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OPTIMIZING THE "SUNSHINE VITAMIN" TO BOOST IMMUNE DEFENSE AGAINST COVID- 19.

Dental Science

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ABSTRACT

In the past few weeks, several studies have appeared that show that the severity of COVID-19 disease and mortality rate are apparently correlated with low levels of vitamin D, whereas people with adequate levels have only mild symptoms. Can vitamin D supplementation have a positive effect on the course of the disease?

KEYWORDS

INTRODUCTION

World is currently going through a major pandemic of corona virus. New CoV infection epidemic started in Wuhan, China in late 2019. First it was called as 2019-nCoV and latter renamed by WHO as COVID 19 on 11th February, 2020[1]. WHO in March 2020 declared the outbreak as pandemic[2]. Considering challenges when comparing data across nations, COVID-19 mortality in some countries is significantly higher than in others. Several factors may play a role in this discrepancy, including disparities in the proportion of the elderly in a community, general health , health care accessibility and efficiency, and socio-economic status. Another often ignored aspect that may affect the COVID-19 outcome is the relative status of populations with vitamin D. Since people are urged to stay as long as possible at home, Great Britain 's government health services have recommended that people during this pandemic to seek proper doses of vitamin D during the summer and autumn. Supplementation of vitamin D may be especially essential for older people, as they are at high risk of poor COVID-19 outcome and vitamin D deficiency. Globally, as of 1:02pm CEST, 24 May 2020, there have been 5,201,549 confirmed cases of COVID-19, including 337,405 deaths, reported to WHO. (Fig. 1)[3]

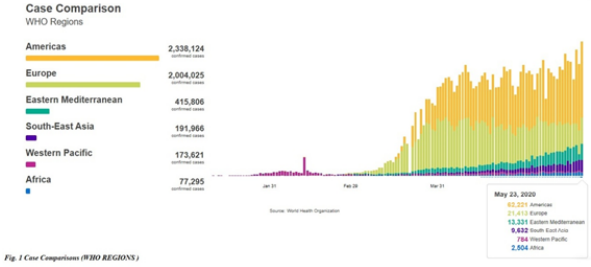

Fig. 1 Case Comparisons (WHO REGIONS)

Vitamin D is a fat soluble secosteroid (steroid with broken rings) which was first discovered in 1919–1924 as an antirachitic agent. It plays a well established role in balancing calcium and phosphates, influencing bone development and turnover. Vitamin D is very important for healthy functioning of immune system leaving numerous individuals to ponder in the case of enhancing with Vitamin D may help diminish the danger of getting the new coronavirus that causes COVID-19.

Observational studies have already reported independent association between levels of Vitamin D and susceptibility to acute respiratory infections. One major exception to this general trend, is for upper respiratory tract infections: A 2017 meta-analysis of individual patient data from 11,321 participants in 25 randomized controlled trials found that vitamin D supplementation was protected against acute respiratory tract infections and that patients with very small (< 25 nmol / L) serum concentrations of 25-hydroxyvitamin D (vitamin D marker) were most effective[4]. In a review of relevant literature on the potential involvement of vitamin D in influenza virus infection prevention, Gruber-Bzura reported that the data created controversy and doubts[11].

Vitamin D a Prohormone

Vitamin D, discovered around 100 years ago as having an anti-rachitic effect, is not a vitamin - the body can make it itself - but a prohormone. Vitamin D arises in the skin from the immediate precursor of cholesterol through a photochemical reaction when it is hit by sunlight with a sufficiently high UVB content (wavelength 280 - 315 nm). In two subsequent enzymatic activation steps, the prohormone is first converted into the hydroxylated product 25-hydroxyvitamin D3 (25 (OH) D3) and then into the biologically active hormone calcitriol (1,25 (OH) 2D3).

Calcitriol works in the same way as the structurally closely related steroid hormones: with its so-called nuclear receptor, it forms a complex that binds in the cell nucleus in a specific way to DNA regions ("response elements") of sensitive genes and controls their expression. Above all, these are genes that play an essential role in the calcium balance - absorption of calcium from the intestine and mineralization of the bones. The consequences of a vitamin D deficiency (see below) are well known and obvious: rickets in children, osteomalacia in adults.

In addition, calcitriol can regulate the expression of an abundance of other genes (of 900 or more genes) that have key functions in important physiological and pathological processes. These include genes that control the growth and differentiation of cells, genes that are essential in the innate and acquired immune response and play an essential role in the defense against infections, required genes in neurophysiological processes and in many other processes in the organism (Fig. 2).

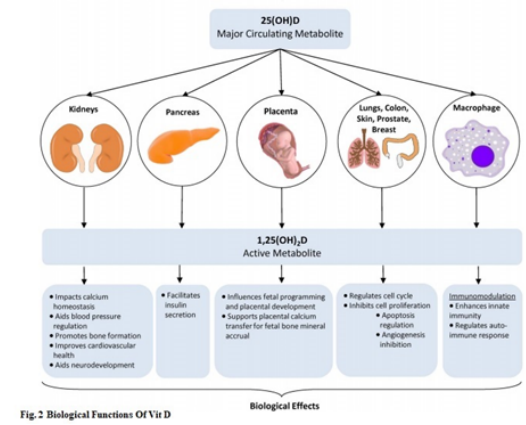

Fig. 2 Biological Functions Of Vit D

EFFECT OF VITAMIN D ON IMMUNE HEALTH:

The biologically active molecule binds to vitamin D nuclear receptors (VDR) to perform its actions. VDRs are present in cells of immune system, bone, kidney and cells of intestine which are ultimately involved in calcium, phosphate and bone metabolism. Bound vitamin D molecules then join with retinoic acid X receptor (RXR) and form a heterodimer – VDR/RXR. This heterodimer serves as a nuclear transcription factor which regulates gene expression (which influence calcium and phosphorus metabolism).

VDR is expressed by keratinocytes of basal and spinous layer of epithelium. Vit D/VDR signalling influences proliferation, differentiation and apoptosis of keratinocytes along with local immune responses[5]. This signalling mediates antiproliferative and prodifferentiation effects. Moreover, MARTIN HEWISON stated the major effect of Vitamin D: its ability to act as a potent modulator of human immune responses on. He made the following observations:

- Numerous cells from both innate and adative immune system communicates the VDR.
- Also, antigen presenting cells i.e. macrophages and dendritic cells also express alpha 1 hydroxylase enzyme which converts biologically inactive molecule of vitamin D to biologically active form that can incite reactions in the cells by binding to their VDRs and advancing transcriptional guidelines[6]. Vitamin D inhibits innate immune system by inhibiting antigen presentation and innate antibacterial activity.

In innate immune response, TOLL LIKE RECEPTORS sense pathogen associated molecular patterns followed by increased synthesis of 1,25(OH)2D3 in macrophages ultimately leading to the generation of antibacterial substances such as cathelicidin and beta-defensins. Wang et al.[7], reported that the expression of cathelicidins and defensins is dependent on plasma concentration of Vitamin D. Vitamin D can promote expression of cathelicidins in diverse cell types such as macrophages, keratinocytes, neutrophils, and T lymphocytes[8]. Deficiency of Vitamin D may weaken innate immune reactions and make individuals prone to infections and low serum centralization of 25(OH)D3 have been connected to irresistible maladies such as tuberculosis.

Vitamin D also influences the adaptive immune response. The activation of CD4 + T-cells increases the VDR expression to five folds, enabling calcitriol to regulate at least 102 identified genes[9]. This regulatory effect decreases the levels of chemokines and cytokines. Vitamin D has strong suppressive effects on IL-2 and IFNγ in a VDR-regulated mechanism. T helper cells(Th1) release (IFNγ), IL-2, IL-12, and tumor necrosis factor alpha Th2 cells express IL-4, IL-5, and IL-13, which further propagate the Th2 response. These Th2-derived cytokines modulate the immune response. The suppression of IL-2 production, in turn, inhibits T-cell proliferation. In general, vitamin D diminishes cell mediated immune response of body. This suppression is enhanced by action of Vitamin D on antigen presenting cells where vitamin D inhibits the production of IL-12 (which enhance Th1 response). Vitamin D acts as a physiological brake on adaptive immunity.

Vitamin D deficiency

The vitamin D present in the human organism is mainly due to its synthesis in the skin and only to a small extent to food supplied - unless one mainly feeds on fatty fish; In addition, supplementation with synthetic vitamin D can take place. A person's vitamin D status is determined based on the blood level of their metabolite 25 (OH) D3. There is consensus about what is to be regarded as a serious deficiency and has an established effect on calcium homeostasis and, above all, on the bone / muscle system – vitamin d blood levels below 10 - 12.5 ng / ml (25 - 30 nM). With regard to adequate levels that are desirable for health, there are different views; a status of > 30 ng / ml (di> 75 nM) is often mentioned.

A prerequisite for the natural synthesis in the skin is a sufficient proportion of UVB radiation in sunlight and this is only the case in the northern hemisphere from around 40 degrees of latitude in the spring and summer months[16]. If the living conditions allow enough sun to reach the skin during this time, the prohormone formed during this time will on average last until autumn; at the beginning of winter, levels below 30 ng / ml up to severe deficiency may already be present. With increasing age, the capacity for vitamin D synthesis decreases; together with a reduced stay outdoors, the vitamin D stores in the organism can be emptied even earlier.

Vitamin D in COVID-19

The potential protective factors are little known. Calcitriol (1,25-dihydroxyvitamin D3) has a marked effect on the ACE2 / Ang(1–7)/MasR axis with increased ACE2 expression[12]. ACE-2 is the receptor for host cells known for mediating SARS-CoV-2 infection. It may mean a higher risk of infection starting from this. This has not been shown to date, however, and previous studies have established correlations between the health outcomes of higher ACE2 rates and better coronavirus disease. ACE2 has been shown to protect against acute lung damage in the lungs[13].

The researchers discovered a clear link between extreme vitamin D deficiency and mortality levels after analyzing global data from the novel coronavirus (COVID-19) pandemic. The study team led by Northwestern University performed a comparative review of data from hospitals and clinics around China, France, Germany, Italy, Iran, South Korea, Spain, Switzerland, UK and the United States[10]. The researchers observed that patients from countries with high COVID-19 death rates, such as Italy, Spain and the United Kingdom, had reduced levels of vitamin D relative to patients in countries not affected as badly. Backman and his team found a clear link between the levels of vitamin D and the cytokine storm — a hyperinflammatory condition caused by an overactive immune system — as well as a link between the vitamin D deficiency and death. The cytokine storm can cause serious lung damage and acute respiratory distress syndrome which leads to death in patients. Researchers claim this is precisely where vitamin D plays a significant part. Vitamin D not only strengthens our inborn immune systems but also protects our immune systems from being overly overactive. This means that having good levels of vitamin D will protect patients from serious complications from COVID-19, including death. With regard to adaptive immune defense, calcitriol can suppress essential inflammation mediators such as interleukin-2 and interferon gamma and, as a whole, intervene in the inflammatory process ("cytokine storm"), which dominates the late heavy phase of COVID-19.

This connection may help to clarify the many questions surrounding COVID-19, for example why children are less likely to die. Children still do not have a fully formed acquired immune system, which is the second line of protection for the immune system and is more likely to overreact. Children rely almost entirely on their innate immune system, which may describe why they have a lower mortality rate.

Vitamin D, however, has many functions in the immune system that can modify the body's response to an infection. Abu-Amer et al, identified the deficiency in vitamin D as impairing the ability of macrophages to develop, produce macrophage-specific surface antigens, produce lysosomal enzyme acid phosphatase, and emit H2O2, an integral feature of their antimicrobial activity[14]. This could in part explain why Martineau et al. observed that vitamin D was protective in hypovitaminosis cases[4].

In a rodent model study, Xie et al. investigated ACE2 expression in the lungs and the effect of ageing and gender on its expression. They described a relatively small decrease in ACE2 between youth and middle-aged groups (25 per cent for males and 18 per cent for females, respectively), but the ACE2 content in older female rats decreases by 67% and even higher by 78% in older male rats compared to younger

rats[15]. The decline in ACE2 with age and gender appears to reflect both the increase in COVID-19 mortality and the higher mortality in the male population.

So is the vitamin D status crucial for the course of the disease?

The data available so far correlate vitamin D deficiency, which occurs particularly in the old population, with a severe course of COVID-19. This is undoubtedly impressive, but should be interpreted with caution. With increasing age there are fundamental changes in our metabolism, essential processes of hormonal regulation stop working, the immune system weakens and the susceptibility to various diseases increases. All of these can contribute to the incidence and course of COVID-19. The correlations that point this out have prompted numerous researchers who now want to test the hypothesis in clinical studies. Since April, 14 such clinical studies have been reported in the https://clinicaltrials.gov/ database, which are expected to run in Spain, Portugal, UK, US, Iran, Turkey and France. (As an example, a multicenter study in France: COvid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D 3 in High-risk COVID-19 Patients (CoVitTrial).

CONCLUSION

Vitamin D deficiency is obvious to be dangerous and can be easily treated with adequate supplementation. This won't stop a patient from contracting the virus, but it will reduce complications and avoid death among those infected. It has already been shown to be safe for acute respiratory infections and has proved to be effective. Nonetheless, it is certainly recommended that all such studies end by supplementing vitamin D or, better still, by allowing sunlight on the skin. In summary, due to the high prevalence of vitamin D deficiency and in order to increase serum concentrations rapidly, safely and significantly, high-dose vitamin D intervention with possible advantages is suggested as a safe and non-invasive treatment for decreasing risk of COVID-19 severity and mortality. Patients would take large doses of vitamin D for a week, followed by a couple of thousand IU / d of vitamin D for a 2 week period. This will ensure that serum vitamin D levels are restored quickly and sustainably, thus potentially triggering an improvement in clinical status and prognosis. Dedicated work on levels of vitamin D in COVID-19 patients with varying degrees of seriousness of disease should be carried out further.

Competing Interest Statement

The authors have declared no competing interest.

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