The association between anxiety and depression with 25(OH)D and thyroid stimulating hormone levels

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ABSTRACT

Objectives: To evaluate the relationships between the serum levels of these parameters and mood disorders, including depression and anxiety.

Methods: One hundred and fifty patients (77 with anxiety and 73 with depression), aged 18 to 79 years old, who were referred to the Neuro Psychiatry Clinic of Uskudar University in Istanbul, Turkey were included in this study from June 2018 to December 2018. According to the Beck Anxiety Inventory and Beck Depression Inventory II results, the anxiety patients met the mild and moderate anxiety criteria and the depression patients met the moderate and severe depression criteria, respectively. Venous blood samples were collected after overnight fasting, and the 25(OH)D and thyroid stimulating hormone (TSH) levels were measured.

Results: The data showed a significantly higher TSH level in the females when compared to their male counterparts in the severe depression subgroup (p=0.011).

Conclusion: A serum TSH evaluation may be considered as a useful biochemical marker for more efficient depression management.

Depression and anxiety are considered to be the most prevalent mental diseases, causing decreased productivity and function of individuals in their daily activities and the loss of economic resources as well. Therefore, a comprehensive program of chronic disease management should be considered for the effective treatment of these disorders. In their meta-analysis, Lim et al. evaluated the depression prevalences in 30 different countries between 1994 and 2014. Their data showed prevalences of 12.9%, 7.2%, and 10.8% for the aggregate point, one-year, and lifetime depression levels, respectively. Additionally, the current prevalence of anxiety disorders has been reported as 7.3% worldwide. During the past decade, various epidemiological studies have indicated that dietary patterns are an underlying cause of the onset of psychiatric symptoms. In this regard, “nutritional psychiatry” mainly discusses the nutritional effects of a single nutrient on mood disorders, including depression and anxiety.
discovery of the systemic role of 25(OH)D opened up a novel area of study for the effects of this vitamin on the regulation of different physiological and pathological processes and on the prevention or treatment of diseases. 6 25(OH)D is supplied through both dietary sources and the photochemical synthesis of epithelial cells. The classical roles of this vitamin have been described as calcium homeostasis modulation and bone metabolism. However, the effect of this molecule on the central nervous system has recently been studied. 6 This vitamin has neuroprotective properties, such as in the synthesis of neuromediators, the production and release of neurotrophins, the homeostasis of intracellular calcium, and nervous tissue protection against oxidative damage. 7 The correlation between a 25(OH)D deficiency and depressive disorders and symptoms has been well-described in recent studies. 8,9 Hoogendijk et al. 10 in a cohort study of 1,200 individuals older than 65 years, observed significantly lower 25(OH)D levels of 14% and 14% in patients with minor and major depression, respectively, when compared to the healthy controls, even after adjusting for the age, sex, body mass index, smoking status, and number of chronic conditions. Moreover, the effects of 25(OH)D supplementation on the depressive symptoms of overweight and obese patients have also indicated a significant improvement in depression in the patients receiving 20,000 IU of cholecalciferol one or twice per week when compared to a placebo group. 11 However, limited studies have been published about the associations between this agent and anxiety disorders. 12 Furthermore, some studies have denied this kind of association. 13 In addition to 25(OH)D, thyroid hormones also play critical roles in adult brain functions, and varying degrees of psychiatric symptoms have been reported in patients with hypo-or hyperthyroidism. Moreover, thyroid dysfunction has been recognized to be implicated in emotional and cognitive disturbances. 14 It has been reported that anxiety disorders were observed in approximately 60% of hyperthyroid patients, while depression symptoms were reported in 31–69% of these patients. 15 In contrast, depression features, cognitive dysfunction, apathy, and psychomotor slowing have been associated with hypothyroidism. 16 In their study, Berthla et al. 17 reported a high prevalence of psychiatric symptoms/disorders in patients with thyroid dysfunctions.

Recent studies have also reported an association between a vitamin D deficiency and thyroid dysfunction. 18 Low 25(OH)D levels have been reported in patients suffering from hypothyroidism and Grave’s disease. 19,20 Two mechanisms have been proposed for this phenomenon: poor vitamin D absorption from the intestine and the improper activation of the body of vitamin D in these patients. 19

Based on the above information, the aim of this study was to evaluate the correlations between the 25(OH)D and thyroid stimulating hormone (TSH) levels and depression and anxiety disorders.

**Methods. Patients.** One hundred and fifty patients (77 with anxiety and 73 with depression), aged 18 to 79 years old, who were referred to the Neuro Psychiatry Clinic of Uskudar University in Istanbul, Turkey were enrolled in this experimental study. When considering a study power of 80% and a confidence interval of 95%, the study population was calculated according to the following formula: sample size=Z1-α/22*P(1-P)/d2. 21 This study was performed according to the tenets of the Helsinki Declaration, and it was approved by the research ethics committee of Uskudar University (Code: 61351342-/2019-80). Written informed consent was obtained from all of the patients prior any clinical examinations.

All of the patients diagnosed with depression and anxiety were included in this study. A history of serum 25(OH)D and TSH altering diseases, such as hepatic dysfunction, renal and thyroid diseases, and diabetes mellitus, or the current use of the aforementioned vitamin supplements were considered to be exclusionary criteria.

**Clinical assessments.** The patients’ moods were evaluated for the presence of depression and anxiety via the Beck Depression Inventory II (BDI-II) and the Beck Anxiety Inventory (BAI), respectively. 22,23 Twenty-nine multiple choice questions were included in each test, and the maximum score for each question was 3. The BDI-II scores lower than 9 were designated as the absence of depression. Depression was classified into 3 subgroups: mild (BDI-II=10–15), moderate (BDI-II=16–23), and severe (BDI-II≥24). The BAI scores of less than 15 were considered to be negative for anxiety. Accordingly, the anxiety status was also categorized as mild (BAI=16–22), moderate (BAI=23–42), and severe (BAI≥43). Those patients with BDI-II scores of ≤9 and BAI scores of <15 were excluded from the study.

**Sampling and laboratory analysis.** Venous blood samples were collected after overnight fasting, and the

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Table 1 - General characteristics of individuals.

| Parameters          | Anxiety n=77 | Depression n=73 |
|---------------------|--------------|-----------------|
|                     | Male n=43    | Female n=34     | Male n=25 | Female n=48 |
| Age (year)          | 36.9±14.42   | 37.38±11.89     | 30.52±7.85 | 38.16±11.88 |
| 25(OH)D (ng/ml)     | 20.4±11.05   | 19.54±10.84     | 20.56±12.61 | 16.1±10.04  |
| TSH (µIU/ml)        | 2.54±1.63    | 2.43±1.47       | 2.29±1.84  | 2.81±1.48   |
| Beck.Depression     | 19.0±7.03    | 19.8±1.98       | 30.0±8.05  | 31.3±6.53   |
| Beck.Anxiety        | 29.18±9.16   | 27.38±7.76      | 14.92±9.15 | 16.85±8.97  |

Data are presented as mean±SD, TSH - thyroid stimulating hormone

Table 2 - Comparison of biochemical parameters between anxiety and depression groups.

| Parameters          | Anxiety n=77 | Depression n=73 | P-value |
|---------------------|--------------|-----------------|---------|
| 25(OH)D (ng/ml)     | 20.02±10.9   | 17.63±11.1      | 0.145   |
| TSH (µIU/ml)        | 2.49±1.55    | 2.63±1.62       | 0.621   |

Data are presented as mean±SD, TSH - thyroid stimulating hormone

Table 3 - Comparison of biochemical parameters between anxiety subgroups.

| Parameters          | Mild anxiety n=18 | Moderate Anxiety n=59 | P-value |
|---------------------|-------------------|-----------------------|---------|
| 25(OH)D (ng/ml)     | 21.79±15.5        | 19.48±9.16            | 0.938   |
| TSH (µIU/ml)        | 2.56±1.44         | 2.47±1.6              | 0.678   |

Data are presented as mean±SD. P<0.05 was considered as statistically significant, TSH - thyroid stimulating hormone

Table 4 - Comparison of biochemical parameters between depression subgroups.

| Parameters          | Moderate depression n=12 | Severe depression n=61 | P-value |
|---------------------|--------------------------|------------------------|---------|
| 25(OH)D (ng/ml)     | 15.92±11.09              | 18.09±11.19            | 0.641   |
| TSH (µIU/ml)        | 1.68±0.79                | 2.81±1.69              | 0.118   |

Data are presented as mean±SD. P<0.05 was considered as statistically significant, TSH - thyroid stimulating hormone

25(OH)D and TSH levels were measured in all of the subjects using a cobas e 411 immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany). 25(OH)D levels of <10, 11–29, and ≥30 ng/ml were categorized as deficiency, insufficiency, and normal, respectively. A 0.3–4.5 µIU/ml interval was considered to be a normal serum TSH level.

Statistical analysis. The data were presented as the mean±standard deviation, and they were analyzed using IBM SPSS Statistics for Windows version 23 (IBM Corp., Armonk, NY, USA). A non-parametric Kruskal-Wallis test was used to compare the means between the groups. A bivariate correlation analysis was also conducted to assess the associations between the clinical variables and the 25(OH)D or TSH levels. A p-value of <0.05 was considered to be statistically significant.

Results. General characteristics of the individuals. Table 1 shows the general information about the participants. There were 77 participants in the anxiety group (43 males and 34 females) and 73 participants in the depression group (25 males and 48 females). The average ages of the males and females in the anxiety group were 36.9±14.42 and 37.38±11.89 years old, respectively. In the depression group, the average ages of the males and females were 30.52±7.85 and 38.16±11.88 years old, respectively. The 25(OH)D and TSH level comparisons showed no significant differences between the anxiety and depression groups (p=0.145 and p=0.621, respectively) (Table 2). 25(OH)D and TSH level comparisons between the anxiety and depression subgroups (Table 3 and Table 4) showed no significant differences between the anxiety and depression groups. As reported, no statistical differences were observed in the 25(OH)D and TSH levels between the two subgroups. In addition, the 25(OH)D and TSH levels among the males and females in the anxiety subgroup showed no significant differences. However, a significantly higher TSH level was observed in the females when compared to the males in the severe depression subgroup (3.01±1.49 µIU/ml versus 2.38±0.02 µIU/ml, respectively, p=0.011) (Table 5 and Table 6).

Correlations between the 25(OH)D and TSH levels and the BDI-II and BAI scores. The correlations between the 25(OH)D and TSH levels and the BDI-II and BAI scores were presented in Table 7 and Table 8. No statistically significant correlations were found between the biochemical parameters and the BDI-II and BAI scores in the studied groups.
Table 5 - Comparison of biochemical parameters between male and female individuals through anxiety sub-groups.

| Anxiety sub-groups n=77 | Male n=10 | Female n=8 | P-value |
|-------------------------|-----------|------------|---------|
| **Mild Anxiety n=18**   |           |            |         |
| 25(OH)D (ng/ml)         | 22.6±16.91| 20.7±14.6  | 0.859   |
| TSH (µIU/ml)            | 2.79±1.6  | 2.28±1.24  | 0.534   |
| **Moderate anxiety n=59**|           |            |         |
| 25(OH)D (ng/ml)         | n=33      | n=26       |         |
| TSH (µIU/ml)            | 19.72±8.83| 19.17±9.74 | 0.939   |
| 25(OH)D (ng/ml)         | 2.47±1.66 | 2.48±1.55  | 0.831   |

Data are presented as mean±SD, TSH - thyroid stimulating hormone.

Table 6 - Comparison of biochemical parameters between male and female individuals through depression sub-groups.

| Depression sub-groups n=73 | Male n=5 | Female n=7 | P-value |
|---------------------------|---------|------------|---------|
| **Moderate depression (n=12)**|          |            |         |
| 25(OH)D (ng/ml)           | 19.77±13.11| 13.72±10.17| 0.345   |
| TSH (µIU/ml)              | 1.83±0.96 | 1.6±0.74   | 0.705   |
| **Severe depression (n=61)**|         |            |         |
| 25(OH)D (ng/ml)           | n=20     | n=41       | p       |
| TSH (µIU/ml)              | 21.34±12.84| 16.5±10.08 | 0.199   |
| 25(OH)D (ng/ml)           | 2.38±2.02 | 3.01±1.49  | 0.011   |

Data are presented as mean±SD, TSH - thyroid stimulating hormone.

Table 7 - Correlation of biochemical parameters with anxiety beck degree.

| Anxiety sub-groups (n=77) | Beck.Anxiety | r       | P-value |
|--------------------------|--------------|---------|---------|
| 25(OH)D (ng/ml)          |              |         |         |
| Mild Anxiety (n=18)      | -0.175       | 0.486   |         |
| Moderate Anxiety (n=59)  | 0.232        | 0.077   |         |
| TSH (µIU/ml)             |              |         |         |
| Mild Anxiety (n=18)      | 0.003        | 0.991   |         |
| Moderate Anxiety (n=59)  | -0.163       | 0.218   |         |

r - Correlation coefficient, TSH - thyroid stimulating hormone.

Table 8 - Correlation of biochemical parameters with depression beck degree.

| Depression sub-groups n=73 | Beck.Depression | r       | P-value |
|----------------------------|----------------|---------|---------|
| 25(OH)D (ng/ml)            |                |         |         |
| Moderate depression (n=12) | 0.525          | 0.097   |         |
| Severe depression (n=61)   | 0.007          | 0.959   |         |
| TSH (µIU/ml)               |                |         |         |
| Moderate depression (n=12) | -0.386         | 0.241   |         |
| Severe depression (n=61)   | -0.145         | 0.265   |         |

r - Correlation coefficient, TSH - thyroid stimulating hormone.

Discussion. The present study was conducted to evaluate the associations between anxiety and depression and the levels of 25(OH)D and TSH. One hundred and fifty patients were divided into depression (77 participants) and anxiety (73 participants) groups according to their BDI-II and BAI scores.

Vitamin D exhibits neuroprotective properties in the brain through the crucial neurotrophic signaling regulations required for neuronal development and health, the modulation of inflammation by inflammatory cytokine inhibition, and reactive oxygen species lowering protein activation. This vitamin also increases the biosynthesis of brain-derived neurotrophic factors (implicated in the schizophrenia pathogenesis) and glial-derived factors (essential for dopaminergic survival and function). Recent studies have suggested that the regional expression of the vitamin D receptor in different parts of the brain is one of the crucial factors in the pathogenesis of psychiatric illnesses. Many of these regions express 1α-hydroxylase, which converts 25(OH)D to 1,25(OH)2D3, and this explains the autocrine and paracrine properties of this vitamin.

Recently, it has been reported that low vitamin D levels are associated with schizophrenia, depression, and anxiety in the general population. In a cohort study conducted between 2015 and 2017, Fond et al. reported hypovitaminosis D in 21.4% of the subjects with no vitamin D supplementation during the previous 12 months. Additionally, this hypovitaminosis D was severely associated with depressive and anxiety symptoms; however, vitamin D supplementation significantly improved these symptoms. In contrast, Choukri et al. in a double blind randomized controlled clinical trial including 152 healthy women, reported the non-beneficial effects of vitamin D supplementation on depressive symptoms and psychological outcomes. Our data also showed lower levels of 25(OH)D in the depression group when compared to the anxiety group. However, this difference was not found to be statistically significant. Moreover, no other significant differences were observed between the 25(OH)D levels and the depression or anxiety subgroups. This may be due to this fact that the average levels of this vitamin were in the insufficiency or sufficient range among the individuals.

Vitamin D has been mainly implicated in bone metabolism and calcium/phosphorous homeostasis. However, the roles of this vitamin in thyroid functions and diseases, including Hashimoto's thyroiditis and Graves' disease, have been studied recently. Moreover, the associations between thyroid malfunctions and psychiatric symptoms, including depression and anxiety, have also been reported previously. Primary thyroid disorders, such as hyperthyroidism and hypothyroidism, may be the underlying causes of various neuropsychiatric symptoms ranging from mild depression and anxiety to...
overt psychosis. Furthermore, anxiety and depression disorders have been found to occur in approximately 60% and 31–61% of hyperthyroidism cases, respectively.15,33

In our study, the mean serum TSH level was within the normal range, but a significantly higher TSH level was observed in the females in the severe subgroup when compared to the males. Lee et al.,34 in a study of 7,270 healthy subjects, also reported higher TSH levels in the females when compared to their male counterparts (2.02±1.01 mU/l versus 1.67±0.87 mU/l, respectively, p<0.01). Some scientists have proposed the “brain hypothyroidism” theory for the pathogenesis of depression.35 In this regard, the occurrence of depression is due to local brain hypothyroidism along with normal serum thyroid hormone levels due to deiodinase type II inhibition and the impairment of T4 transport across the blood brain barrier.35

Although several studies have pointed to a significant association between mood disorders and a vitamin D deficiency, the different perspectives are not fully understood, and they remain controversial. Several studies have also shown a correlation between a vitamin D deficiency and depression symptoms. However, it remains unclear whether low vitamin D levels are the cause or the effect of depression. In the United States, more than 50% of psychiatric inpatients have vitamin D deficiencies of less than 10 ng/ml.36 We measured the vitamin D levels in psychiatric outpatients, and we did not find any relationships between the vitamin D level and the mood disorder severity. However, the lack of statistical significance in the measured parameters among the studied population may have been due to the small population size, which was one of the limitations of our study. Therefore, a larger population should be considered in future studies. Additionally, the presence of a healthy control group could help provide a better interpretation of the data.

In conclusion, patients with depression or anxiety may exhibit low vitamin D levels due to lower outdoor activity levels or reduced nutrient intakes. However, an evaluation of vitamin D receptor genetic mutations is recommended for future studies in order to better understand the possible mechanisms between the vitamin D biology and mood disorders with regard to thyroid functions.

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