Mini Review

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Archives of Medicine
ISSN 1989-5216

2020
Vol.12 No.6:37

DOI: 10.36648/1989-5216.12.6.338

Vitamin D as a Possible Factor that Reduces COVID-19 Complications

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Citation: Alfadil Mohamed AM, Abdelrahman Mohammed NM, Mohammed Hamad MN (2020) Vitamin D as a Possible Factor that Reduces COVID-19 Complications. Arch Med Vol. 12 No.6:37

Abstract

Corona Virus Disease 19 (COVID-19) remains a serious health problem worldwide cause by a novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) which rapidly declared on 30-Jan-2020 as a global pandemic by WHO. Unfortunately, there is no effective treatment or vaccine available so far. The only preventive measure to break the spreading of the virus is by physical distancing, wearing masks, and lockdown of countries. All of the above mentioned measures implemented in European and African countries, despite that, the outbreak of the African countries has resulted in quite a few number of cases. Sever cases of COVID-19 is resulted from acute lung injury and cytokine storm. Vitamin D is well-known to inhibit the pathological inflammatory immune response by suppressing the activation of Th1 cells and activation of T regulator cells, as a result of that, vitamin D could minimize the occurrence of the cytokine storm. African countries has a privilege of sunshine most of the year seasons that help synthesizing Vitamin D_3 which could explain the low number COVID-19 cases compared to European countries.

Keywords: Vitamin D; COVID-19 complications

Received: September 24, 2020; **Accepted:** October 23, 2020; **Published:** October 30, 2020

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) also known as 2019-nCoV or HCoV-19 is one of the most contagious coronaviruses identified so far, which declared on 30-Jan-2020 as a global pandemic by World Health Organization (WHO) [1,2]. This novel - causes the most prevalent infection among other coronavirus family (Severe Acute Respiratory Syndrome-1 (SARS CoV-1) and Middle East Respiratory Syndrome-CoV (MERS-CoV) in which these members culminated in outbreaks during the past two decades. SARS-CoV-2 belongs to the family coronaviridae, genus betacoronavirus together with SARS-CoV-1. Both CoV-1 and CoV-2 cross the animal reservoir to the human [2,3]. Corona Virus Disease 2019 (COVID-19) is a term used to describe the disease caused by SARS-CoV-2 which has first been discovered in Wuhan city, Hubei province, China in December 2019 [3].

COVID-19 remains a highly infectious disease which rapidly transmitted from human to human through different modes including: Contact, droplet, airborne, fomite, fecal-oral, blood-borne, mother-to-child, which enable the COVID-19 to be disseminated all over the world but with different effects and inimitableness. The only preventive measure to reduce the spread of the virus is by mass quarantine and lockdown of countries. This policy has been taken almost everywhere in world countries [4].

Literature Review

Till date as on 22-Aug-2020, the European region has reported (3,633,633) confirmed cases and (208,959) death, while in Africa the confirmed cases (1,246,185) and (29,586) death [5]. Currently, there is no effective treatment or vaccine for the treatment of COVID-19. Although all of the lockdown procedures have been implemented by the European and African countries, the outbreak of the African countries has resulted in quite a few number of cases compared to the European outbreak. This little quantity

is levitation a lot of questions in order to more understand the situation [6]. Because the occurrence of severe COVID-19 disease is quite different between patients, it has been proposed that immune system manage the COVID-19 infection differently. It is well-known that vitamin D plays an important role in protection against acute respiratory tract infections which hypothesized that vitamin D deficiency may significantly compromises the immune response against respiratory infections [7].

This review is a narrative one, which assumes that increase the concentration of Vitamin D, which in turn increased by sunlight exposure, could drastically decrease the symptoms of the disease, and even more decrease the number of deaths.

COVID-19 can be divided into three phases; an asymptomatic phase, non-severe symptomatic phase with upper respiratory tract involvement, and severe potentially lethal disease with hypoxia "ground glass" infiltrates in the lung and progression to Acute Respiratory Distress Syndrome (ARDS) [8]. Recent clinical data suggest that these severe symptoms are due to over activation of the immune response leading to the cytokine storm which is responsible for the development of ARDS [9].

Cytokine storm is an uncontrolled inflammatory response usually culminating from the secretion of proinflammatory cytokines and chemokines by the immune effector cells (i.e., T helper 1 (Th1) leading to ARDS, multiple organ failure and finally death [8]. The proinflammatory cytokines (IL1B, IFN, CXCL10, TNF and CCl_2) that are responsible for the cytokine storm were found higher in COVID-19 patients requiring ICU admission compared to those who did not require ICU admission [10].

Vitamin D (VD) is a fat-soluble prohormone vitamin. There are two major forms of vitamin D; vitamin D_2 (Ergocalciferol), and vitamin D_3 (Cholecalciferol). Vitamin D_2 is consumed in a plant-derived diet (fungi and mushrooms irradiated with ultra-violet light "UVB"), and it is the main form of fortified food [11].

The natural Cholecalciferol (vitamin D_3) is obtained in a small amount from animal food but mainly synthesized in the skin from 7-Dehydrocholesterol (7-DHC) precursor after exposure to sunlight (UVB, 280-315 nm), this exposure isomerizes the 7-DHC and is converted into pre-vitamin D_3, followed by thermal sensitive isomerization to form vitamin D_3, immediately binds to Vitamin D Binding Protein (DBP) and transported to liver [12-14].

The production of vitamin D_3 is influenced mainly by the intensity of UVB, duration of sun exposure, skin pigmentation and skin surface area available for exposure, "A recent study of sun-protective behaviour in the USA showed that wearing long sleeves or staying in the shade reduced vitamin D status" [13].

Cholecalciferol is a biologically inactive form which undergoes hydroxylation in the liver, at the C-25 position to produce Calcidoil "25-hydroxyvitamin D_3" (25[OH]D_3). This hydroxylation is regulated by hepatic enzymes, three of them are microsomal CYP2R1, CYP2J2 and CYP3A4, the fourth enzyme CYP27A1, is a mitochondrial type. This 25-(OH)-D_3 is a major circulatory form of vitamin D with a half-life of 15 days and its serum level reflects both dietary and skin contributions as well as body stores [12].

Vitamin D activation

The activation of vitamin D takes place in the kidney after the second hydroxylation by the enzyme 1-α hydroxylase (CYP27B1) which is under strict control of parathyroid hormone to produce 1α, 25-(OH)-2D (calcitriol). 1α, 25-(OH)-2D can also be produced in extra-renal tissues as colon, prostate, muscle, immune system and pancreas. In these organs vitamin D acts in paracrine/autocrine manner [13,14].

Calcidiol and calcitriol are inactivated by CYP24A1 hydroxylase enzyme which catalyzes the hydroxylation at C-24 and C-23 of both Calcidiol and calcitriol producing calcitroic acid and lactone excreted in bile [15].

The classical functions of vitamin D are to regulate calcium and phosphate level through their intestinal absorption, calcium bone mobilization and renal excretion. Over the last decades, it has become increasingly recognized that vitamin D has a pleiotropic functions through regulation of different cellular processes, as cardiovascular functions, malignant cells and innate and adaptive immunity [16].

Vitamin D exerts its actions through Vitamin D Receptor (VDR); a nuclear receptor, which present in almost every tissue, "When activated by 1α, 25-(OH)-2D, VDR dimerizes with the Retinoid X Receptor (RXR) forming a VD-VDR-RXR complex which binds up or down to Vitamin D-Responsive Elements (VDREs) regulating the transcription of various genes in the target cells" [17].

Vitamin D has an immunological action beyond its classical role on bone metabolism. It is well known that Vitamin D receptor is highly expressed in T and B lymphocytes, giving it a plausible role to modulate the pathological immune response in patients with inflammatory diseases. Study by Laird E et al. showed a shifting of immune response from a pro- to anti-inflammatory cytokines in adults is attributable to a sufficient serum vitamin D level [18,19].

Vitamin D boosts the innate immunity through direct induction of cathelicidin (hCAP18) and defensin β_2 (DEFB) which promote the intracellular killing of the target pathogen, especially the viruses [20,21]. Moreover, vitamin D inhibits the antigen presentation by the Antigen Presenting Cells (APCs) especially the Dendritic Cells (DC) through suppressing the release of pro-inflammatory cytokines (IL-1, IL-6, IL-12 and TNFα) leading to less activation of adaptive immunity and eventually reducing the cytokines storm. Additionally, vitamin D inhibits DC differentiation and maturation giving it a tolerogenic property [11,16,22].

Vitamin D is known to be responsible for T cell proliferation suppression and could also affect the phenotype of T-cells, through inhibition of Th1 cells, which modulates the production of the cytokine storm, at the same time, vitamin D triggers the anti-inflammatory cytokine associated with Th2 (IL3, IL4, IL5) [10]. In the other hand, vitamin D stimulates the production of IL-10 that exerts a dual effect of increasing the production of T regulatory cells (Treg) as well as suppressing the production of (IL-2, IFNγ) which in turn inhibit the Th1 activation.

Beside that vitamin D plays a significant role in protection of

acute lung injury through modulating the expression of renin-angiotensin system e.g. ACE2 in lung tissue. Therefore, we suggest that vitamin D could help limit the occurrence of the cytokine storm and protect lung form the acute injury [21,22].

Recent studies have shown that vitamin D status is associated with COVID-19 mortality rate and prognosis [23]. Furthermore, vitamin D has been involved in reducing the risk of respiratory tract infections, especially COVID-19. Therefore, we strongly postulated that vitamin D could improve the severely-ill COVID-19 patients who displayed decrease regulatory T cells and may overwork beneficial effect on COVID-19 cytokine storm [24]. Some researchers suggest that vitamin D supplements will improve outcomes in COVID-19 patients [25,26].

Discussion and Conclusion

COVID-19 infection is more prevalent in Europe compared to Africa; which most probably attributed to difference in immunity. Studies conducted in Africa generally, showed adequate or even high mean serum vitamin D concentration, whereas in Europe, it has been found to be suboptimal especially in southern Europe (Spain and Italy). There is a possible role of vitamin D to suppress the pathological immune response culminating from COVID-19 disease. The ability of vitamin D "as an immune modulator" to decrease the cytokines storm (the potential cause of death in COVID-19 infection) is found to be the key factor which reduces the number of severe cases and death in Africa.

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