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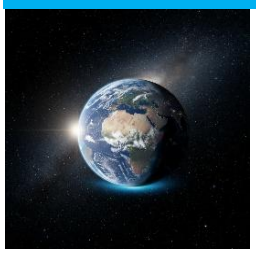

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Subclinical Hypothyroidism as an overlooked contributor to depression and mood disorders

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Abstract

Introduction and Purpose: Thyroid hormones regulate metabolism and brain function, including mood and cognition. Subclinical hypothyroidism (SCH), defined by elevated TSH with normal fT3 and fT4, often goes unnoticed due to vague symptoms. This review

investigates the possible link between SCH and mood disorders, particularly depression, and outlines potential neurobiological mechanisms.

Materials and Methods: A narrative review of the literature was conducted using clinical trials, meta-analyses, and epidemiological data. The focus was on studies assessing the psychiatric impact of SCH and the effects of levothyroxine (L-T4) treatment on depressive symptoms in these patients.

State of Knowledge: Evidence suggests that individuals with SCH—especially women and older adults—may experience increased depressive symptoms, fatigue, and cognitive impairment. Proposed mechanisms include disrupted serotonin and dopamine pathways, reduced neurotrophic factors, and HPT axis dysregulation. While some studies report benefits from L-T4 therapy, others find no significant effect, indicating the need for personalized treatment decisions.

Conclusion: SCH may contribute to mood disorders, though a causal relationship remains unconfirmed. Thyroid function assessment should be considered in patients with unexplained depression. Personalized therapy and interdisciplinary collaboration are key, and more large-scale research is needed.

Keywords: “Subclinical hypothyroidism”, „depression”, „mood disorders”, “thyroid hormones”, “neuropsychiatry”, “levothyroxine therapy”.

Introduction

Thyroid hormones play a key role in the regulation of metabolism and the function of many body systems, including the central nervous system (CNS). Their influence on neurotransmission, neurogenesis, and synaptic plasticity means that disorders of their secretion can have significant psychological and neurological consequences. In recent years, there has been increasing attention to the potential link between thyroid dysfunction and mood disorders, including depression and anxiety disorders. (1)

Hypothyroidism, in both overt and subclinical forms, is a condition with a complex pathogenesis, involving autoimmune mechanisms, iodine deficiency, or iatrogenic damage to the thyroid gland. Subclinical hypothyroidism (SNT), defined as elevated levels of thyrotropic hormone (TSH) with normal levels of free thyroid hormones (fT3 and fT4), is of particular interest because it can be sparsely symptomatic or manifest with nonspecific symptoms such as fatigue, weakness, difficulty concentrating, or mood swings. Many of these symptoms overlap with the symptomatology of depression, raising questions about a potential cause-and-effect relationship between SNT and psychiatric disorders. (2)

The purpose of this review paper is to analyze the available scientific research on the effects of subclinical hypothyroidism on mental function, with a particular focus on depression and mood disorders. The paper discusses the neurobiological mechanisms through which thyroid hormones can affect the psyche, presents current data on the diagnosis and treatment of SNT in a psychiatric context, and addresses the controversy surrounding the appropriateness of treating this disease entity in patients with depressive symptoms. (3)

Physiology of thyroid hormones

Production and regulation of thyroid hormones (hypothalamic-pituitary-thyroid axis)

Thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are synthesized and secreted by the thyroid gland under the control of the hypothalamic-pituitary-thyroid (HPT) axis. This process begins in the hypothalamus, which secretes thyroglobulin (TRH), which stimulates the pituitary gland to produce thyrotropin-stimulating hormone (TSH). (4)TSH stimulates the follicular cells of the thyroid gland to uptake iodine, synthesize thyroglobulin, and iodinate it, leading to the formation of thyroid hormones. The hormones secreted into the bloodstream circulate mostly bound to transport proteins, mainly thyroxine-binding globulin (TBG), while

their biologically active fraction remains in free form (fT3 and fT4). The concentration of thyroid hormones is tightly regulated by a feedback mechanism - elevated levels of T3 and T4 inhibit the secretion of TSH and TRH, preventing overproduction of the hormones, while their decreased concentration stimulates the pituitary gland to increase TSH secretion, stimulating the thyroid gland to work more intensively. (5)

Mechanisms of action of T3 and T4 at the cellular level

The main action of thyroid hormones takes place at the cellular level through the regulation of gene expression. T3 is the biologically active form of thyroid hormone, while T4 acts as a precursor and is converted to T3 in peripheral tissues by deiodinase enzymes. After entering the cell, T3 binds to nuclear receptors (TRα and TRβ), which act as transcription factors regulating the expression of numerous genes related to metabolism, proliferation, and cell differentiation. (6)The effect of these processes is to increase mitochondrial protein synthesis, enhance energy metabolism, and accelerate cellular metabolism. In addition, thyroid hormones affect the activity of enzymes involved in the metabolism of glucose, lipids, and proteins, which is crucial for the proper functioning of the body. (7)

Effects of thyroid hormones on metabolism, cardiovascular, nervous, and mental systems

Thyroid hormones play a key role in regulating metabolism, controlling metabolic rate, oxygen consumption, and heat production. They stimulate lipolysis, enhance gluconeogenesis, and increase glucose uptake by cells, which provides the body with adequate energy resources. Effects on the cardiovascular system include an increase in heart rate, strength of myocardial contraction, and a decrease in peripheral resistance, leading to an increase in cardiac minute capacity and better blood supply to tissues. Within the nervous system, T3 and T4 are essential for normal brain development, especially during fetal and early childhood, when they condition myelination of nerve fibers, development of neurons, and their synaptic connections. (8)In adult life, they regulate the activity of neurotransmitters such as serotonin, dopamine, and

norepinephrine, which are responsible for the control of mood, emotions, and cognitive functions. That's why abnormal levels of thyroid hormones can lead to behavioral changes, concentration problems, memory disorders, emotional lability, and even the development of depression and other mental disorders. (9)

Hypothyroidism - pathogenesis and classification

Causes of hypothyroidism (autoimmune, iatrogenic, iodine deficiency, etc.).

Hypothyroidism is an endocrine disorder resulting from insufficient production of thyroid hormones or their reduced action at the cellular level. Among its most common causes is chronic autoimmune thyroiditis, known as Hashimoto's disease, in the course of which there is a lymphocytic infiltration of the gland and gradual destruction of its parenchyma. (10) The autoimmune process is associated with the presence of antibodies to thyroperoxidase (anti-TPO) and thyroglobulin (anti-Tg), which lead to damage to the follicular cells of the thyroid gland and a progressive reduction in the synthesis of thyroxine (T4) and triiodothyronine (T3). (11)

In addition to autoimmune etiology, iatrogenic factors play an important role in the pathogenesis of hypothyroidism. Treatment of hyperthyroidism with radioactive iodine (I-131), thyroidectomy, and the use of drugs that inhibit thyroid hormone synthesis (e.g., thiamazole, propylthiouracil) can lead to permanent gland failure. (12)In addition, some pharmacological substances, such as lithium, amiodarone, or tyrosine kinase inhibitors, can disrupt thyroid function by inhibiting hormone synthesis and release or modifying their peripheral conversion. Deficiency of iodine, a key substrate for the synthesis of T3 and T4, remains a significant cause of hypothyroidism in regions with a low supply of this element, although in many countries, its effective prevention has been achieved through iodized table salt supplementation programs. (13)

Division into primary, secondary, and tertiary forms

Hypothyroidism can be primary, secondary, or tertiary, depending on the location of the pathological process within the hypothalamic-pituitary-thyroid axis.

Primary hypothyroidism results from damage to the thyroid gland and is the most common form of the disease. It is characterized by elevated levels of thyrotropic hormone (TSH) with decreased levels of free thyroid hormones (fT3 and fT4), resulting from a compensatory mechanism of the pituitary seeking to stimulate the dysfunctional gland. (14)

Secondary hypothyroidism is caused by failure of the pituitary gland, leading to inadequate TSH secretion and a secondary reduction in T3 and T4 concentrations. It can result from pituitary tumors, craniocerebral trauma, Sheehan's syndrome, or infiltrative disease processes such as histiocytosis or sarcoidosis. (15)

Tertiary hypopituitarism, the rarest form of this disorder, results from damage to the hypothalamus and impaired secretion of thyroxine (TRH). It can be caused by hypothalamic tumors, inflammation, or blood supply disorders. Both secondary and tertiary hypothyroidism are characterized by low or normal TSH levels with decreased T3 and T4 levels, which distinguishes them from the primary form. (16)

Type of hypothyroidism	Cause	TSH concentration	fT4 concentration	fT3 concentration
Primary hypothyroidism	Damage to the thyroid gland (e.g., autoimmune thyroiditis, radioactive iodine treatment, thyroidectomy, iodine deficiency)	Elevated	Decreased	Decreased
Secondary hypothyroidism	TSH deficiency due to pituitary dysfunction (e.g., pituitary tumors, Sheehan's syndrome, traumatic brain injury, infiltrative disease)	Decreased or normal	Decreased	Decreased
Tertiary hypothyroidism	TRH deficiency resulting from damage to the hypothalamus (e.g., hypothalamic tumors, inflammation, vascular disease)	Decreased or normal	Decreased	Decreased
Subclinical hypothyroidism	An early form of hypothyroidism, often of autoimmune origin	Elevated	Normal	Normal

(1)

Table 1 Division of hypothyroidism and characteristics of endocrine disorders.

TSH, fT4, and fT3 values in each form of hypothyroidism reflect the pathogenetic mechanism underlying the disorder. In primary hypothyroidism, elevated TSH results from a compensatory mechanism of the pituitary, while in secondary and tertiary forms, TSH is unable to properly stimulate the thyroid gland. In the case of subclinical hypothyroidism, despite the elevated TSH, the levels of free hormones remain within normal limits, which can make it difficult to make a clear diagnosis and indicate indications for treatment. (17)

Subclinical hypothyroidism - definition, diagnostic criteria, epidemiology

Subclinical hypothyroidism (SNT) is an intermediate state between normal thyroid function and overt hypothyroidism. It is characterized by elevated TSH levels with preserved normal levels of free thyroid hormones (fT3 and fT4). Clinically, SNT may be asymptomatic or manifest with nonspecific symptoms such as fatigue, impaired concentration, weakness, or mood swings. (18)

Diagnostic criteria for SNT include determination of TSH and fT4. Subclinical hypothyroidism is considered to be TSH above the upper limit of normal (usually >4.5 mIU/L), with concomitant normal fT4 values. Depending on the degree of TSH elevation, SNT is divided into mild (TSH 4.5-10 mIU/L) and pronounced (>10 mIU/L), with the latter being associated with a higher risk of progression to overt hypothyroidism. (19)

Epidemiological studies indicate that the prevalence of SNT in the general population is about 4-10%, with women more commonly affected, especially in the elderly. (20) There is evidence to suggest that SNT may be an important risk factor for mood disorders, including depression, but research findings remain inconclusive. Therefore, there is ongoing debate regarding the need to treat this form of hypothyroidism, especially in the context of its potential impact on mental function. (21)

Effects of hypothyroidism on mental function and mood disorders

Neurobiological mechanisms of the effects of thyroid hormones on central nervous system function

Thyroid hormones play a key role in the normal functioning of the central nervous system (CNS) by regulating the processes of neurogenesis, myelination, and neuronal plasticity. (22)Receptors for triiodothyronine (T3) are widely distributed in brain structures responsible for regulating emotion and cognitive function, such as the prefrontal cortex, hippocampus, and

amygdala. (23)Thyroid hormone deficiency leads to impaired synthesis of neurotransmitters, including serotonin, dopamine, and norepinephrine, which can result in lowered mood, impaired cognitive function, and increased susceptibility to stress. (24)In addition, T3 affects the expression of neurotrophic factors, such as brain-derived nerve growth factor (BDNF), which plays an important role in neuronal adaptation and resistance to stress factors. (25)

Link between hypothyroidism and depression and other psychiatric disorders

Several studies indicate a strong link between hypothyroidism and the risk of developing depressive disorders and other psychiatric conditions, such as anxiety disorders and dysthymia. Patients with overt hypothyroidism often exhibit depressive symptoms, which may be due to both neurotransmitter dysfunction and a general slowing of metabolic processes in the CNS. (26)There is also evidence of milder mood disorders in patients with subclinical hypothyroidism, although findings in this regard are inconclusive. Neuroimaging studies indicate changes in the activity of limbic structures in hypothyroid patients, which may explain their increased susceptibility to emotional disturbances. (27)

Subclinical hypothyroidism and depression, and mood disorders

A review of clinical studies on the association of SNT with depression and other psychiatric disorders

Some studies suggest a potential link between subclinical hypothyroidism (SNT) and the occurrence of depression and other mood disorders. Meta-analyses suggest that people with SNT are more likely to experience depressive symptoms, chronic fatigue, and reduced motivation compared to those with normal thyroid function. Population-based epidemiological

studies have shown that patients with elevated TSH but normal fT4 have an increased risk of affective disorders, especially women and the elderly. At the same time, some studies do not show a clear effect of SNT on mental health, raising questions about the real role of thyroid dysfunction in the pathogenesis of depression. (28)

Possible mechanisms through which SNT may contribute to mood disorders

The mechanism by which SNT affects mood disorders is not fully understood, but the regulation of the hypothalamic-pituitary-thyroid axis and its effects on the hypothalamic-pituitary-adrenal axis are thought to play a key role. Thyroid hormones affect serotonergic and dopaminergic neurotransmission, and their deficiency can lead to neurotransmission disorders typical of depression. In addition, reduced triiodothyronine (T3) activity in the central nervous system may contribute to a decrease in the expression of brain-derived neurotrophic factor (BDNF), which negatively affects neuroplasticity and mood. Reduced metabolic activity in brain structures such as the hippocampus and prefrontal cortex may also explain the observed depressive symptoms in patients with SNT.(29)

Controversy and discrepancies in research results - does SNT play a role in the pathogenesis of depression?

Despite numerous studies on the effects of SNT on mental health, there is still no conclusive evidence supporting its direct role in the pathogenesis of depression. Some studies suggest that levothyroxine (L-T4) therapy can improve the well-being of patients with SNT and depressive symptoms, but other analyses show no significant improvement after implementing treatment. There are hypotheses that SNT may not be the primary cause of mood disorders, but only one of the factors modulating their course. Moreover, in some cases, depressive symptoms may be due to a general deterioration in the quality of life of patients with SNT, rather than a direct effect of thyroid dysfunction on the central nervous system. Therefore, further research is needed to precisely determine the impact of SNT on health. (30)

The importance of subclinical hypothyroidism in the pathogenesis of mood disorders

Subclinical hypothyroidism (SNT) is of particular interest in the context of psychiatry because abnormal TSH values can affect mental function, even if free thyroid hormone concentrations remain within normal limits. Some studies indicate that patients with SNT are more likely to have symptoms of depression, impaired concentration, and reduced motivation. (31) In addition, people with SNT may exhibit greater sensitivity to stress and mental strain, which may be due to subtle changes in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Although levothyroxine (L-T4) replacement therapy in SNT remains a matter of debate, there are reports suggesting that in some patients its use may improve cognitive function and mood, especially if TSH exceeds 10 mIU/L. (32)

Diagnosis and treatment of hypothyroidism in the context of psychiatric disorders

Diagnostic methods - assessment of thyroid function and differential diagnosis

Hypothyroidism diagnosis is based on laboratory evaluation of the hypothalamic-pituitary-thyroid axis, including determination of thyrotropin (TSH) levels and free fractions of thyroid hormones (fT3, fT4). In primary hypothyroidism, TSH elevation with decreased fT4 is characteristic, while in the subclinical form, isolated TSH elevation with normal fT4 and fT3 levels is observed. Differential diagnosis includes evaluation of anti-TPO and anti-Tg antibodies to identify an autoimmune etiology and, if necessary, additional imaging studies (thyroid ultrasound, pituitary MRI). In the context of psychiatry, it is particularly important to differentiate depressive symptoms resulting from thyroid dysfunction from primary affective disorders, so that treatment can be targeted accordingly. (33)

Treatment of hypothyroidism and its impact on the patient's mental state

The mainstay of hypothyroidism treatment is levothyroxine (L-T4) substitution, the dose of which is individually selected based on TSH levels, body weight, and the patient's clinical condition. Optimization of thyroid hormone concentrations not only normalizes the body's

metabolic functioning but can also significantly improve mental status, reducing the severity of depressive symptoms, anxiety, and cognitive impairment. In some cases, especially in patients with treatment-resistant depressive disorders, the use of triiodothyronine (T3) preparations is being considered as adjunctive therapy, but its efficacy and safety require further study. (34)

Dilemmas of treating subclinical hypothyroidism in patients with mood disorders

The treatment of subclinical hypothyroidism remains a matter of debate, particularly in the context of psychiatric disorders. The indications for levothyroxine therapy in patients with SNT depend on TSH levels, age, comorbidities, and symptom severity. Current guidelines recommend considering treatment for TSH >10 mIU/L or in patients with symptoms suggesting the impact of thyroid dysfunction on psychological well-being. (35)Studies suggest that hormone therapy may be beneficial in reducing depressive symptoms and improving cognitive function, but not all analyses support unequivocal efficacy. Therefore, the decision to treat SNT should be made on an individual basis, taking into account the risk of progression to overt hypothyroidism and the potential impact on the patient's mental health. (36)

Clinical implications and therapeutic options

Should patients with subclinical hypothyroidism be treated?

The question of treating patients with subclinical hypothyroidism (SNT) remains a matter of debate in the medical community. Most guidelines suggest that the decision to institute levothyroxine (L-T4) therapy should depend on the patient's age, TSH level, and the presence of clinical symptoms. In patients with TSH levels above 10 mIU/L, treatment is usually recommended, while for mildly elevated TSH (4.5-10 mIU/L), management is more

individualized. In high-risk groups, such as pregnant women or those with cardiovascular disease, it is recommended that therapy be considered even at lower TSH levels. However, in the psychiatric context, there are still no clear recommendations, and the treatment decision should be made after a thorough clinical evaluation. (37)

Review of studies on levothyroxine therapy in the context of improving depressive symptoms

Studies on the efficacy of L-T4 treatment in patients with SNT and depressive symptoms have yielded conflicting results. Some studies suggest that hormone therapy can lead to an improvement in mood, a reduction in depressive symptoms, and a decrease in feelings of chronic fatigue. In contrast, other analyses show no significant difference between groups receiving L-T4 and placebo, suggesting that the impact of the treatment may be limited to selected subgroups of patients. (38) Meta-analyses indicate that the benefit may be greatest in those with higher TSH and patients with more severe depressive symptoms at baseline. However, large randomized clinical trials are still lacking to clearly define the role of L-T4 therapy in the treatment of mood disorders in patients with SNT.(39)

The role of a multidisciplinary approach in treating patients with psychiatric disorders and SNT

Given the multifactorial etiology of mood disorders and their potential association with endocrine dysfunction, interdisciplinary collaboration between psychiatrists, endocrinologists, and primary care physicians is crucial for the effective diagnosis and treatment of patients with SNT. Patients with depressive symptoms should undergo evaluation of thyroid function, especially if standard psychiatric treatment is unsuccessful. (40)On the other hand, in patients with established SNT, a detailed analysis of psychiatric symptoms is necessary before hormone

therapy is included. A holistic approach, incorporating both pharmacotherapy and psychotherapeutic interventions, can help improve patients' quality of life and optimize their treatment. (41)

Summary and conclusions

Key findings on the relationship between SNT and depression

Available research suggests that subclinical hypothyroidism (SNT) may be associated with the occurrence of mood disorders, including depression and anxiety. Patients with SNT are more likely to experience depressive symptoms, fatigue and psychomotor retardation, suggesting a potential impact of thyroid dysfunction on central nervous system functioning. (42)Possible mechanisms for this association include changes in serotonergic and dopaminergic neurotransmission, reduced metabolic activity in brain structures, and dysregulation of the hypothalamic-pituitary-thyroid axis. However, despite several studies, the role of SNT in the pathogenesis of depression is not unequivocally confirmed, and the effect of hormone treatment on improving psychological well-being remains an open question. (43)

Limitations of available studies and need for further analysis.

Despite the plethora of studies on the relationship between SNT and mood disorders, many of them have significant methodological limitations. There is a lack of large, randomized clinical trials to determine whether SNT is a cause of depression or merely a comorbid factor. There are also discrepancies regarding the efficacy of levothyroxine treatment, with some studies showing significant improvement in mental status after implementation of therapy, while others show no significant difference compared to placebo. An additional limitation is the heterogeneity of the patient groups studied and the different diagnostic criteria used in the analyses. Therefore, further well-designed studies are needed to accurately determine the impact of SNT on mental health and to identify optimal therapeutic strategies. (44)

Clinical applications - is it worth considering thyroid testing in patients with mental disorders?

The current state of knowledge indicates that assessment of thyroid function should be part of the differential diagnosis in patients with depression and chronic fatigue, especially in cases refractory to standard psychiatric treatment. (45)Testing TSH and fT4 levels is a simple and widely available tool that can help identify patients with a potential endocrine basis for their symptoms. Although there are no clear guidelines recommending routine L-T4 supplementation in all patients with SNT and depression, individualization of therapy and interdisciplinary collaboration between endocrinologists and psychiatrists can significantly improve the quality of patient care. Further research is needed to develop precise guidelines for the management of this group of patients, allowing for more effective treatment of both thyroid disorders and comorbid psychiatric problems. (46)

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Authors' contribution:

Conceptualization: Aleksandra Cieplak
Methodology: Aleksandra Cieplak
Software: Aleksandra Cieplak
Check: Aleksandra Cieplak
Formal analysis: Aleksandra Cieplak

Investigation: Aleksandra Cieplak
Resources: Aleksandra Cieplak
Data curation: Aleksandra Cieplak
Writing -rough preparation: Aleksandra Cieplak
Writing -review and editing: Aleksandra Cieplak
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