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CLINICAL STUDY

25-hydroxyvitamin D levels are low but not associated with disease activity in chronic spontaneous urticaria and depression

Vurgun E[a,1], Memet B[b,2], Kocaturk E[b,2], Guntas G[a,c]

Medical Biochemistry, Sorgun State Hospital, Yozgat, Turkey. **eren_vurgun@hotmail.com**

ABSTRACT

AIM: To evaluate vitamin D levels in patients with chronic spontaneous urticaria (CSU), depression and both of them, thus to find out whether vitamin D may be a common causative factor of CSU and depression.

METHODS: Thirty patients with CSU, 30 patients with depression, 30 patients with both CSU and depression and 30 healthy volunteers as control group were involved in the study. Serum 25-hydroxyvitamin D (25(OH) D) levels of these groups were measured and compared. Correlations between 25(OH)D levels and the activity of CSU and depression were analyzed.

RESULTS: Healthy controls' 25(OH)D levels (17.2±8.8 ng/mL) were higher than patients with CSU (9.1±5.1 ng/mL), depression (8.9±6.1 ng/mL) and CSU with depression (7.7±4.7 ng/mL) ($p<0.001$, $p<0.001$ and $p<0.001$, respectively). There were no differences in 25(OH)D levels between CSU patients with and without depression, between depression patients and CSU patients with and without depression ($p=0.43$, $p=0.82$ and $p=0.92$, respectively). There were no correlations between 25(OH)D levels and the activity of CSU or depression ($p=0.99$ and $p=0.76$, respectively).

CONCLUSION: Lower 25(OH)D levels in CSU and/or depression may appear as a secondary phenomenon, which means being result of these diseases rather than the cause *(Tab. 1, Fig. 2, Ref. 41)*. Text in PDF *www.elis.sk*

KEY WORDS: vitamin D, vitamin D deficiency, chronic urticaria, depression.

Introduction

Urticaria is a disorder characterized by the appearance of wheal and flare reaction lasting less than 24 hours (1). The disease is termed as acute urticaria if it lasts less than six weeks and chronic urticaria if it lasts longer than six weeks and with almost every day presentation (2). The primary effector cell is the mast cell and the main mediator is histamine (3). Basophils also contain histamine, but the most important source of histamine are the skin mast cells (2).

Although the central role of vitamin D in bone physiology is well known, it has been reported to show various immunomodulatory actions on both natural and acquired immunity via plasma membrane (mVDR) and nuclear (nVDR) receptors on the epithelial cells, monocytes, macrophages, T and B lymphocytes, dendritic cells and mast cells (4,5). In addition to its roles in other parts of immune system, it has also been shown that vitamin D affect the proliferation, survival, differentiation and function of the mast cells (4,6).

Chronic urticaria is often associated with psychological conditions such as depression, anxiety and stress, which may play a role not only in the genesis of the disease but also in its evolution (7). Depression is strongly associated with morbidity, mortality and health expenditures. Although biological, physiological, and environmental theories have been developed, the underlying pathophysiology of depression is still not fully understood, and it is likely that more than one different mechanism plays a role in the pathogenesis (8).

Vitamin D receptors are found on neurons and glial cells which are located in many brain regions including the cingulate cortex and the hippocampus which are involved in the pathophysiology of depression (9). The presence of vitamin D in a number of brain processes such as neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development makes biologically reasonable that vitamin D might have an implication on the occurrence of depression (10). Vitamin D is a unique neurosteroid hormone that may have an important role in the pathogenesis of depression.

[a]Department of Medical Biochemistry, Okmeydani Training and Research Hospital, Istanbul, Turkey, [1]Medical Biochemistry, Sorgun State Hospital, Yozgat, Turkey, [b]Department of Dermatology, Okmeydani Training and Research Hospital, Istanbul, Turkey, [2]Department of Dermatology, Koc University School of Medicine, Istanbul, Turkey, and [c]Kırklareli University School of Health, Kirklareli, Turkey

Address for correspondence: E. Vurgun, Medical Biochemistry, Sorgun State Hospital, postal code: 66700, Yozgat, Turkey.
Phone**:** +905377188596

Tab. 1. Comparative table of demographic characteristics of groups.

	Control	Depression	CSU without depression	CSU with depression
n	30	30	30	30
Age	32 (26.7–35.7)	34.5 (25.7–43.2)	41.5 (31.7–58.2)*	40.5 (32.7–53.7)*$^{\Delta}$
Female/Male	22/8	27/3	22/8	28/2
UAS7 score	—	—	14 (5.0–28.5)	22.5 (14.7–38.0)$^{\#}$
BDI score	7 (2.7–9.2)	28 (24.7–38)**$^{\#\#}$	7 (2.7–9.2)	27.5 (24–32.7)**$^{\#\#}$

* $p < 0.05$ and ** $p < 0.001$ when compared to control group, $^{\Delta}$ $p < 0.05$ when compared to depression group, $^{\#}$ $p < 0.05$ and $^{\#\#}$ $p < 0.001$ when compared to CSU without depression group

The first aim of this study was to determine vitamin D levels in patients with chronic spontaneous urticaria (CSU), depression and both of them and to compare them with healthy controls. The second aim was to investigate the relationships between 25-hydroxyvitamin D (25(OH)D) levels and the activity of CSU and depression, thus to find out whether vitamin D may be a common causative factor of CSU and depression.

Methods

Participants

The study was conducted at the Dermatology Clinic of Okmeydani Training and Research Hospital which is an Urticaria Centre of Reference and Excellence (UCARE) (11) between September 2015 and March 2016. All patients who were volunteered to participate in the study were administered a Beck Depression Inventory (BDI) (12). Thirty CSU patients whose scores were < 17 points on the BDI were included in the study as "CSU without depression". The CSU patients whose scores were ≥ 17 points on the BDI were directed to the psychiatry clinic. Thirty patients who were diagnosed as depression by the psychiatrist were included in the study as "CSU with depression". All CSU patients' urticaria activity scores of last seven days (UAS7) (13) at the time of enrollment to the study were recorded.

Thirty patients whose scores were ≥ 17 points on the BDI and who were diagnosed with depression by the psychiatrist from the Psychiatry Clinic of our hospital were included in the study as "depression group". In addition, thirty healthy volunteers who had < 17 points on the BDI were included in the study as "control group". All participants were between 18–64 years old and have not taken any vitamin D supplementation within last six months. CSU patients who were enrolled into the study were taking antihistamine treatment alone. Subjects who were on continuous corticosteroid or immunosuppressive treatment or on regular non-steroid anti-inflammatory drugs or on antidepressants for the last six months were not included in the study.

Measurement of 25(OH)D

Serum 25(OH)D levels were measured by using Zivak 25-OH Vitamin D2/D3 LC-MS/MS analysis kit (Zivak Technologies, Istanbul, Turkey) in fully automated Zivak Multitasker LC-MS/MS (Zivak Technologies, Istanbul, Turkey) (14). Inter-assay and intra-assay CVs for 25(OH)D measurement were ≤ 3.4 % and ≤ 4.4 %, respectively.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from Okmeydani Training and Research Hospital Ethics Committee of Clinical Investigations (No: 522).

Statistical analysis

Thirty participants were included in each group for the effect size of 0.65 with type I error rate of 0.05 and type II error rate of 0.20. Sample size was calculated by G*Power 3.1 (GPower, Dusseldorf, Germany).

Age, UAS7 and BDI scores were not normally distributed, so they were expressed as median (25–75 percentile). Non-parametric Kruskal–Wallis test was used to compare the age and BDI scores of groups. Mann–Whitney U test was used for pairwise comparisons of age, BDI and UAS7 scores. Chi-square test was used when female/male ratios were compared, and Fisher's Exact test was used if necessary conditions were not met.

25(OH)D levels were not normally distributed; after logarithmic transformation was applied, the distribution was in accordance with normality by histogram and Kolmogorov–Smirnov test. As a result, 25(OH)D levels were compared using logarithmically transformed data, but were expressed as untransformed mean ± standard deviation for ease of understanding. Comparisons were made using the one-way ANOVA test because the logarithmic values were normally distributed and the variances were homogeneous by Levene's test. Tukey HSD test was used in post hoc evaluations because the group numbers were equal.

The correlations between 25(OH)D levels and UAS7 or BDI scores were analyzed by Spearman's correlation test. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, USA) and values of $p < 0.05$ were considered significant.

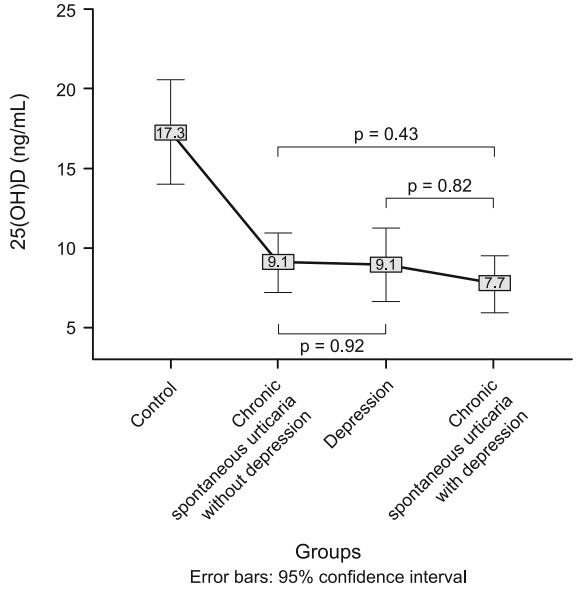

Fig. 1. 25(OH)D levels of groups.

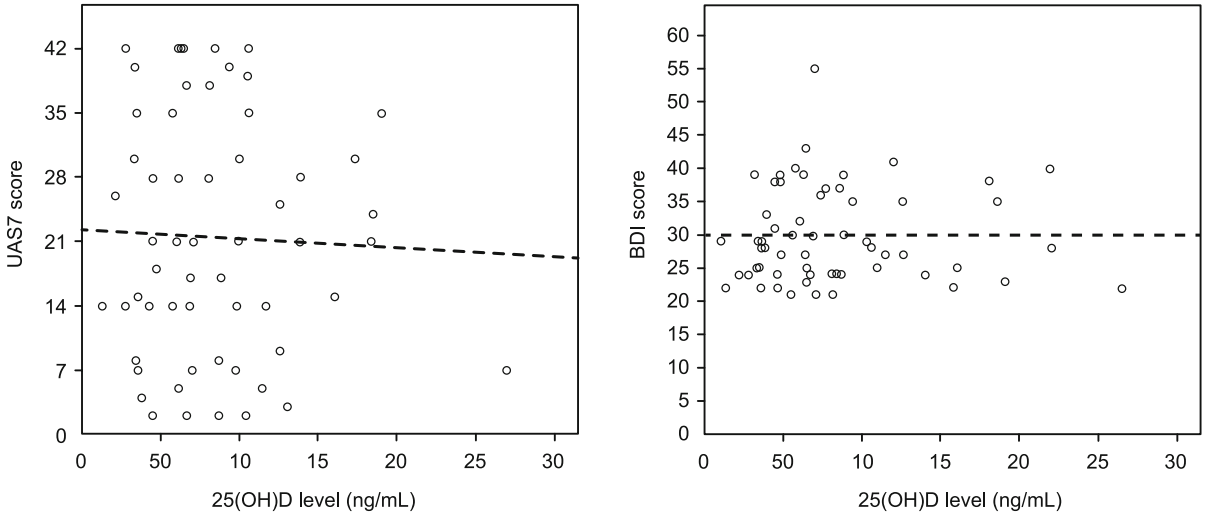

Fig. 2. Distributions of 25(OH)D levels with UAS7 (A) and BDI (B) scores with their fit lines.

Results

Demographic characteristics of control and patient groups are shown in Table 1.

Serum 25(OH)D levels were lower in all patient groups compared to the control group

Serum levels of 25(OH)D were lower in patients with CSU, depression and CSU with depression groups when compared to the control group ($p < 0.001$ for each). There were no differences in 25(OH)D levels between the patient groups ($p = 0.92$, $p = 0.43$ and $p = 0.82$), as shown in Figure 1.

Serum 25(OH)D levels were not correlated with UAS7 and BDI scores

There were no correlations between 25(OH)D levels and UAS7 scores in all CSU patients ($r = 0.002$, $p = 0.99$) as well as there were no correlations between 25(OH)D level and BDI scores in all depression patients ($r = 0.041$, $p = 0.76$) as shown in Figure 2.

Discussion

In this study, 25(OH)D levels were shown to be lower in both CSU patients and depression patients compared to the healthy controls nevertheless there were no correlations between 25(OH)D levels and the activity of urticaria and/or depression. Vitamin D does not seem to be a common causative factor of CSU and depression. In recent years, 25(OH)D levels in chronic urticaria and depression have been in the focus of many researchers. Similarly, 25(OH)D levels of chronic urticaria patients have been found to be lower than in controls in studies conducted in different populations (15-20). In order to evaluate this observation, we examined the relationship between the disease activity (by UAS7) and the levels of 25(OH)D but there was no correlation between them. In concordance with our results, many of these studies haven't found any correlation between the activity of urticaria and 25(OH)D levels (15–19).

The role of vitamin D supplementation in chronic urticaria has also been investigated by researchers. Currently there is not sufficient evidence to support vitamin D supplementation in chronic urticaria patients due to the limited number of studies highlighting the benefits of vitamin D in chronic urticaria as indicated in a review by Quirk et al (21). These results do not demonstrate that vitamin D is involved in the etiopathogenesis of urticaria because the mechanism of action of vitamin D supplementation is not clear. These findings suggest that vitamin D does not interact directly with the clinical presentation of urticaria. Even so, the exact mechanism of the relevance between vitamin D deficiency and chronic urticaria remains unclear so far. As mentioned by Grzanka et al (17), lower levels of 25(OH)D may therefore appear as just a secondary phenomenon, expressed as a result of the disease process itself including inflammation or immune activation and as such, may not contribute in any way to the pathogenesis of the disease.

Consistent with our result, several studies have found lower 25(OH)D levels in depression (22–26). In order to evaluate this observation, we examined the relationship between the activity of depression (BDI score) and the levels of 25(OH)D but we found no correlation between them. Lower 25(OH)D levels were associated with an increased risk of depression as a finding in a meta-analysis (27). Nevertheless, other studies did not support this association (28–30). Only one of four meta-analyses examining the effect of vitamin D supplementation on depression has supported a beneficial effect (31). The other three meta-analyses have showed no overall beneficial effects of vitamin D supplementation (32–34). Thereby, these results do not support the findings obtained from observational studies of an important role of vitamin D in the pathogenesis of depression.

In our study, urticaria activity scores of CSU patients with depression were shown to be higher than those without. Depression accompanying urticaria in these patients may have increased the

activity of urticaria. However, the lack of difference in 25(OH)D levels between CSU with and without depression and correlation between 25(OH)D levels and UAS7 scores indicate that the higher activity of urticaria in CSU with depression group was independent of 25(OH)D level.

Furthermore, the number of disorders associated with low levels of 25(OH)D has constantly increased (35). The discrepancy between observational studies and randomized controlled trials brings to mind that low 25(OH)D might be the result, rather than the cause, of physiological disruptions relevant to some diseases (36). From this point of view, Autier et al (35) suggest that low 25(OH) D could be a marker of ill health. 25(OH)D levels are significantly reduced during acute health events which are characterized by severe inflammation and multiorgan failure, especially in critically ill patients (37–38). Similar decreases in 25(OH)D levels have been reported in many inflammatory diseases (39). Inflammation appears to be the common factor of these various non-skeletal diseases. It can be speculated that vitamin D levels decreases due to the inflammatory processes occurring in the pathogenesis of the diseases and that could explain why low vitamin D status is reported in a wide range of diseases.

We have some limitations such as age differences between CSU patients and the other groups. One possible reason of this difference might be that CSU is most common between the ages 20–40 (40). However, it is not expected that there will be a physiological change in 25(OH)D levels between the ages of 32 and 40 years. 25(OH)D levels are known to be affected by age so that the levels have been shown to decrease in the elderly people (> 65 years) (41). Nevertheless, we don't think that age difference has an effect on the findings of our study because there were no elderly people (> 65 years), neither among patients, nor controls.

Conclusion

The results of this study have shown lower 25(OH)D levels in CSU and depression. There were no correlations between 25(OH) D levels and the activity of urticaria and/or depression. Moreover, the lack of differences in 25(OH)D levels between CSU without depression, depression and CSU with depression patients support the hypothesis that lower 25(OH)D levels in CSU and/or depression may appear as a secondary phenomenon which means to be a result of these diseases rather than the cause. In order to clarify this hypothesis, further studies are needed to monitor the vitamin D levels of CSU and depression patients before treatment and after recovery.

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