The role of vitamin D for the management of depression in the Western Ukrainian population with autoimmune thyroiditis and hypothyroidism

Background. Hashimoto’s thyroiditis is known to be an essential endocrine disease that affects the population and may lead to hypothyroidism. This disease is one of the most common autoimmune diseases. Hypothyroid patients frequently experience signs of depression, which is prevalent among other symptoms in hypothyroidism. Data from recent research has proved that vitamin D deficiency may cause depression manifestations in the population. The aim of our work is to study the effect of cholecalciferol on the level of depression in the Western Ukrainian population with autoimmune thyroiditis and hypothyroidism. Materials and methods. The study included 56 patients with hypothyroidism caused by autoimmune thyroiditis. We identified the severity of depression levels using the Hamilton Depression Rating Scale. Examinations were performed at the beginning and by the end of a 12-week treatment. Results. In patients of group 1 who received cholecalciferol and L-thyroxine, the level of depression on the Hamilton Depression Rating Scale decreased by 40%, while in those who received only L-thyroxine, by 25%. In addition, there was a significant difference between patients in groups 1 and 2 after treatment ($p = 0.003$). That is, additional cholecalciferol on the background of L-thyroxine was more effective than therapy with L-thyroxine alone. Analysis of the effect of treatment in group 1 with the additional administration of cholecalciferol on the background of L-thyroxine has shown that depression disappeared in 21.4% of patients. In addition, there was a decrease in depression in other participants from this group. Thus, in the remaining patients, the severity of depressive manifestations decreased from moderate to mild depressive disorder. At the same time, after treatment with L-thyroxine alone, depressive disorder of moderate severity decreased from 78.6 to 35.7%, but complete disappearance of depression in this group of patients after treatment was not observed. Conclusions. Vitamin D supplementation should be administered in patients suffering from autoimmune thyroiditis and hypothyroidism, which may correct depression disorders.

Keywords: depression; autoimmune thyroiditis; hypothyroidism; vitamin D
The aim of our work is to study the effect of cholecalciferol in patients with autoimmune thyroiditis and hypothyroidism in the Western Ukrainian population on the level of depression 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 byAIT. These patients were distributed into two groups. Patients in 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 in 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 Rights (amended in 2008). The participants completed and signed a written informed consent before enrolling voluntarily in the research.

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 anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) were detected [8].

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 antibodies (normal range 0–30 IU/mL) and anti-TG antibodies, 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 depression levels using the Hamilton Depression Rating Scale (HDRS), which is reliable for depression assessment. Due to the HDRS, scores of 0–7, 8–13, 14–18, 19–23, and 23–53 are regarded as normal, mild, medium, severe, and very severe, correspondingly [9].

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

In our study, after treatment, there was a decrease in anti-TPO levels in patients taking cholecalciferol and L-thyroxine by 31.25% (p < 0.001), while in patients in group 2 who received only L-thyroxine, anti-TPO levels decreased only by 14.1% (p < 0.05).

When comparing anti-TG after treatment, there was a probable decrease in anti-TG levels in patients receiving cholecalciferol and L-thyroxine by 18.84% (p < 0.001), while in patients of group 2 who received only L-thyroxine anti-TPO level decreased by only 8.82%.

Table 1. Analysis of depressive disorders on the Hamilton scale

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Me</th>
<th>Q₁–Q₃</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of depression on the Hamilton scale</td>
<td>Group 1</td>
<td>15.00</td>
<td>12.00–16.00</td>
<td>28</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td></td>
<td>Group 1 after treatment</td>
<td>9.00</td>
<td>7.00–12.00</td>
<td>28</td>
<td>p₉₁ — Group 1 after treatment — Group 1 &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Group 2</td>
<td>16.00</td>
<td>15.00–16.00</td>
<td>28</td>
<td>p₉₂ — Group 2 — Group 1 after treatment &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Group 2 after treatment</td>
<td>12.00</td>
<td>12.00–15.00</td>
<td>28</td>
<td>p₉₂ — Group 2 after treatment — Group 1 after treatment = 0.003</td>
</tr>
</tbody>
</table>

Note: * — differences are statistically significant (p < 0.05).
We performed analysis of depression conditioning on presence of depression on the Hamilton scale (Table 1).

After treatment, there is a decrease in the level of depression on the Hamilton scale (figure 1). Thus, in patients of group 1 who received cholecalciferol and L-thyroxine, the level of depression on the Hamilton scale decreased by 40 %, while in patients who received only L-thyroxine, the level of depression decreased by 25 %. In addition, there was a significant difference between patients in groups 1 and 2 after treatment (p = 0.003). That is, treatment with additional cholecalciferol on the background of L-thyroxine was more effective than treatment with L-thyroxine alone (table 2).

Analyzing the effect of treatment in patients with Group 1 with the additional appointment of cholecalciferol on the background of L-thyroxine in 21.4 % of patients disappeared depression. In addition, there was a decrease in depression in other patients in this group. Thus, in the remaining patients the severity of depressive manifestations decreased from moderate severity to mild depressive disorder.

At the same time, after treatment only L-thyroxine depressive disorder of moderate severity decreased from 78.6 to 35.7 % to mild depressive disorder, but complete disappearance of depression in this group of patients after treatment was not observed (figure 2).

**Discussion**

Thyroid dysfunctions are closely connected with deterioration of brain function [10]. The valuable insights on the correlation between thyroid hormone deficiency with depression have been discussed substantially in various credible studies [11]. Symptoms of depression tend to coincide in patients. However, the treatment of these disorders remains controversial. Vitamin D deficiency is a universal health problem. The prevalence of vitamin D deficiency or insufficiency exceeds a billion worldwide [12].

Hashimoto’s thyroiditis characterized by lymphocytic infiltration, which may finally lead to the progressive loss of thyroid tissue [1]. Some studies prove that HT is the outcome of the united action of genetic susceptibility and environmental factors, but the precise route is still not established [13]. One study claimed that in the case of normal thyroid function, AIT could also induce neuro-inflammation, resulting in emotional alterations [14]. Nowadays, the possibilities of AIT are also growing; most subjects do not manifest symptoms, which are commonly observed at the physical checkups. Some studies have favored that vitamin D produces a positive protective influence on autoimmune thyroid diseases and thyroid malignancies, but the mechanism has not been elucidated [15].

One essential of the numerous functions of vitamin D implies the regulation of nervous system development in addition to being involved in calcium regulation [16]. Vitamin D attenuates and easily passes the blood-brain barrier [17]. Vitamin D receptors are widely found in different brain sites, i.e., the prefrontal cortex, substantia nigra, and hypothalamus [18]. Vitamin D is also closely connected with the synthesis of monoamines, such as serotonin, dopamine, and norepinephrine, and its steroid properties enable modulating the activity of GABA-A receptors [18–20]. Furthermore, several studies have suggested that vitamin D is related to nerve growth factor enhancement and antioxidant effects in the central nervous system [20–22].

A meta-analysis identified the impact of vitamin D administration on depression. The findings reported positive results of vitamin D for the treatment of depression [23].

**Table 2. Analysis of depressive disorders on the Hamilton scale**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Presence of depression on the Hamilton scale</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Milt depressive disorder</td>
<td>Group 1 - 28.6</td>
<td>Group 1 after treatment - 22(78.6)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0(0.0)</td>
<td>6(21.4)</td>
</tr>
<tr>
<td></td>
<td>Depressive disorder of moderate severity</td>
<td>20(71.4)</td>
<td>0(0.0)</td>
</tr>
</tbody>
</table>

**Note** * — differences are statistically significant (p < 0.05).
In our study, after treatment with additional administration of cholecalciferol on the background of L-thyroxine in 21.4% of patients disappeared depression. In addition, there was a reduction in depression in other patients in this group. Thus, in the remaining patients the severity of depressive symptoms decreased from moderate to mild depressive disorder.

For the last three decades, a complicated association between peripheral immune activation, neuroinflammation, and changes in brain circuits linked to depression has been traced [24]. In this respect, vitamin D is considered a well-known regulator of innate immunity that acts not only as transcription and a growth factor but also interacts with surface receptors in different immune cells [25]. Therefore, numerous positive effects of vitamin D influencing the behavior might be related to its capability to stabilize peripheral and central nervous system (CNS) immune responses.

In the CNS, 1,25(OH)D is often connected with neuroprotective properties. A contemporary study proved that 1,25(OH)D was able to inhibit serotonin reuptake transport and monoamine oxidase-A gene expression (MAO-A; the enzyme which is in charge of monoamine degradation) in cultured rat serotoninergic neuronal cell lines, presupposing that calcitriol tends to act similarly to antidepressants [26].

In our study after treatment, there is a decrease in the level of depression on the Hamilton scale. Thus, in patients of Group 1 who received cholecalciferol and L-thyroxine, the level of depression on the Hamilton scale decreased by 40%, while in patients who received only L-thyroxine, the level of depression decreased by 25%. That is, treatment with additional cholecalciferol on the background of L-thyroxine was more effective than treatment with L-thyroxine alone. Regarding that vitamin D contributes to neuro-immunomodulation and neuroplasticity and may decrease oxidative stress [27], it has been researched as a possible strategy for the treatment of symptoms of depression.

Conclusions

Considering our results, vitamin D, supplementation should be administered in patients suffering from autoimmune thyroiditis and hypothyroidism which may correct depression disorders in these patients. Ongoing and prospective long-term randomized controlled trials are necessary to gain insight into the effectiveness and safety of vitamin D as a therapeutic agent for these thyroid disorders and the prevention and treatment of neurological complications.

Acknowledgments

Ethical approval. Our study was conducted according to the Declaration of Helsinki adopted in 1975 and revised in 2008, and the ethical principles were entirely respected.

Consent to participate. Written informed consent was obtained from the participants.

Data availability. The data of this study is available by request.

Conflict of interest. The authors declare that there is no conflict of interest.

References

У дослідження було включено 56 пацієнтів з гіпотиреозом, спричиненим АІТі. Ми зосередилися на вивченні впливу вітаміну D на тлі L-тироксину у 21,4 % пацієнтів зникли прояви депресії. 

Вступ.

Тиреоїдит Хашимото — одне з найчастішими захворюваннями серед населення західноукраїнської популяції на рівень депресії. Дани останніх досліджень довели, що дефіцит вітаміну D може викликати прояви депресії в населені. Хоча вітамін D може призвести до депресії, вона може впливати на нервовий рост. 

Вітамін D регулює синтез GDNF, Ret, FoxO3a, і Sirtuin1 в Хашимото Тиреоїдиті та відповідності до відповідної патології. Вітамін D сперва серотонин, 1,25-дійоксивітамін D рефлекти серотонин уythake r (SERT) і MAO-A генов. 

Резюме.

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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Висновок.

Роль вітаміну D у лікуванні депресії у хворих на автоімунний тиреоїдит і гіпотиреоз серед населення західноукраїнської популяції

Резюме. Вступ. Тиреоїдит Хашимото — одне з найчастішими ендокринних захворювань, що може призвести до депресії. Це захворювання також є одним з найбільш поширенних у хворих на гіпотиреоз. Висновки. 

Ключові слова: депресія; гіпотиреоз; вітамін D