

## Vitamin D Deficiency in Chronic Idiopathic Urticaria

Masoud Movahedi<sup>1</sup>, Marzieh Tavakol<sup>2</sup>, Armin Hirbod-Mobarakeh<sup>3,4</sup>, Mohammad Gharagozlou<sup>1</sup>,  
Asghar Aghamohammadi<sup>1,5</sup>, Zahra Tavakol<sup>6</sup>, Kaveh Momenzadeh<sup>4</sup>, Mohammad Nabavi<sup>7</sup>,  
Abbas Dabbaghzade<sup>1</sup>, Asieh Mosallanejad<sup>8</sup> and Nima Rezaei<sup>3,5</sup>

<sup>1</sup> Department of Allergy and Clinical Immunology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Department of Allergy and Clinical Immunology, Shahid Bahonar Hospital, Alborz University of Medical Sciences, Karaj, Iran

<sup>3</sup> Molecular Immunology Research Center, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

<sup>4</sup> Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>5</sup> Research Center for Immunodeficiencies, Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran

<sup>6</sup> Student' Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran

<sup>7</sup> Department of Allergy and Immunology, Rasool-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

<sup>8</sup> Imam Hosein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 2 April 2014; Received in revised form: 21 June 2014; Accepted: 12 August 2014

### ABSTRACT

Chronic urticaria is the most common skin disease, characterized by chronic cutaneous lesions which severely debilitates patients in several aspects of their everyday life. Vitamin D is known to exert several actions in the immune system and to influence function and differentiation of mast cells, central role players in the pathogenesis of chronic idiopathic urticaria.

This study was performed to evaluate the relationship between vitamin D levels and susceptibility to chronic idiopathic urticaria. One hundred and fourteen patients with chronic idiopathic urticaria were recruited in this study along with one hundred and eighty seven sex-matched and age-matched healthy volunteers as the control group. For each patient, urticaria activity score was calculated and autologous serum skin test was done.

Vitamin D metabolic statue was measured in serum as 25 hydroxyvitamin D using enzyme immunoassay method. Patients with chronic idiopathic urticaria significantly showed lower levels of vitamin D. Vitamin D deficiency was significantly associated with increased susceptibility to chronic idiopathic urticaria. There was a significant positive correlation between vitamin D levels and urticaria activity score.

This study showed that patients with chronic idiopathic urticaria had reduced levels of vitamin D, while vitamin D deficiency could increase susceptibility to chronic idiopathic urticaria.

**Keywords:** Cholecalciferol; Mast cells; Urticaria; Vitamin D; Vitamin D deficiency

**Corresponding Author:** Marzieh Tavakol, MD;  
Shahid Bahonar Hospital, Azimieh, Karaj, Iran.

Tel: (+9826) 32527 575, Fax: (+9826) 3254 7128,  
E-mail: marzieh.tavakol@yahoo.com

### INTRODUCTION

Chronic urticaria is a heterogeneous cutaneous condition, which its main presentations are transient pruritic swellings of the skin (wheal or hive) in superficial dermal layer in different locations of body.<sup>1-5</sup> In half of the occasions, angioedema which is swelling of deep subcutaneous tissues accompanies the hives.<sup>2-5</sup> This condition must affect the patient for more than 6 weeks at least 2 times a week to deserve the term chronic.<sup>2-5</sup> Chronic urticaria as one of the most common skin diseases impairs several aspects of everyday life of affected patients.<sup>2,3,5-8</sup> At least, 75 % of cases have chronic idiopathic urticaria (CIU), in which no triggering event was found to be responsible for the spontaneous appearance of wheals.<sup>3,8</sup> This condition usually affects females in their midlife.<sup>2,5</sup> Presence of some autoantibodies makes a distinction between 30–50% of patients who have autoimmune chronic urticaria (AICU) and the remainder having true CIU.<sup>3,9,10</sup>

In patients with AICU, IgG antibodies against  $\alpha$  chain of the high-affinity immunoglobulin E (IgE) receptor on mast cells or IgE itself are found to be responsible for the presentation of disease.<sup>3,9,10</sup> However, in patients with true CIU factors remained to be identified which are responsible for increased releasability of mediators from mast cells.<sup>3,9,10</sup>

Although Vitamin D is well known by its central role in the bone physiology, it can exert several immunomodulatory actions in both innate and adaptive immunity primarily by affecting its nuclear (nVDR) and plasma membrane receptors (mVDR) on epithelial cells, mast cells, monocytes, macrophages, T-cells, B-cells, and dendritic cells.<sup>11-14</sup> Apart from its role in other parts of the immune system, vitamin D is known to extensively influence proliferation, survival, differentiation, and function of mast cells.<sup>11,15</sup> Recently, an increasing body of literature showed paradoxical relationships between vitamin D and allergic diseases like food allergy, rhinosinusitis, recurrent wheeze, asthma, atopic dermatitis and eczema.<sup>14,16-22</sup> Some studies suggested that vitamin D inhibits development of allergic diseases and can be a potential treatment for allergy.<sup>17-23</sup> On the other hand, some studies showed vitamin D supplementation as a possible cause for increased rate of allergic disorders and allergy pandemic.<sup>16-22</sup> Bearing in mind a 10% prevalence of vitamin D deficiency and 50% prevalence of vitamin D

insufficiency.<sup>24,25</sup> This study was performed to evaluate vitamin D levels in true CIU and AICU comparing to control group.

### PATIENTS AND METHODS

#### Study Population

In this study, patients with chronic urticaria were diagnosed in the Immunology and Allergy clinic of the Children Medical Center Hospital, the Pediatrics Center of Excellence in Tehran, Iran, between November 2012 and February 2013 in order to avoid seasonal influence. They showed urticarial symptoms at least twice a week for more than six weeks. After exclusion of well-known causes including drug, food, infection, neoplastic or systemic disorders and patients with exercise related urticaria, physical urticaria, urticarial vasculitis, and hereditary angioedema, 114 patients with CIU were recruited in the study. Other exclusion criteria were pregnancy, history of bone disease and use of vitamin supplements or corticosteroids in the previous six months. For each patient, complete medical history was taken and physical examination was done and a questionnaire regarding the characteristics of the disease and exacerbating factors was completed. Urticaria Activity Score (UAS), which is a clinical tool to assess disease severity based on patient-reported outcomes for symptoms, were calculated for patients.<sup>26</sup> Total serum IgE concentration was measured by enzyme-linked immunosorbent assay (ELISA) method (Genesis Diagnostics ELISA kit, England) and Autologous Serum Skin Test (ASST), which is a simple and cost-effective *in vivo* test for detection of autoimmune nature of urticaria, was carried out for each patient as previously described.<sup>27</sup> One hundred and eighty seven sex-matched and age-matched healthy volunteers from hospital visitors with no history of urticaria or using vitamin supplements were included in the study as the control group. Informed consents were obtained from all the participants after receiving verbal and written information regarding aim of study. All the principles of the Declaration of Helsinki were applied in the study and the study was approved by the Ethical Committee of Tehran University of Medical Sciences.

#### Vitamin D Status

Blood samples were taken from patients and controls into EDTA treated tubes after an overnight

fast. Vitamin D was measured as 25 hydroxy vitamin D, the best circulating biomarker of vitamin D metabolic status, using enzyme immunoassay method (EIA) [immunodiagnostic system; IDS (LTD), UK]. Values less than 20 ng/ml were considered as vitamin D deficiency and vitamin D insufficiency were defined as values of 25-hydroxyvitamin D of 20 to 30 ng/ml.<sup>24</sup>

### Statistical Analysis

Statistical analyses were done using SPSS statistical software, version 18 (SPSS Inc., Chicago, Illinois, USA). The chi-square test was used to determine association between vitamin D deficiency and disease. Independent T test was used to compare vitamin D levels between groups. Pearson test was used to evaluate relationship between vitamin D levels and disease severity. A *p* value less than 0.05 was considered statistically significant.

## RESULTS

The characteristics of both patients and control group are presented in the Table 1. Patients showed the symptoms of urticaria on average for 54 months (54.6±8.6), while 91 patients (79.8%) experienced symptoms of the disease daily.

Patients with CIU and particularly with true CIU significantly showed lower levels of 25 (OH)D in comparison with the control group (*p*=0.005) (Figure 1). However, considering AICU patients separately, there was no significant differences in vitamin D levels between them and the control group (*p*=0.11). Vitamin D deficiency was significantly associated with increased susceptibility to CIU (*p*=0.001). Individuals with vitamin D deficiency showed a 2.4-fold (95%CI: 1.4-4) risk of having CIU. In addition, vitamin D deficiency significantly increased susceptibility to true CIU (*p*=0.001, OR=2.7, 95%CI: 1.4-5.1). However, slight significant difference was detected between the controls and the AICU patients regarding vitamin D deficiency (*p*=0.048, OR=2.04, 95%CI: 0.99-4.2) (Table 2).

There was not any significant difference in vitamin D levels in male patients and female patients. However, patients who reported longer duration for their symptoms (>24h) showed significantly lower levels of vitamin D (*p*=0.046).

There was a significant correlation between vitamin D levels and UAS (*r*=0.2, *p*=0.042). Considering patients with AICU separately, there was also a fair correlation between vitamin D levels and UAS (*r*=0.3, *p*=0.034). There was not any significant relationship between IgE levels and vitamin D levels.

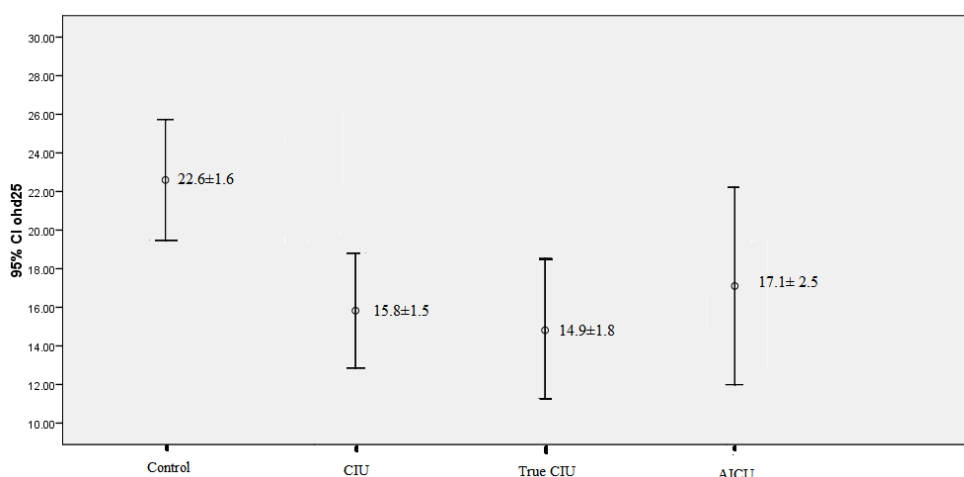
**Table 1. Clinical characteristics of patient group and control group**

Characteristics	Patients with CIU (n=114)	Controls (n=187)
Age (y), (mean±SE)	29.4±1.3	32.8±1
Gender (Male/ Female)	19/95	23/164
BMI (Kg/M <sup>2</sup> ), (mean±SE)	24.1±0.5	-
AICU	47 (41.2%)	-
UAS (mean±SE)	3.5±0.15	-
AICU	3.7±0.26	-
True CIU	3.3±0.18	-
Serum IgE levels (IU/mL), (mean±SE)	142.7±16.6	-
AICU	120.1±20.3	-
True CIU	163.3±25.6	-
Family history of Urticaria	41 (36%)	-
AICU	21 (44.7%)	-
True CIU	20 (29.9%)	-
Presence of angioedema	72 (63.2%)	-
AICU	37 (78.7%)	-
True CIU	35 (52.2%)	-

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**Table 2. Vitamin D status in patients and controls**

Characteristics	Controls (n=187)	Patients (n=114)	P	Patients with true CIU (n=67)	P	Patients with AICU (n=47)	P
Vitamin D deficiency	107 (57.2%)	86 (75.4%)		53 (79.1%)		33 (70.2%)	
Vitamin D insufficiency	31 (16.6%)	18 (15.8%)	0.001	9 (13.4%)	0.002	9 (19.1%)	0.11
Vitamin D sufficiency	49 (26.2%)	10 (8.8%)		5 (7.5%)		5 (10.6%)	



**Figure 1. Vitamin D levels in controls in comparison with patients with CIU, true CIU and AICU**

### DISCUSSION

This study showed a significant relationship between vitamin D deficiency and susceptibility to CIU, particularly susceptibility to true CIU. This finding is in accordance with the findings of Thorp et al study on 25 patients with chronic urticaria.<sup>28</sup> Goetz et al reported a case series of 63 patients with idiopathic pruritus, rash, and urticaria and low levels of vitamin D whose cutaneous manifestations improved upon vitamin D supplementation.<sup>29</sup> More recently, Sindher et al reported resolution of chronic urticaria following treatment with vitamin D in a patient with severe vitamin D deficiency.<sup>30</sup>

Vitamin D beyond its role in bone physiology, directly and indirectly influences several elements of both innate and adaptive immunity.<sup>11,14,16,18</sup> It has an undeniable role in immunity against pathogens through effects on growing and differentiation of several types of the immune cells and expression of several antimicrobial agents like Defensins and Cathelicidin.<sup>12-14</sup>

Vitamin D plays a central role in regulating inflammation and tissue damage in the skin therefore

its deficiency may result in excess inflammation leading to simultaneous degranulation of mast cells.<sup>18,31</sup> Vitamin D inhibits expression of costimulatory molecules like CD40 and CD80/CD86 on dendritic cells and therefore induces tolerance via immature and tolerogenic dendritic cells.<sup>11,14,16,18</sup> Vitamin D enhances both number of Tregs and their immunosuppressive activity.<sup>11</sup> In addition, several parts of cytokine network can be influenced by vitamin D levels. Vitamin D inhibits production of IL-1, IL-6, IL-12, IL-23, IFN- $\gamma$  and Regulated on Activation, Normal T Expressed and Secreted (RANTES).<sup>11,14,16,18</sup> On the other hand, it enhances production of tolerogenic cytokines like IL-10 and TGF- $\beta$  by Tregs, dendritic cells and more interestingly mast cells.<sup>11,21</sup> Interestingly, patients with CIU have increased circulatory levels of IL-1, IL-6 and IL-12.<sup>2</sup> Vitamin D is reported to enhance anti-inflammatory effects of corticosteroids.<sup>16</sup> In addition, in the skin, vitamin D enhances keratinocyte differentiation, improves integrity of epidermal barrier and reduces UVB induced oxidative damage by increasing glutathione peroxidase.<sup>13,14,22</sup>

In patients with CIU and especially true CIU, increased releasability and degranulation of mast cells

is central in presentations like wheals and angioedema.<sup>2,4,32</sup> Vitamin D enhances ICAM-3 expression in mast cells which can result in modulation of proliferation, apoptosis, spreading, cytokine production of mast cells in addition to their adhesion to matrix components.<sup>33</sup>

Vitamin D regulates maturation of mast cells via inducing apoptosis in mast cell precursors and inhibiting mast cell differentiation in various stages though triggering VDR in mast cells.<sup>34</sup> Previously, in vivo studies in mice showed absence of VDR signaling, resulted in accelerated maturation of mast cells and an increase in the number of dermal mast cells.<sup>22</sup> These studies also showed that these mast cells are more responsive and have increased releasability.<sup>22</sup> Vitamin D can decrease IL-1 and RANTES which are two known Histamine-releasing factors (HRF) believed to be the factor responsible for CIU.<sup>8</sup> However, some studies reported that vitamin D enhances release of active mediators from mast cells induced by cross linking of IgE receptors or calcium ionophore alone.<sup>35</sup>

In conclusion, this study showed reduced levels of vitamin D in patients with CIU. One limitation of our study was using ASST test which has a 70% sensitivity and specificity of about 80% to determine autoimmune nature of urticaria instead of using the gold standard test of in vitro.<sup>9</sup> It is important to note that several genetic, hormonal, individual or environmental factors (like VDR polymorphisms) are involved in immunomodulatory role of vitamin D,<sup>18,21</sup> therefore, further studies are needed to replicate this association in different populations.

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