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Review

Depression and autoimmune thyroiditis - their relationship and the effects of treating psychiatric and thyroid disorders on changes in clinical and biochemical parameters including BDNF and other cytokines – a systematic review.

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Abstract: Various autoimmune diseases, including autoimmune hypothyroidism (AHT), are associated with a higher risk of developing mood disorders throughout life. Depression is accompanied by the changes in the levels of inflammatory and trophic factors, including interleukines (IL-1beta, IL-2, IL-6), interferon alpha (IFN-alpha), tumor necrosis factor alpha (TNF-alpha), C-reactive protein (CRP) and brain derived neurotrophic factor (BDNF). Similar disturbances in the cytokine profile as in AHT patients are present in their relatives. Disclosure of the relationship between the coexistence of depression and autoimmune subclinical thyroiditis indicates that the pathomechanism of depression may be related to the changes in the immune system, it is also possible that both conditions may be caused by the same immune processes. The above hypothesis is indirectly supported by the observations that the treatment with both antidepressants and levothyroxine leads to a decrease in the levels of proinflammatory cytokines with an increase in BDNF concentrations, simultaneously correlating with an improvement in the clinical parameters. However, so far there are no long-term studies determining the causal relationship between depression, thyroid autoantibodies, and cytokine profile, which could bring us closer to understanding the interrelationships between them and facilitate the use of an adequate pharmacotherapy, not necessarily psychiatric. We consider the above issues insufficiently investigated but of great importance. This article is an overview of the available literature as well as an introduction to our research project.

Keywords: depression, chronic autoimmune thyroiditis; BDNF

1. Introduction

The relationship between thyroid function and depression has been known for a long time [1-3]. It was first described in 1825 by Parry, who noted an increased number of "nerve strokes" in thyroid disease. Seagull in 1873 showed a link between myxoedema and psychosis, which was confirmed in 1888 by the Committee of the Clinical Society. In 1949 Asher introduced the term "myxedema madness" to describe mental state changes in patients with hypothyroidism [4]. It is currently well known that thyroid dysfunction can significantly affect the mental state, including emotions and cognitive functions. Both the excess and the deficiency of thyroid hormones can cause mood disorders, including depressive disorders, which can be usually resolved with an appropriate treatment of dysthyreosis. Depression may, in turn, be accompanied by various degrees of thyroid dysfunction. An overt hypothyroidism is present in 1-4% of patients with affective disorders, while subclinical hypothyroidism occurs in 4-40% of this population. According to Boswell, the frequency of depressive symptoms in patients with hypothyroidism reaches 50% [5], while depression of significant clinical severity occurs in over 40% of people suffering from hypothyroidism [6]. What is practically very important, and what prompted us to

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undertake the research, the depressive states associated with broadly understood thyroid dysfunction are usually at least partially resistant to antidepressive treatment, with the causal treatment being the key here. Thyroid hormones are also usually recommended as an adjunctive therapy in the treatment of depression in treatment algorithms [7].

2. Autoimmune hypothyroidism (AHT) and depression

AHT is a progressive disease of the thyroid gland. Dense lymphocytic infiltration covering the gland is involved in the pathogenesis of this type of chronic thyroiditis [8]. Activated B cells produce antibodies against several major thyroid antigens. AHT is characterized by a combination of typical clinical features (Table 1) [9], increased serum TSH (thyroid-stimulating hormone) levels, decreased fT4 (free thyroxine) levels, presence of antibodies to thyroid antigens, and decreased ultrasonographic echogenicity of the thyroid parenchyma [10].

Table 1. Autoimmune hypothyroidism - symptoms, assessment, and diagnostic findings

Symptoms	Assessment Findings	Diagnostic Findings
Depression	Dry, coarse skin	Hyponatremia
Fatigue	Reduced body and scalp hair	Macrocytic anemia
Weight gain	Dull facial expression	Decreased memory
Constipation	Bradycardia	Hyperprolactinemia
Muscle cramps, arthralgias	Goiter	Elevated creatine kinase level
Menorrhagia	Macroglossia	Pituitary gland enlargement
Infertility	Ascites	Delayed bone age
Sexual dysfunction	Galactorrhea	Hypercholesterolemia
Cold intolerance	Slow relaxation of tendon reflexes	
Carpal tunnel syndrome	Nonpitting edema of lower extremities	
Sleep disorders	Hoarseness	

AHT is the most common organ autoimmune disorder, with an estimated prevalence at approximately 2%, women suffer more frequently. Thyroid peroxidase (TPO) is the main autoantigen, and antibodies to TPO (Anti-TPO) are present in almost all AHT patients and may precede onset of the clinical phase by up to several years. Subclinical AHT (with the presence of Anti-TPO, elevated TSH and normal fT4 levels) is more frequent and affects approximately 9% of general population [10].

Depression, including severe depression, is more common in patients with euthyroid chronic AHT comparing to subjects without this condition [8]. Frequent simultaneous presence of depressive and anxiety disorders in patients with Hashimoto's disease (over 90% of AHT) in the euthyroid stage has also been confirmed [11]. A large Danish epidemiological study has shown that various autoimmune diseases, including AHT, are associated with a higher occurence of mood disorders throughout life [12]. It has been shown that it is not only the decreased level of thyroid hormones that determines the occurrence of mood disorders. We also know that even in patients with normal thyroid function but with elevated Anti-TPO antibodies, their presence correlates with a higher risk of anxiety and mood disorders [13]. An increased levels of anti-thyroid antibodies has been documented in 20% of patients with depression, while the incidence in the general population ranges from 5 to 10% [14,15]. In patients with bipolar disorder, regardless of the use of lithium (having “anti-thyroid” properties), the presence of Anti-TPO and AHT is also more frequent [16,17]. Also, the offspring of people with bipolar disorder have a higher incidence of Anti-TPO, even if they do not have mental disorders [18,19]. There are also data showing an increased level of Anti-TPO and antibodies blocking the TSH receptor in patients with depressive disorders without thyroid dysfunction, but who were resistant

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to antidepressant treatment [20]. Several hypotheses are proposed to explain above observations. Decrease in the secretion of thyroid hormones is interpreted as a result of dysregulation of TSH secretion circadian rhythm (physiologically TSH levels are higher at night). This suggests that some depressed patients may have central hypothyroidism (pituitary and hypothalamus dependent - secondary and tertiary, respectively). Moreover, sleep deprivation used in the treatment of depression leads to the restoration of the nocturnal rise in TSH levels and, consequently, an increase in fT3 (free triiodothyronine) and fT4 levels. According to another hypothesis, autoimmune thyroid diseases are associated with the hypothalamic-pituitary-adrenal axis and are mediated by changes in the concentration of pro-inflammatory and anti-inflammatory cytokines. TNF-alpha (tumor necrosis factor), interleukines IL-1 and IL-6 (all pro-inflammatory agents) increase the release of CRH (corticoliberin) and AVP (arginine vasopressin) leading to increase of glucocorticosteroids (GCS) secretion from the adrenal cortex. Chronic high GCS levels induce receptor resistance to GCS, subsequently causing further increase in their secretion and disturbances in the functioning of the hypothalamic-pituitary-adrenal axis increasing the susceptibility to autoimmune processes and depression [21,22]. Next hypothesis connects the frequent postpartum recurrence of depression with the end of immune tolerance present in pregnancy [23,24]. Unfortunately, currently there are no studies showing a relationship between postpartum thyroiditis and postpartum depression and convincingly explaining the etiopathogenetic relationships but indicate the existence of common elements of the immune pathogenesis of both AHT and mood disorders.
The results of the summary on depression, anxiety and AHT indicate, that in the United States the prevalence of AHT is 4-13%, AHT more often affects women, its occurrence increases with age reaching 20% in the group of older women [25]. Prevalence of depression reached 6.6%, and anxiety disorders 18.1% in this study. It was also found that depression occurs in 16.8% of patients suffering from AHT, while the criteria for anxiety disorders were met by 35.7% of patients. The recently published meta-analysis of the comorbidity of hypothyroidism and depression did not show a statistically significant relationship between the autoimmunity of the thyroid gland and the incidence of depressive disorders [26]. The study of the relationship between morphological changes in the central nervous system in AHT patients with hypothyroidism using positron emission tomography (PET) also did not show any direct relationship between specific changes caused by AHT and the development of depressive disorders [2,27].

Figure 1 shows the PRISMA flow chart for study screening and selection.
Literature Search Strategy: the literature search was completed on 16 August 2021, from 5 databases: EMBASE, PubMed, Cochrane library, SCOPUS, and Web of Science. The search was restricted to peer-reviewed publications of original research written in English and German from 1990–2021, both years included.

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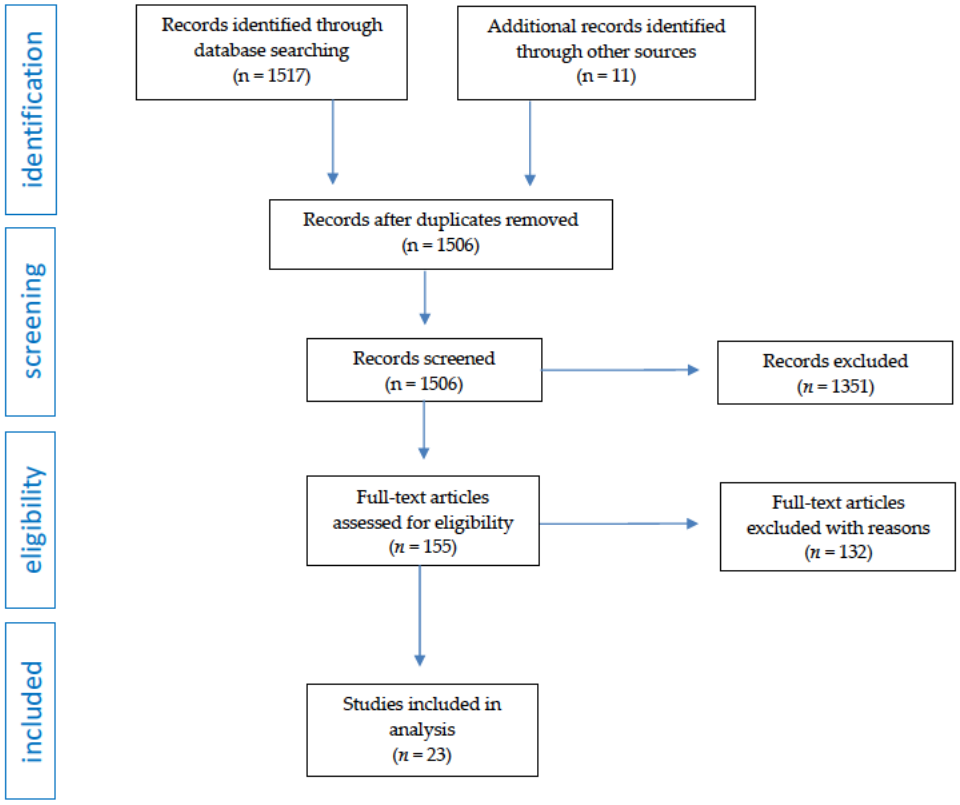

Table 2 shows the characteristics of all included studies.

Table 2. Studies investigating various aspects of depression and ATH comorbidity.

Author	Year	Sample size	Characteristic of Participants	Results and Conclusions	Reference
Pop et al.	1998	583 women	58 women had elevated levels of anti-TPO antibodies. Age group: 47-54 years old.	This study showed that women with elevated levels of anti-TPO antibodies are more prone to developing depression, while postmenopausal age does not increase this risk.	[28]
Zetting et al.	2003	76	41 patients with autoimmune thyroiditis and 35 patients in the control group	Brain impaired perfusion has been confirmed in patients with AHT. The presence of cerebral hypoperfusion suggests cerebral vasculitis as the most likely pathogenic cause.	[29]
Carta et al.	2004	222	16.6% of the studied patients had elevated levels of anti-TPO antibodies.	A relationship has been demonstrated between the presence of a lifetime diagnosis of depressive disorders and the level of anti-TPO antibodies.	[13]
Carta et al.	2005	190	19 patients diagnosed with Hashimoto's disease (HD) in euthyroidism, 19 patients with euthyroid neutral goiter, 152 people in the control group	Patients diagnosed with HD in euthyroidism showed a higher incidence of depressive episodes throughout life.	[11]
Engum et al.	2005	30175	995 of the study group had elevated levels of anti-TPO antibodies. Age group: 40-84.	In the group with elevated levels of anti-TPO antibodies, the incidence of depression was not higher than in the general population.	[30]

Gulseren et al.	2006	160	33 patients with overt hypothyroidism, 43 patients with subclinical hypothyroidism, 51 patients with overt hyperthyroidism, 13 patients with subclinical hyperthyroidism and a healthy control group of 20 patients.	Achieving euthyroidism reduces depressive symptoms. In this study, the causes of hypothyroidism were not mentioned - the levels of TSH, fT3 and fT4 were examined.	[31]
Bunevicius et al.	2007	474	Of the 474 randomly selected primary care patients, 348 were female, 95 of them were postmenopausal, 67 had a history of endocrine disease; 68 patients had a history of mental disorders. 84 patients used psychotropic drugs, including 69 benzodiazepines; none of the patients used lithium. 6 women were diagnosed with hypothyroidism and were treated with L-thyroxine.	The results of this study indicate that ultrasound-assessed thyroid autoimmunity is associated with the symptoms of mood disorders in primary care patients, especially in premenopausal women.	[32]
Schinhammer et al.	2010	107	67 patients diagnosed with HD and 30 patients in the control group, age group 18-80.	Patients with HD have an increased risk of developing depression. This study showed that the MTHRF 1298C/C gene polymorphism in patients with HD may be associated with the etiology of depression. There seems to be an association between the MTHFR 677C/C and COMT A/A polymorphisms and Hashimoto's disease. Gene polymorphism in the folate/homocysteine system appears to play a role in HD and associated depressive disorders.	[33]
Kirim et al.	2012	201	Patients diagnosed with HD in the euthyroid stage, age group 18-65 years.	Increased frequency and severity of symptoms of depression in patients diagnosed with Hashimoto's disease in the euthyroid stage.	[8]
Franke et al.	2013	57	36 patients diagnosed with HD and 21 patients diagnosed with neutral goiter.	The study shows increased expression of the ADA (adenosine deaminase gene) and ADAR (adenosine deaminase gene, RNA specific) genes in patients diagnosed with HD compared to patients with neutral goiter, which may explain the increased incidence of depression in patients with HD.	[34]
Giynas Ayhan et al.	2014	164	51 patients diagnosed with HD in euthyroidism, 45 patients with euthyroid neutral goiter, 68 patients in the control group.	Depressive disorders are more common in euthyroid patients diagnosed with HD, suggesting that they may be associated not only with abnormal levels of thyroid hormones, but also with the process of autoimmunity.	[35]
Medici et al.	2014	7983	1,503 people had the level of anti-TPO tested, the study included Caucasian	Older people with low normal TSH levels have more comorbid depressive symptoms and a	[36]

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			people aged 55+ (people with dementia were excluded).	significantly increased risk of developing a depressive syndrome later in life. Low TSH levels are an important risk factor for the development of depression in the elderly. Autoimmunity of the thyroid gland (as assessed by elevated levels of anti-TPO antibodies) was not associated with an increased risk of depression.	
Demartini et al.	2014	246	123 patients with subclinical hypothyroidism, including 106 patients diagnosed with HD, 12 with non-autoimmune hypothyroidism and 5 with nodular goiter, and 123 controls without diagnosed thyroid disease. Patients diagnosed with intellectual disability and dementia were excluded.	More than twice more patients diagnosed with subclinical hypothyroidism had at least mild depression.	[37]
Quinque et al.	2015	36	18 patients treated for AHT and 18 patients in the control group. Structural and functional MRI and neuropsychological tests were performed to assess mood and cognitive function.	Properly treated patients report more depressive symptoms compared with healthy controls. Mood changes were not associated with brain structure and function in brain regions specific to depression. Higher levels of anti-TPO are associated with higher gray matter density in the right amygdala and increased connections between the cortex subcallosum and the left posthypocampal gyrus. Duration of treatment was associated with the development of structural and functional changes in brain areas associated with depression and untreated hypothyroidism. Autoimmunity and the duration of treatment are possible factors explaining the occurrence of psychiatric symptoms in patients receiving long-term treatment for hypothyroidism.	[38]
Itterman et al.	2015	2142	The analysis included 498 patients with previously diagnosed thyroid dysfunction - 247 people were taking medication, 223 had thyroid nodules, 74 were diagnosed with hyperthyroidism, and 70 with hypothyroidism - without specifying the causes of the disorders.	Untreated, diagnosed hypothyroidism is associated with a higher risk of depressive symptoms. TSH and anti-TPO levels were not significantly associated with the risk of depression.	[39]

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Fjaellegaard et al.	2015	8214	The patients were divided into 4 groups: 1.Euthyroid patients with normal levels of anti-TPO antibodies (7015 patients) 2.Euthyroid patients with elevated levels of anti-TPO antibodies (619 patients), 3. Patients with subclinical hypothyroidism and normal levels of anti-TPO antibodies (378 patients), 4. Patients with subclinical hypothyroidism and elevated levels of anti-TPO antibodies (202 patients).	This study showed no significant differences in the incidence of depression in euthyroid patients and patients diagnosed with subclinical hypothyroidism. It was shown, however, that euthyroid women with elevated levels of anti-TPO antibodies had statistically significantly better well-being than patients with normal levels of anti-TPO antibodies.	[40]
Van de Ven et al.	2016	906	Age group 50-70, relationship between the presence of anti-TPO antibodies, TSH and fT4 levels and the risk of depression was examined.	Presence of anti-TPO antibodies may be a marker of susceptibility to depression. Lack of correlation between thyroid function and incidence of depression.	[41]
Krysiak et al.	2016	86	Age group: women aged 20-40, 68 patients were divided into three groups: 1. Patients in euthyroidism diagnosed with HD, 2. Patients with non-autoimmune hypothyroidism, 3. Patients with autoimmune hypothyroidism, Control group - 18 patients	The Beck Depression Inventory (BDI) total score was highest in group 3, and higher in groups 1 and 2 than in group 4. Anti-TPO antibody levels were directly proportional to serum TSH levels and the BDI total score and the number of patients with depressive symptoms.	[42]
Delitala et al.	2016	3138	The group included patients who were not taking thyroid medications or antidepressants. The levels of TSH, fT4 and anti-TPO antibodies were assessed.	No relationship was found between the level of anti-TPO antibodies and the occurrence of depressive symptoms. On the other hand, a U-shaped relationship was found between the level of fT4 and the occurrence of depressive symptoms in comparison with the average values of fT4 - both high and low values of fT4 were associated with a greater number of depressive symptoms.	[43]
Yalcin et al.	2017	124	93 patients diagnosed with euthyroid HD for at least 3 months and 31 patients in the control group.	The level of TSH was statistically higher in patients diagnosed with HD, no differences in the level of fT4 were observed in the group of patients with HD and in the control group. In 17.3% of patients diagnosed with HD and in 4.3% of patients in the control group, depression was diagnosed. Thus, it has been shown that autoimmunity itself may have an impact on the risk of depression in patients diagnosed with HD in the euthyroid stage.	[44]

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Tayde et al.	2017	66	33 patients with autoimmune hypothyroidism and 33 patients from the control group.	In 57% of patients diagnosed with AHT, mild to moderate depression was diagnosed (MADRS> 11 points). After 6 months of treatment with tyroxin, 42% of these patients had remission of symptoms. The decrease in inflammatory markers correlated with the remission of depression.	[4]
Lee et al.	2019	1651	The study group was divided into 3 groups depending on the level of TSH. Anti-TPO antibodies and fT4 levels were also tested in all patients.	Depressive symptoms were observed less frequently in patients with positive anti-TPO antibodies and the highest TSH concentrations than in the group of patients with the lowest TSH concentrations. Men with the highest TSH level were less than twice as likely to develop depressive symptoms than in the group with the lowest TSH levels. On the other hand, in women with the highest TSH level 35% less often depressive symptoms than in the group with the lowest TSH level. Gender may play an important role in the relationship between TSH levels and depressive symptoms.	[45]
Dersch et al.	2020	100	100 patients with unipolar endogenous major depression or treatment-resistant depression, including: 25 patients with first depressive episode (6 of them patients with psychotic symptoms) and 75 patients with recurrent depression (18 of them were patients with psychotic symptoms)	This study provides evidence of intrathecal synthesis of anti-thyroid antibodies in a subset of patients with unipolar depression. This may indicate central immunization in a subset of patients diagnosed with HD.	[46]

Abbreviations: TPO - thyroid peroxidase; ATH - autoimmune hypothyroidism; HD - Hashimoto's disease; TSH - thyroid-stimulating hormone, fT3- free triiodothyronine, fT4 - free thyroxine, MRI – magnetic resonance imaging, MARDS – The Montgomery–Åsberg Depression Rating Scale.

3. Inflammatory processes, growth factors and cytokines

Common etiological basis for both thyroid autoimmunity and mood disorders are also seen in similar changes of growth and differentiation in the hematopoietic and neuronal system cells and similar changes in the cytokine profile [10]. Numerous studies indicate that depression activates the inflammatory response system through increased production of pro-inflammatory cytokines such as IL-1beta, IL-2, IL-6, IFN-alpha (interferon alpha), TNF-alpha and their receptors (IL-6R, IL-1RA) [47]. Stress induces production of pro-inflammatory cytokines leading to neuroendocrine and neurotransmitter changes resembling symptoms of depression. IFN-alpha immunotherapy (e.g., used previously in hepatitis C) often causes depressive symptoms and autoimmune thyroid disorders with the appearance of anti-TPO and anti-TG (anti-thyroglobulin) antibodies [48].
The presence of acute phase proteins and cytokines may be associated with inflammation within the brain. Peripherally produced cytokines can cross the blood-brain barrier [49,50], and after crossing it, they are able to participate in stress response modulation and regulation of neurogenesis [48]. One of their potential mechanisms of action on mood is the attenuation of neurogenesis within hippocampal neurons, which is believed to be a key mechanism in the pathophysiology of depression and its treatment [51-53]. The

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weakening of neurogenesis may, over time, contribute to the reduction of the gray matter volume in hippocampus, often observed in depression [54]. It is still unclear whether the presence of acute phase proteins may be the cause, consequence or only accompanying the depression.

Studies of changes in cytokines and other inflammatory parameters in the population with the concomitant occurrence of AHT with depression (also during pharmacological inteventions) are very limited. A study conducted in patients with hypothyroidism after thyroidectomy due to cancer showed increased levels of the pro-inflammatory cytokines IL-6, IL-10. IL-17, TNF-alpha and CRP (C-reactive protein). Levothyroxine therapy (used in hypothyroidism) resulted in a decrease in the level of these cytokines, but their levels were still higher than in healthy subjects [55]. In patients treated with levothyroxine, a simultaneous reduction in the level of pro-inflammatory cytokines and an increase in the levels of anti-inflammatory cytokines has been also demonstrated [56]. Interestingly, primary AHT is characterized by increased values of pro-inflammatory cytokines such as IL-2, IL-6, IL-15, TNF-alpha and CRP [7,56-58]. During treatment with levothyroxine, a significant decrease in the levels of IL-1, IL-2, IL-6, IL-12, IFN-gamma, TNF-alpha and a significant increase in IL-10 (anti-inflammatory cytokine) was observed [7,56]. In the Polish study the incidence of mild and moderate depression among patients with hypothyroidism was initially 57%. After 6 months of levothyroxine therapy and achieving euthyroidism nearly half of the group (42%) remitted depressive symptoms [7].

Use of selective serotonin reuptake inhibitors (SSRI), our most frequently used group of antidepressants, reduces promoting-depression effect of pro-inflammatory cytokines. Fluoxetine has been shown to reduce the expression of IL-1beta, IL-6, and TNF-alpha, but interestingly subsequently increasing the level of IL-10 [59]. Desipramine (tricyclic antidepressant, TCA) reduces levels of TNF-alpha in the hippocampus and brainstem [60], and its clinical efficacy has been associated with its ability to alter the sensitivity of noradrenergic neurons to TNF-alpha [61]. In conclusion, studies evaluating the effects of SSRIs (selective serotonin reuptake inhibitors) and other antidepressive drugs indicate that inflammatory factors contribute to the pathogenesis of depression, and that various antidepressants have ability to reduce the release of pro-inflammatory cytokines as eg., IL-1beta. The results of the few published studies indicate that various antidepressants affect the level of thyroid hormones differently in patients with depression, which is probably due to differences in mechanisms of action between the drugs [62]. The results of a study evaluating the effects of reboxetine, venlafaxine and sertraline on TSH and thyroid hormones (T4 – thyroxine and fT4) levels before and after treatment in severely depressed patients showed large discrepancies between drugs, although improvement in depressive symptoms occurred in all groups. A decrease in TSH levels, an increase in fT4 and T4 was observed in patients treated with reboxetine, no changes in hormone levels were observed in those treated with venlafaxine, while patients taking sertraline had an increase in TSH levels, a decrease in fT4, and T4 levels [63]. The effect of SSRIs on thyroid function was summarized by a meta-analysis that included clinical studies that measured levels of thyroid parameters (TSH, T4, fT4, or fT3) before and after treatment with SSRIs (as a group). It was shown that after treatment with these drugs, patients had lower levels of T4, fT4 and fT3 with no change in TSH values [64]. So far, the mechanism of inducing hypothyroidism during SSRI treatment has not been established. One hypothesis is that SSRIs stimulate the activity of the type 2 iodothyronine deiodinase enzyme, which converts T4 to T3 (trioiodothyronine) in various tissues, including the brain [65]. Also, the relief of depressive symptoms causes biological effects that may modulate the thyroid axis. It has been documented that there is an association of the effect of venlafaxine treatment with polymorphisms in the NR3C2 gene and elevated TSH levels [66]. Studies on the effect of thyroid hormones on the speed of action of antidepressants indicate that accelerating the response to antidepressants is not possible for all classes of antidepressants. T3 accelerates responses to TCAs (tricyclic antidepressants) but does not have the same effect when used with SSRIs. In a meta-analysis of four RCTs of controlled depression patients, there was no evidence of a faster onset of response when T3 was added to SSRIs [67]. The reasons

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for a discrepancy between the effects of T3 on TCA versus SSRIs remain unknown [68]. However, we do not have data on the effect of treatment with antidepressants on the biochemical parameters of the thyroid gland, including the levels of anti-thyroid antibodies in patients with AHT.

It is worth noting, that preliminary data suggest that anti-inflammatory drugs may be useful in mood disorders - it has been reported that in patients treated with rofecoxib and celecoxib, the depressive symptoms improvement was more pronounced than in the group not treated with these drugs [63,64]. This effect at least partially may be related to the analgesic effect of the COX-2 inhibitors, but studies on rats showed that use of rofecoxib leads to serotonin increase in frontal, parietal, and temporal cortex, which may indicate their other-than-analgesic mechanism of action [63]. So far, no studies have been conducted to assess the effect of anti-inflammatory drugs on the biochemical parameters of thyroid function in AHT. Even if not all depressive states have an inflammatory etiology, according to the available data there is possibly a separate subtype of depression of inflammatory origin or manifestation of inflammatory process is able to clinically mimics depression. Biological anti-inflammatory drugs, including anti-TNF-alpha antibodies as e.g., infliximab, adalimumab and guselkumab potentially may be useful to treat those types of depression. Those particles have an ability to reduce severity of inflammation (e.g., in rheumatic diseases, psoriasis and Crohn's disease) very effectively. However, the conclusions from limited depression trials are ambiguous, although patients with high initial levels of pro-inflammatory cytokines may have more benefit with this treatment [69-71]. Tocilizumab (IL-6 receptor blocker) studies show potential to decrease levels of depressive symptoms in patients with rheumatoid arthritis [72,73], but in patients with haematological problems the results were completely different - depressive symptoms exacerbated with this drug [74]. Interestingly, hallucinogens (increasingly studied in depression) and bupropion have an ability to block TNF-alpha or decrease its production [75].

Scarce data from studies concerning the thyroid gland function during use of TNF-alpha antibodies showed mostly neutral results (no changes in TSH, T3, anti-TPO and anti-TG levels, decrease in fT4 levels) [76]. We need to underline here that depression (also with increased suicidal risk) and thyroiditis (new onset or its exacerbation) are among common side effects of TNF-alpha blockers.

Studies involving relatives of patients with AHT force even deeper reflections about common origin of both ATH and depression. Euthyroid women being relatives of AHT patients have abnormal serum levels of hematopoietic and neural growth and differentiation factors important in etiology of depression – BDNF (Brain-derived neurotrophic factor), IGFBP-2 (insulin-like growth factor binding protein), EGF (epidermal growth factor) and SCF (stem cell factor) [10].

4. Brain-derived neurotrophic factor (BDNF) and depression, AHT and gender

BDNF needs a broader description as a crucial element in current understanding of development and dynamics of depressive symptomatology. This particle belongs to the group of neurotrophins, proteins synthesized in the cells of the central and peripheral nervous system and involved in the development, function, and protection of nerve cells. It regulates many processes in our body, including the development and growth of neurons, inhibiting apoptosis, promoting neurogenesis, neuroregeneration, and stimulating the formation of dendritic connections. BDNF participates in the regulation of neuronal plasticity related to learning and memory processes, influencing the process of synaptic long-term potentiation and long-term depression in the hippocampus. It also influences the development of serotonergic, dopaminergic, noradrenergic, and cholinergic neurons. Dopaminergic neurons of the substantia nigra and striatum have been found to be the main source of BDNF secretion. BNDF easily cross the blood-brain barrier [77].

Preclinical studies show that stress reduces BDNF expression in the rat hippocampus, while a single two-sided direct infusion of BDNF into the rat hippocampus has an antidepressant effect in animal models of depression [78]. In humans, BDNF plays a significant role in the pathophysiology of mental disorders, especially depression, where its key role

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is undisputable. Patients with severe depressive symptoms show lower levels of BDNF compared to controls. Moreover, BDNF levels are correlated with the reduction of the hippocampal volume [79]. We also know that BDNF expression is lower in the prefrontal cortex and hippocampus of people who died committing suicide compared to the control group matched in terms of sex and age [80]. The use of sertraline, escitalopram, and venlafaxine in the study by Matrisciano et al. resulted in significant clinical improvement despite varying effects on peripheral BDNF levels. A relationship was also found between an increase in BDNF serum levels and an improvement in the Hamilton Depression Rating Scale, thus indicating that a higher BDNF level in the blood serum corresponds to recovery [80]. It has been shown that BDNF levels were directly related to antidepressant responses, and people who responded well to treatment (> 50% improvement in the scores of depression severity scales) had higher BDNF levels before treatment than non-responders, indicating that BDNF can be a potential predictor of the antidepressant response [79]. It was also confirmed that the concentration of BDNF and its changes are not rigidly correlated with improvement in depression, but that the level of BDNF generally increases during antidepressant treatment. Studies on rapid-acting antidepressant - ketamine - having different mechanism of action than SSRIs and TCAs, showed that the rapid antidepressant response after its administration is mediated by an increase in BDNF levels [81]. Research directly linking BDNF to thyroid disorders is scarce at present. Rats with early-onset hypothyroidism exhibited lower levels of BDNF in the brain [82]. Preclinical studies conducted by Hung indicate that thyroxine protects against white matter damage by increasing the level of BDNF [83]. In clinical trials, higher TSH levels were associated with a more discrete increase in serum BDNF levels in depressed patients during antidepressant therapy [78], and lower baseline TSH levels correlated with greater improvements after fluoxetine and sertraline [84]. It has also been shown that observed clinical results were better among patients who had lower TSH levels during sertraline and triiodothyronine therapy [85]. On the other hand, the only study evaluating the effect of thyroid hormones on changes in BDNF in serum, plasma, and platelets over the 3-month period of treatment with antidepressants in patients without thyroid disease showed that higher TSH levels correlated with a lower increase in serum levels of BDNF during antidepressive treatment. It was additionally indicated that with TSH increase BDNF concentrations decreased throughout the observation period [78]. In patients participating in this study, no such relationship was found between the levels of triiodothyronine (T3), thyroxine (T4), corticotropic hormone (ACTH), cortisol, prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), estrogen and progesterone. A study evaluating similar relationships in patients with hypothyroidism and subclinical hypothyroidism has not been conducted so far.

In conclusion, it can be hypothesized that thyroid hormones may affect the response to antidepressant therapy through its influence on BDNF, but so far there are no sufficient data to confirm this hypothesis unequivocally.

Due to the epidemiology of depression and AHT, it is worth emphasizing that the relationship between the level of BDNF and depression may depend on gender. It has been shown that reduced BDNF values are more pronounced in women with depression, and long-term antidepressant use selectively raises its concentration in women. Therefore, it is possible that the more frequent occurrence of depression in women may be related to this mechanism and interactions with female sex hormones, especially since it has been shown that BDNF expression can be reduced by exogenous administration of estradiol [78].

5. Summary

People with higher risk of developing mood disorders, including depressive disorders, are at the same time more likely to develop autoimmune thyroid disease and vice versa, what may indicate a common pathogenetic roots. An abnormal profile of haemopoietic and neuronal growth factors, including BDNF, is observed in patients with mood disorders as well as in those at risk of developing ATH. Similar observations apply to the

cytokine profile in patients with both diseases, in whom we observe an increase in the concentrations of pro-inflammatory interleukins, e.g., IL-1beta, IL-2, IL-6, and TNF-alpha. From the clinical perspective, the conclusion that seems to be of particular importance is that in euthyroid patients with autoimmune thyroiditis and elevated levels of anti-thyroid antibodies, the incidence and severity of depression is significantly higher [8]. Treatment with both antidepressants and levothyroxine leads to a decrease in the level of pro-inflammatory cytokines, an increase in the level of BDNF, correlating with an improvement in clinical parameters of depression. Hence one of the hypotheses that depression may belong to the spectrum of inflammatory and degenerative disorders [86].

For the above reasons, patients with depression and anxiety disorders should be tested for autoimmune hypothyroidism, and patients with AHT should be screened for psychiatric symptoms [25]. However, it is necessary to conduct long-term studies (as our team is planning now) to determine the causal relationship between depression, thyroid autoantibodies, and cytokine levels, which would help us bring us closer to understanding the interrelationships between them and facilitate the use of adequate pharmacotherapy, not necessarily psychiatric. At the same time, it would be possible to identify groups of higher risk for the occurrence of both frequent and very burdensome diseases, and from psychiatric perspective to help prevent the development of full-blown depression and finally to predict the therapeutic response to particular treatment (drugs or groups of drugs).

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