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Vitamin D in the treatment of anxiety in patients with autoimmune thyroiditis and hypothyroidism in the West-Ukrainian population

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Thyroid diseases are reported as the most common endocrine abnormalities, and autoimmune thyroiditis (AIT) are perhaps among the most prevalent autoimmune diseases [1]. AIT is relatively spread organ-specific autoimmune disorder that induces diseases varying in severity from hypothyroidism to hyperthyroidism [2]. As an immune modulator, vitamin D is implicated in the onset and development of AIT [3].

A recent study has reported notable comorbidity between anxiety disorders and thyroid disorders experienced by patients with hypothyroidism [4]. Further, several studies have reported an association between low serum levels of vitamin D and the risk of anxiety symptoms [5, 6]. Data from recent research has proved that vitamin D deficiency may cause anxiety manifestations in the population generally [7]. People lacking vitamin D are more likely at the risk of experiencing anxiety disorders. Therefore, vitamin D supplementation is endorsed for the prevention and treatment of such conditions. Although preclinical investigations demonstrate limited and poor-quality evidence on the feasible mechanisms based on the favorable effects of vitamin D for the therapy of these disorders, most of the clinical studies prove that vitamin D supplementation enhances the reduction of the prevalence of anxiety symptoms [8].

In a cohort study, N. C. Bozkurt et al. found that insufficient intake of vitamin D deficiency had a notable impact on the development of AIT [9]. Other studies have demonstrated a significant interaction between vitamin D deficiency and thyroid autoimmunity in all age groups and reduced Thyroid Peroxidase Autoantibodies (anti-TPO) levels after cholecalciferol administration, which is carried out in AIT patients with vitamin D deficiency [10].

The purpose of our work is to evaluate the effects of Vitamin D in patients with autoimmune thyroiditis and hypothyroidism in the general Western Ukrainian population and approach the problem of predicting the development of disorders leading to anxiety in these patients.

MATERIALS AND METHODS

Our research was conducted in Bukovinian State Medical University, Chernivtsi Regional Endocrinology Center, and I. Horbachevsky Ternopil National Medical University, Ukraine. The study included the 56 patients with hypothyroidism caused by AIT. These patients were distributed into two groups. Patients of the first group (n = 28) received cholecalciferol at a dose of 4000 IU/day (28,000 IU/week) and L-thyroxine (88.39 ± 12.70 μg/day). Patients of the second group (n = 28) were prescribed only L-thyroxine (87.50 ± 12.73 μg/day). Examinations were performed at the beginning and end of the 12-week treatment.

Ethical approval. The study fully ensured standards described in the 1975 Helsinki Declaration of Human

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Rights (amended in 2008). The participants completed and signed a written informed consent before enrolling voluntarily in the research. The Ethics Committee of the HSEEU «Bukovinian State Medical University», I. Horbachevsky Ternopil National Medical University, and Chernivtsi Regional Endocrinology Center, Ukraine, have approved this study.

To diagnose hypothyroidism, we were guided by recommendations required by the American Association of Clinical Endocrinologists 2012. The corresponding clinical features were considered when verifying AIT, namely the results of a sonogram of the thyroid gland (reduced echogenicity) and circulating antibodies to thyroid antigens, anti-TPO, and anti-thyroglobulin autoantibodies (anti-TG) were detected [11].

Blood samples from patients and controls were taken in the morning (8 to 10 am) after a night fast. Using STAT FAX303/Plus analyzer (Awareness Technology Inc, USA), we determined levels of free thyroxine (fT4, normal range 6.0—13.0 pmol/l for males and 7.0—13.5 pmol/l for females), thyroid-stimulating hormone (TSH, normal range 0.3—4.0 mIU/ml), anti-TPO (normal range 0—30 IU/ml) and anti-TG (normal range 0—65 IU/ml) in each individual who participated in the study.

Study exclusion criteria were the following: less than 18 years of age, malignancy, inflammation resulting from rheumatic diseases or acute/chronic infection, diabetes mellitus, vascular, chronic diseases of liver and kidneys, and pregnancy. Individuals administering drugs that could influence thyroid function were also ruled out from the study.

We identified the severity of anxiety levels using the Hamilton rating scale for anxiety (HAMA), which is reliable for anxiety assessment. Due to the HAMA, each item is scored on a basic numeric scoring of 0 (not present) to 4 (severe) [12].

The optimal HAMA score ranges were: mild anxiety = 8—14; moderate = 15—23; severe ≥ 24 (scores ≤ 7 were considered to represent no/minimal anxiety) [13].

When determining 25-OH Vitamin D levels in the serum of the patients and healthy individuals, we applied the ELISA using the 25-OH Vitamin D Total (Vit D-Direct) Test System ELISA Kit (Monobind Inc.®, United States, Product Code: 9425—300) on E. I. A. Reader Sirio S (Seac, Italy).

Statistical analysis. Quantitative variables were assessed for normality using the Shapiro-Wilk test (when the number of subjects was less than 50) or the Kolmogorov-Smirnov test (when the number of subjects was more than 50). Quantitative variables following non normal distribution were described using median (Me) and lower and upper quartiles (Q1 — Q3). Comparisons of three or more groups on a quantitative variable whose distribution differed from normal were made using the Kruskal-Wallis test and Dunn's criterion with Holm correction as a post-hoc method. Comparison of frequencies in the analysis of multifield contingency tables was performed using Pearson's chi-square test (for expected values greater than 10).

RESULTS

When assessing the level of anxiety on the Hamilton scale after treatment in patients of Group 1 who received holecalciferol with L-thyroxine there was a statistically significant reduction in anxiety by 48.27 %, while after treatment with only L-thyroxine anxiety decreased by 18.25 %. That is, the additional appointment of holecalciferol significantly reduced the level of anxiety compared with treatment with only L-thyroxine ($p < 0.001$). In accordance with the presented Table and Figure 1, patients in Group 1 after treatment showed a statistically significant reduction in anxiety on the Hamilton scale.

Thus, no symptoms of moderate anxiety were observed in Group 1 patients after treatment. Anxiety disappeared in 42.9 % of Group 1 patients, while Mild anxiety remained in 57.1 %. At the same time, 21.4 % of Group 2 patients had Moderate anxiety and 78.6 % had Mild anxiety on the Hamilton scale (Figure 2). Thus, there was a statistically significant reduction in anxiety on the Hamilton scale in Group 1 patients compared with Group 2 patients after treatment.

DISCUSSION

Since mood and anxiety disorders are observed relatively often and are connected with a notable deterioration in health conditions and the limitations of modern methods of treatment, there is a great demand for new compounds with antidepressant and anxiolytic properties. In this context, vitamin D has been studied as a prospective strategy for treating these disorders.

A meta-analysis identified the impact of vitamin D administration on anxiety. The findings reported positive results of vitamin D for the treatment of anxiety [14].

Although a causal relationship between vitamin D, immunomodulation anxiety symptoms has not yet been established, some of the positive effects of vitamin D on psychiatric symptoms may likely appear due to neuro-immune interactions.

Table

Analysis of Anxiety conditioning on the Hamilton scale

Group		Value
1 (n = 28)	Before treatment	14.5 (12.0—18.0)
	After treatment	7.5 (6.0—10.0)*
2 (n = 28)	Before treatment	16.0 (13.0—17.0)
	After treatment	13.0 (11.0—13.0)**#

Note. Data are presented as median and lower and upper quartiles (Me (Q_1 — Q_3)).

The difference to the value before treatment is statistically significant: * $p < 0.001$; ** $p < 0.05$

The difference to the indicator value of Group 1 after treatment is statistically significant: # $p < 0.001$.

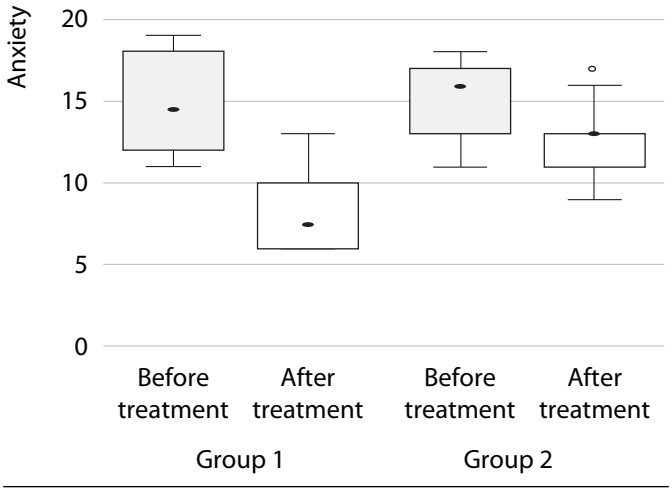

Figure 1. *Analysis of Anxiety conditioning on the Hamilton scale*

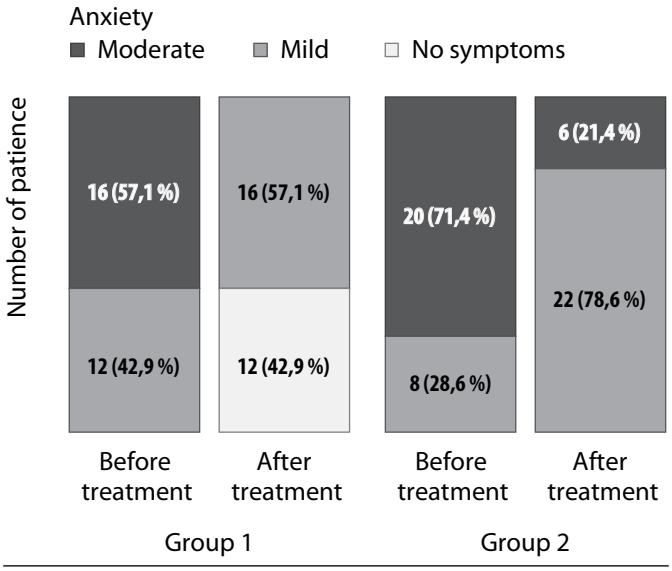

Figure 2. *Analysis of Presence of anxiety on the Hamilton scale*

The vast majority of research assessing anxiety-related symptoms in different populations provides insight into an interconnection between lack of levels of vitamin D and anxiety [15, 16].

Some studies reported vitamin D supplementation is connected with reduced anxiety symptoms [17]. Meanwhile, others didn't manage to find an interrelation between vitamin D supplementation and a decrease in anxiety symptoms [18, 19].

In our study, patients in Group 1 after treatment with cholecalciferol and L-thyroxine showed a statistically significant reduction in anxiety on the Hamilton scale. Thus, no symptoms of moderate anxiety were observed in Group 1 patients after treatment. Anxiety disappeared in 42.9 % of Group 1 patients, while Mild anxiety remained in 57.1 %. At the same time, 21.4 % of Group 2 patients had Moderate anxiety and 78.6 % had Mild anxiety on the Hamilton scale. Thus, there was a statistically significant reduction in anxiety on the Hamilton scale in Group 1 patients compared with Group 2 patients after treatment.

It is necessary to point out that most of the studies were worked out to assess anxiety symptoms related to different clinical conditions. So far, no clinical trials have been performed in patients suffering from anxiety disorders and vitamin D supplementation.

Given the significant reduction in thyroid autoantibodies and the lack of reported adverse events during vitamin D therapy, vitamin D treatment may be the right option for AIT and hypothyroidism, especially in patients with vitamin D deficiency. We expect more appropriate randomized double trials to be performed in the future blinded placebo-controlled studies with longer follow-up to confirm the effect of vitamin D supplementation on thyroid autoantibody levels in the treatment of AIT.

CONCLUSIONS

Considering our results, vitamin D supplementation should be administered in patients suffering from autoimmune thyroiditis and hypothyroidism to correct anxiety disorders in these patients.

Conflicts of interest: *none.*

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ABSTRACT

Objective — to study the effects of cholecalciferol on the level of anxiety in patients with autoimmune thyroiditis and hypothyroidism in the Western Ukrainian population.

Materials and methods. The study included 56 patients with hypothyroidism caused by autoimmune thyroiditis. Hypothyroidism was diagnosed under the guidance of recommendations of the American Association of Clinical Endocrinologists 2012. To verify autoimmune thyroiditis, the following was taken into account: related clinical signs, sonograms of the thyroid gland (reduced echogenicity) and reveal of the circulating antibodies to thyroid peroxidase and thyroglobulin. The patients were divided into two groups. Patients of the first group (n = 28) received cholecalciferol in a dose of 4000 IU/24 hours (28 000 IU/week) and L-thyroxine ((88.39 ± 12.70) mkg/24 hours). Patients of the second group (n = 28) were administered L-thyroxine only ((87.50 ± 12.73) mkg/24 hours). Presence of anxiety was assessed using the Hamilton rating scale for anxiety (HAMA). Examinations were performed at the baseline and after 12 weeks of treatment.

Results. Assessment of the anxiety level by Hamilton scale after the treatment of patients of the first group demonstrated the significant reduction of anxiety level by 48.27 %, whereas in the second group by 18.25 % ($p < 0.001$). In the patients of the first group after treatment, anxiety disappeared in 42.9 % of subjects, and mild anxiety according to the Hamilton scale

remained in 57.1 %. At the same time, in the second group 21.4 % of patients had moderate anxiety, 78.6 % had mild anxiety. Thus, there was a significant decrease in the anxiety level according to the Hamilton scale after the treatment of patients of the first group compared to the subjects of the second group..

Conclusions. Patients suffering from autoimmune thyroiditis and hypothyroidism should be administered vitamin D supplementation with the purpose of attenuation of anxiety disorders.

Keywords: autoimmune thyroiditis, hypothyroidism, anxiety, vitamin D.

РЕЗЮМЕ

Вітамін D у лікуванні тривожності у хворих на автоімунний тиреоїдит та гіпотиреоз у західноукраїнській популяції

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Мета роботи — вивчити вплив холекальциферолу на рівень тривожності у хворих на автоімунний тиреоїдит та гіпотиреоз у західноукраїнський популяції.

Матеріали та методи. У дослідження було залучено 56 пацієнтів з гіпотиреозом, спричиненим автоімунним тиреоїдитом. Для діагностики гіпотиреозу керувалися рекомендаціями Американської асоціації клінічних ендокринологів 2012 р. Для верифікації автоімунного тиреоїдиту враховували відповідні клінічні ознаки, результати сонограми щитоподібної залози (знижена ехогенність) та виявлення циркулюючих антитіл до тиреопероксидази і тиреоглобуліну. Пацієнтів розподілили на дві групи. Пацієнти першої групи (n = 28) отримували холекальциферол у дозі 4000 МО/добу (28 000 МО/тиж) і L-тироксин ((88,39 ± 12,70) мкг/добу). Пацієнтам другої групи (n = 28) призначали лише L-тироксин ((87,50 ± 12,73) мкг/добу). Наявність тривоги визначали за допомогою шкали тривоги Гамільтона (HAMA). Обстеження проводили на початку та в кінці 12-тижневого лікування.

Результати. При оцінці рівня тривожності за шкалою Гамільтона після лікування у пацієнтів першої групи зареєстровано статистично значуще зниження рівня тривоги на 48,27 %, тоді як у хворих другої групи — на 18,25 % (p < 0,001). У пацієнтів першої групи після лікування тривожність зникла у 42,9 % осіб, легка тривожність за шкалою Гамільтона зберігалася у 57,1 %, у другій групі у 21,4 % пацієнтів мала місце помірна тривожність, у 78,6 % — легка, тобто спостерігалося статистично значуще зниження рівня тривожності за шкалою Гамільтона після лікування у пацієнтів першої групи порівняно з хворими другої групи.

Висновки. Пацієнтам, які страждають на автоімунний тиреоїдит та гіпотиреоз, слід призначати холекальциферол з метою зниження тривожних розладів.

Ключові слова: автоімунний тиреоїдит, гіпотиреоз, тривога, вітамін D.

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