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REVIEW ARTICLE

Subclinical thyroid dysfunction and major depressive disorder

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Abstract

Purpose This review attempts to investigate the link between subclinical thyroid dysfunction (SCH) and major depressive disorder (MDD). It has been speculated that SCH may be related to MDD through an autoimmune mechanism.

Methods A comprehensive literature search was conducted in the PubMed database for relevant research and review articles.

Results There appears to be an association between an autoimmune mechanism, possibly involving the thyroid gland, and depressive disorders, but the available evidence is so far inconclusive.

Conclusion Lifetime prevalence of depression is significantly higher in patients with SCH, a finding reflecting a possible effect of SCH in lowering the threshold for the emergence of MDD. The relationship between SCH and MDD is, however, not clear, with large and well-designed studies investigating possible links between reference-range thyroid hormone levels and MDD having as yet found no relation between the two.

Keywords Major depressive disorder · Thyroid function · Subclinical · Psychoneuroendocrinology

Introduction

Higher rates of subclinical hypothyroidism (SCH) have been observed among patients with depression [1]. SCH seems to affect the severity of major depressive disorder (MDD) and the effectiveness of antidepressants [2]. In addition, SCH possibly decreases the threshold for the emergence of depression. The relationship of subclinical thyroid dysfunction with MDD is thought to be mediated by an autoimmune mechanism, possibly involving the thyroid gland, but currently, the available evidence is non-conclusive [1]. This review aims to ascertain whether SCH could cause MDD, since the relationship between SCH and the development of depression remains to date largely controversial.

Methods

A literature search was carried out in PubMed/Medline up to 20 May 2021 by using the following key terms: “major depressive disorder” [MeSH Terms] AND “subclinical thyroid dysfunction” [MeSH Terms] OR “thyroid dysfunction” [All Fields] AND “5 – HT” [All Fields] OR “GABA-A receptor” [All Fields] AND “thyroid axis” [All Fields] OR “MDD” [All Fields] AND “thyroid hormones” [All Fields] OR “augmentative” [All Fields] OR “therapy” [All Fields] AND “antidepressant agents” [All Fields] OR “effect on thyroid function” [All Fields] AND (“meta-analysis”[All Fields] AND “cohort study”[All Fields] AND “systematic review"[All Fields].

Two authors (GK and EMT) examined the extracted articles and decided on study inclusion. The criteria for inclusion of studies were as follows: English language; systematic reviews; research topic addressing thyroid dysfunction and depression; adult participants; thyroid axis dysregulation and depressive symptomatology; and the primary outcome was the highlighting of the relationship between SCH and MIDD.

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The collected articles were then thoroughly examined for content to confirm that they met the inclusion criteria. The references in the retrieved articles were scanned to identify additional relevant studies. The following data were extracted from each article: subclinical thyroid dysfunction and depressive symptomatology, thyroid axis dysregulation in MDD, and thyroid hormone effects as augmentation to treatment with antidepressants.

Any discrepancies regarding inclusion of articles and extraction of data were resolved by discussion between all authors.

Thyroid function and depressive disorder

It has been estimated that MDD will be the leading cause of disease burden worldwide by the year 2030 [3]. Depression is thought to be accompanied by mild neuroendocrinological disorders, including disorders of the thyroid. Missing a diagnosis of SCH may contribute not only to depression or mood cycling, but also to delayed treatment response. Furthermore, autoimmune thyroiditis often causes hypothyroidism in patients with depression, particularly in the postpartum period [4]. The question, however, remains whether MDD is the cause of thyroid dysfunction or vice versa.

In patients with MDD, mild elevations in thyroid hormone levels and blunting of the TSH response to TRH stimulation are common. Furthermore, in MDD, there is frequently an absence of the nocturnal surge of TSH, reversed either by sleep deprivation or after remission of an acute episode of depression [5]. Evidence concerning the autoimmune pathology associated with MDD has revealed to date specific variations of the iodothyronine deiodinase 1 (*DIO1*) gene, a possible genetic candidate for thyroid dysfunction [6].

Strenuous exercise, pregnancy, the postnatal period, anxiety, and mood disorders, as well as acute or chronic stress, are known to trigger the emergence of autoimmune diseases or to aggravate existing ones. The effect of stress on autoimmune mechanisms is mediated by changes in the systemic pre-/anti-inflammatory cytokine balance [7].

As MDD is often comorbid with autoimmune thyroiditis, MDD could be seen as a possible autoimmune disorder or as a disorder affecting the immune system. Many patients with depression have been found to have abnormally high levels of antithyroid antibodies [5]. Moreover, microsomal antibodies are frequently detected in patients with chronic lymphocytic thyroiditis. In patients with hypothyroidism, additional thyrotropin receptor (TSHR) antibodies that block TSH action may occasionally cause hypothyroidism [8]. Furthermore, patients with celiac disease [9] tend to present with higher rates of personality disorders and MDD; thus, subclinical thyroid dysfunction could be an additional specific risk factor for them [10].

An association between SCH, raised anti-TPOs, and MDD has been hypothesized, but anti-TPO levels have failed to represent a general biomarker for MDD [11]. In addition to their association with extra-thyroidal diseases such as Graves' ophthalmopathy or Hashimoto's encephalopathy, however, antithyroid antibodies, and especially TSH receptor antibodies, have been associated with depression and could be considered as an immune dysfunction biomarker in MDD. Regarding interleukin-17 (IL-17) levels, they do not seem to be associated with TSH receptor antibody levels or MDD severity [12].

Thyroid-binding inhibitory immunoglobulins prevent TSH from binding to its receptor and thereby contribute to the induction of hypothyroidism. High levels of these immunoglobulins and microsomal antibodies are observed in atypical depression, and both have been associated with treatment resistance [13]. Moreover, depression is accompanied by a modified thyrotropin-releasing hormone (TRH) response, as increased TRH concentrations have consistently been found in the cerebrospinal fluid of patients with depression [5, 14]. Microsomal antibody and TSH-blocking immunoglobulin levels are elevated in patients with atypical depression, while FT3, FT4, and TSH levels vary within the normal range in the same patients [15].

The association between depression and thyroid dysfunction in pregnancy is well known [16]. Microsomal antibodies have been associated with postpartum thyroid dysfunction and postpartum depression [17]. Transient postnatal hyperthyroidism is often followed by hypothyroidism in women who present with high levels of antithyroid antibodies and are, therefore, predisposed to hypothyroidism [18]. It has also been suggested that the lower range of concentrations of free and total T4 during pregnancy is associated with depressive symptomatology during the postnatal period [19].

Interestingly, childhood sexual abuse possibly represents an important risk factor for hypothalamic-pituitary-thyroid (HPT) axis disturbances and thyroid autoantibodies in women who develop postpartum depression [20]. Relapse prediction factors antenatally include serum levels of FT4 and the FT4 + thyroxine-binding globulin (TBG) combination, but the evidence remains poor [6].

Partial sleep deprivation (PSD) has a known antidepressant effect, and research concerning PSD, TSH, and thyroid hormone concentrations indicates a possible common underlying neurochemical mechanism [21]. It has been suggested that 5-HT1A receptors in the rat limbic area modulate the HPT axis, but how this could affect the emergence of clinical depression remains unclear [22]. HPT dysregulation in patients with MDD could be regarded as a compensatory mechanism for diminished central 5-HT activity [23]. Thyroid hormones are also thought to interact with the 5-HT1A

receptor and play a role in the hippocampal expression of brain-derived neurotrophic factor (BDNF) [24]. In addition, in depression, decreased BDNF and 5-HT levels mediated by increased thyroid peroxidase antibodies (TPOAbs) have been reported in mouse prefrontal cortex, a finding possibly related to subsequent postpartum depression (PPD) [25].

Thyroid hormones influence gamma aminobutyric acid-A (GABA-A) receptor binding and function in cerebral neurons. Studies in mice indicate that thyroid hormones have effects on multiple components of the GABA system, such as the degradation or synthesis of GABA, the expression and function of GABA-A receptor, and GABA release and reuptake. In the adult brain, hypothyroidism increases GABA levels, but hyperthyroidism does not always have the opposite effect. In vitro evidence suggests that the presence of thyroid hormones in the synapse may prolong the action of GABA following its release. Such evidence supports the hypothesis of reciprocal regulation in vertebrates by the thyroid and GABA systems [26]. T3 and T4 might also have non-genomic mechanisms of action [27]. In cultures of cortical and hippocampal neurons, they seem to modulate inhibitory neurotransmission directly, acting as negative allosteric modulators at the GABA-A receptor [28].

Overt hypothyroidism and SCH are relatively common comorbid disorders accompanying MDD, especially in females [29]. The comorbidity is possibly responsible for treatment resistance, higher severity of MDD, psychotic phenomenology, and somatic symptoms [6]. In patients with MDD, thyroid function test results vary within the reference range [15, 30], and mild thyroid dysfunction does not affect the therapeutic effects, at least of tricyclic antidepressants [31]. Patients with MDD may manifest activation of the immune system, leading to autoimmune thyroiditis [32], and subsequently to thyroid dysfunction. It is well documented that patients with hypothyroidism and MDD, in particular treatment-resistant patients or/and patients with atypical symptoms, may benefit from thyroid hormone replacement therapy [6]. Conversely, affective as well as wider neuropsychiatric symptomatology is common in overt hypothyroidism [33], and it has been hypothesized that subclinical autoimmune thyroid dysfunction could possibly have a causal role in MDD [13].

The hypothesis that MDD may be part of the etiopathogenesis of thyroid dysfunction proposes that thyroid function changes in patients with depression are determined by the severity of symptoms, the duration of the disease, and remission-favoring factors [5]. Furthermore, changes in regional gray matter volumes are correlated to altered variants of thyroid hormone genes and depression. Specifically, left occipital gray matter volume in patients with MDD is influenced by altered variants of thyroid hormone genes and their transporters (single nucleotide polymorphisms—SNPs, *rs496549* and *rs479640*) [34]. TSH level abnormalities possibly emerging early during MDD could also be correlated with neuronal dysfunction in prefrontal white matter, although it is not yet clear if they are actually related to the neuropathology of this psychiatric disorder [35].

A reverse hypothesis, relevant to the pathogenetic mechanism of MDD, suggests that it could be attributed to a state of local cerebral hypothyroidism with normal peripheral thyroid hormone concentrations. This hypothesis is expressed by many researchers with the term "brain hypothyroidism" and is mainly based on the observation of type II deiodinase inhibition in the brain and of impaired T4 transport across the blood–brain barrier in depressed patients. Furthermore, there is evidence concerning functional alterations such as loss of nocturnal thyrotropin (TSH) rise, blunted TSH response to thyrotropin-releasing hormone (TRH) stimulation, and slight elevation of serum thyroxine (T4) [36]. Clinically, MDD is more frequent following thyroidectomy for thyroid cancer [37].

Increased suicide risk, suicidal intent, violent suicide attempts, and higher lethality have all been associated with a lower TSH response to TRH, mostly in depressed women. It has indeed been suggested that TSH, antithyroglobulin (TgAb), and TPOAb levels could be used as biomarkers of suicidality in MDD [38]. Furthermore, TSH response to TRH (delta max TSH) has been correlated with cerebrospinal fluid (CSF) homovanillic acid (HVA) in suicide attempters [39]. The role of thyroid dysfunction in suicidal behavior, however, remains obscure.

Thyroid axis dysregulation in depression

Depressive symptomatology is not significantly related to HPT axis activity [40], but changes in its components and predisposition to autoimmune thyroiditis have been correlated with MDD [41, 42]. These changes concern baseline TSH, loss of nocturnal TSH rise, blunted TSH response to TRH stimulation (measured by delta max TSH representing maximal TSH response to 400 μg TRH), and a small elevation of serum thyroxine (difference of T4 level between 09.00 h and 13.00 h) [41].

The "brain hypothyroidism" hypothesis [43] is based on the idea that impaired T4 transportation across the blood–brain barrier and brain type II deiodinase inhibition in cerebral tissue may represent a state of regional brain hypothyroidism related to depression but in a euthyroid condition. In this context, blunted TSH response to TRH stimulation in MDD could be attributed in reduced intracerebral serotonin (5-HT) levels [41].

Using the dexamethasone suppression test (DST) in depression, patients who fail to suppress cortisol after the DST challenge exhibit significantly lower grade

suppression of basal TSH values [44]. In patients with depression, blunted TSH response seems to remain consistent even after DST positivity returns to the normal range [45]. Additionally, research using cultured hypothalamic tissue demonstrated a paradoxical increase of TRH production after glucocorticoid stimulation. An inhibitory feedback loop to the thyroid axis could be active in patients with MDD. In these patients, a probable glucocorticoid activation of the TRH neuron leading to downregulation of thyrotropic cell TRH receptors in the anterior pituitary could result in a weakened TSH response to exogenous TRH [46].

The DeltaDeltaTSH (ΔΔTSH) test is an improved method to detect HPT axis dysregulation in MDD [23]. It measures the difference in TSH response to TRH tests on the same day between 23:00 h and 08:00 h. Following 2 weeks of antidepressant treatment, alterations in the HPT axis were associated with treatment resistance. Indeed, clinical remission followed the chronobiological restoration of HPT axis activity [23]. Nevertheless, measuring thyroid axis hormones at various times during the day is not thought to be reliable in patients with MDD [47].

Regarding age and gender, in patients with depression, there were no significant differences between basal TSH and thyroid hormones, but free thyroxine (FT4) concentrations seemed to be significantly related with severity of depression. It has been proposed that lower secretion of TSH and HPT-axis dysregulation observed especially during the acute phase of MDD reflects a neuroendocrine-immune response to a non-thyroidal pathophysiological mechanism [44].

Pretreatment with transcranial magnetic stimulation (TMS) lowers TSH levels, leading to improved therapeutic efficacy [46]. Data from animal studies show that agents, such as resveratrol, acting on both the HPT axis and the Wnt/beta-catenin pathway are known to exert antidepressant-like effects [48]. An increase in T4 and a decrease in TSH and T3 serum levels are observed in methamphetamine abusers, who present with high rates of depression after abstinence [49]. Severe hypoxia in patients with the obstructive sleep apnea–hypopnea syndrome results in a decrease in serum FT3 and FT4 levels, and this has recently been associated with depressive-like symptomatology in this group of patients [50]. Depressive symptomatology in patients (especially males) with coronary artery disease appears to be associated with changes in thyroid axis function [16]. Moreover, electroconvulsive therapy (ECT), an effective treatment for severe MDD, is known to reverse complicated hormonal dysregulations, thus highlighting a dual effect both in MDD and in endocrine illness [51].

SCH

SCH is defined biochemically as an increased serum thyrotropin concentration with normal serum free T4 concentration in asymptomatic patients, or higher TSH than FT3 and FT4 levels. SCH, which is also known as mild or borderline thyroid failure, or grade II hypothyroidism [52], is the most common thyroid dysfunction in the general population [53]. The relationship between SCH and depression is to date largely unclear [54], but it has been associated with increased risk of MDD in those over 50 years old [55]. SCH possibly represents a risk factor for MDD [56]. Clinically, a significant difference between patients with MDD and SCH comorbidity and patients with MDD without SCH is that the first tend to present with comorbid panic disorder and a poorer response to antidepressant therapy [57]. Depressive-like symptomatology secondary to SCH could be attributed to reduced hippocampal triiodothyronine (T3) preceding the reduction of serum thyroid hormone levels [48]. Current evidence, however, supports the hypothesis that depression in SCH is not associated with it. It presents either an independent psychiatric diagnosis or a response to the newly diagnosed thyroid disease and its sequelae [29, 58]. Moreover, variations in thyroid function within the normal thyroid function range seem to be related to the neurocognitive deficits associated with depression but not with the emergence of the disorder per se [30]. SCH has also been associated with treatment-resistant depression (TRD). Evidence indicates that patients with TRD express higher rates of SCH and higher serum TSH levels [2, 59]. Methodological errors have led previous studies to report inconsistent or controversial results as to whether SCH increases the relative risk of MDD. More recent evidence, based on multivariate logistic regression analysis, has revealed high serum TPO antibody levels, SCH, and Graves' eye syndrome as risk factors for MDD [60].

Large and well-planned studies have failed to find a relation between MDD and SCH [33, 55, 61]. An extensive study, even though not concerning MDD but incident depression [61] ($n = 92,206$) without known thyroid disease or depression, revealed that the prevalence of incidental depression occurred in 8% of the participants, while no association between presence of SCH and development of depression during a mean follow-up of 2 years was found. One more significant conclusion of a sub-analysis in a large euthyroid group ($n = 87,822$) of the same study was that there was no association between increased risk of incidental depression and thyroid hormone levels [61].

A relatively recent meta-analysis including over 36,000 participants concluded that patients with autoimmune thyroiditis are more prone to develop depressive symptomatology [62]. A second meta-analysis failed to replicate these results; however, age of participants seemed to be an

important confounder, such that MDD and SCH were related only in the younger (< 60 years old) subjects [58].

Thyroid hormones as add-on therapy in treatment-resistant depression

Clinical practice guidelines recommend that SCH should be treated at TSH levels over 10 mIU/L [63]. However, antidepressant therapy augmentation with thyroid hormones remains controversial, with several studies reaching conflicting conclusions [64].

The possible mechanism of HPT axis-based antidepressant treatment is a field of research based on either the peripheral modulation of endocrine systems or the central effects of hormones on non-endocrine cerebral circuitry [3]. Metabolic dysfunction of cerebral neurons has been hypothesized as a vulnerability coefficient for MDD. In this context, effects of thyroid hormones on cellular metabolism could contribute to the recession of MDD [65]. Nevertheless, although hypothyroidism is associated with MDD's severity and its psychopathologic features, it seems that it is not linked strongly to antidepressant treatment response [66]. The effectiveness of thyroid hormone adjunctive therapy to other categories of antidepressant agents other than TCAs and SSRIs is to date not extensively documented.

T3 stimulates neurogenesis and cellular metabolism. T3 monotherapy or its combination with fluoxetine possibly modulates gene transcription, resulting in changes in mRNA coding for 5-HT1A and 5-HT1B receptors [67]. It is also thought to directly act as a neurotransmitter. Type 1 deodinase (DIO1) is one of the enzymes assisting the conversion of T4 to T3. Genetic polymorphisms in *DIO1* may help in discriminating potential responders to T3 augmentation [68].

Add-on T3 administration at doses smaller than the endogenous 24-h production is reported to be effective, but it increases the risk of clinical hyperthyroidism [6, 69]. T3 augmentation responders, who are within the euthyroid range, tend to have (prior to any antidepressant treatment) higher levels of T4 and free thyroxine index (FTI) and lower levels of TSH compared to non-responders [70]. T3 adjuvant personalized therapeutic strategies could, therefore, be effective, particularly in patients with depression and elevated T4 and serum FTI levels before the onset of antidepressant therapy. Adding T3 to treatment as usual in MDD seems to have some effect in TRD [69, 71]. Moreover, T3 seems to be superior to T4 in TRD [72].

T4 has also been proposed as an adjunctive therapy in depressed patients with SCH and/or autoimmune thyroiditis, and as substitution therapy in patients who take lithium [73]. The current evidence is, however, that T4 add-on in TRD might be less effective than T3 [69]. Enhancement of antidepressant therapy with T4 in patients with SCH remains largely undocumented [1].

It has been postulated that both T3 and T4 mediate serotoninergic effects, most probably through desensitization of the 5-HT1A autoreceptor [22]. T3 plus T4 combination therapy is more effective than T4 monotherapy for the treatment of persistent hypothyroidism, found in approximately 5–10% of patients. This effect is mainly attributed to two polymorphisms in *DIO2* and monocarboxylate transporter 10 (*MCT10*) genes [74].

Interestingly, a recent meta-analysis found that there is not sufficient evidence to support the enhancement of antidepressant therapy with adjunctive thyroid hormones in TRD [64]. Moreover, there was no improvement in maternal depressive symptomatology with the addition of prenatal T4 replacement therapy [75].

Evidence of the clinical effectiveness of add-on thyroid hormone in depression therefore leads to the possibility that SCH may not constitute a direct cause of unipolar depression [76].

The effect of antidepressants on thyroid function

Various antidepressants have different effects on serum thyroid hormone levels in patients with MDD, this differential result possibly being attributable to the specific mechanism of action of each antidepressant [77]. It has been reported that thyroid dysregulation is frequent in patients with bipolar disorder regardless of which pharmacological agent is used in their treatment [78], and that tricyclic antidepressants (e.g., desipramine) "normalize" thyroid axis dysregulation often present in depression [79]. Escitalopram may cause transient SCH [80]. An association between decline in T3 levels and response to fluoxetine has also been reported, but fluoxetine has not been significantly related to thyroid function dysregulation in perimenopausal women with depression [81]. Regarding the effect of SSRIs on thyroid function, a recent meta-analysis providing preliminary evidence concluded that it possibly concerned an inhibitory mechanism [82].

Moreover, there is not to date sufficient evidence to support an improvement of thyroid function following effective treatment with antidepressants. FT3 levels have been shown to be higher in responders to antidepressant medication compared to poor responders [15]. This was, however, not true for FT4, TSH, and TBII levels in the same patients [15]. Furthermore, there is a recent report linking venlafaxine treatment outcome with *NR3C2* gene polymorphisms and increased TSH concentrations [83], while BDNF serum levels, known to decrease during depression [84, 85], have been shown to climb back to normal levels in the brain with

effective antidepressant (fluoxetine and agomelatine) treatment [85]. Hence, the connection between BDNF and TSH levels in patients with MDD seems a promising research field.

Conclusions

SCH is commonly comorbid with MDD, especially in females. In MDD, SCH affects severity, resistance to treatment, psychotic phenomenology, and somatic symptoms. On the other hand, depression is known to affect thyroid function, mediating mild elevations in thyroid hormone levels, blunting of the TSH response to TRH stimulation, and frequent absence of the nocturnal surge of TSH. However, thyroid function in patients with MDD fluctuates within the reference range, and mild thyroid dysfunction does not seem to influence the therapeutic effects of antidepressant agents. MDD is likely to induce activation of autoimmune processes, leading to a predisposition to autoimmune thyroiditis and, subsequently, to thyroid dysfunction. A reverse hypothesis proposes that a state of local cerebral hypothyroidism with normal peripheral thyroid hormone concentrations ("brain hypothyroidism") could be one cause of MDD, among others. Moreover, variations of the *DIO1* gene might represent a possible link between thyroid dysfunction and MDD.

MDD is often comorbid with autoimmune thyroiditis, indicating either that MDD may be an autoimmune disorder or that it may cause modifications to the immune system. Furthermore, microsomal antibodies are related to atypical depressive features in late pregnancy-postpartum depression. High levels of peroxidase antibodies and lower levels of T4 have been associated with the development of depression in women in the premenopausal period. Decreased levels of BDNF and 5-HT due to elevated TPOAbs might be related to postpartum depression, but the relevant evidence is sparse and, additionally, the relationship between BDNF levels and TSH in patients with MDD is also not yet clear.

Although SCH is associated with the severity of MDD and its psychopathology, it does not seem to be linked to antidepressant treatment response. Various antidepressants have different effects on serum thyroid hormone levels in patients with MDD, and this differential result is likely to be attributable to the specific mechanism of action of each agent. While evidence supporting antidepressant treatment augmentation with add-on thyroid hormones for treatment-resistant unipolar depression is insufficient, it is possibly beneficial for improving the cognitive deficits associated with MDD. L-thyroxine replacement therapy seems to be effective in addressing depressive symptoms in SCH, but augmentation of antidepressant therapy with L-thyroxine remains controversial. According to the current evidence, levothyroxine use among depressed patients with SCH should be individualized.

The relationship between SCH and MDD remains thus far controversial. Lifetime rates of depression are significantly higher in those who meet the criteria for SCH, and SCH may cause a decrease in the threshold for the emergence of MDD symptoms. Improvement of clinical or subclinical thyroid dysfunction following successful antidepressant therapy needs further study with large well-designed longitudinal studies.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Grigorios N. Karakatsoulis, Calypso Mitkani, and Prof. Konstantinos N. Fountoulakis. The first draft of the manuscript was written by Grigorios N. Karakatsoulis, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Code availability Not applicable.

Declarations

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Consent to participate Not applicable (the research did not involve human participants).

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Ethical statement This article does not contain studies with patients or animals performed by the authors.

Consent for publication All authors read and approved the manuscript for publication.

Conflict of interest The authors declare no competing interests.

References

1. Loh HH, Lim LL, Yee A et al (2019) Association between subclinical hypothyroidism and depression: an updated systematic review and meta-analysis. BMC Psychiatry 19:12. https://doi.org/10.1186/s12888-018-2006-2
2. Cohen BM, Sommer BR, Vuckovic A (2018) Antidepressant-resistant depression in patients with comorbid subclinical hypothyroidism or high-normal TSH levels. Am J Psychiatry 175:598–604. https://doi.org/10.1176/appi.ajp.2017.17080949
3. Dwyer JB, Aftab A, Radhakrishnan R et al (2020) Hormonal treatments for major depressive disorder: state of the art. Am J Psychiatry 177(8):686–705. https://doi.org/10.1176/appi.ajp.2020.19080848

4. Le Donne M, Mento C, Settineri S et al (2017) Postpartum mood disorders and thyroid autoimmunity. Front Endocrinol (Lausanne) 8:91. https://doi.org/10.3389/fendo.2017.00091
5. Hage MP, Azar ST (2012) The link between thyroid function and depression. J Thyroid Res 2012:590648. https://doi.org/10.1155/2012/590648
6. Trifu S, Popescu A, Dragoi AM et al (2020) Thyroid hormones as a third line of augmentation medication in treatment-resistant depression. Acta Endocrinologica (Bucharest) 16:256–261. https://doi.org/10.4183/aeb.2020.256
7. Elenkov IJ, Chrousos GP (2002) Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. Ann N Y Acad Sci 966:290–303. https://doi.org/10.1111/j.1749-6632.2002.tb04229.x
8. McLachlan SM, Rapoport B (2013) Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. Thyroid 23:14–24. https://doi.org/10.1089/thy.2012.0374
9. Slim M, Rico-Villademoros F, Calandre EP (2018) Psychiatric comorbidity in children and adults with gluten-related disorders: a narrative review. Nutrients 10:875. https://doi.org/10.3390/nu10070875
10. Ch'ng CL, Jones MK, Kingham JG (2007) Celiac disease and autoimmune thyroid disease. Clin Med Res 5:184–192. https://doi.org/10.3121/cmr.2007.738
11. Fjaellegaard K, Kvetny J, Allerup PN et al (2015) Well-being and depression in individuals with subclinical hypothyroidism and thyroid autoimmunity - a general population study. Nord J Psychiatry 69:73–78. https://doi.org/10.3109/08039488.2014.929741
12. Fam J, Rush AJ, Burt T et al (2015) Thyroid autoimmune antibodies and major depressive disorder in women. Annals, Academy of Medicine, Singapore 44:284–289
13. Fountoulakis KN, Iacovides A, Grammaticos P et al (2004) Thyroid function in clinical subtypes of major depression: an exploratory study. BMC Psychiatry 4:6. https://doi.org/10.1186/1471-244X-4-6
14. Kirkegaard C, Faber J, Hummer L et al (1979) Increased levels of TRH in cerebrospinal fluid from patients with endogenous depression. Psychoneuroendocrinology 4:227–235. https://doi.org/10.1016/0306-4530(79)90006-4
15. Fountoulakis KN, Kantartzis S, Siamouli M et al (2006) Peripheral thyroid dysfunction in depression. World J Biol Psychiatry 7:131–137. https://doi.org/10.1080/15622970500474739
16. Bunevicius AK, Pop L, Victor J et al (2009) Screening for antenatal depression with the Edinburgh Depression Scale. J Psychosom Obstet Gynecol 30:238–243. https://doi.org/10.3109/01674820903230708
17. Wesseloo R, Kamperman AM, Bergink V et al (2018) Thyroid peroxidase antibodies during early gestation and the subsequent risk of first-onset postpartum depression: a prospective cohort study. J Affect Disord 225:399–403. https://doi.org/10.1016/j.jad.2017.08.058
18. Keely EJ (2011) Postpartum thyroiditis: an autoimmune thyroid disorder which predicts future thyroid health. Obstetric medicine 4:7–11. https://doi.org/10.1258/om.2010.100041
19. Smith A, Eccles-Smith J, D'Emden M et al (2017) Thyroid disorders in pregnancy and postpartum. Aust Prescr 40:214–219. https://doi.org/10.18773/austprescr.2017.075
20. Plaza A, Garcia-Esteve L, Ascaso C et al (2010) Childhood sexual abuse and hypothalamus-pituitary-thyroid axis in postpartum major depression. J Affect Disord 122:159–163. https://doi.org/10.1016/j.jad.2009.07.021
21. Baumgartner A, Gräf KJ, Kürten I et al (1990) Thyrotropin (TSH) and thyroid hormone concentrations during partial sleep deprivation in patients with major depressive disorder. J Psychiatr Res 24:281–292. https://doi.org/10.1016/0022-3956(90)90001-7
22. Bauer M, Heinz A, Whybrow P (2002) Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. Mol Psychiatry 7:140–156. https://doi.org/10.1038/sj.mp.4000963
23. Duval F, Mokrani MC, Erb A et al (2015) Chronobiological hypothalamic-pituitary-thyroid axis status and antidepressant outcome in major depression. Psychoneuroendocrinology 59:71–80. https://doi.org/10.1016/j.psyneuen.2015.05.005
24. Vaidya VC, Elena Pei Q et al (2001) Influence of thyroid hormone on 5-HT1A and 5-HT2A receptor-mediated regulation of hippocampal BDNF mRNA expression. Neuropharmacology 40:48–56. https://doi.org/10.1016/S0028-3908(00)00094-0
25. Zhou Y, Wang X, Zhao Y et al (2016) Elevated thyroid peroxidase antibody increases risk of post-partum depression by decreasing prefrontal cortex BDNF and 5-HT levels in mice. Front Cell Neurosci 10:307. https://doi.org/10.3389/fncel.2016.00307
26. Wiens SC, Trudeau VL (2006) Thyroid hormone and gamma-aminobutyric acid (GABA) interactions in neuroendocrine systems. Comp Biochem Physiol A Mol Integr Physiol 144:332–344. https://doi.org/10.1016/j.cbpa.2006.01.033
27. Giammanco MD, Liegro CM, Schiera G et al (2020) Genomic and non-genomic mechanisms of action of thyroid hormones and their catabolite 3,5-diiodo-l-thyronine in mammals. Int J Mol Sci 21:4140. https://doi.org/10.3390/ijms21114140
28. Puia G, Losi G (2011) Thyroid hormones modulate GABA(A) receptor-mediated currents in hippocampal neurons. Neuropharmacology 60:1254–1261. https://doi.org/10.1016/j.neuropharm.2010.12.013
29. Samuels MH (2018) Subclinical hypothyroidism and depression: is there a link? J Clin Endocrinol Metab 103:2061–2064. https://doi.org/10.1210/jc.2018-00276%J
30. Samuels Mary, Kolobova Irina et al (2016) Effect of thyroid function variations within the laboratory reference range on health status, mood, and cognition in levothyroxine-treated subjects. Thyroid 26:1173–1184. https://doi.org/10.1089/thy.2016.0141
31. Sauvage MF, Marquet P, Rousseau A et al (1998) Relationship between psychotropic drugs and thyroid function: a review. Toxicol Appl Pharmacol 149:127–135. https://doi.org/10.1006/taap.1998.8367
32. Jucevičiūtė N, ŽilaitienėAniulienė BR et al (2019) The link between thyroid autoimmunity, depression and bipolar disorder. Open Med (Warsaw, Poland) 14:52–58. https://doi.org/10.1515/med-2019-0008
33. Samuels MH (2014) Psychiatric and cognitive manifestations of hypothyroidism. Curr Opin Endocrinol Diabetes Obes 21:377–383. https://doi.org/10.1097/MED.0000000000000089
34. Dixson L, Ridler K, Nichols TE et al (2011) Thyroid hormone transporter genes and grey matter changes in patients with major depressive disorder and healthy controls. Psychoneuroendocrinology 36:929–934. https://doi.org/10.1016/j.psyneuen.2010.12.002
35. Jia Y, Zhong S, Wang Y et al (2015) The correlation between biochemical abnormalities in frontal white matter, hippocampus and serum thyroid hormone levels in first-episode patients with major depressive disorder. J Affect Disord 180:162–169. https://doi.org/10.1016/j.jad.2015.04.005
36. Bauer M, Goetz T, Glenn T et al (2008) The thyroid-brain interaction in thyroid disorders and mood disorders. J Neuroendocrinol 20:1101–1114. https://doi.org/10.1111/j.1365-2826.2008.01774.x
37. Choi KW, Kim Y, Fava M et al (2019) Increased morbidity of major depressive disorder after thyroidectomy: a nationwide population-based study in South Korea. Thyroid 29:1713–1722. https://doi.org/10.1089/thy.2019.0091
38. Shen Y, Wu F, Zhou Y et al (2019) Association of thyroid dysfunction with suicide attempts in first-episode and drug

naïve patients with major depressive disorder. J Affect Disord 259:180–185. https://doi.org/10.1016/j.jad.2019.08.067
39. Jokinen J, SamuelssonNordström MA-L et al (2008) HPT axis, CSF monoamine metabolites, suicide intent and depression severity in male suicide attempters. J Affect Disord 111:119–124. https://doi.org/10.1016/j.jad.2008.02.001
40. Rubin RT, Poland RE, Lesser IM et al (1987) Neuroendocrine aspects of primary endogenous depression—IV. Pituitary-thyroid axis activity in patients and matched control subjects. Psychoneuroendocrinology 12:333–347. https://doi.org/10.1016/0306-4530(87)90062-X
41. Foltyn W, Nowakowska-Zajdel E, Danikiewicz A et al (2002) Hypothalamic-pituitary-thyroid axis in depression. Psychiatr Pol 36:281–292
42. Fischer S, Ehlert U (2018) Hypothalamic-pituitary-thyroid (HPT) axis functioning in anxiety disorders A systematic review. Depress Anxiety 35:98–110. https://doi.org/10.1002/da.22692
43. Talaei A, RafeeRafei NF et al (2017) TSH cut off point based on depression in hypothyroid patients. BMC Psychiatry 17:327. https://doi.org/10.1186/s12888-017-1478-9
44. Maes M, D'HondtBlockx PP et al (1994) A further investigation of basal HPT axis function in unipolar depression: effects of diagnosis, hospitalization, and dexamethasone administration. Psychiatry Res 51:185–201. https://doi.org/10.1016/0165-1781(94)90038-8
45. Sarandöl A, Taneli B, Sivrioğlu Y (2003) Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axis findings in depressive disorder. Turk Psikiyatri Derg 14:116–124
46. Kito S, Hasegawa T, Fujita K et al (2010) Changes in hypothalamic-pituitary-thyroid axis following successful treatment with low-frequency right prefrontal transcranial magnetic stimulation in treatment-resistant depression. Psychiatry Res 175:74–77. https://doi.org/10.1016/j.psychres.2008.10.002
47. Sullivan PF, Wilson DA, Mulder RT et al (1997) The hypothalamic-pituitary-thyroid axis in major depression. Acta Psychiatr Scand 95:370–378. https://doi.org/10.1111/j.1600-0447.1997.tb09648.x
48. Ge J-F, Xu Y-Y, Qin G et al (2016) Resveratrol ameliorates the anxiety- and depression-like behavior of subclinical hypothyroidism rat: possible involvement of the HPT axis, HPA axis, and Wnt/β-catenin pathway. Front Endocrinol 7:44–44. https://doi.org/10.3389/fendo.2016.00044
49. Li SX, Yan SY, Bao YP et al (2013) Depression and alterations in hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axis function in male abstinent methamphetamine abusers. Hum Psychopharmacol 28:477–483. https://doi.org/10.1002/hup.2335
50. Liang Y, Xu JH, Li WY et al (2019) The effect of hypothalamic-pituitary-thyroid axis hormone levels and depression in obstructive sleep apnea-hypopnea syndrome. Zhonghua Jie He He Hu Xi Za Zhi 42:591–595. https://doi.org/10.3760/cma.j.issn.1001-0939.2019.08.006
51. Eslami MH, Afkhami-Ardekani M, Akbari M (2008) Effects of electroconvulsive therapy on thyroid function parameters in depressed patients. SSU Journal 16:312–312
52. Wiersinga WM (2015) Guidance in subclinical hyperthyroidism and subclinical hypothyroidism: are we making progress? European thyroid journal 4:143–148. https://doi.org/10.1159/000438909
53. Polat Canbolat I, Belen E, Bayyigit A et al (2017) Evaluation of daily blood pressure alteration in subclinical hypothyroidism. Acta Cardiologica Sinica 33:489–494. https://doi.org/10.6515/acs20170220b
54. Baumgartner C, Blum MR, Rodondi N (2014) Subclinical hypothyroidism: summary of evidence in 2014. Swiss Med Wkly 144:w14058. https://doi.org/10.4414/smw.2014.14058
55. Tang R, Wang J, Yang L et al (2019) Subclinical hypothyroidism and depression: a systematic review and meta-analysis. Front Endocrinol 10:340–340. https://doi.org/10.3389/fendo.2019.00340
56. Haggerty JJ Jr, Stern RA, Mason GA et al (1993) Subclinical hypothyroidism: a modifiable risk factor for depression? Am J Psychiatry 150:508–510. https://doi.org/10.1176/ajp.150.3.508
57. Joffe RT, Levitt AJ (1992) Major depression and subclinical (grade 2) hypothyroidism. Psychoneuroendocrinology 17:215–221. https://doi.org/10.1016/0306-4530(92)90060-K
58. Zhao T, Chen BM, Zhao XM et al (2018) Subclinical hypothyroidism and depression: a meta-analysis. Transl Psychiatry 8:239. https://doi.org/10.1038/s41398-018-0283-7
59. Hickie I, Bennett B, Mitchell P et al (1996) Clinical and subclinical hypothyroidism in patients with chronic and treatment-resistant depression. Aust N Z J Psychiatry 30:246–252. https://doi.org/10.3109/00048679609076101
60. Yu J, Tian A-J, Yuan X et al (2016) Subclinical hypothyroidism after 131I-treatment of Graves' disease: a risk factor for depression? PLoS ONE 11:e0154846–e0154846. https://doi.org/10.1371/journal.pone.0154846
61. Kim JS, Zhang Y, Chang Y et al (2018) Subclinical hypothyroidism and incident depression in young and middle-age adults. J Clin Endocrinol Metab 103:1827–1833. https://doi.org/10.1210/jc.2017-01247
62. Siegmann E-M, MüllerLuecke HHOC et al (2018) Association of depression and anxiety disorders with autoimmune thyroiditis: a systematic review and meta-analysis. JAMA Psychiat 75:577–584. https://doi.org/10.1001/jamapsychiatry.2018.0190
63. Calissendorff J, Falhammar H (2020) To treat or not to treat subclinical hypothyroidism, what is the evidence? Medicina (Kaunas) 56:40. https://doi.org/10.3390/medicina56010040
64. Lorentzen R, Kjær JN, Østergaard SD et al (2020) Thyroid hormone treatment in the management of treatment-resistant unipolar depression: a systematic review and meta-analysis. Acta Psychiatr Scand 141:316–326. https://doi.org/10.1111/acps.13154
65. Głombik K, Detka J, Kurek A, et al (2020) Impaired brain energy metabolism: involvement in depression and hypothyroidism. Front Neurosci 14:586939. https://doi.org/10.3389/fnins.2020.586939
66. Fugger G, Dold M, Bartova L et al (2018) Comorbid thyroid disease in patients with major depressive disorder - results from the European Group for the Study of Resistant Depression (GSRD). Eur Neuropsychopharmacol 28:752–760. https://doi.org/10.1016/j.euroneuro.2018.03.011
67. Lifschytz T, Gur E, Lerer B et al (2004) Effects of triiodothyronine and fluoxetine on 5-HT1A and 5-HT1B autoreceptor activity in rat brain: regional differences. J Neurosci Methods 140:133–139. https://doi.org/10.1016/j.jneumeth.2004.03.028
68. Cooper-Kazaz RV, der Deure W, Medici M et al (2009) Preliminary evidence that a functional polymorphism in type 1 deiodinase is associated with enhanced potentiation of the antidepressant effect of sertraline by triiodothyronine. J Affect Disord 116:113–116. https://doi.org/10.1016/j.jad.2008.10.019
69. Touma KTB, Zoucha AM, Scarff JR (2017) Liothyronine for depression: a review and guidance for safety monitoring. Innovations in clinical neuroscience 14:24–29
70. Sokolov ST, Levitt AJ, Joffe RT (1997) Thyroid hormone levels before unsuccessful antidepressant therapy are associated with later response to T3 augmentation. Psychiatry Res 69:203–206. https://doi.org/10.1016/s0165-1781(96)02941-1
71. Voineskos D, Daskalakis ZJ, Blumberger DM (2020) Management of treatment-resistant depression: challenges and strategies.

Neuropsychiatr Dis Treat 16:221–234. https://doi.org/10.2147/NDT.S198774
72. Cooper R, Lerer B (2010) The use of thyroid hormones in the treatment of depression. Harefuah 149(8):529–534, 550, 549
73. Bschor T, Bauer M (2013) Side effects and risk profile of lithium: critical assessment of a systematic review and meta-analysis. Nervenarzt 84:860–863. https://doi.org/10.1007/s00115-013-3766-z
74. Wiersinga WM (2019) T4 + T3 combination therapy: any progress? Endocrine 66:70–78. https://doi.org/10.1007/s12020-019-02052-2
75. Costantine MM, Smith K, Thom EA et al (2020) Effect of thyroxine therapy on depressive symptoms among women with subclinical hypothyroidism. Obstet Gynecol 135:812–820. https://doi.org/10.1097/aog.0000000000003724
76. Tost M, Monreal JA, Armario A et al (2020) Targeting hormones for improving cognition in major mood disorders and schizophrenia: thyroid hormones and prolactin. Clin Drug Investig 40:1–14. https://doi.org/10.1007/s40261-019-00854-w
77. Eker SS, Akkaya C, Sarandol A et al (2008) Effects of various antidepressants on serum thyroid hormone levels in patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 32:955–961. https://doi.org/10.1016/j.pnpbp.2007.12.029
78. Lambert CG, Mazurie AJ, Lauve NR et al (2016) Hypothyroidism risk compared among nine common bipolar disorder therapies in a large US cohort. Bipolar Disord 18:247–260. https://doi.org/10.1111/bdi.12391
79. Brady KT, Anton RF (1989) The thyroid axis and desipramine treatment in depression. Biol Psychiatry 25:703–709. https://doi.org/10.1016/0006-3223(89)90241-2
80. Bazigh I, Dharmapuri S, Cosme RM (2019) Transient subclinical hypothyroidism and acute suicidal ideation following treatment with escitalopram. Cureus 11:e5144–e5144. https://doi.org/10.7759/cureus.5144
81. Cortes EM, Llanes-González L, Aguilar-Faisal JL, Asbun-Bojalil J et al (2017) Is metabolic dysregulation associated with antidepressant response in depressed women in climacteric treated with individualized homeopathic medicines or fluoxetine? The HOMDEP-MENOP study. Homeopathy 106:3–10. https://doi.org/10.1016/j.homp.2016.11.002
82. Caye A, Pilz LK, Maia AL et al (2020) The impact of selective serotonin reuptake inhibitors on the thyroid function among patients with major depressive disorder: a systematic review and meta-analysis. Eur Neuropsychopharmacol 33:139–145. https://doi.org/10.1016/j.euroneuro.2020.01.011
83. Yuan F, Yuan R, Ren D et al (2020) A novel NR3C2 polymorphism and the increased thyroid-stimulating hormone concentration are associated with venlafaxine treatment outcome in Chinese Han MDD patients. Psychiatry Res 284:112690. https://doi.org/10.1016/j.psychres.2019.112690
84. Baek JH, Kang ES, Fava M et al (2014) Thyroid stimulating hormone and serum, plasma, and platelet brain-derived neurotrophic factor during a 3-month follow-up in patients with major depressive disorder. J Affect Disord 169:112–117. https://doi.org/10.1016/j.jad.2014.08.009
85. Prova EM, Das Z, Nishuty R, Lovely N et al (2020) Reduced serum BDNF levels are associated with the increased risk for developing MDD: a case–control study with or without antidepressant therapy. BMC Res Notes 13:83. https://doi.org/10.1186/s13104-020-04952-3

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