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Vitamin D supplementation: a potential booster for urticaria therapy

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Chronic urticaria is a common skin condition whereby the etiology remains largely idiopathic and the mainstay therapy is symptomatic control with antihistamines. There have been a limited number of small studies suggesting a potential role for vitamin D in chronic urticaria, and this this editorial review will discuss the current supporting evidence. Associations for decreased serum vitamin 25 hydroxyvitamin D levels in subjects with chronic urticaria have been reported. In addition to observational reports, there has been a randomized, prospective, blinded trial demonstrating symptom improvement when high vitamin D3 supplementation was utilized as an add-on therapy for urticarial management. More research is needed to address mechanisms of action and to investigate vitamin D supplementation in larger and longer duration human trials.

Chronic urticaria is a skin condition that is defined as experiencing urticarial wheals daily or nearly daily for a duration of greater than 6 weeks. The lifetime prevalence of this disorder in the general population is 1–3% and may dramatically impair the quality of life [1,2]. The underlying etiology of these skin manifestations is a complex interaction of inflammatory and allergic mediators in the peripheral tissue milieu. There are multiple subtypes of chronic urticaria that include physical, idiopathic, autoimmune, vasculitic and infectious. Autoimmune etiologies account for 30–60% of chronic urticaria with the presence of functional autoantibodies to the high affinity IgE receptor or IgE, and up to 12% are associated with thyroid autoantibodies such as antithyroid peroxidase antibody and antimicrosomal antibody. Approximately 50% of cases of chronic urticaria remain largely idiopathic [1,3].

The association between vitamin D and multiple medical conditions has been receiving much attention, which was well summarized by Holick in 2007 [4]. He reviewed the potential associations with vitamin D deficiency in a variety of solid tumors, arthritis, transplant rejection, and autoimmune diseases including Crohn's disease, multiple sclerosis and type 1 diabetes [4]. However, large randomized controlled trials are largely lacking to validate these potential associations. In fact, in early 2014 a systemic review of randomized trials assessing the role of vitamin D supplementation in various medical conditions failed to demonstrate significant benefit for vitamin D, with the exception of reduced all-cause mortality in elderly women [5]. However, there is a growing body of evidence linking vitamin D with allergic diseases. Notably, in 2007, Camargo *et al.* published a study tracking the regional distribution of 2.5 million epinephrine pens prescribed in a calendar year in the USA [6]. They reported significantly more prescriptions and filled prescriptions in the northern states, with a strong north to south gradient. The authors proposed that sunlight exposure was the important factor because this north–south gradient was demonstrated despite controlling for variables such as population, number of healthcare providers and number of other medication prescriptions [6]. Vitamin D has also been associated with asthma control, but interventional studies demonstrating benefit with supplementation are lacking. Namely, Sutherland and colleagues enrolled 54 adults with asthma and

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measured vitamin D levels and reported that reduced vitamin D levels are associated with impaired lung function, increased airway hyperresponsiveness and reduced glucocorticoid response [7]. Airway hyperresponsiveness was significantly improved in subjects with 25(OH)D levels greater than 30 ng/ml (p = 0.01) [7].

To date there are a limited number of studies examining the role of vitamin D in the etiology and treatment of chronic urticaria. Our group originally reported in 2007 that serum vitamin D (25(OH)D) levels were significantly reduced in subjects with chronic urticaria as compared to subjects with allergic rhinitis (p = 0.016) [8]. More recently, Grzanka *et al.* in Poland investigated vitamin D levels in healthy adults (n = 33) and chronic urticaria subjects (n = 35) and reported similar findings that patients with chronic urticaria had increased prevalence rates of vitamin D deficiency, defined as 25(OH)D less than 20 ng/ml [9]. In this study, chronic urticaria was further defined as mild and moderate to severe; however, there was no difference between those groups and vitamin D level. Lastly, Chandrashekar in south India also found that vitamin D levels were lower in subjects with chronic urticaria as compared to healthy controls, and also found that autoreactive status of chronic urticaria disease might be important in this association [10]. There have been two observational studies commenting on a potential beneficial role for vitamin D supplementation in the treatment of subjects with chronic urticaria. In 2011, Goetz reported in a retrospective case series that 70% of subjects with chronic urticaria (n = 57) had treatment success of their idiopathic urticaria with supplementation of vitamin D 50,000 IU weekly followed by daily supplementation [11]. Sindher and colleagues reported in a case report that a 58-year-old man with chronic urticaria and severe vitamin D deficiency (25(OH)D level 4.7 ng/ml) had complete resolution of his symptoms after supplementation of vitamin D with repeat 25(OH)D level of 65 ng/ml [12].

In early 2014, we reported on potential benefits of vitamin D supplementation in subjects with chronic urticaria in the first double-blind, randomized controlled clinical trial to our knowledge [13]. A total of 42 adult subjects with chronic urticaria were enrolled with or without baseline vitamin D deficiency to either a high-dose (4000 IU) or low-dose (600 IU) vitamin D_3 supplement daily for 12 weeks. At the trial onset, all subjects, regardless of the treatment group, were initiated on the triple drug therapy of ranitidine, montelukast and a high dose of cetirizine. Urticaria symptoms were recorded at weeks 1, 6 and 12 in addition to tracking the number of medication pills required to control symptoms. There was a 33% reduction in total urticaria severity score (USS) at 1 week post-enrollment in both treatment groups [13]. Importantly, there was a further significant reduction (~40%) in total USS in subjects treated with high-dose, but not low-dose, vitamin D supplementation at 3 months compared to 1 week post-enrollment. Compared to the low treatment group, there was a trend (p = 0.052) toward reduced total USS at week 12. On further evaluation of the individual questions comprising the USS, there was a significant improvement in several items including degree of hives in the past week (p = 0.03), body distribution of hives on an average day (p = 0.003) and body distribution of hives on the worst day (p = 0.008). Trends were observed for improving the degree of pruritus in the past week (p = 0.09) and nights of hives with sleep interference (p = 0.07). However, we found no difference in the number of allergy pills taken on a daily basis between the treatment groups. In addition, the measured serum 25(OH)D levels correlated with the USS. There were also no significant adverse events with high (or low) vitamin D dosing in these subjects [13].

These few studies do provide evidence of a potential relationship between chronic urticaria and vitamin D; however, these studies are small with only one randomized controlled clinical trial reported in the literature. Our randomized, interventional study was limited in the number of subjects, and importantly, limited in subject diversity that was predominately overweight-obese, Caucasian females [13]. In addition to recommending further multicenter studies, investigations with diverse ethnic and racial populations such as Hispanic and African American are necessary as these groups are more commonly vitamin D deficient [4]. Other potential limitations of our study included time of the year subjects were enrolled (summer, winter), average minutes of daily sunlight per subject and baseline nutritional status, which contribute to vitamin D metabolism. This study was also limited in duration, and therefore we would suggest that future studies extend the observational window to 1 year.

Despite these collective studies suggesting a beneficial role of vitamin D in chronic urticaria, the explanation for why vitamin D would be beneficial is not clear. It is possible that downstream effects of vitamin D signaling pathways are augmenting other factors involved with urticaria. Vitamin D receptors (VDRs) have been identified on most cells of the immune system including T cells, B cells, neutrophils, macrophages and dendritic cells (DCs) [14], which might impact immune suppression. Vitamin D has been shown to have an inhibitory effect on DC migration and decreased IL-6, IL-12, IL-23, C-reactive protein, TNF-α and IgE production [14–17]. There is also evidence for a possible role continues to be acquired about a possible role for Vitamin D appears to induce Treg cells with the ability of VDR-agonists to increase the induction of Treg *in vitro* [18]. Moreover, there have been reports of vitamin D-treated human DCs exhibiting the ability to convert $CD4^+$ T cells into IL-10 secreting Treg cells, which may have the capability to suppress skin inflammation [19]. It is known that vitamin D stimulates the production of cathelicidin, which is an antimicrobial peptide of the innate immune system that has been shown to have an effect on atopic dermatitis [20].

Expert commentary

Vitamin D is an immunoregulatory and anti-inflammatory agent that might play a beneficial role in chronic urticaria. Currently, there is not enough evidence to strongly support assessing serum vitamin D levels in all chronic urticaria subjects or to strongly recommend supplementation with vitamin D. Nonetheless, vitamin D3 represents a relatively safe and inexpensive

therapy with clinical evidence to support its consideration and use as an add-on therapy for subjects suffering from chronic urticaria. There is a clear need for larger, multicenter clinical studies with longer study duration as well as investigations to understand the mechanisms of potential clinical benefit.

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