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The Possible Role of Vitamin D in Prevention and Treatment of COVID-19 Disease

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Abstract

Preliminary studies suggest an inverse link, between serum vitamin D levels and the severity, and mortality in Covid-19 patients. Such patients are suffering from inflammation storm caused by the excess production of cytokines by the immune system. The present review provides indications for the anti-inflammatory activity of 1,25-Dihdroxyvitamin D_3. This vitamin D active metabolite, down-regulates the expression of TNFα in human macrophages. TNFα is a major mediator of host response to pathogens, since it initiates a powerful pro-inflammatory cascade. However, excessive production of TNFα over-activates inflammation accompanied by a cytokines storm, as occurs in the Covid-19 disease. These findings provide a biological basis and possible mode of action by which vitamin D makes its impact on the Covid-19 disease, and emphasize the possible role of vitamin in preventing Covid-19, or at least moderates its severe symptoms. Hence, it is suggested to prevent vitamin D deficiency by vitamin D supplementation for the general population, with a special care for the elderly. In case of acute Covid-19 disease, It is suggested to treat patients with the active metabolite of vitamin D, $1,25(OH)_2D_3$, or with its less calcaemic synthetic analogs.

Keywords: COVID-19, Vitamin D, $1,25(OH)_2D_3$, Cytokines, TNFα, NF-κB, Macrophages, respiratory infection

Recent preliminary observations suggest a role for vitamin D in the prevention of Covid-19 disease and mortality [1,2]. Although, no clinical studies on vitamin D supplementation in Covid-19 disease are available, some observations reveal a possible association between vitamin D deficiency and the frequency and severity of the disease [1]. The purpose of the present review is to describe some indications that may provide a biological basis and possible mode of action by which vitamin D makes its impact on the Covid-19 disease.

Patients in second stage of Covid-19 disease, suffer from a severe unregulated inflammation storm caused by the excess production and secretion of cytokines by the immune system. These cytokines include the Tumor Necrosis Factor alpha (TNFα) and a variety of interleukins (IL), including IL-6. Indeed, this is the reason for the experimental therapeutic treatments of Covid-19 patients with steroids, and with IL-6 antibodies (Actemra), in order to moderate this cytokines storm.

In a previous study we have demonstrated in vitro the anti-inflammatory activity of vitamin D in human macrophages [3]. It was shown on this study that the active metabolite of vitamin D, namely 1,25-Dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) downregulates the expression of TNFα in human macrophages. TNFα is a major mediator of host response to pathogens since it initiates a powerful pro-inflammatory cascade. However, excessive production of TNFα leads to over–activated inflammation accompanied by a cytokines storm, as occurs in the Covid-19 disease. In a following study we have exposed the mechanism by which $1,25(OH)_2D_3$ downregulates the TNFα expression [4]. Transcriptional activation of the TNFα gene in macrophages is dependent on the transcriptional factor NF-κB. In the resting situation NF-κB bound to its inhibitor IκB, remains in the cell cytoplasm. Following pathogens invasion, or polysaccharide activation, IκB is degraded, and the free NF-κB is trans-located to the cell nucleus and activates the transcription of specific genes responsible for the immune and inflammatory responses. It was found by us that $1,25(OH)_2D_3$, as well as its less calcaemic vitamin D_2 analog ($1,24(OH)_2D_2$), inhibit the degradation of IκB. As a result, the translocation of the NF-κB to the nucleus is decreased, TNFα expression is reduced, and the inflammation became moderated [4]. Moreover, earlier studies have demonstrated that the active metabolite of vitamin D, $1,25(OH)_2D_3$, is produced not only in the kidney, but also by human peritoneal

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macrophages [3,5] and by human alveolar macrophages [6]. It means that in this case there is an autocrine effect. The $1,25(OH)_2D_3$ which is produced in the macrophage regulates the TNFα expression in the same cell. The regulation of cytokines expression by $1,25(OH)_2D_3$ is not limited to TNFα Similar down-regulation effect was described for IL-12 in human monocytes [7].

Although there are no direct clinical experiments concerning the effect of vitamin D on the regulation of cytokines production in general, and no such direct experiments in the case of Covid-19, there is a significant number of reports about the positive effect of vitamin D in the treatment of acute respiratory tract infections [8,9] which is the main complication of the Covid-19 disease. This phenomenon is summarized in an extensive meta-analysis of 25 randomized, double blind. placebo controlled trials with a total of 11,321 participants, supplemented by vitamin D [10]. The authors, A.R. Martineau, *et al.* [10], emphasize that vitamin D supplementation was safe, and reduced the risk of acute respiratory tract infection among all participants. However, patients with a deep vitamin D deficiency before intervention, got the most significant benefit by the vitamin D supplementation. We believe that our in vitro results concerning the downregulation of cytokines expression in human macrophages by the active metabolite of vitamin D provides the biological and physiological basis for the clinical findings described above. Moreover, we do believe that our results open the gate for the possible treatment of Covid-19 patients with vitamin D, with its metabolites, or with its analogs.

No doubt that in the present Covid-19 disease situation, there is a reduction in the serum vitamin D levels. Home quarantines and the limitations of movements outside, decrease significantly exposure to sunshine. As a result, there is a reduction in the endogenous production of vitamin D. The situation is more serious among the elderly population, specifically those who live in elderly houses. In general, old people are less exposed to sunshine, their endogenous production is decreased with age, and their intestine ability to absorb vitamin D from their diet is also reduced. Even residing in a sunny area, does not guarantee adequate vitamin D levels, as people avoid sunshine in order to prevent skin cancer, or use U.V. protective creams for the same purpose. It is possible of course, and desirable to correct, and normalized, vitamin D levels by vitamin D supplementations. This conclusion is particularly important today with the global spread of the Covid-19 pandemic.

This was concluded also by Dr. Umhau from NIH in a short review that was published on last March 2020 [2]. On this review, Dr. Umahau emphasizes the point that the sunshine deficiency during the winter months increases the frequency of respiratory tract infections. In light of this situation, obese, or elderly people, as well as people with dark skin should be supplemented with significant amounts of vitamin D in order to get protection against respiratory tract viral infections. As we know, respiratory tract infections is the main complication of Covid-19 disease, and correction of serum vitamin D levels may prevent or decrease the risk of this disease.

It is well known that the severity of the Covid-19 disease is different in various patients. There are patients that pass the disease with light symptoms, while others are experiencing very serious symptoms. It will not come as a surprise for me if it will be found out that some of the seriously ill patients have a vitamin D deficiency status. Moreover, most of the Covid-19 patients and specifically most of the mortality are concentrated in the elderly population. As established already in the literature and in practice, this population suffers from vitamin D deficiency. This is of course not the only reason for this phenomenon, but in light to the above indications, vitamin D deficiency at least contributes to this serious situation. In order to clarify this point, it should be advisable to perform dedicated studies concerning vitamin D serum levels in Covid-19 patients with different degree of disease severity.

In conclusion, it is suggested to prevent vitamin D deficiency by vitamin D supplementation and to keep the normal serum vitamin D levels in the general population, with a special care of the elderly, the obese, and people with dark skin, in order to prevent, or to reduce, at least, the serious symptoms of the Covid-19 disease,. It should be remembered that vitamin D has more known advantages in keeping body minerals homehostasis, prevention of bone diseases such as rickets and osteoporosis. Recent data suggest that vitamin D has more recognized activities, such as its anti-carcinogenic activity, as well as its effects on the immune system, as described above. So, it is important to keep the correct serum vitamin D level, anyway.

In case of acute Covid-19 disease a different strategy is suggested. It is known very well that vitamin D is an inert material, and that it should be metabolized in the liver and in the kidney to become the active metabolite $1,25(OH)_2D_3$. Hence, vitamin D supplementation will not be enough. First of all the production of $1,25(OH)_2D_3$ in the kidney is highly regulated and its limited endogenous production will not be sufficient for reducing the cytokines storm. Beside this, there are clinical reports about possible damage to the kidney during Covid-19 disease. Such a damage will reduce further the $1,25(OH)_2D_3$ level. Due to these limitations, it makes sense to treat acute Covid-19 patients with the active metabolite $1,25(OH)_2D_3$, or with its synthetic analog 1α-Hydroxyvitamin D_3. However, such

a treatment should be carried out carefully in order to prevent hypercalcaemia. Another alternative treatment in this case, is the use of less calcaemic analogs of the active metabolite of vitamin D.

No doubt that more clinical trials are required in order to shed a light on the role of vitamin D in prevention and treatment of the Covid-19 disease.

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