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ROLE OF VITAMIN D AS AN IMMUNO-MODULATOR IN COVID-19.

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ABSTRACT:

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) DISEASE (COVID-19). The current outbreak of coronavirus disease (COVID-19) got reported first from Wuhan, China, on 31 December 2019. A novel coronavirus disease 2019 (COVID-19) outbreak is a global dramatic pandemic that is immeasurably impacting our communities. Considering massive health and economic burden of the COVID-19 pandemic, any means by which to improve the condition of patients to accelerate recovery and to reduce the risk of deterioration and death would be considered of significant clinical and economical importance. In the absence of approved marketed drugs against coronaviruses, the treatment and management of this novel CoV disease (COVID-19) worldwide is a challenge. Vitamin D is an immune-modulator, acting through the innate immune cells called dendritic cells as well as the adaptive T cells. This leads to higher clearance of the virus from the body as well as suppression of the inflammatory responses which lead to symptomatic illness. Direct virus-targeted antiviral agents target specific nucleic acid or proteins of the virus while host-based antivirals target either the host innate immune responses or the cellular machineries that are crucial for viral infection. Both the approaches necessarily interfere with viral pathogenesis. The emergence of SARS-CoV-2 has once again exposed the weaknesses of global health systems preparedness, ability to respond to an infectious threat, the rapidity of transmission of infections across international borders and the ineffectiveness of knee- jerk policy responses to emerging/re-emerging infectious disease threats. The study concludes with the key learning points from the ongoing efforts to prevent and contain COVID-19 and identifies the need to invest in health systems, role of Vitamin D as an Immuno-modulator and the need for preparedness and global health security.

Key words: - Immunomodulator, coronavirus, vitamin, cholecalciferol, human health.

INTRODUCTION:

Coronavirus disease (COVID-19) is an infectious disease caused by a new virus that had not been previously identified in humans. COVID-19 has been declared as a pandemic by WHO due to the alarming levels of spread and severity. Till date, there is no specific medicine to treat or prevent COVID-19. In response to the outbreak, there is an urgent need to accelerate development of diagnostics, vaccines, novel therapeutics and re-purposing of drugs for this novel coronavirus. In view of the limited current level of knowledge about the new virus, critical research questions need to be answered urgently, and ways have to be found to fund priority research that can contribute to curtail this outbreak and prepare for future outbreaks. Urgent need to develop safe and effective countermeasures that can be available, accessible and suitable for use in populations most in need. Research is an important integral component of the response to be able to identify key knowledge gaps and research priorities, and thereby accelerate the generation of critical scientific information and the most needed medical products to contribute to the control of 2019-nCoV emergency (1,2).

Vitamins are substances required for the good health but these are not synthesized in the human body. While cholecalciferol is called a vitamin, and it actually function as hormone. The discovery of vitamins is a breakthrough in the understanding the relationship between diseases and health. Vitamin D also known as sun shine vitamin was first identified as a vitamin early in the 20th century. Discovery of vitamin D is linked with studies on rickets; in 1920's vitamin D was identified as a preventing agent against rickets(1). Vitamin D is well known for calcium absorption and to maintain bone mineral dentistry. The importance of vitamin D for the human health

and its potential beneficiary effects on the health have been established by a lot of research work in the past decade. From different epidemiological studies it has been evident that vitamin D plays a crucial role in several other physiological processes including cellular differentiation and proliferation, immune regulation, central nervous system function and cardiovascular health. Beside its effect on calcium and phosphorus homeostasis vitamin D is also involved in providing immunity against microbial pathogens(2). Role of vitamin D in auto immune and metabolic disorders has also been established in many studies. Many research groups tried to establish the role of vitamin D in management and fighting against TB(3).

Vitamin D is a fat-soluble substance of steroidal nature that is essential for the human organism. Its origin can be endogenous, produced from skin-derived 7-dehydrocholesterol that is converted to vitamin D3 or cholecalciferol by ultraviolet sunlight, or exogenous, from the intake of vegetables (vitamin D2 or ergocalciferol) or foods of animal origin (cholecalciferol) and their subsequent absorption via the intestine. The active form of vitamin D or calcitriol is synthesized within the organism after transformation of its precursor cholecalciferol, which is biologically inert and requires two hydroxylations for its activation. The first hydroxylation takes place in the liver, where cholecalciferol is transformed into calcidiol or 25hydroxycholecalciferol by mitochondrial enzyme 25-hydroxylase (CYP 2R1). The second hydroxylation is in the kidney, where enzyme 1αhydroxylase (CYP27B1) metabolizes calcidiol into calcitriol or 1-α,25- dihydroxycholecalciferol, which can bind to its nuclear receptor in different cell populations and modify various functions of these cells(1).

The evolutionary story of vitamin D started more than a billion years ago as an inert molecule being an end product of a photochemical reaction. Since more than 500 million years vitamin D gained via the nuclear receptor VDR endocrine functions. The role of vitamin D in bone health is well known but represents only one aspect of the pleiotropic functional profile of the molecule. The immune-regulatory function of vitamin D developed even earlier to its role in calcium homeostasis and seems to have a comparable impact. Moreover, as the evolutionary history indicates and also genome-wide experimental data demonstrate, the original and likely still central function of vitamin D is to regulate genes involved in energy metabolism. Due to the since ancient times preferred non-marine diet of humans, different genetic admixture and the rather recent indoor lifestyle, vitamin D_3 became the most important supplement to compensate for insufficient sun exposure(4).

Vitamin D and autoimmunity

Various studies have demonstrated the beneficial effect of vitamin D against the development of some ADs. All immune system cells express the VDR and are therefore susceptible to calcitriol-mediated modulation. In addition, some immune cells can synthetize calcitriol by expressing 1α-hydroxylase, including dendritic cells (DCs), macrophages, and B and T cells. Calcitriol can affect the maturation and migration of different DC subtypes and their production of cytokines and chemokines, giving them an immune-regulatory and tolerogenic role. The interaction of calcitriol with its receptor, VDR, halts DC differentiation and maturation of DCs and enhances their tolerogenic status, reducing the production of pro-inflammatory cytokines (IL6, IL-12, IL-23) and tumor necrosis factor α (TNF-α), increasing the production of anti-inflammatory

cytokines (IL-8, IL-10), and diminishing the expression of major histocompatibility complex class I and II and surface costimulatory molecules (CD40, CD80, CD83, CD86)(1,5).

Calcitriol inhibits the differentiation of B cells into plasma cells and their production of antibodies. It can also act on T cells when these express VDR after their activation. Specifically, Th1 and Th17 subpopulations are reduced and Th2 differentiation is promoted in $CD4^+$ T cells, producing IL-4. Calcitriol also stimulates the activity of regulatory cells that suppress the immune response. These effects on immune cells may explain the beneficial effect of vitamin D observed against certain autoimmune diseases(6). the findings are suggestive that ritonavir and lopinavir may have good potential for repurposing as SARS-CoV-2 protease inhibitors. Molecular dynamics simulation studies for the complexes obtained in this study would be essential to identify specific interactions between the enzyme and drug in the stable complexes and observe the hydrogen bond pattern, especially in the presence of solvent molecules. Additionally, studies need to be undertaken for the binding analyses of the other protease inhibitors, specific RdRp inhibitors and inhibitors of other enzymatic targets. The results would help gain an in-depth understanding of the relative binding affinity and design of derivatives with greater binding potential at the enzyme active site.

Vitamin D insufficiency or deficiency is associated with the onset and progression of some ADs. Most studies on vitamin D supplementation have observed beneficial preventive or curative effects. The ideal supplementation dose of vitamin D for patients with ADs remains under debate; however, there is consensus on the need to promote healthy habits in the population to increase their levels of this vitamin as a preventive measure against ADs and other diseases. Therefore, considering the importance of vitamin D for the function of the immune system, it is reasonable to recommend maintenance of adequate vitamin D status for the general population. Vitamin D is known to have a large impact on innate immunity, for example, by regulating the expression of antimicrobial peptides, such as cathelicidin (CAMP). Moreover, the critical co-receptor of toll-like receptor (TLR) 4, CD14, is a prominent vitamin D target gene in monocytes. These actions of vitamin D on innate immunity had already been established in fish. Furthermore, antigen-presenting dendritic cells are another cellular component of innate immunity that is very responsive to vitamin D. Dendritic cells interact with T cells, i.e., they modulate the actions of adaptive immunity. Thus, the vitamin D responsiveness of the evolutionary older part of the immune system nowadays still has a major impact on efficient pathogen defense. Interestingly, the human leukocyte antigen (HLA) locus cluster on human chromosome 6 was detected as a “hotspot” of epigenome-wide. In the course of evolution the biologically active form of vitamin D_3, 1, $25(OH)_2D_3$, became a pleiotropic compound that regulates not only genes involved in cellular metabolism but also in calcium homeostasis and bone mineralization as well as in innate and adaptive immunity. A pharmacologic application of 1, $25(OH)_2D_3$ or its synthetic analogs over a prolonged time period is often limited by the risk of causing hypercalcemia. Therefore, the main aim for developing vitamin D analogs is to dissociate their function, e.g., to activate the immune system without increasing calcium absorption. For a few analogs, such as topically applied calcipotriol (marketed as “Dovonex”, “Daivonex” and “Psorcutan”) against psoriasis, this had been successful. However, the molecular

basis of the achieved selectivity is not based on any differential activation of the VDR but on the pharmacokinetic profile of the compound leading to rapid degradation.

Therapeutic perspectives(3,4,&7).

Vitamin D supplementation

Local vitamin D metabolism allows immune cells to modulate immune responses autonomously when regulation is required, but optimal functioning of this autocrine and/or paracrine circuit crucially depends on the availability of circulating 25(OH)D_3. The exact levels of circulating 25(OH)D_3 needed to meet the requirements of vitamin D sufficiency are still a matter of debate, especially in the light of the non-classical effects of vitamin D(4,5). Nevertheless, it is generally accepted that vitamin D insufficiency or even deficiency are highly prevalent in many populations across the globe. Therefore, vitamin D supplementation represents an attractive strategy to ensure sufficient 25(OH)D_3 levels for adequate immune function, thereby eliminating one of the proposed risk factors that may underlie disorders such as chronic infections and autoimmunity(8,10).

RESULT & DISCUSSION

Results of epidemiological studies and in vitro studies are suggested to indicate that the vitamin might have much broader effects on health, including cancer, cardiovascular diseases, autoimmune diseases and infections(9). The renewed interest in Vit D has led to a large increase in the number of studies published over the last two decades. However, in this rapidly growing scientific area several uncertainties remain regarding effects, status and function of Vit D. After the discovery of the VDR in many tissues, the possible role of vit D in different diseases has been studied extensively. The role of Vit D in cellular Proliferation, differentiation, apoptosis and the innate and adaptive immune system was recognized.

CONCLUSION:

The findings are in support of the finding that a low vitamin D level boosts the risk of COVID-19, but treatment that adequately addresses the deficiency reduces the risk. This conclusion is strengthened by the finding that those who were treated with higher doses after having a low vitamin D level at their last test were not at higher risk. Their chances were comparable to those whose last test results and treatment history suggested adequate vitamin D levels at the time of COVID-19 testing.Vitamin D is now believed to play a role in the development (or prevention) of several autoimmune diseases, based on its immune-modulatory properties(7). As well, the increasing incidence of autoimmune disease as one moves away from the equator, may be due to the lack of sunlight, which is crucial for the maintenance of normal vitamin D levels. A deficiency in vitamin D levels or vitamin D receptors is commonly indicated in autoimmune diseases, with multiple sclerosis (MS) being one of the best-studied and well-known examples(8). However, the role of vitamin D in other autoimmune diseases is not well defined, including autoimmune liver diseases such as primary biliary cirrhosis, autoimmune hepatitis, and primary sclerosing cholangitis. It will become clear that vitamin D likely plays a role in the development of autoimmune liver disease, but this area requires further investigation.

Conflicts of Interest: *Dept. of Technology, Savitribai Phule Pune University*

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Fig.1 Vitamin D (calcitriol)