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Vitamin D and COVID-19

Dr Arup Halder

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Though the SARS-CoV-2 is also known as 'novel' coronavirus, we don't have any novel drugs for treatment or prevention of this disease. The only drug which has shown proven benefit in reducing the mortality is steroid, though the timing of application is key to get an optimal outcome. While this is used in a proven COVID patient in dysregulated immune stage, we still do not have any drug which can prevent the infection. Though many of the drugs are being proposed to modulate the immune system and thus can reduce the severity of the disease. One of such drug is Vitamin D. Here in this article we will try to look at Vitamin D and COVID relationship.

Different forms of Vitamin D

There are many confusion in relation to Nomenclature and measuring units of Vitamin D. First we will need a clear view on that aspect.

1) There are three main sources of Vitamin D, plant source and animal source and sunlight.
2) The Vitamin D from plant sources are called **Ergocalciferol or Vitamin D2**. The Vitamin D from animal or sunlight is called **Cholecalciferol or Vitamin D3.**
3) Both of Vitamin D2 or D3 undergo 25 hydroxylation in the liver to f**orm 25 Hydroxy Cholecalciferol or 25(OH)D or Calcifediol.**
4) This Calcifediol or 25(OH) D is further hydoxylated in position 1 to form **1, 25(OH)2D or 1, 25 Dihydroxy Vitamin D or also known as Calcitriol.** This Calcitriol is the main active form of Vitamin D and modulates various physiological actions while acting through Vitamin D receptors or VDR.
5) When we measure Vitamin D levels in blood we generally measure the Calcifediol level, means the 25 Hydroxy form. It is measured either as nanogram/ ml (ng/ml) or nanomol/Litre (nmol/L). The first unit is used in US and the second unit is used in UK. The conversation from ng/ml to nmol/L can be done as follows ng/ml × 2.5= nmol/L, example Higher blood level is considered as 33 ng/ml (33×2.5)= 82.4 nmol/L. Lower blood level is considered as 12 ng/ml (12×2.5)= 30 nmol/L
6) The therapeutic dose of Vitamin D is measured in two units. It is measured either in International Units (IU) or in micrograms (mcg).
   1 mcg= 40 IU of Vitamin D
7) According to US endocrine society 4 Vitamin D status have been described depending on blood levels.

Deficiency: <20 ng//ml
Insufficiency: 21 to 29 ng/ ml
Sufficiency: >30 ng/ ml
Toxicity: >150 ng/ ml

Vitamin D and COVID-19

The role of Vitamin D to prevent Acute Respiratory infections (ARI) were shown in many studies. A meta-analysis published in 2017 in BMJ [1] identified 25 eligible RCTs (n=11321). They showed Vitamin D supplementation reduced the risk of ARI among all participants (adjusted Odds Ratio 0.88, 95% CI 0.81- 0.96, $p < 0.001$). In subgroup analysis, protective effect of Vitamin D were shown in those receiving daily or weekly doses of Vitamin D without additional bolus doses, but not in those receiving one or more bolus doses. Vitamin D was well tolerated by the participants in the study. A recent study has shown that Vitamin D sufficiency was associated with reduced risks of adverse outcomes in COVID-19 [2]. After adjusting for the confounding factors, the study found, there was a significant association between Vitamin D sufficiency and reduction of clinical severity, inpatient mortality, CRP levels and increase in lymphocyte percentage. Only 9.7% of patients older than 40 years who were Vitamin D sufficient succumbed to the infection compared to 20% who had a Vitamin D Insufficiency (<30ng/ml).

Another recently published study described the effect of Calcifediol treatment in patients hospitalized for COVID 19 [3]. 76 consequetive patients hospitalized for COVID were allocated to two groups. Both arm received HCQS+ Azithromycin, but only one arm received Calcifediol in addition. Of the 50 patients treated with Calcifediol, only 1 required (2%) admission to the ICU, while of 26 patients not on Calcifediol, 13 required (50%) admission to ICU, a p value < 0.001. In the Calcifediol arm no patient died, while 2 patients died among the 13 patients who were not on Calcifediol and admitted to the ICU. A recent unpublished study on 5000 patients defined the role of Vitamin D on suppression of inflammation in COVID [4]. They stated that elimination of severe Vitamin D deficiency reduces the risk of high CRP level (OR 2) in COVID patients.

But what is the possible mechanism of action of Vitamin D in COVID 19?

We already know that Vitamin D is required for the maintenance of normal blood levels of Calcium and Phosphate, that are required for mineralization of bones, muscle contractions, nerve conduction and general cellular functions [5]. It is also important for immune function, inflammation, cell proliferation and differentiation [6, 7]. The possible role of Vitamin D in COVID 19 and other infectious diseases is explained by its regulatory effects on Innate and Adaptive immune responses [8]. In Innate arm, Vitamin D is produced in macrophages in response to stimulation of Toll like receptors by binding of the infectious agent. Vitamin D synthesized binds to VDR and augments production of Antimicrobial peptides like Defensins and Cathelecidins [9]. These peptides have antiviral effects. In Adaptive immune response, Vitamin D inhibits activation of B Cells [10] promotes T Regulatory cells. These ultimately lead to suppression of Th1 and Th17 types of responses and promotes Th2 type of response, thus

have a calming effect on inflammatory system. Vitamin D also regulates Invariant NK T cells which are thought to be a link between Innate and Adaptive arms [11].

Vitamin D deficiency pandemic

It is clear from above discussions that Vitamin D has a role in infectious diseases, like COVID 19 by modulating the immune responses. But how common is the Vitamin D deficiency among general population?

Hilger J et al in 2014, estimated 88.1% of the world population would have a Vitamin D below 30 ng/ml, and 37% would have a Vitamin D levels below 20 ng/ ml [12]. Though in our country India we have a lot of scorching sunlight, yet Vitamin D deficiency is rampant in our country. The community based studies have shown a prevalence of Vitamin D deficiency ranging from 50 to 94% [5]. Hospital based studies in our country have found a prevalence of Vitamin D deficiency from 37 to 99% [5].

But what me the reasons for such a huge prevalence of Vitamin D deficiency ?

1) Increased indoor lifestyle
2) Pollution can hamper the Vitamin D synthesis by skin
3) Changing food habits contribute to low dietary calcium and Vitamin D intake
4) Phytates and Phosphates which are present in fiber rich diet, can deplete Vitamin D stores and increase Calcium requirement [13].
5) Increased melanin and skin pigmentation reflect UV rays more and decrease the synthesis of Vitamin D in skin. Sunscreen applications do similar effects.
6) Cultural practices of covering the body with clothing.

Vitamin D sources, requirement and dosing

Cholecalciferol (Vitamin D3) or Ergocalciferol (Vitamin D2) are native sources of Vitamin D [14]. Cholecalciferol is obtained by ingesting foods mostly from animal origin, mainly oily fish, egg yolk, fungi or meat. Ergocalciferol is obtained mainly from vegetables [15, 16]. **But 90% of required Vitamin D is synthesized in the body under sun exposure**. The UVB light (290 – 320 nm) from sun exposure converts 7 Dehydrocholesterol, present in skin, to pre Vitamin D3, which undergoes thermal isomerization into Cholecalciferol.

Atleast 5 to 30 minutes of sun exposure between 10 am to 3 pm for atleast twice a week to the face, arms, legs or back without sunscreen, usually synthesize sufficient Vitamin D [17]. But numerous factors reduce the ability of skin to make Vitamin D, like time of the day, whether, skin color, advanced age etc. Sunlight exposure through glass is ineffective in producing Vitamin D because glass filters out UV light necessary for conversion. Sunscreen with SPF >8 may block Vitamin D producing UV rays.

The Recommended Daily Allowance (RDA) of Vitamin D is around 800 IU/ Day. This RDA is calculated assuming that it will be obtained from dietary exposure and not through the sunlight. This RDA corresponds to lower cutoff of Vitamin D concentration in blood, that is a value of 20 ng/ml. The National Heath and Nutritional Examination Survey (NHANES) in US has estimated that women in US of more than 70 years of age have an average total Vitamin D intake from foods of only 156 IU/Day [18].

The tolerable upper limit of intake is 4000 IU/ Day. Some groups recommend 800 IU to 2000 IU / Day, but few groups recommend even higher doses of 5000 IU or even 10000 IU per day without any symptoms of toxicity [19, 20]. It takes several months to reach a steady state plasma concentration when Vitamin D is administered in standard daily doses. So various studies have been published with loading doses protocol. One protocol studied the administration of 100000 IU of Vitamin D3 administered every 2 weeks for a total 4 doses. It is after 7th day of 4th doses subjects reached sufficient Vitamin D concentration who were initially deficient [21]. So it took almost 2 months to achieve sufficient serum concentration with the bi weekly loading doses. Another study has demonstrated a weekly loading dose of Vitamin D can achieve the serum concentration after 5 weeks of administration. This is why one study used ‘Vitamin D hammer’ in treating patients with Influenza, they used 1 time 50000 IU of Vitamin D3 or 10000 IU for 3 times daily for 2 to 3 days [22]. Given this time lag to achieve the optimum serum concentration, it is really difficult to say how far it will be effective when administered after diagnosis of COVID 19. A preventive approach may be more useful than therapeutic approach.

The optimal doses of Vitamin D should be determined after consultation with a doctor and according to the serum levels. Increased self administered doses may be associated with toxicity as this is a fat soluble Vitamin and get stored in the body [17]. **Toxicity** can include non specific symptoms like anorexia, weight loss, polyuria and irregularities of heart rhythm. There may be elevation of serum Calcium leading to calcification of blood vessels and tissue calcification. A RCT has shown high doses of Vitamin D supplementation increase risk of fracture and falls, and kidney stones. Some epidemiologic investigations have reported adverse association of high Vitamin D levels with Prostate cancer and pancreatic cancer.

But in case of Vitamin D the risk/ benefit ratio is always skewed in favor of benefits when administered in proper doses and forms. The benefits ranges from maintaining bone metabolism to reducing the prevalence of colon cancer.

Though mostly for supplementation Cholecalciferol (Vitamin D3) is used widely, but for patients with liver disease or intestinal problems, Calcifediol (25OHD3) should be used which will skip the liver hydroxylation phase and have a good Intestinal absorption. Similarly in kidney disease the active form of Vitamin D, that is Calcitriol (1, 25 Dihydroxy Vitamin D) should be used.

Conclusion

In COVID 19 disease the evidences are still emerging. There are paucity of RCTs and most evidences are based on cross-sectional studies. They are often considered as anecdotal evidences and prescription of any drugs based on these evidences are not recommended in medical science. But any drug which has a logical and scientific rationale and devoid

of serious adverse effects may warrant a judicious use in selected patients, specially if the patients are deemed to be deficient of that particular agent. Vitamin D is one such drug. This Vitamin D, which behaves as 'secosteroid' or a steroid like molecule with broken rings, is truly a fascinating molecule [23].

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