Role of Vitamin D Supplementation in Immuno-modulation and Improvement of Symptoms of Patients with Chronic Spontaneous Urticaria

Thesis

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List of Abbreviations

25(OH) D	25-hydroxyvitamin D
AE	Adverse event
APR	Acute phase response
ASST	Autologous serum skin test
ASST	Autologous serum skin test
BD	Bis die (twice daily)
CAPS	Cryopyrin-associated periodic syndromes
CIU	Chronic idiopathic Urticaria
CRP	C-reactive protein
CSU	Chronic spontaneous urticaria
CU-Q2oL	Chronic Urticaria quality-of-life questionnaire
DCs	Dendritic cells
DLQI	Dermatology life quality index
DPU	Delayed pressure Urticaria
DQOLS	Dermatology quality of life scales
DSQL	Dermatology specific quality of life
ECP	Eosinophilic cationic protein
ENT	Ear, nose, throat.
FACS	Familial cold auto inflammatory syndrome
Ga2len	Global Allergy and Asthma European Network
GC	Glucocorticoids
GIT	Gastrointestinal
H1RA	Histamine 1 receptor antagonist
H2RA	Histamine 2 receptor antagonist
HC	highly cytokinergic
IgE	Immunoglobulin E
IL	Interleukin

List of Abbreviations *(Cont ..)*

ISS	Itch severity score
IV IG	Intravenous immunoglobulin
LTRA	Leukotriene receptor antagonists
MetS	Metabolic Syndrome
MIID	Minimum important difference
MMP	Matrix metalloproteinases
MTX	Methotrexate
NOMID	Neonatal onset multisystem inflammatory disease
nsAH	Non-sedating antihistamines
NSAIDs	Non-steroidal anti-inflammatory drugs
QOL	Quality of life
RXR	Retinoid X receptor
SLE	Systemic lupus erythematous
TCSA	TNFα & Complement system Abs
TLR	Toll like receptor
TNF	Tumor necrosis factor
UAS	Urticaria activity score
UAS7	Urticaria activity score over 7 days
USS	Urticarial severity score
UV	Urticarial vacuities
VAS	Visual analogue score
VDRE	Vitamin D response elements
VDRs	Vitamin D receptors
	WAO World allergy organization

ABSTRACT

Background: Chronic Spontaneous Urticaria (CSU) is an allergic auto-immune disease with more than 6 weeks of continuous symptoms, it is known to trigger allergic wheal formations and angioedema. Vitamin D at optimal levels plays an important role in adjusting innate immunity thus People who has deficient or insufficient levels of serum vitamin D suffer from disturbance in immune system. Accordingly, studies have been established to explore the effect of vitamin D on CSU. Aim of the Study: To determine the effect of 12 weeks daily oral vitamin D supplementation [high (4,000 IU/d) versus low (600 IU/d) dose of orally administered vitamin D3] on Urticaria activity score (UAS-7), quality of life (QOL) and medication burden in patients with chronic spontaneous urticaria, and to assess the relationship between vitamin D levels and CRP in these patients. Patients and methods: This single blind randomized prospective study conducted to 50 patients with CSU, admitted to Ain shams hospital, 50 patients were divided into 2 groups according to the dose of vitamin D orally administrated to these subjects, the first was group A , patients have received vitamin D orally in High dose 4000 IU/Day compared to group B , which included 25 cases received oral vitamin D in a low dose concentration 600 IU/d , Patients has been followed up in 3 times at baseline (0 week) , 6 weeks and 12 weeks intervals. Results: Serum vitamin D levels in Group were higher than Group B (44.48±12.86 vs 34.45±5.43). Medication consumption was higher in group A compared to group B, thus favors orally low dose administration of vitamin D at first 6 weeks in the beginning of treatment course. UAS7 score in group A was better than Group B from baseline) to 6 weeks (P=0.*009 vs 0.239)* and from 6 weeks to 12 weeks. *(P= 0.011 vs <0.0011)*. There was no significant difference in serum CRP between group A and group B as regards to CRP, furthermore there was no statistically correlation between 3 times intervals in group A and group B separately (12.71±1.47 vs 13.11±1.45). Conclusion: Improvement of both quality of life, and UAS7 score after receiving of High dose 4000 IU/d vitamin D orally in Group A, could benefit patients with CSU and decrease the complication of this disease. It was also found Serum Vitamin D level has no significant relation with C Reactive protein level, thus we couldn't relay on evaluation the chronicity of urticarial by measuring its value in serum blood with patients suffering from chronic spontaneous idiopathic urticaria.

Keywords: Vitamin D, Urticaria, auto-immune diseases, Immunomodulation.

Introduction

Chronic urticaria with or without angioedema (CU) is a common allergic skin condition associated with considerable morbidity and burden on health care expenditure. CU is defined as urticarial wheals occurring daily or almost daily and lasting longer than 6 weeks. It has been estimated that 10% to 20% of the population develop an acute episode of urticaria in their lifetime and 1% to 3% develop CU ***(Khan and David, 2013).*** Through a comprehensive approach, cutaneous symptoms sometimes can be ascribed to drug, food, aeroallergen, contact allergen, or autoantibodies to the high-affinity IgE receptor or to free IgE. However, in most cases, the diagnosis remains idiopathic ***(Sanchez-Borges et al., 2012).***

Chronic spontaneous urticaria (CSU) is an inflammatory disease, characterized by acute phase response (APR) and in many cases by the immune-activation. C-reactive protein (CRP) is a marker of systemic CSU activity, reflecting the systemic effects of inflammatory mediators associated with the disease, including IL-6 ***(Kasperska-Zajac, 2011).***

Chronic spontaneous urticaria and other chronic forms of urticaria do not only cause a decrease in quality of life, but also affect performance at work and school ***(Zuberbier et al., 2009).***

Treatment options are limited, and the mainstay of therapy is symptomatic control with antihistamines. Systemic corticosteroids, anti-leukotrienes, hydroxychloroquine, cyclosporine, dapsone, anti-IgE monoclonal antibody therapy, and other anti-inflammatory agents may be used, which themselves can pose substantial adverse events and cost. A potential alternative and safe immune-modulator is vitamin D ***(Rorie et al., 2014a).***

There has been increasing evidence showing that vitamin D deficiency/insufficiency is associated with increased incidence and severity/activity of the immune-inflammatory disorders. Vitamin D has immunomodulatory properties and is able to suppress the inflammatory milieu, including IL-6 and CRP synthesis. In the clinical practice, vitamin D status is assessed by measurement of the circulating level of 25-hydroxyvitamin D [25(OH)D], considered as the best indicator of vitamin D status, including its availability ***(Grzanka et al., 2014).***

Vitamin D plays key roles in innate and adaptive immunity through the stimulation of Toll-like receptors,

increasing pro-inflammatory cytokine production, and possibly enhancing T helper type 2 responses. These mechanisms may explain the growing body of evidence connecting vitamin D to allergic diseases, including asthma, food allergies, and allergic rhinitis. As with many of the atopic diseases, there are conflicting data surrounding the effect that vitamin D has on the development of allergic skin diseases. Most of the studies to assess the impact of vitamin D on allergic skin diseases focus on atopic dermatitis (AD). Current data demonstrate the importance of screening for vitamin D deficiency measured by serum concentration of 25(OH) D in chronic urticaria patients. In addition, such observations may have certain therapeutic implications. Interestingly, it has been demonstrated that in patients suffering from idiopathic chronic urticaria, isolated pruritus, and rash with low 25(OH)D level, the symptoms resolution is often possible with oral supplementation of vitamin D ***(Goetz, 2011).***

To date very few randomized, prospective trials have investigated the role of vitamin D supplementation in patients with CU and whether vitamin D supplementation decreases CU symptoms in patients with vitamin D insufficiency.

Aim of the work

To determine the effect of 12 weeks daily oral vitamin D supplementation [high (4, 000 IU/d) versus low (600 IU/d) dose of orally administered vitamin D3] on urticaria activity score (UAS-7), quality of life (Q2OL) and medication burden in patients with chronic spontaneous urticaria, and to assess the relationship between vitamin D levels and CRP in these patients

Chapter (1)
Chronic Urticaria

Urticaria, defined as the occurrence of wheals, angioedema, or both, It is characterised by a red, raised, itchy rash resulting from vasodilatation, increased blood flow, and increased vascular permeability, consequent upon mediator release from mast cells. Urticarial wheals can vary in size from a few millimetres to large lesions (10–20 centimetres), which may be single or numerous, and are intensely itchy. While urticaria occurs in the superficial dermis, angioedema refers specifically to localized deep tissue swelling. Chronic urticaria is defined as the development of daily or almost daily repeated urticarial episodes lasting for 6 weeks or longer The exact incidence and prevalence of chronic Urticaria are unknown, although it occurs in at least 0.1% and possibly up to 3% of the population. ***(Zuberbier et al., 2014)***

Approximately one third of cases are thought to involve autoimmune mechanisms such as skin mast cell activation by immunoglobulin (Ig) G autoantibodies to IgE or to the asub unit of the high affinity IgE receptor (FceR1a).Chronic infections, auto-allergic mechanisms, and

intolerance to food components are other known causes of CSU. However, many patients are not investigated for underlying causes. ***(Rosen and Clifford , 2011)***

The natural history of chronic urticaria varies, and some patients suffer with it for years or even decades. Chronic urticaria impairs quality of life and causes a high burden of suffering in affected patients. The etiology of chronic urticarial has been attributed to an immense number of factors including foods, drugs, aeroallergens, infections, contact allergens, and auto-antibodies to the high affinity immunoglobulin E (IgE) receptor or free IgE Mast cells are the major effector cells in chronic urticaria. The wheals and angioedema associated with the disease are in part due to the release of histamine and other vasoactive substances from dermal mast cells besides mast cells, basophils, dendritic cells, monocytes, neutrophils and numerous cytokines have been implicated in the pathogenesis of chronic urticaria. ***Sabroe and Greaves, 2006*** reported that basophil numbers are inversely related to disease severity, and observed that paradoxical suppression of FcεRI mediated antiFcεRI/antiIgE antibody induced release of histamine from basophils during the active disease. ***(Greaves and Malcolm, 2014)***

Futata et al., 2012 indicated that chronic urticaria may be affected by immune dysregulation through functional impairment of plasmacytoid dendritic cells. In addition, increased levels of circulating pro-inflammatory cytokines, such as tumor necrosis factor α, interleukin (IL) 1, IL6, and IL12, and high monocyte responsiveness through CCL2/CXCL8 expression have been observed in patients with chronic urticaria. Moreover, an elevated level of IL6 is significantly associated with the clinical severity of chronic urticaria. Therefore, it is supposed that cytokines and chemokines are the implicating factors contributing to the skin lesions observed in chronic urticaria, while also influencing the behavior and properties of the inflammatory cells involved. One third of patients with chronic urticaria were found to have circulating functional histamine releasing IgG autoantibodies against the FcεRIα receptor on dermal mast cells and basophils, which allows them to be classified as having chronic autoimmune urticaria. ***(Autier et al., 2014)***

It has been supposed that several etiological factors of chronic urticaria act synergistically or sequentially, as either independent or interlinked mechanisms, to activate mast cells through the release of preformed mediators and the secretion of newly synthesized vasoactive molecules, producing the