitamin deficiency and these conditions[30,31].

However, rather than study of D3 serum levels, the polymorphisms of vitamin D binding protein (DBP), a specific transport protein which could influence on the plasma vitamin D and DBP concentrations, may possibly influence the results of these such studies and should be considered in study participants and checked out by genotyping[32].

For invasion host's cells, SARS-CoV-2 uses the angiotensin-converting enzyme 2 as the entry receptor and Transmembrane Protease Serine 2 (TMPRSS2) for S protein priming through Renin-Angiotensin-System which could be elevated by vitamin D deficiency which could increase the risk of COVID-19 infection[33].

In addition, the lack of vitamin D is a risk factor for the development of autoimmune and neuropsychiatric disorders[41].

Some studies confirm association of vitamin D deficiency with greater severity and higher mortality with higher rates of hospital admissions with longer hospital stays of COVID-19 patients. The severity of COVID-19 infection is measured by rates of mortality, hospital admission and duration of hospital stay.

Vitamin C deficiency

In spite of most of animals, human is unable to synthesis vitamin C in liver. Thus, it should be obtained regularly as an essential nutrient by people. Contrary to popular belief, studies show that vitamin C deficiency is likely to be common globally particularly in low-income countries[34,35]. In addition to low vitamin C diet, pregnancy, breastfeeding, overactive thyroid, inflammation, diarrhea, surgery, burns and smoking are mentioned as causes of vitamin C deficiency.

As an infection, COVID-19 has been studied for status of vitamin C deficiency among patients. The results showed sever depleted vitamin C status and interestingly elevated markers of oxidative stress among patients[36].

The clinical evidences confirmed reduced plasma levels of vitamin C in critically ill and ICU COVID-19 patients[37].

However, there are challenges on short-term administration of intravenous vitamin C in treating patients with COVID-19. Some results showed that this strategy could not reduce the risk of severity and mortality in patients with COVID-19[38].

Other studies showed that vitamin C therapy didn't reduce major health related outcomes in COVID patients and no significant benefit were observed on severity of illness and mortality[39,40].

Discussion

Prevention and treatment, COVID-19 pandemic has become the first topic for world health. Several strategies and clinical trials are suggested to decline rates of severity and its complications and necessary mortality of COVID-19 infection.

The vitamin D is the well-known supplementation for decreasing risk of SARS-CoV-2 infection due to several roles that mentioned for this supplement. It has shown that vitamin D receptor expressed in innate immune cells including monocytes, macrophages, DCs and could increase the differentiation of monocytes to macrophages. It also stimulates these immune cell proliferation and cytokine production. Vitamin D mainly has inhibitory effects in adaptive immunity on proliferation of B-cells, generation of plasma cell and secretion of immunoglobulin, Th1 cytokines and Th17 differentiation. It also increased apoptosis of B-cells[41].

These roles could explain the results that confirm vitamin D deficiency leads to exacerbated respiratory disease and severity and mortality of COVId-19 infection[42].

Vitamin C as an effective antioxidant factor could eliminate reactive oxygen and reactive nitrogen species. It also increases regeneration of other important antioxidants such as glutathione and vitamin E to their active state. This vitamin also improves innate immune system by promoting collagen synthesis to support the integrity of epithelial barriers. It also stimulates production, function and movement of neutrophils, lymphocytes and phagocytes. The emerge function in activity of NK cells that has important role in COVID-19 infection. It could also enhance differentiation and proliferation of lymphocytes[43].

Both vitamins could disrupt binding of SARS-Cov-2 virus to host cells through ACE2 by altering associated genes and downregulating signaling cascades. Deficiency of them could increase efficiency of cytokine storm that cause higher severity and eventually death in patients[44]. Overview of several studies concluded that supplementation with vitamins C and D improve the inflammatory response and decrease the severity of disease in patients with COVID-19[45].

Concluding remarks

Critical role of vitamin D and vitamin C in regulation and modulation of immune system in viral infections including covid-19 has been observed in studies.

Vitamin D could modulate immune cells and induce immune tolerance and has beneficial effects on immune function in autoimmunity. Following, the studies found that vitamin D deficiency modulates the number of immune cells in COVID-19 patients particularly in the number of NK cells[46]. The association of vitamin D deficiency with COVID-19 severity has been also confirmed[47]. A strong association was also found between lower 25(OH)D levels and increased rate of SARS-CoV-2 positivity and COVID-19 severity[48].

There is a controversial whether vitamin D level deficiency could increase risk of severe COVID-19 or the low vitamin level is a consequence of COVID-19. However, in both conditions, the treatment of vitamin D deficiency is highly recommended by clinical trials to prevent SARS-CoV-2 infection and also to achieve significant decrease in inflammatory marker[49].

In spite of numerous reported observational studies, fewer comprehensive studies have been conducted on vitamin C supplement in COVID-19 infection which increases the challenges and discussions about it. Considering the results, it seems that vitamin C with several immune supportive role showed minimal effect on risk of SARS-CoV-2, but could shorten duration of illness and decrease severity of COVID-19 infection and importantly prevent progression to more severe conditions such as pneumonia, ARDS, sepsis and COVID-19[50].

Conflict of interest

Authors do not have any conflict of interest to declare.

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