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Possible Role of Vitamin D Supplementation in Chronic Urticaria Management

Basma Ahmed Mohamed El Azhary, Ashwak Mohamed Fouad Abo Taleb, Randa Saddek Abd El Latif, Mai Mohamed Malek

Medical Microbiology and Immunology Department, Faculty of Medicine - Zagazig University, Egypt

Corresponding author: Basma Ahmed Mohamed El Azhary

Email: basmaahmedelazhary@gmail.com

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Abstract: Background: The etiology of chronic urticaria is mostly unknown, and antihistamines are the mainstay of treatment. Some small studies have suggested that vitamin D may play a role in the condition, and this editorial review will discuss the available evidence. Observational reports and a randomized, prospective, blinded trial have both shown that subjects with chronic urticaria have lower serum 25 hydroxyvitamin D levels. A randomized, prospective, blinded trial also showed that patients with chronic urticaria had better symptomatic relief when high vitamin D3 supplementation was used as an additional therapy for urticarial management. Further research is necessary to determine the mechanisms of action and to explore vitamin D supplementation

Keywords: *Vitamin D, Chronic Urticaria Management*

Introduction

Vitamin D is a fat-soluble vitamin that has been historically known as a molecule. A deficiency in vitamin D might lead to bone diseases, primarily rickets. The discovery of vitamin D dates back to the first half of the 20th century and, despite it still being named as a vitamin, it is well known that it is truly a pro-hormone, with complex endocrine regulation [1].

Indeed, it binds to cytosolic receptors, located mainly in intestinal cells, and osteocytes, but also in several other tissues, such as muscle cells, hematopoietic cells, and the brain. Vitamin D is consequently transported to the cell nucleus, where is able to interact with DNA and modulate the expression of more than 900 genes [1].

The most important effects of vitamin D are on calcium metabolism and bone mineralization; however, it is involved in several physiological and pathological processes, such as cancer, immune modulation cardiovascular diseases, and metabolic syndrome [1].

Most vitamin D effects are mediated by vitamin D receptors, which are able to regulate a large number of target genes, influencing, consequently, many cellular pathways. Interestingly, VDRs are actually expressed in almost every type of human cell, and they have been found to modulate the transcription of about 3% of human genes.

Moreover, there is increasing evidence of the potential role of several VDR polymorphisms in a huge number of diseases , such as hypertension, non-alcoholic fatty liver disease, cancer, obesity, and many more [1].

Vitamin D Physiology and metabolism:

Vitamin D was initially described as a substance that was able to cure rickets and was termed 'D' as it was the fourth in the sequence of vitamins discovered. The two main chemical structures of vitamin D are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). There are several exogenous ways to obtain vitamin D, including dietary sources, such as oily fish (vitamin D3), mushrooms (vitamin D2), or enriched foods (vitamin D2 and vitamin D3). However, the dietary vitamin D assumption provides only a minor portion of the total daily human intake**.** The main source of vitamin D is the production in the skin layers, through exposure to the sun's ultraviolet B rays [1].

Vitamin D3 is produced in the skin through the action of sun rays on a derivative of cholesterol, 7-dehydrocholesterol, to produce previtamin D3. Then, previtamin D3 is slowly isomerized to vitamin D3; cholecalciferol. This dual source of Vitamin D, through sunlight in the skin and diet intake, secures sufficient levels of Vitamin D in the body, although the major source for production of vitamin D3 is through the skin [2]. Exposure of the precursor 7-dehydrocholesterol in the basal and suprabasal layers of the epidermis to ultraviolet B (UVB) light with a wavelength of 290-315 nm is needed for the formation of the previtamin D3. Thus, the level of production of vitamin D3 in the skin is mainly affected by the amount of UVB radiation to which the skin is exposed. Other factors affecting this cutaneous synthesis of vitamin D3 include geographical area, season of the year and time of the day [2].

Vitamin D3 itself is biologically inactive. Thus, after being synthesized in the skin, vitamin D3 binds to the vitamin D-binding protein (DBP) in the blood to be transported into the liver where the first hydroxylation at position 25 occurs producing the major circulating metabolite 25-hydroxy vitamin D3 (25(OH)D3). The responsible enzyme is CYP2R1, located in the liver endoplasmic reticulum, which can 25-hydroxylate either vitamin D2 or vitamin D3. Interestingly, CYP27A1 displays a similar enzymatic activity, but is distributed throughout the whole body, and is not able to 25-hydroxylate vitamin D2. The measurement of the circulating levels of 25 (OH)D is considered the best marker for assessing vitamin D status [2].

The hormonally active form of vitamin D is derived from the additional hydroxylationof a C1-carbon atom, in the proximal renal tubule, leading to the production of 1, 25-hydroxy vitamin D3 (1,25(OH)D). CYP27B1 is responsible for this metabolic step; although the major expression is predominant in the kidney, it has also been found in other sites, including the placenta, monocytes, and macrophages [3].

Interestingly, the extra-renal production of 1,25(OH)D is not dependent on parathyroid hormone (PTH) action; thus, the serum availability and sufficiency of 25(OH)D are the limiting factors for the extrarenal synthesis of calcitriol ***(Cross, 2007)***.Although the circulating level of 25(OH)D3 is 500-1000-fold greater than thesubsequent 1 α, 25 dihydroxy D3, but its bioactivity is 3 times less than the active one. This might be explained on the basis that the serum DBP has more affinity to 25(OH)D3, rendering it biologically inactive in vivo [2].

The kidney is also the main site at which vitamin D catabolism takes place. There are more than 35 additional vitamin D3 metabolites are formed by the body. However, it is evident now that all these metabolites are either less active or rapidly cleared and they are considered intermediates in the degradation of the active form, 1, 25(OH)2D3. The most important of these metabolites are 24, 25- (OH)2D3 and 1, 24, 25-trihydroxyvitamin D3 produced by the enzyme CYP24, which is induced by the vitamin D hormone itself .The 24,25-(OH)2 D3 has been shown to be an essential hormone in the process of bone fracture healing [3].

Experiencing urticarial wheals on a daily or almost daily basis for more than six weeks is characterized as chronic urticaria, a skin disorder. This condition may severely diminish quality of life and has a lifetime prevalence of 1-3% in the general population [1,2]. Inflammatory and allergic mediators interact intricately in the peripheral tissue milieu to cause various skin symptoms. Physical, idiopathic, autoimmune, vasculitic, and viral subtypes of chronic urticaria are all present. Up to 12% of chronic urticaria cases are linked to thyroid autoantibodies, including antithyroid peroxidase and antimicrosomal antibodies, and 30-60% of these cases

include functional autoantibodies to the high affinity IgE receptor or IgE. Idiopathic causes account for over half of all cases of chronic urticaria [1,3].

Holick provided a useful summary of the research on the link between vitamin D and various health problems in 2007 [4]. Several autoimmune disorders, such as Crohn's disease, multiple sclerosis, and type 1 diabetes, as well as solid tumors, arthritis, and transplant rejection, were evaluated by him in relation to vitamin D deficiency [4]. To validate these possible correlations, however, substantial randomized controlled trials are mostly absent. With the exception of a decrease in all-cause mortality in older women, a systematic analysis of randomized trials evaluating the function of vitamin D supplementation in different medical disorders did not find substantial benefit for vitamin D in early 2014 [5]. Nonetheless, research connecting vitamin D with allergic disorders is increasing. An important study that followed the distribution of 2.5 million epinephrine pens prescribed in the US in a year was published in 2007 by Camargo et al. [6]. There was a sharp north-south gradient in the number of prescriptions written and completed in the northern states. This north-south gradient persisted after the authors controlled for demographics, healthcare provider density, and the total number of prescriptions for all medications [6], leading them to conclude that sun exposure was the critical component. There is a lack of interventional trials showing that supplementing with vitamin D helps with asthma management, while there is some evidence that it may help. In particular, Sutherland et al. [7] found that low vitamin D levels are linked to worse lung function, more airway hyperresponsiveness, and less glucocorticoid response in a study of 54 persons with asthma. Subjects whose 25(OH)D levels were higher than 30 ng/ml showed a marked improvement in airway hyperresponsiveness ($p = 0.01$). [7].

Vitamin D has only been the subject of a small number of investigations on the causes and treatments for chronic urticaria. In 2007, our research found that compared to patients with allergic rhinitis, those with chronic urticaria had significantly lower serum vitamin D (25(OH)D) levels ($p = 0.016$) [8]. A more recent study conducted in Poland by Grzanka et al. [9] compared vitamin D levels in healthy adults ($n = 33$) and subjects with chronic urticaria ($n = 35$). The results showed that patients with chronic urticaria were more likely to have vitamin D deficiency, which is defined as 25(OH)D less than 20 ng/ml. There was no correlation between vitamin D level and the two subgroups of chronic urticaria (mild and moderate to severe), which were further described in this study. Finally, Chandrashekar in southern India reported that people with chronic urticaria had lower vitamin D levels than healthy controls, and he also suggested that the autoreactive condition of the disease may play a significant role in this correlation [10]. Vitamin D supplementation may be useful in the treatment of chronic urticaria, according to two observational studies. Goetz documented in a 2011 retrospective case series that supplementing with vitamin D at 50,000 IU weekly, and then daily, successfully treated idiopathic urticaria in 70% of patients ($n = 57$) with chronic urticaria [11]. In a case study, Sindher and colleagues described how vitamin D administration, along with a repeat 25(OH)D level of 65 ng/ml, completely alleviated the symptoms of chronic urticaria in a 58-year-old man who had significant vitamin D insufficiency (25(OH)D level 4.7 ng/ml) [12].

The first randomized controlled clinical trial that we are aware of that examined the effects of vitamin D supplementation on individuals with chronic urticaria was published in early 2014 [13]. In this 12-week study, 42 adults suffering from chronic urticaria were randomly assigned to take a 4000-or 6000-iu daily dose of vitamin D3 supplement, depending on whether they had a vitamin D shortage to begin with. The trial began with the administration of ranitidine, montelukast, and a high dose of cetirizine to all individuals, irrespective of the treatment group. At weeks 1, 6, and 12, urticaria symptoms were documented along with the quantity of tablets needed to treat them. Both therapy groups showed a 33% decrease in total urticaria severity score (USS) one week after enrollment [13]. Notably, when comparing the results at 3 months compared to 1 week after enrollment, patients treated with high-dose vitamin D supplementation had a significantly lower total USS (~40%), but those treated with low-dose vitamin D supplementation did not. At week 12, there was a trend toward lower total USS compared to the low therapy group ($p = 0.052$). A number of items, including the degree of hives in the past week ($p = 0.03$), the body distribution of hives on an average day ($p = 0.003$), and the body distribution of hives on the worst day ($p = 0.008$), showed a significant improvement upon additional review

of the individual questions that make up the USS. There were trends in reducing the severity of itching during the previous week ($p = 0.09$) and in the number of nights when hives disrupted sleep ($p = 0.07$). The quantity of allergy tablets taken daily did not change across the treatment groups, though. Furthermore, there was a correlation between the USS and the detected serum 25(OH)D levels. Vitamin D dosage had no discernible negative effects on these individuals, either at high or low levels [13].

There is some evidence from a small number of studies suggesting a possible link between vitamin D and chronic urticaria. However, it is important to note that there is only one randomized controlled clinical trial documented in the literature. There were just a small number of individuals in our randomized interventional study, and more significantly, the majority of those subjects were overweight or obese white women [13]. Investigations involving varied ethnic and racial populations, including Hispanics and African Americans, are important, in addition to advocating future multicenter research, because these groups are more typically deficient in vitamin D [4]. Time of year of enrollment (summer or winter), average daily sunshine minutes per individual, and baseline nutritional status were other possible limitations of our study that affect vitamin D metabolism. Due to the short period of this study, we recommend that future research use a longer observational window of at least one year.

The reason why vitamin D would be helpful in chronic urticaria remains unclear, even though these combined trials imply a favorable function for vitamin D. Vitamin D signaling pathway downstream effects may be amplifying other urticaria-related variables. The majority of immune system cells, including T cells, B cells, neutrophils, macrophages, and dendritic cells (DCs), have vitamin D receptors (VDRs) [14]. These VDRs may influence immune suppression. Vitamin D has been demonstrated to reduce the production of IL-6, IL-12, IL-23, C-reactive protein, TNF-α, and IgE and to impede the migration of DCs [14–17]. Further evidence is being accumulated about the potential role of vitamin D in inducing regulatory T cells (Tregs), which can be enhanced in vitro by VDR-agonists [18]. Plus, some research suggests that human DCs treated with vitamin D can transform CD4+ T cells into IL-10 secreting Treg cells, which could potentially reduce inflammation in the skin [19]. One known effect of vitamin D on atopic dermatitis is an increase in the production of cathelicidin, an innate immune system antimicrobial peptide [20].

The immunoregulatory and anti-inflammatory effects of vitamin D suggest it may be useful in the treatment of chronic urticaria. There is insufficient data to endorse vitamin D supplementation or to strongly suggest testing serum vitamin D levels in all individuals with chronic urticaria at this time. Still, there is clinical evidence to suggest that vitamin D3 is a safe and cost-effective medication that could be considered and used as an adjunctive treatment for individuals with chronic urticaria. To fully comprehend the processes of possible therapeutic benefit, there must be more extensive, multicenter clinical trials with longer research durations.

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