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ORIGINAL ARTICLE

Vitamin D as a Marker for Disease Severity in Chronic Urticaria and Its Possible Role in Pathogenesis

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Background: Chronic urticaria is defined as repeated episodes of wheals lasting for 6 weeks or longer. Nowadays, the role of vitamin D in various chronic diseases is a matter of great interest, but limited data is available on the vitamin D status in patients with chronic urticaria. **Objective:** The goal of this study was to investigate the relationship between vitamin D status and clinical characteristics of chronic urticaria. **Methods:** The clinical records of 72 patients with chronic urticaria, 26 with acute urticaria and 26 with atopic dermatitis, along with 72 healthy controls, were retrospectively reviewed. **Results:** The serum 25-(OH)D_3 level was found to be significantly reduced in patients with chronic urticaria compared to those in the other groups. In particular, the proportion of patients with critically low vitamin D levels (< 10 ng/ml) was significantly higher in the chronic urticaria group than in the other groups. The serum vitamin D levels showed significant negative associations with urticaria activity score and disease duration. In addition, serum vitamin D levels were significantly lower in subjects with a positive autologous serum skin test than in subjects with a negative result. **Conclusion:** In conclusion, the serum vitamin D level was more likely to be critically low in patients with chronic urticaria, and an inverse relationship with disease severity and disease duration was observed. These findings may open up the possibility of the clinical use of vitamin D as a contributing factor in the pathogenesis of chronic urticaria and a predictive marker for disease activity in chronic urticaria. **(Ann Dermatol 27(4) 423～430, 2015)**

-Keywords-
Chronic urticaria, Vitamin D, 25-(OH)D_3

INTRODUCTION

Urticaria is characterized by transient, red, and itchy wheals[1]. Chronic urticaria is defined as the development of daily or almost daily repeated urticarial episodes lasting for 6 weeks or longer[2]. 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[3]. The natural history of chronic urticaria varies, and some patients suffer with it for years or even decades. Gaig et al.[4] demonstrated that 50% of patients with chronic urticaria were symptom free after a period of 3 months. However, 11% of the patients still suffered after 5 years[4]. Owing to its chronic nature and intractable course, chronic urticaria impairs quality of life and causes a high burden of suffering in affected patients.

The etiology of chronic urticaria has been attributed to an immense number of factors including foods, drugs, aeroallergens, infections, contact allergens, and autoantibodies to the high affinity immunoglobulin E (IgE) receptor or free IgE[5,6]. 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[7]. Besides mast cells, basophils, dendritic cells, monocytes, neutrophils and numerous cytokines have been implicated in the pathogenesis of chronic urticaria. Sabroe et al.[8] reported that basophil numbers are inversely related to disease severity, and observed that paradoxical suppression of FcεRI mediated, anti-FcεRI/anti-IgE antibody-induced release of

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histamine from basophils during the active disease. Futata et al.[9] 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, IL-6, and IL-12, and high monocyte responsiveness through CCL2/CXCL8 expression have been observed in patients with chronic urticaria[10,11]. Moreover, an elevated level of IL-6 is significantly associated with the clinical severity of chronic urticaria[12,13]. 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[14].

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 final clinical expression of chronic urticaria[15]. However, despite the enormous numbers of studies, the exact etiology and prognostic factors of chronic urticaria remain unclear.

Vitamin D is a secosteroid with a well-known mechanism of action in mineral homeostasis and bone metabolism. As vitamin D has been demonstrated to have potential immunomodulatory activity, the modulation of several types of immune cells by vitamin D may have clinical implications in determining susceptibility to autoimmune disease[16]. The role of vitamin D in various chronic diseases such as malignancies, infectious diseases, autoimmune diseases and allergic disease, including atopic dermatitis and asthma, has been a matter of great interest[17].

Brehm et al.[18] observed that vitamin D insufficiency is relatively frequent in children with asthma, even in the equatorial population of Costa Rica. In this group, lower vitamin D levels were associated with increased markers of allergy and asthma severity. Concerning atopic dermatitis, patients with atopic dermatitis were found to have significantly lower values of vitamin D than healthy control subjects and patients with psoriasis[19]. In one clinical study, 1,600 IU vitamin D was administered to 30 patients with atopic dermatitis. After administration, significant improvement in the SCORAD and TIS were observed. This study concluded that supplementation with oral vitamin D dramatically improved the disease severity in patients with atopic dermatitis[20].

Based on such reports, it seems reasonable to suspect that vitamin D may also play a role in the pathomechanism of chronic urticaria. However, limited data is available on the vitamin D status of patients with chronic urticaria. Therefore, the purpose of this study was to examine the relationship between serum vitamin D status and chronic urticaria. In addition, we aimed to evaluate which, if any, of the clinical characteristics may be affected by the vitamin D status.

MATERIALS AND METHODS

Subjects

A retrospective review was carried out on the clinical records of patients with chronic urticaria who visited the outpatient clinic of the Department of Dermatology, Eulji University Hospital. As there might be seasonal variation in serum vitamin D levels, we planned to conduct the chart review on patients whose blood samples had been taken repeatedly during a period of 1 year, from December 2013 to October 2014, which included South Korea's four seasons. Patients were diagnosed as having chronic urticaria according to the EAACI/GALEN/EDF criteria[21]. Among the available records, the data from 72 patients with chronic urticaria who had performed an autologous serum skin test (ASST) and laboratory tests including serum levels of 25-(OH)D_3, eosinophil, calcium, phosphorous, alkaline phosphatase and total IgE were included in this study. The medical records of patients with acute urticaria and atopic dermatitis in our outpatient clinic during the same period of time were also reviewed. Among these cases, 26 patients with atopic dermatitis and 26 with acute urticaria had undergone laboratory tests, including analysis of serum 25-(OH)D_3, and were included as the positive controls. For the negative healthy control group, the data from healthy subjects who visited the department of family medicine, Eulji University Hospital, for routine health checkups within the same period of time were collected. Among the available records, 72 age and sex matched healthy subjects were selected to decrease the possible errors. All subjects were residents of Daejeon (36.36^{o} N, 127.44^{o} E), South Korea. The following exclusion criteria for the subjects were implemented: patients with inducible urticaria, patients with abnormal serum calcium, phosphate, or alkaline phosphatase levels, and subjects with a history of any of the following conditions: diabetes mellitus, hypertension, cerebro-vascular disease, gastrointestinal malabsorption, and malignancies. This study was approved by the institutional review board of Eulji University Hospital (IRB No. 2014-10-009).

Clinical and laboratory analysis

The clinical records of the subjects were examined for age, sex, disease duration, and laboratory parameters, including serum levels of 25-(OH)D_3, eosinophil, calcium, phosphorous, alkaline phosphatase and total IgE, as well as for the results of the ASST. The urticaria activity score (UAS) of each patient, which was recorded in the medical records, was also reviewed. Using the UAS, which was estimated according to the number of wheals and pruritus intensity based on the EAACI/GA2LEN/EDF guidelines[21], the patients' disease severity levels were graded as mild (0～14), moderate (15～29), and severe (30～42). To assess the vitamin D status, the subjects were divided into four groups according to serum 25(OH)D_3 levels: critically low (＜10 ng/ml), deficiency (＜20 ng/ml), insufficiency (between 20 and 29 ng/ml), and sufficiency (≥30 ng/ml)[17,22].

Statistics

IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA) was employed for all analyses. The mean and standard deviation were used for evaluating the baseline characteristics of the study population. The Kruskal-Wallis test and Mann-Whitney U test were used to compare the differences between groups. The chi square test was used to evaluate the differences in the proportions of each category of serum 25-(OH)D_3 status between the groups. Jonckheere-Terpstra test wasused to evaluate the association between serum 25-(OH)D_3 levels and chronic urticaria. The results were expressed as the mean±standard deviation (SD). A *p*-value of less than 0.05 was considered to be significant.

RESULTS

Clinical characteristics of subjects

The baseline characteristics of the study population are listed in Table 1. Among the 72 patients with chronic urticaria, the ages ranged from 8 to 84 years (median 37.9 years). Eight patients were children (age ＜18 years), 60 were adults (between 18 and 60 years), and 4 were elderly (＞60 years). No significant differences were observed in the baseline characteristics for age, sex, or serum levels of calcium, phosphorus, alkaline phosphate and white blood cells among the groups. The levels of serum total IgE were significantly higher in the atopic dermatitis patients compared with the chronic urticaria patients ($p=0.008$).

The serum 25-(OH)D_3 levels in subject groups

The serum 25-(OH)D_3 levels were significantly lower in the chronic urticaria group (11.86±7.16 ng/ml; mean±SD) compared with the acute urticaria group (14.12±5.56 ng/ml, $p=0.024$), the atopic dermatitis group (16.12±8.09 ng/ml, $p=0.008$) and healthy controls (20.77±9.74 ng/ml, $p<0.001$) (Fig. 1). Among the 10 patients initially diagnosed as acute urticaria and whose vitamin D level was critically low, in 5 patients (50%) their urticarial symptoms lasted for over 6 weeks, and they were reclassified as having chronic urticaria.

Comparison of vitamin D status in chronic urticaria and other groups

To assess the vitamin D status, subjects were divided into four groups according to their serum 25(OH)D_3 levels (as mentioned in material and methods). In the chronic urticaria patients, 35 subjects (49%) were grouped as having critically low vitamin D, 28 subjects (39%) were grouped

Table 1. Characteristics of the study population

	Chronic urticaria (n=72)	Acute urticaria (n=26)	Atopic dermatitis (n=26)	Healthy control (n=72)	*p*-value
Age (yr)	37.89±16.13	29.07±17.07	21.83±9.44	38.61±15.12	0.07
Male/female (n)	28/44	12/14	13/13	28/45	0.3
Calcium (mg/dl)	9.5±0.5	9.4±1.0	9.3±0.3	9.3±0.9	0.3
Phosphorous (mg/dl)	5.2±0.8	4.8±1.0	5.1±0.7	5.2±0.9	0.7
Alkaline phosphate (mg/dl)	607±284	610±543	623±294	600±341	0.1
Total immunoglobulin E (IU/ml)	237±56	319±108	877±213	Unchecked	0.02
White blood cells (cells/ml)	7,292±247	8,374±578	8,224±457	6,500±345	0.06
Serum eosinophil (cells/mm^3)	202±239	142±143	451±406	116±131	＜0.001
Serum eosinophil (%)	2.58±1.82	2.08±2.56	5.26±3.68	1.79±2.40	＜0.001
25-(OH)D_3 (ng/ml)	11.86±7.16	14.12±5.56	16.12±8.09	20.77±9.74	0.008

Values are presented as number or mean±standard deviation.

as vitamin D deficient, 7 subjects (10%) were grouped as vitamin D insufficient, and 2 subjects (2%) were grouped as vitamin D sufficient. Among the healthy control subjects, 5 subjects (8%) were grouped as having critically low vitamin D, 32 subjects (45%) as vitamin D deficient, 20 subjects (27%) as vitamin D insufficient and 15 subjects (20%) as being vitamin D sufficient.

The proportion of subjects with a critically low vitamin D status was significantly higher in those with chronic urticaria (49%) than in those with acute urticaria (26%) ($p<0.002$), atopic dermatitis (28%) ($p<0.004$), or in healthy controls (8%) ($p<0.001$) (Fig. 2; Table 2).

Association between ASST result and serum 25-(OH)D_3 levels in patients with chronic urticaria

In the chronic urticaria group, 28 subjects (38%) tested positive in the ASST. The serum 25-(OH)D_3 levels were found to be significantly lower in the ASST positive subjects (9.12±4.25 ng/ml) than in the ASST negative subjects (13.33±7.09 ng/ml) ($p=0.034$) (Fig. 3). More specifically, the proportion of those with critically low vitamin D status was higher in the ASST positive group (60%) than in the ASST negative group (32%) ($p=0.021$) (Fig. 4).

Association between disease severity and serum 25-(OH)D_3 levels in patients with chronic urticaria

In chronic urticaria patients, the serum 25-(OH)D_3 levels tended to have a significant negative correlation with the UAS ($p<0.001$; Jonckheere-Terpstra test) (Fig. 5). When we grouped disease severity according to the UAS as mild, moderate and severe, the proportion of subjects with critically low vitamin D status was significantly higher in the moderate/severe UAS group than in the mild UAS group ($p=0.03$).

Association between disease duration and serum 25-(OH)D_3 levels in patients with chronic urticaria

In patients with chronic urticaria, the mean duration of chronic urticaria was 25.86 months. Among these patients, a disease duration of less than 6 months was observed in 49% of patients (n=36), less than 1 year in 19% (n=13), less than 3 years in 16% (n=12), and more than 3 years in 16% (n=12). The serum 25-(OH)D_3 levels showed

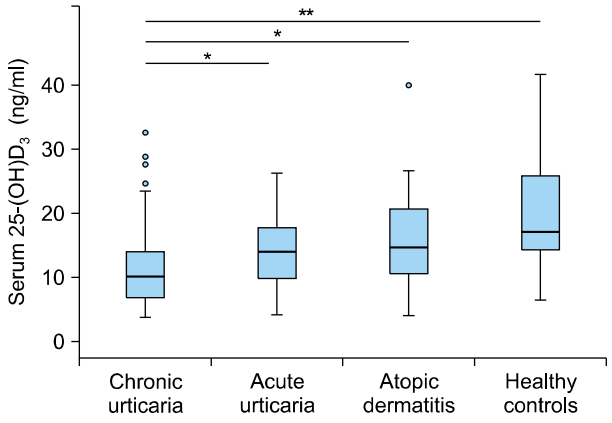

Fig. 1. Levels of serum 25-(OH)D_3 in patients with chronic urticaria, acute urticaria, atopic dermatitis and healthy controls. Serum 25-(OH)D_3 levels were significantly reduced in patients with chronic urticaria compared with acute urticaria ($p=0.024$), atopic dermatitis ($p=0.008$) and healthy controls ($p<0.001$). Data are presented as Box and Whisker plots ('○' representing data points >1.5 interquartile range). Sample sizes were as follows: chronic urticaria, n=72; acute urticaria, n=26; atopic dermatitis, n=26; healthy control, n=72. *$p<0.05$, **$p<0.001$.

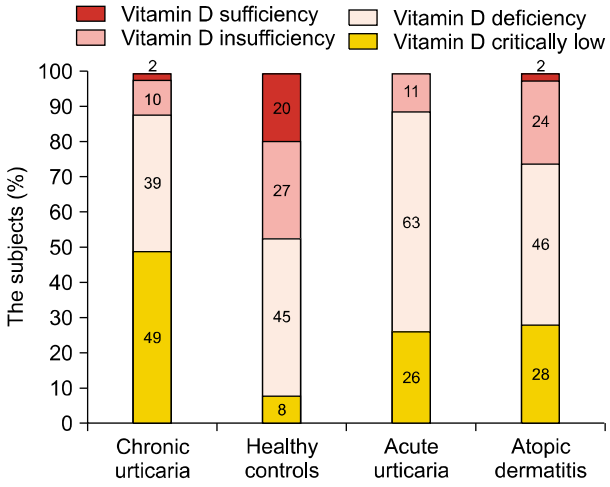

Fig. 2. Proportion of the subjects in chronic urticaria, healthy control, acute urticaria and atopic dermatitis in the serum vitamin D level groups. The proportion of subjects with critically low vitamin D was significantly higher in patients with chronic urticaria (49%) compared to patients with acute urticaria (26%) ($p<0.002$), atopic dermatitis (28%) ($p<0.004$) and healthy controls (8%) ($p<0.001$).

Table 2. Proportion of critically low vitamin D status in chronic urticaria patients compared with other groups

Serum 25-(OH)D_3 status	Chronic urticaria (n=72)	Healthy controls (n=72)	Acute urticaria (n=26)	Atopic dermatitis (n=26)	*p*-value (CU vs. HC)
Critically low (<10 ng/ml)	35 (49)	5 (8)	6 (26)	7 (28)	<0.001

Values are presented as number (%). CU: chronic urticaria, HC: healthy controls.

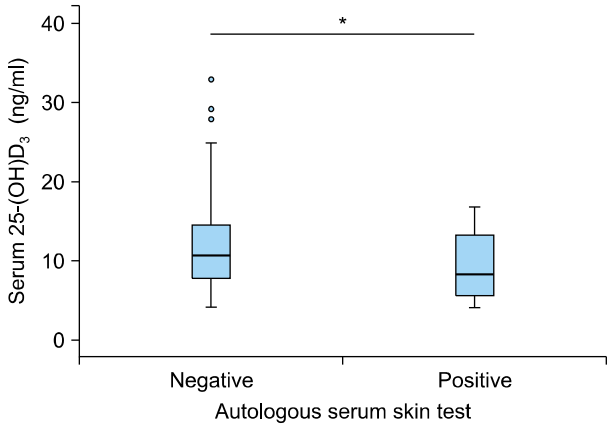

Fig. 3. Serum 25-(OH)D_3 levels of chronic urticaria patients according to autologous serum skin test (ASST) results. The serum 25-(OH)D_3 levels were significantly lower in ASST positive subjects than ASST negative subjects ($p=0.034$), *$p<0.05$. Data are presented as Box and Whisker plots. Sample sizes were as follows: ASST negative, n=44; ASST positive, n=28.

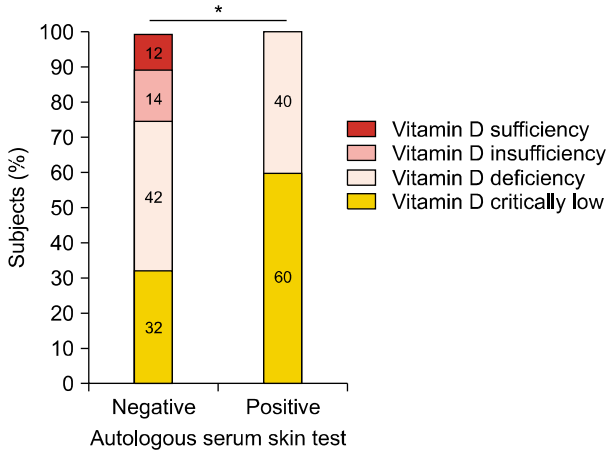

Fig. 4. Patients with chronic urticaria grouped according to the autologous serum skin test (ASST) and serum vitamin D levels. The proportion of patients with critically low vitamin D was higher in the ASST positive group (60%) than the ASST negative group (32%) ($p=0.021$), *$p<0.05$.

a significant negative trend in association with the disease duration ($p=0.008$; Jonckheere-Terpstra test) (Fig. 6).

Others

In patients with chronic urticaria, the mean serum 25-(OH)D_3 level was the lowest in children (9.67±5.50 ng/ml) and the highest in the elderly (13.05±10.03 ng/ml); however, there was no significant correlation between age and serum 25-(OH)D_3 levels ($p=0.94$). The serum 25-(OH)D_3 levels were significantly lower in females (9.95±5.56 ng/ml) than males (14.86±8.33 ng/ml) ($p=0.003$). The proportion of patients with critically low vitamin D status was higher in females than males ($p=0.041$).

There was also a significant difference in serum 25-(OH)D_3 levels according to the season. In all seasons, the serum 25-(OH)D_3 levels in patients with chronic urticaria (summer, 16.12±7.10; autumn, 12.79±7.80; spring, 11.64±5.99; winter 8.35±4.91; mean±SD) were significantly lower than the healthy controls (summer, 22.06±6.20; autumn, 19.39±6.50; spring, 16.32±7.63; winter, 15.28±3.02) (Fig. 7).

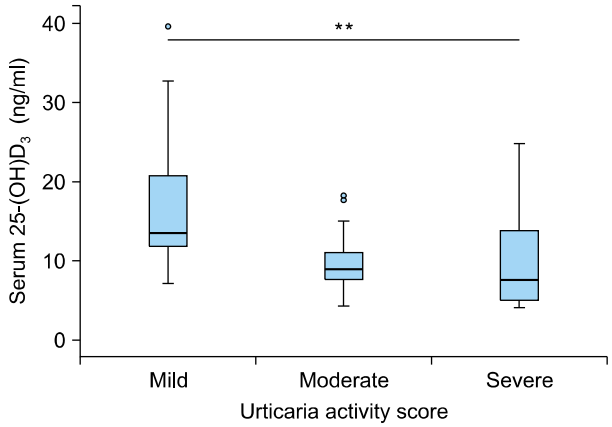

Fig. 5. The trend of association between urticaria activity score (UAS) and serum 25-(OH)D_3 levels in patients with chronic urticaria. The serum 25-(OH)D_3 levels showed a significant negative trend of association with UAS in chronic urticaria patient ($p<0.001$; Jonckheere-Terpstra test). Data are presented as Box and Whisker plots, **$p<0.001$. Sample sizes were as follows: mild, n=22; moderate, n=25; severe, n=26.

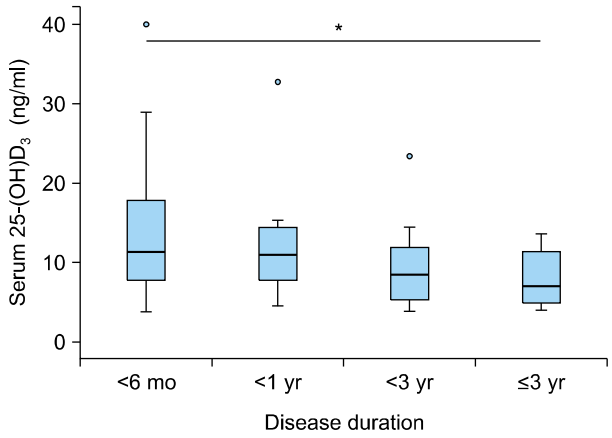

Fig. 6. The trend of association between disease duration and serum 25-(OH)D_3 levels in patients with chronic urticaria. The serum 25-(OH)D_3 levels showed a significant negative trend of association with disease duration ($p=0.008$; Jonckheere-Terpstra test). Data are presented as Box and Whisker plots, *$p<0.05$. Sample sizes were as follows: <6 months, n=36; <1 year, n=13; <3 years, n=12; ≥3 years, n=12.

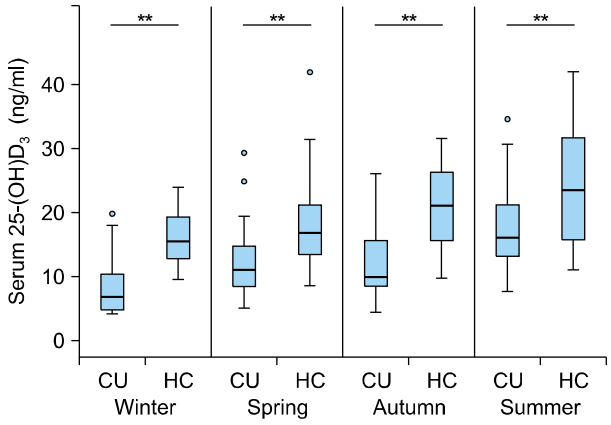

Fig. 7. Serum 25-(OH)D_3 levels in patients with chronic urticaria and healthy controls according to the season. Patient with chronic urticaria had significantly lower serum 25-(OH)D_3 levels than the healthy control group. Sample sizes were as follows: In patients with chronic urticaria, winter, n=17; spring, n=23; autumn, n=14; summer, n=18; in healthy controls, winter, n=16; spring, n=23; autumn, n=15; summer, n=18. Data are presented as Box and Whisker plots, $^{**}p<0.01$. CU: chronic urticaria, HC: healthy controls.

DISCUSSION

In the field of dermatology, numerous studies have been carried out to investigate the association of vitamin D with certain diseases, such as atopic dermatitis and psoriasis[19,20,23,24]. Vitamin D is known to have modulatory effects on dendritic cells and monocytes, and the functional impairment of these cells interferes with the production of various cytokines. This led us to suspect that the impaired function of various immunocytes due to low vitamin D levels might lead to increase of circulating pro-inflammatory cytokines and imbalance of regulatory T-cell cytokine production, which might cause worsening of chronic urticaria. However, studies on the vitamin D status in patients with chronic urticaria are scarce[25-27]. In previous reports, the vitamin D level was found to be reduced in chronic urticaria patients when compared with normal healthy controls[25-27]. In this report, a significant reduction of the serum 25-(OH)D_3 level was observed in patients with chronic urticaria compared with healthy controls, which is a similar result to the previous studies[25-27]. In addition, this study included not only a healthy control group, but also other disease control groups for comparison. Comparison with patients suffering from atopic dermatitis and acute urticaria also demonstrated that the chronic urticaria patients displayed significantly reduced serum 25-(OH)D_3 levels. Previous studies focused only on vitamin D deficiency[25-27]; however, in the present study, the vitamin D status was further subdivided to allow more in-depth analysis. In the Korean population, mean serum vitamin D levels are around 21.2 ± 7.5 ng/ml in males and 18.2 ± 7.1 ng/ml in females[28], which are very close to the referential range for vitamin D deficiency. In this study, emphasis was placed not only on the proportion of patients with vitamin D deficiency, but also on the proportion of patients with critically low vitamin D levels. Through this approach, it was found that the proportion of patients with critically low vitamin D was significantly higher in the group with chronic urticaria than in the other control groups. Altogether, it was demonstrated that critically low levels of vitamin D can commonly be found in patients with chronic urticaria.

In the current era of dermatology, the involvement of reduced vitamin levels in atopic dermatitis is well known[23,24], but no papers yet exist comparing the levels of vitamin D in patients with chronic urticaria and with atopic dermatitis. In this report, these two patient groups were compared, and it was found that the vitamin D levels were significantly lower in the patient with chronic urticaria.

Among 10 patients initially diagnosed as having acute urticaria with critically low vitamin D levels, 5 patients (50%) displayed urticarial symptoms which lasted for over 6 weeks, causing them to be regrouped as having chronic urticaria. As vitamin D is considered not only as a marker for chronic inflammatory disease, but also for the acute phase of inflammation[29], it could be suspected that low vitamin D levels among patients initially presenting with acute urticaria may provide a marker for predicting higher probability to progression to the chronic form.

In patients with chronic autoimmune urticaria, the ASST is the best clinical test for *in vivo* detection of functional circulating autoantibodies to FcεRIα. Thorp et al.[25] and Grzanka et al.[27] observed no differences in the levels of 25-(OH)D_3 between the ASST-positive and -negative groups. However, the ASST-positive patients in the present study were found to have significantly lower levels of 25-(OH)D_3 when compared with the negative patients. This finding agrees with the study of Chandrashekar et al.[26], who observed that the mean 25-(OH)D_3 level was significantly lower in the ASST-positive group. Herein, it was newly found that the proportion of patients with critically low vitamin D was higher in the ASST-positive group than in the ASST-negative group. This finding might suggest that vitamin D deficiency, especially when at critically low levels (<10 ng/ml), might be used as an auxiliary marker suggesting autoimmune urticaria. Although no differences in serum vitamin D levels between the ASST-positive and -negative groups were observed by Thorp et al.[25] and Grzanka et al.[27], we suspect that this might be due to the small sample sizes and lack of subdivision of the vitamin D deficiency status in these studies.

Although Thorp et al.[25] did not observed a relationship between the severity of urticaria and vitamin D, an inverse relationship between the severity and serum levels of 25-(OH)D_3 was observed herein, which seems to support the previous findings of Chandrashekar et al.[26]. In addition, a negative association between disease duration and vitamin D was also found in the chronic urticaria patients: the longer the disease duration, the lower the serum 25-(OH)D_3 levels.

A potential limitation of the present study is that the patient groups were recruited from the outpatient clinic of a tertiary center hospital, which raises the possibility of the study being limited by small sample size, selection and detection bias. Several factors that affect the levels of serum vitamin D such as smoking, daily sunlight per subject, baseline nutritional status, time of blood sampling, body mass index and levels of serum parathyroid hormone should be always considered[17]. However, due to the retrospective design of this, it is necessary to acknowledge that we cannot analyze the above confounding factors. Therefore, further well-designed prospective studies with large samples should be performed. A further additional *in vitro* study regarding vitamin D supplementation in chronic urticaria is also needed. Although Sindher et al.[30] reported that daily supplementation of cholecalciferol improved the urticarial symptoms of one patient with chronic urticaria, further studies with larger samples are necessary to determine whether vitamin D supplementation may improve the symptoms of those with chronic urticaria, or provide benefits as an add-on therapy for chronic urticaria.

Although, the exact mechanism of the relationship between vitamin D deficiency and chronic urticaria is so far not clear, we suspect that besides the direct action of vitamin D, its modulatory function on various inflammatory cells might partially explain the association of vitamin D deficiency with chronic urticaria. We believe that this study may provide potential pathways for future research on understanding the role of vitamin D in chronic urticaria. Additional large-scale studies are needed to assess whether vitamin D could be used as an auxiliary marker to predict the disease severity and clinical course in chronic urticaria patients. Furthermore, vitamin D supplementation might be used to improve the symptoms of those with chornic urticaria, or to provide benefits as an add on therapy in the treatment of chronic urticaria.

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