doi: 10.4183/aeb.2020.256

THYROID HORMONES AS A THIRD LINE OF AUGMENTATION MEDICATION IN TREATMENT-RESISTANT DEPRESSION

S. Trifu[1,*], A. Popescu[2], A.M. Dragoi[2], A.I. Trifu[3]

[1]"Carol Davila" University of Medicine and Pharmacy - Neurosciences, [2]"Alex. Obregia" Clinical Hospital for Psychiatry - Psychiatry, [3]Medical Military Institute - General Medicine, Bucharest, Romania

Abstract

Introduction. Clinical or subclinical hypothyroidism dictates the severity of depressive episodes and more frequently overlaps psychotic phenomenology. There are also major depressive episodes resistant to treatment in patients with euthyroidism, in which supplementation of antidepressant medication with thyroid hormones is beneficial.

Material. Systematization of meta-analyses from perspectives: hypothyroidism and depression, autoimmune and depression pathology, gestational and puerperal pathology in association with hormonal and dispositional changes, presentation of therapeutic schemes.

Results. Hypothyroidism is more commonly comorbid with major depression in women. It associates the need for hospitalizations, psychotic phenomenology, resistance to treatment, somatic comorbidities. Autoimmune pathology is associated with depression and requires thorough investigation. A possible genetic candidate for thyroid dysfunction is the DIO1 gene. FT4 may be a predictor, but the combination of FT4 + TBG measured during the prenatal period has a higher prognostic power for a future depressive episode.

Conclusion. The article presents psychiatric medication schemes that combine antidepressants and antipsychotics of various classes with other enhancers, an important role going back to step three, which includes thyroid hormones, mainly T3. The doses used are smaller than the amount of endogenous production of T3 daily, with a small risk of inducing clinical hyperthyroidism.

Keywords: hypothyroidism, depression, autoimmune pathology, DIO1 gene, antidepressant, thyroid hormones.

Dear Editor,

This letter bring to your attention a relationship between thyroid function and depressive episodes, which has already been recognized historically 200 years ago, though controversial, with an insufficiently known mechanism.

Both hypo - and hyperthyroidism can cause mood disorders; 1-4% of patients with affective disorders have been shown to have clinical hypothyroidism, while subclinical hypothyroidism occurs in 4% to 40% of these patients (1). Traditionally, the most common documented abnormalities accompanying anxiety and depression are high levels of T4 with low T3, along with a reduced TSH (thyrotropin) response to TRH (thyrotropin-releasing hormone), positive anti-thyroid antibodies and increased concentrations of cerebrospinal fluid TRH.

Sometimes, the mood disorders encountered in thyroid dysfunction are a side effect of the treatment. Steroids, for example, used as a treatment for subacute thyroiditis, can aggravate depression. Beta blockers prescribed for hyperthyroid-related heart rhythm disorders can exacerbate fatigue, attention and concentration disorders, and sad mood.

Hypothyroidism

The psychopathological disorders encountered range from irritability and agoraphobia to depression with melancholic elements and can reach dementia, in almost all patients with untreated hypothyroidism. It has been shown that the effect of prolonged hypothyroidism on the brain functioning can be severe and possibly irreversible. Moreover, due to the insidious onset with minor and non-specific manifestations at first presentation, the diagnosis may be delayed.

Given the modern tests that quantify thyroid hormone levels, it has been determined that there is a larger group of patients with borderline hypothyroidism from a biochemical point of view. They have few specific symptoms, that is why treatment management remains unclear. Some studies say that despite adequate treatment with thyroxine substitution, residual symptoms of the pathology may still persist.

Hypothyroidism is more common in women,

*Correspondence to: Simona Trifu MD, "Carol Davila" University of Medicine and Pharmacy, Neurosciences, 37 Dionisie Lupu Str., Bucharest, 020021, Romania, E-mail: simonatrifu@yahoo.com

with an incidence rate of 8:1.

From a clinical point of view, the physical appearance is characteristic, with swollen eyelid, skin pallor and dark circles under the eyes. The skin is dry and hard, with generalized edema. Hair loss occurs, and the hair is thin. The ideo-verbal rhythm is slown down, the tone of the voice has no inflections. The patient's disposition seems to be impassive, lost. Among the first patient's complaints is intolerance to low temperatures. Often encountered are menorrhagia in women and impotence in men.

Etiology of psychic disturbances

The specific pathophysiology that explains the emotional and behavioral disturbances of patients with hypothyroidism remains unknown in detail. Old studies show that cerebral arterial flow is low by 38% and that there is a consumption of 27% less oxygen and glucose in patients with hypothyroidism. The nuclear receptors for triiodothyronine are found in the brain and are in high concentrations in the amygdala and hippocampus, areas associated with modulation of mood. The associated mental symptomatology can be broadly correlated with changes in brain metabolism, regardless of the cause. These changes can also be highlighted in the EEG analysis and should be monitored in the substitution treatment. Symptoms of severe affective illness and schizophrenia are often caused by organic, genetic or environmental factors. There are cases of psychiatric symptomatology with absent obvious lesions, in which there is probably a cerebral metabolic defect. However, the mechanism is not fully elucidated; there are patients having clear depressive symptoms, without showing hypothyroidism, who have responded to thyroxine treatment after other forms of treatment have failed.

The therapeutic algorithm for acute depressive episode

The first line of treatment:

A) When we consider that serotoninergic phenomenology predominates (depression of mild or moderate intensity, accompanied by diffuse anxiety, restlessness, irritability, irascibility, rumination with sad content in existential context and search for solutions, easy crying and externalizing of experiences):

1. We can start with SSRI, which acts on serotonin transporters or presynaptic reuptake transporters;

2. We can start with tricyclic AD / tetracyclic AD, which have multireceptorial action (they are more potent, but also act on histamine and muscarinic receptors), causing more adverse reactions.

B) When we consider that the noradrenergic effects predominates and we talk about a depression characterized by: apathy, loss of interest, loss of pleasure, loss of vital momentum, we start with a dual antidepressant. This may be a SNRI - serotonin-norepinephrine reuptake inhibitor (Venlafaxine) or a NaSSA - noradrenergic and specific serotonergic antidepressant (Mirtazapine). The latter two are used in mixed forms of depression or when somatic problems are associated.

In case of non-liability, the treatment line is switched to Line II. This includes initially increasing doses.

If we do not get the expected answer, the change of antidepressant is intended. Usually from SSRI (Selective Serotonin Reuptake Inhibitor) in dual AD or SSRI in tricyclic / tetracyclic AD.

If depression is associated with obsessional phenomena, the choice is considered Sertraline or Clomipramine. We wait for 4-6 weeks.

In case of non-responsiveness, the organic resistance factors are searched and, in the absence of them, we go to line III of treatment, which implies:

1) enhanced associations of two ADs, both with action on serotonergic and noradrenergic receptors.

2) association of Lithium.

3) association of Pindolol.

4) association of thyroid hormones.

In case of pharmacological non-liability, it is passed to the IV line of the treatment, which implies the increase of AD with enhanced antipsychotic medication, for example:

- SSRI + Olanzapine (example: 80 mg Fluoxetine + 20 mg Olanzapine)

- SSRI + tricyclic / tetracyclic AD

- "Heroic" combinations, for example: 45 mg Mirtazapine + 225 mg Venlafaxine + 15 mg Olanzapine.

In the opposite situations, when hypothyroidism is the main cause of the dispositional changes in the depressive sense, its treatment is beneficial; the behavioral disorders respond well to the adequate therapy with thyroxine, although initially it is helpful to have a supplement with an antidepressant or a minor neuroleptic. There were cases of patients (2) that returned to euthyroidism, whose deficits of mood, memory and intellect did not improve. These patients were those who remained psychiatrically undiagnosed for a long period of time or had insufficient psychiatric treatment.

In most patients with hypothyroidism,

cognitive dysfunction is markedly improved with substitution treatment. However, studies have shown that residual symptoms may occur despite adequate thyroxine treatment, thus increasing the possibility of increased triiodothyronine treatment.

The introduction of thyroxine into the treatment plan needs to be done carefully, especially in the elderly, as it can cause myocardial distress.

Very rarely, a maniacal or, more rarely, psychotic disorder may occur at the initiation of treatment. Symptoms begin on days 4-7 of thyroxine treatment and recover within 1-2 weeks, without any special therapeutic interventions. The patients in question are completely cured. They usually have a family or personal history of psychiatric disorder.

Despite adequate thyroxine therapy, with TSH levels within normal limits, many patients with hypothyroidism have persistent apathy and co-existing psychopathological symptoms.

Combination therapy with triiodothyronine and thyroxine has resulted in increased cognitive performance, improved mood and general well-being compared to patients receiving thyroxine-only therapy (3). However, other clinical trials on the same topic have failed to replicate these findings, which suggests that it is possible that only patients with absent thyroid function will benefit from combination therapy.

We present a review of medical literature focused on the following areas:

I. Depression as a consequence of hypothyroidism.

II. Autoimmune thyroiditis and depression.

III. Postnatal depression - level of thyroid hormones antepartum and during pregnancy.

IV. Hormonal treatment in depression.

RESULTS

Depression as consequence of hypothyroidism

Gernot Fuggera's 2018 study (4), which investigated the comorbidity of thyroid disorders with major depressive episodes in a sample of European patients with treatment-resistant depression, indicates a prevalence rate of 13.2% of comorbidity of hypothyroidism with major depressive disorder, on a batch of 183 patients diagnosed with both diseases, out of 1410 patients investigated. Comparatively, the prevalence rate between hyperthyroidism and major depressive disorder is 1.6%. Patients with comorbid hypothyroidism with major depression were significantly older (mean 55.58 years) and in a greater number of women (85.2%).

Of the patients with hypothyroidism-depression comorbidity, 17.5% associated psychotic phenomena, 50.3% required hospitalization, 68.9% were diagnosed with somatic comorbidities, of which 32.2% with hypertension and 10.9% with heart disease. This was also the subset of patients who required a greater number of concomitant medications.

The study of Seref Gulseren (5) investigated the quality of life regarding anxiety depressive disorders in patients with subclinical thyroid dysfunction and included a group of 160 subjects (33 with manifest hypothyroidism, 43 with subclinical hypothyroidism, 51 with manifest hyperthyroidism and 13 with subclinical hyperthyroidism). The evaluation was done with the Hamilton scales for anxiety and depression, with SF36 (36-Item Short Form Health Survey) and with the Brief Disability Questionnaire. The results showed that anxiety and depression were more severe in patients with manifest hypothyroidism and hyperthyroidism and, as a result of treatment, the groups of patients with hypothyroidism or clinical hyperthyroidism had a greater improvement than the patients in the subclinical groups.

The study of Sanisah Saidia Siti (6) investigated the relationship between TSH level, age, sex and depression symptoms among patients with thyroid disorders, measuring their levels of anxiety, depression and stress through DASS-21 (Depression Anxiety Stress Scales). It was a retrospective cohort study, which included 13017 subjects (7913 men and 5100 women), aged 17-84 years, investigated in the hospital environment. It was found that the risk of depression was increased in subjects with high levels of TSH, compared with subjects with low TSH. The results were statistically demonstrated only among women. In other words, the level of TSH as a continuous variable significantly predicted depressive symptoms only in women.

Hypothyroidism is more common in women (7), and the risk of developing hypothyroidism following subclinical thyroid dysfunction is also higher in women than in men. Moreover, the thyroid reserve in response to depression can be mobilized more effectively in men than in women. In this regard, a suboptimal functioning thyroid may increase the vulnerability to the development of clinically significant depressive symptoms, especially in women.

Panicker *et al.* tested whether genetic variation affecting thyroid function also influences free thyroid hormones and vulnerability to depression. As an

initial step, to establish a strong biological basis, 12 SNPs were genotyped, including two selected for their association with FT4 (8) and 10 selected for their association with TSH (9). Genome-wide analyses were performed and the association of these genotypes with thyroid indices in the studied population was examined. In other studies, the two SNPs associated with FT4 levels, including cSNP rs11206244, were also evaluated in the study population. These findings are encouraging because DIO1 is a critical gene in thyroid hormone production, responsible for the conversion of thyroxine to triiodothyronine (10), and has strong validity as a candidate gene for major depression, given the literature (in large epidemiological studies and meta-analyses) that support the hypothesis of thyroid hormone action in the etiology of major depression (11).

In this study, the researchers focused on the DIO1 gene, more specifically on the rs11206244 polymorphism, for three reasons:

a) first, because it is a cSNP found in 3′UTR of DIO1 that has been assumed to be functional in molecular assays, probably by modifying mRNA stability.

b) secondly, the genotype of this SNP was associated with the response to the growth of thyroid hormones.

c) third, current genetic information has not been sufficient to reliably impute more accurate haplotypes. However, the current findings confirm previous findings that the T allele of this polymorphism is associated with increased FT4, but not with increased TSH levels (12). Furthermore, it should be noted that other polymorphisms, including intronic rs2235544 polymorphism, are also related to the linkage imbalance of rs11206244 and that further studies are indicated to determine the nature of the functional variant of this haploblock.

Autoimmune thyroiditis and depression

Despite the growing interest in the psychiatric implications of autoimmune diseases (AI), most published studies still focus on their somatic effects.

Up to 50% of patients with autoimmune diseases report a decrease in quality of life (QOL) and have symptoms similar to depression. The immune system not only causes inflammation in the affected organs, but also mediates disorders of mood and nictemeral rhythm.

By quantitatively summarizing the results of current studies on AI diseases as a possible root of mood disorders, awareness of this association increases and adequate thyroid treatment beyond antidepressants and psychotherapy can be implemented. Furthermore, screening tests for symptoms of depression and anxiety in patients with AI disease and for AI disease in patients with depression and anxiety may be established.

A recent study by Robert Krysiak (13), investigated sexual function and depressive symptoms in young women with autoimmune thyroiditis and subclinical hypothyroidism. Beyond measuring serum hormone levels and thyroid antibody titers, the index of female sexual function - FSFI and the presence and severity of depressive symptoms (with the BDI-II scale) were calculated. The results suggest that both thyroid autoimmunity and mild thyroid insufficiency, especially if they occur together, can adversely affect female sexual function and depressive symptoms.

Siegmann *et al.* (14) investigated the association of depressive and anxiety disorders with autoimmune thyroiditis, represented a meta-analysis that included 19 studies, including 21 independent samples, with a total number of 36,174 participants (35,168 diagnosed with depression, 34094 diagnosed with anxiety disorder). Patients with autoimmune disease, Hashimoto's thyroiditis, subclinical or manifest hypothyroidism had significantly higher scores on the instruments for identifying and measuring depression. For them, the scores on the anxiety scale were above average, but lower than those obtained on the depression scale.

The study of Gold (15) refers to autoimmune thyroiditis in depression and specifies that patients with clinically silent autoimmune thyroiditis may also be euthyroid (15% of patients met the criteria for subclinical hypothyroidism, of these 60% had thyroid peroxidase antibodies. Depression or other psychiatric disorders may be the basis for suspicion of autoimmune disease.

Postnatal depression - level of thyroid hormones antepartum and during pregnancy

Mood disorders are common among pregnant women as well as postpartum. The prevalence of depression (major and minor) according to DSM-IV and RDC (Research Diagnostic Criteria) is about 14% during pregnancy, cumulative with the first three months after birth (16). Hormonal changes associated with the perinatal period have long been suspected to play an etiological role in the onset of postpartum depression. Studies of hormonal correlates of postpartum depression have over time focused

mainly on estrogen, progesterone or cortisol (17). At present, there are relatively few studies that examined the relationship of thyroid variables with postpartum mood disorders. This is surprising because thyroid function has many connections with depression, and it is well known that the hypothalamic-pituitary-thyroid axis (HPT) undergoes considerable changes during pregnancy and postpartum (18). High estrogen levels in pregnancy cause approximately 150% increase in thyroid hormone binding proteins, respectively thyroxine binding globin, requiring the thyroid gland to produce much more hormone to occupy the larger "binding space" and to keep hormone levels free in the normal range. Thus, the total serum thyroxine concentration increases to the upper limit of the normal range, while the free thyroxine concentration usually decreases during pregnancy. Subsequently, the total thyroxine concentration decreases for approximately six weeks after birth, until it reaches the pre-gestational levels.

Hormonal treatment in depression

TRH (Thyrotropin-Releasing Hormone)

TRH has been tested as an antidepressant, due to stimulation of the hypothalamic-pituitary-thyroid axis, as well as due to its independent effects on brain function. Most studies have used TRH alone, but there have been studies regarding the use of TRH along with electroconvulsive therapy (ECT). TRH has been administered intravenously. Depressed patients who are treated with tricyclic AD and T3 can be twice as responsive to the combined treatment compared to the control groups, according to a meta-analysis of eight studies that totaled 292 patients supporting the use of T3, specifying the limitations of the studies examined (19, 20).

General clinical manifestations

Depressive episode

Hypothyroidism is frequently associated with depressive mood. Several visible metabolic and behavioral changes in hypothyroidism are common to depression, which is why changes in the pituitary-thyroid axis may play a role in modulating mood. The most common thyroid function abnormality in patients with depression is a moderate increase in serum thyroxine concentration, which decreases with the clinical response to treatment (21). Low thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) has been repeatedly described in approximately 25% of patients with major depression (22). Traditionally, the most commonly documented abnormalities are elevated T4 levels, low T3, elevated rT3, a blunted TSH response to TRH, positive antithyroid antibodies, and elevated CSF TRH concentrations (23).

Mild hypothyroidism also occurs frequently in bipolar affective disease, in 25% of cases. Supplementation of thyroxine treatment has been shown to help reduce the number of episodes.

Management of major depressive disorder

The evaluation considers: clinical form, intensity, comorbidities, somatic problems, suicide risk, level of social functioning. The diagnosis is made according to ICD 10 and DSM-5.

Monitoring involves the evaluation of the general condition, of the psychiatric symptoms and the somatic state, the level of compliance and the social functioning.

In conclusion, thyroid hormones are involved in many psychiatric functions, and could be considered as adjuvant treatment for psychiatric disorders, especially in depression and cognitive changes.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Wolkowitz OM, Rothschild AJ. The Scientific Basis of Clinical Practice. Psychoneuroendocrinology: 1st edition. Washington DC: American Psychiatric Publishing. 2003.
2. Magner JA. Pituitary–Thyroid Relationships. Principles of Medical Biology 1997; 10: 165-189.
3. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJJr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med. 1999; 340(6):424-429.
4. Fuggera G, Dolda M, Bartova L, Kautzky A, Souery S, Mendlewicz J, Serrettie A, Zoharf J, Montgomeryg S, Freya R, Kasper S. Comorbid thyroid disease in patients with major depressive disorder - results from the European Group for the Study of Resistant Depression (GSRD). European Neuropsychopharmacology. 2018; 28(6):752-760.
5. Gulseren S, Gulserena L, Hekimsoy Z, Cetinay P, Ozena C, Tokatlioglu B. Depression, Anxiety, Health-Related Quality of Life and Disability in Patients with Overt and Subclinical Thyroid Dysfunction. Archives of Medical Research. 2006; 37(1):133-139.
6. Siti SS, Jaafara NI, Ramli AD, Noor MN, Ahmad FN. Relationship between levels of thyroid stimulating hormone, age, and gender, with symptoms of depression among patients with thyroid disorders as measured by the Depression Anxiety Stress Scale 21 (DASS-21). Enfermería Clínica. 2018; 28(S1):180-183.
7. Flynn RW, MacDonald TM, Morris AD, Jung RT, Leese GP. The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. J Clin Endocrinol Metab. 2004; 89(8):3879-3884.

8. Panicker V, Cluett C, Shields B, Murray A, Parnell KS, Perry JR, Frayling TM. A common variation in deiodinase 1 gene DIO1 is associated with the relative levels of free thyroxine and triiodothyronine. The Journal of clinical endocrinology and metabolism. 2008; 93(8):3075–3081.
9. Hwang SJ, Yang Q, Meigs JB, Pearce EN, Fox CS. A genome-wide association for kidney function and endocrine-related traits in the NHLBI's Framingham Heart Study. BMC Med Genet. 2007; 19(8):1-10.
10. Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, Zeöld A, Bianco AC. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocr Rev. 2008; 29(7):898-938.
11. Forman-Hoffma V, Philibert RA. Lower TSH and higher T4 levels are associated with current depressive syndrome in young adults. Acta Psychiatr Scand. 2006; 114(2):132-139.
12. Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab. 2003; 88(7):3202-3211.
13. Krysiak R, Drosdzol-Cop A, Skrzypulec-Plinta V, Okopien B. Sexual function and depressive symptoms in young women with thyroid autoimmunity and subclinical hypothyroidism. Clin Endocrinol (Oxf). 2016; 84(6):925-931.
14. Siegmann E, Müller HHO, Luecke C, Philipsen A, Kornhuber J, Grömer TW. Association of Depression and Anxiety Disorders With Autoimmune Thyroiditis. A Systematic Review and Meta-analysis. JAMA Psychiatry. 2018; 75(6):577–584.
15. Gold MS, Pottash AL, Extein I. "Symptomless" autoimmune thyroiditis in depression. Psychiatry Res. 1982; 6(3):261-269.
16. O'Hara MW, Swain AM. Rates and risk of postpartum depression-A meta-analysis. International Review of Psychiatry. 1996; 8(1):37–54.
17. Hendrick V, Altshuler LL, Suri R. Hormonal changes in the postpartum and implications for postpartum depression. Psychosomatics. 1998; 39(2):93-101.
18. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev. 1997; 18(3):404-433.
19. Iosifescu DV. MSc Supercharge' antidepressants by adding thyroid hormones. Current Psychiatry. 2006; 5(7):15-25.
20. Morin AK. Triiodothyronine (T3) supplementation in major depressive disorder. Mental Health Clinician. 2015; 5(6):253-259.
21. Bauer MS, Whybrow PC. Rapid cycling bipolar affective disorder. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. Arch Gen Psychiatry. 1990; 47:435–440.
22. Gillette GM, Garbutt JC, Quade DE. TSH response to TRH in depression with and without panic attacks. The American Journal of Psychiatry. 1989; 146(6):743–748.
23. Hage MP, Azar ST. The Link between Thyroid Function and Depression. J Thyroid Res. 2012; 2012:590648.
24. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications 4th Edition, Cambridge University Press, Cambridge. 2013.