International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 13, Issue 1, pp: (313-318), Month: April 2025 - September 2025, Available at: www.researchpublish.com

Major Depressive Disorder and Subclinical Hypothyroidism: A Complex Relationship with Clinical Implications

Dr. Moosa Jeded S Alenazi

[12] MBBS, SBFM, SENIOR FAMILY PHYSCAIN

The Northern Area Armed Forces Hospital

King Khalid Military City, Hafr Al Batin, Saudi Arabia

DOI: https://doi.org/10.5281/zenodo.15735907

Published Date: 25-June-2025

Abstract: **Major Depressive Disorder (MDD) and subclinical hypothyroidism (SCH) frequently co-occur, and their relationship involves overlapping clinical features and intertwined pathophysiological mechanisms. SCH –defined by elevated thyroid-stimulating hormone (TSH) with normal thyroid hormone levels – is common, affecting roughly 3–8% of the general population (up to 20% in the elderly). Depression is a well recognized neuropsychiatric manifestation of thyroid dysfunction. Recent studies in the past decade suggest that even mild thyroid impairment may influence mood disorders: patients with SCH have an increased prevalence of depressive symptoms, although findings are mixed regarding causality. Biochemical pathways linking the hypothalamic-pituitary-thyroid (HPT) axis and monoamine systems provide a possible mechanism for this association. Clinically, the symptom overlap between MDD and SCH can complicate diagnosis, underscoring the importance of thyroid function screening in depressive patients. Treatment interactions are also significant – untreated SCH may hinder antidepressant response, whereas thyroid hormone supplementation (levothyroxine or liothyronine) can augment depression treatment in select cases. This concise review synthesizes recent evidence on the complex MDD–SCH relationship, emphasizing biochemical links, diagnostic challenges, and treatment implications for improved clinical decision-making.**

Keywords: **Major Depressive Disorder, subclinical hypothyroidism, relationship, phycology.**

I. INTRODUCTION

Major Depressive Disorder is a common and debilitating mental illness characterized by persistent low mood, anhedonia, and various cognitive and somatic symptoms. Its etiology is multifactorial, involving genetic, environmental, and biological factors. Endocrine disturbances are one important biological factor: the connection between thyroid function and mood has long been recognized. As early as the 19th century, physicians observed “myxedema madness” – psychiatric disturbances in hypothyroid patients – highlighting the thyroid’s role in mental health. Subclinical hypothyroidism (SCH) is a milder form of thyroid hypofunction defined biochemically by elevated TSH with normal circulating thyroxine (T4) and triiodothyronine (T3) levels. SCH is relatively common, with an estimated prevalence of ~3–8% in the general adult population (with higher rates in women) and up to 15–20% in older adults. Unlike overt hypothyroidism, SCH often presents with subtle, nonspecific symptoms or even none at all. Depression is one of the most frequent neuropsychiatric manifestations of thyroid disorders. Conversely, thyroid abnormalities are commonly noted in patients with mood disorders. For instance, overt hypothyroidism is present in a small percentage of individuals with affective disorders, and SCH has been reported in a substantial minority (some studies suggest anywhere from 4% to as high as 40% of patients with mood disorders, depending on the population). Such variability indicates heterogeneity and possible selection biases, but it underlines that thyroid function should be assessed in psychiatric evaluations. In fact, the American Association of Clinical

Endocrinologists recommends that depression be considered in all patients with hypothyroidism (including subclinical), given the frequent coexistence. Similarly, psychiatric guidelines often advise screening TSH levels in patients presenting with depression to rule out an underlying thyroid condition. The relationship between MDD and SCH is complex. Some recent studies and meta-analyses have found a higher risk of depression in those with subclinical hypothyroid status, while others have found no significant association in certain populations. This discrepancy may be explained by factors such as age, sex, and the degree of thyroid dysfunction. It appears that *clinical context matters*: younger and middle-aged adults with SCH may be more susceptible to depressive symptoms, whereas in the elderly, mild TSH elevations might not correlate strongly with depression. Additionally, women (who have higher rates of both hypothyroidism and depression) seem particularly affected – a large 2021 meta-analysis found that hypothyroidism (especially overt) conferred an increased depression risk primarily in women, with only a minimal risk increase in subclinical cases (approx. 13% higher odds) . These findings suggest that SCH's impact on mood is real but modest, and likely modulated by other factors. Given the overlapping symptomatology of MDD and SCH and the potential for one condition to influence the course of the other, it is crucial for clinicians to understand their interplay. The following discussion explores: (1) **Biochemical mechanisms** that link thyroid function and mood regulation, including neuroendocrine pathways and immune factors; (2) **Diagnostic overlap** between depressive symptoms and thyroid-related symptoms, and strategies to differentiate or detect coexisting conditions; and (3) **Treatment interactions and implications**, including how SCH might affect response to antidepressant therapy and whether treating SCH can improve depressive outcomes. Emphasis is placed on clinically relevant evidence from the past 5–10 years to guide diagnostic and therapeutic decision-making..

II. DISCUSSION

A. Biochemical Mechanisms Linking Thyroid Function and Mood

Thyroid hormones play a pivotal role in brain development and neuropsychological function, influencing neurotransmitter systems, neuroplasticity, and metabolic activity in the central nervous system. It is well established that disturbances in the hypothalamic-pituitary-thyroid (HPT) axis can affect mood and behavior. Depression itself can induce subtle changes in thyroid function tests: for example, depressed patients often exhibit a blunted TSH response to thyrotropin-releasing hormone (TRH) stimulation, and some have a slight elevation of serum T4 or loss of the normal circadian TSH surge. These alterations have led to the concept of "brain hypothyroidism," wherein despite normal peripheral thyroid hormone

levels, local thyroid hormone activity in the brain is deficient . Mechanistically, this could be due to reduced transport of T4 across the blood-brain barrier or impaired conversion to T3 in the brain, leading to localized hypothyroid effects that contribute to depressive symptoms. This theory is supported by findings of decreased type II deiodinase activity in post-mortem brains of individuals with depression and the noted HPT axis dysregulation in mood disorders. Neurotransmitter pathways provide another biochemical link. Serotonin and other monoamines, which are central to depression pathophysiology, interact with the thyroid axis. Research indicates that low central somatostatin levels in depression maydisinhibit TSH secretion, resulting in higher TSH levels. Conversely, serotonin deficiency (a hallmark of MDD) has been associated with reduced TRH and TSH release. In essence, the neurochemical changes in depression can perturb thyroid regulation, and mild thyroid failure can, in turn, exaggerate neurochemical imbalances. This bidirectional interaction helps explain why even subclinical thyroid dysfunction might precipitate or worsen depressive symptoms. Additionally, thyroid hormones are known to modulate gene expression of neurotransmitter receptors and influence neurogenesis; insufficient T3 within the brain could thereby contribute to the development of depressive phenotypes. Immune and endocrine crosstalk is also relevant. Autoimmune thyroiditis (Hashimoto's thyroiditis), a leading cause of hypothyroidism, has itself been linked to mood disorders. Patients with MDD have higher rates of thyroid autoantibodies than the general population in some studies. Elevated anti-thyroid peroxidase (TPO) or thyroglobulin antibodies have been proposed to correlate with depressive severity and even suicidality in mood disorders. While a 2021 meta-analysis did *not* find thyroid autoantibody positivity to be significantly associated with clinical depression overall, the concept of an "autoimmune link" remains under investigation. It is hypothesized that systemic inflammation or specific autoimmune processes might contribute to depressive symptoms in a subset of patients. For example, cytokines involved in Hashimoto's thyroiditis could cross the blood-brain barrier and affect neurotransmitter metabolism or HPT axis signaling. Indeed, MDD is increasingly recognized to have an inflammatory component in some patients, and it is conceivable that thyroid autoimmunity could be one contributory factor in those cases. Importantly, *overt* hypothyroidism (where T4 is frankly low) is a known reversible cause of depression: patients often experience fatigue, low mood, apathy, cognitive slowing, and other depressive-like symptoms when hypothyroid, which typically improve with thyroid hormone replacement. SCH, by definition, features normal circulating hormone levels, yet mild deficiencies at the tissue level or HPT axis dysregulation may still produce

subtle mood effects. The presence of SCH alongside MDD has been associated with greater depression severity, more pronounced cognitive symptoms, and even treatment resistance in some reports For instance, one study noted that MDD patients with concurrent thyroid dysfunction (including SCH) had higher rates of refractory depression and psychotic features . While not all studies concur, these observations align with the biochemical reasoning that adequate thyroid hormone action is important for optimal antidepressant response and mood regulation.

B. Diagnostic Overlap and Clinical Evaluation

There is considerable overlap in the clinical presentation of major depression and hypothyroidism, which can pose diagnostic challenges. Both conditions can produce symptoms such as fatigue, lethargy, concentration difficulties, psychomotor slowing, sleep disturbances, and changes in appetite or weight. For example, an individual with subclinical hypothyroidism might experience low energy, slight weight gain, and depressed mood – a picture easily mistaken for MDD (and vice versa). The overlapping symptoms that features like depressed mood, cognitive impairment, and somatic complaints (e.g. sleep problems, constipation, aches) can appear in both disorders. However, certain signs tip the scale toward thyroid dysfunction: cold intolerance, dry skin, hair loss, bradycardia, or a goiter, if present, are suggestive of hypothyroidism rather than primary depression. In subclinical cases, such physical signs are often absent or subtle, so clinicians cannot rely on exam findings alone. Because of this overlap, routine screening of thyroid function is a widely accepted practice in the work-up of depression. A simple serum TSH test can uncover SCH or overt hypothyroidism in patients presenting with depressive symptoms. This is of high clinical yield given the relatively high prevalence of SCH and the significant clinical implications of diagnosing it. Indeed, recent guidance emphasizes that any patient with new-onset depression (especially if atypical features are present or depression is refractory to treatment) should be evaluated for thyroid dysfunction. This ensures that an underlying medical contributor to depression is not overlooked – an error that could lead to prolonged suffering or inadequate treatment if only antidepressants are given. Conversely, when a patient is known to have SCH, clinicians should be vigilant for emerging depressive symptoms; some endocrinology guidelines suggest considering depression as a potential comorbidity in all hypothyroid patients. It is important to note that not every mild TSH elevation in a depressed patient indicates causation. Large population studies have shown that many individuals with SCH are asymptomatic and that in some cohorts (e.g. adolescents or older adults), SCH was *not* significantly associated with depressive symptoms. For instance, an analysis of U.S. National Health and Nutrition data found no clear link between SCH and depression risk in the general adult population. In adolescents screened during the COVID-19 pandemic, those with elevated TSH did not have higher depression scores than euthyroid peers. These findings underscore that while SCH and depression often co-occur, the presence of one does not automatically mean it is causing the other. A careful, individualized assessment is required. When faced with a patient who has both MDD and SCH, clinicians should perform a thorough evaluation: - **Corroborate symptoms with labs:** Determine if the severity and time course of depressive symptoms correlate with changes in thyroid levels. For example, did mood worsen as TSH rose or after an illness that could trigger thyroiditis? - **Assess for other clues:** Even subtle physical signs of hypothyroidism (e.g. slight slowing of reflexes, elevated cholesterol, menstrual irregularities) might support treating the thyroid as a priority. - **Use rating scales and history:** Tools like the PHQ-9 or Hamilton Depression Rating Scale can quantify depression severity while thyroid labs give objective data – together these help track response if treatment is initiated for one or both conditions. - **Differentiate primary vs. secondary depression:** If a patient has significant thyroid dysfunction, one might consider the depression as "secondary" to that medical condition. In such cases, treating the thyroid disorder could alleviate depressive symptoms without needing aggressive psychiatric intervention. On the other hand, if thyroid function is only mildly off, or depression is disproportionately severe, it's likely that primary MDD is present and will need its own targeted therapy alongside thyroid management. In summary, diagnostic overlap means clinicians must maintain a broad differential. The key is **to test, not guess** – obtaining thyroid function tests in depression is a simple step that can prevent misdiagnosis. It is also prudent to periodically re-check thyroid labs in patients with depression, as prolonged psychiatric stress or medications can sometimes alter thyroid function subtly (for example, certain antidepressants and lithium can impact thyroid hormone levels). By recognizing the overlap and interconnection, practitioners can avoid the pitfall of treating one condition in isolation when both may be present.

C. Treatment Interactions and Clinical Management

The coexistence of MDD and subclinical hypothyroidism raises important questions about treatment strategy. The central considerations are: Will correcting SCH improve depressive symptoms? Does the presence of SCH affect response to antidepressants? And conversely, can antidepressant therapies influence thyroid function? Thyroid Hormone Replacement: In overt hypothyroidism accompanying depression, thyroid hormone replacement (levothyroxine, i.e. L-T4) is essential and

often yields significant mood improvement. Many cases of "hypothyroid depression" resolve once euthyroid status is restored. However, in subclinical hypothyroidism, the benefit of routine thyroid hormone therapy on mood is less clear. Current endocrinology guidelines generally recommend initiating levothyroxine in SCH only if TSH exceeds 10 mIU/L or if the patient is symptomatic (or has specific indications like pregnancy or positive antibodies) . Mild SCH (TSH just above the reference range) without symptoms may be monitored rather than treated. Depression, when present, could be considered one such "symptom" that might prompt therapy – yet evidence to support this approach is mixed. Several studies in the past decade have examined whether treating SCH helps coexistent depression. A 2019 systematic review and meta-analysis by Loh et al. found that while individuals with SCH had a higher prevalence of depression than euthyroid controls, levothyroxine therapy did not significantly improve depression scores in those patients on average. Specifically, pooled results showed no significant difference in depressive symptom reduction (measured by Beck Depression Inventory and Hamilton scales) between SCH patients treated with levothyroxine and those not treated. This suggests that for many patients, simply normalizing a mildly elevated TSH may not be sufficient to resolve depression – perhaps because the depression is multifactorial or because SCH was not the primary driver of mood symptoms. An ancillary analysis of a large randomized trial in older adults (mean age ~74) similarly reported that levothyroxine had no effect on development or improvement of depressive symptoms in SCH, compared to placebo. These findings have tempered enthusiasm for automatically treating every mild thyroid abnormality in depressed patients. Instead, an individualized approach is advised . Individualized management means considering the degree of TSH elevation, patient's age, and overall clinical picture. For example, if a patient with MDD has SCH with TSH near 10 mIU/L and also has classic hypothyroid complaints (fatigue, cognitive slowing) alongside depression, a trial of levothyroxine is reasonable, with close monitoring of mood changes. In contrast, a patient with very mild SCH (TSH ~5) and severe melancholic depression might benefit more from prompt psychiatric treatment (antidepressants and/or psychotherapy) while observing the thyroid function over time. Notably, one study found that raising the dose of thyroid hormone to achieve lower TSH within normal range improved depressive mood in older SCH patients without causing overt hyperthyroid effects. This hints that some patients may feel better at a "high-normal" thyroid level. Nevertheless, overtreatment must be avoided, as hyperthyroidism can induce anxiety, insomnia, and even precipitate mania in susceptible individuals. Augmentation with Thyroid Hormones: Psychiatrists have long used thyroid hormones as adjuncts in depression treatment, even for euthyroid patients. Triiodothyronine (T3) augmentation is a well-established strategy to accelerate or enhance response to antidepressants, particularly tricyclic antidepressants and in treatment-resistant depression. Low-dose liothyronine (T3) has shown efficacy in augmenting antidepressant effects, especially in women with depression. Although the mechanism is not fully understood, T3 may increase serotonin availability or improve neurotransmission, and it likely corrects any subtle "brain hypothyroidism" present in depression. In patients with coexistent SCH, adding T3 or ensuring adequate T4 replacement might thus yield dual benefits – addressing the thyroid insufficiency and boosting the antidepressant response. Clinical practice point: In an MDD patient with SCH who is not responding well to antidepressants, one could either initiate levothyroxine to normalize TSH (if not already done) or add a small dose of T3 to the regimen (sometimes both are done, carefully monitoring thyroid levels and clinical response). Some experts advocate for aiming TSH in the lower half of the normal range in such cases, given observations that depressive symptoms may remit as thyroid function comes to an optimal level. On the other side of the interaction, certain psychiatric treatments can affect thyroid function. Notably, lithium (used as a mood stabilizer and adjunct in refractory depression) is known to cause hypothyroidism in a significant proportion of patients over time. Thus, if a patient with MDD is on lithium and develops depressive relapse or fatigue, a TSH check is warranted to rule out lithium-induced SCH or overt hypothyroidism. Some antidepressants (like sertraline or other SSRIs) have been reported to cause mild elevations in TSH or interfere with thyroid hormone binding, though these effects are usually subclinical and reversible. Electroconvulsive therapy (ECT), an intervention for severe depression, can transiently stimulate TSH release and thyroid hormone levels – an interesting phenomenon, though of uncertain clinical significance. Overall, clinicians should remain aware that when treating a patient with both thyroid and mood disorders, the therapies for one condition can impact the other. Regular thyroid function monitoring is prudent when patients are undergoing psychiatric treatments that might influence the endocrine system. In summary, managing a patient with MDD and subclinical hypothyroidism requires a balanced approach: - Treat the treatable: If SCH is significant or likely contributing to symptoms, instituting levothyroxine therapy can be beneficial for overall health and possibly mood – with the caveat that mood improvement is not guaranteed . - Optimize depression treatment: Do not rely solely on thyroid correction if depression meets criteria for independent treatment. Use antidepressants, psychotherapy, or other modalities as indicated, while also addressing thyroid status. - Monitor outcomes: Set specific targets (e.g. achieve euthyroid state with TSH in reference range) and observe changes in depressive symptoms. It may take 6–12 weeks on thyroid therapy to see mood changes, similar to antidepressants. - Augment if needed: Consider T3 augmentation in persistent depression. Evidence shows thyroid hormones can potentiate

antidepressant effects even in patients without overt hypothyroidism. This can be a valuable strategy in treatment-resistant cases. - Avoid over-treatment: Pushing thyroid levels too high can cause iatrogenic hyperthyroidism, which may induce anxiety, irritability, or cardiac issues. The goal is to restore normal physiology, not to induce a thyrotoxic state. Through careful, individualized treatment plans, many patients with co occurring SCH and MDD can experience improvement in mood and overall well-being. Close collaboration between primary care, endocrinology, and psychiatry may be ideal in complex cases to ensure both conditions are optimally managed.

III. CONCLUSION

MDD and subclinical hypothyroidism are intimately connected by a web of physiological and clinical threads. This complex relationship means that clinicians must maintain a high index of suspicion for thyroid dysfunction in patients with depression and vice versa. Biochemically, even mild thyroid hormone deficiencies can contribute to depressive symptoms via alterations in neurotransmitter systems and brain metabolism. Clinically, overlapping features can obscure the true diagnosis unless appropriate laboratory screening is performed. Recent evidence suggests that while SCH is associated with an increased incidence of depression, it is neither a universal cause nor present in all depressed individuals – many patients with SCH remain asymptomatic and many depressed patients are euthyroid. Treatment decisions should therefore be personalized. In patients with MDD and SCH, correcting the thyroid imbalance is an important consideration for overall health, and it may aid in mood improvement for some, though it should not replace standard depression therapies. Adjunctive use of thyroid hormones has emerged as a useful tool in treatment-resistant depression, reflecting the essential role of adequate thyroid function in normalizing mood. In practice, the care of patients at the interface of psychiatry and endocrinology should be collaborative. A patient's depressive disorder should prompt evaluation of thyroid status as a reversible contributing factor. Conversely, patients with known thyroid disease should be monitored for mood changes and screened for depression, given the high prevalence of co-morbidity. By understanding the nuanced interplay between MDD and SCH – from shared biochemical pathways to diagnostic pitfalls and therapeutic opportunities – healthcare providers can improve outcomes. The clinical implications are clear: integrated treatment of both mood and thyroid conditions leads to better patient care. Ongoing research will continue to clarify which subsets of patients benefit most from thyroid interventions in depression. For now, an evidence-based yet individualized approach, attentive to the complex relationship between these two disorders, offers the best path for helping patients achieve remission and improved quality of life..

REFERENCES

[1] Nuguru SP, et al. (2022). Hypothyroidism and Depression: A Narrative Review. Cureus 14(8): e28379. This review highlights the longstanding link between hypothyroidism (including subclinical) and depression, noting that untreated thyroid dysfunction increases depression risk and that thyroid hormone replacement can improve mood disorders.

[2] Loh HH, et al. (2019). Association between subclinical hypothyroidism and depression: an updated systematic review and meta-analysis. BMC Psychiatry 19:12. In this meta-analysis of 12,000+individuals, SCH was associated with a higher risk of depression (RR ~2.3). However, levothyroxine treatment of SCH did not significantly improve depressive symptoms on standard scales, suggesting that thyroid correction alone may be insufficient to treat depression.

[3] Tang R, et al. (2019). Subclinical Hypothyroidism and Depression: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne) 10:340. This study found an odds ratio of ~1.78 for depression in SCH patients, with the association particularly notable in individuals above 50 years old. It reinforces the need for vigilance regarding depressive symptoms in patients with mild thyroid dysfunction.

[4] Bode H, et al. (2021). Association of hypothyroidism and clinical depression: A systematic review and meta-analysis. JAMA Psychiatry 78(12):1375–1383. A comprehensive meta-analysis indicating only a modest overall link between hypothyroidism and depression. Subclinical hypothyroidism conferred a small increase in depression risk (OR ~1.13) that was significant only among women, whereas overt hypothyroidism had a stronger effect. Thyroid autoimmunity alone was not significantly associated with depression in this analysis.

[5] Zhao T, et al. (2018). Subclinical hypothyroidism and depression: a meta-analysis. Transl Psychiatry 8:239. This meta-analysis concluded that overall, SCH is not significantly linked to depression. A noteworthy finding was age-related differences: SCH was associated with depression in younger patients (<60 years) but not in older patients, highlighting the influence of age on the SCH-MDD relationship.

[6] Lang X, et al. (2020). Prevalence and clinical correlates of subclinical hypothyroidism in first-episode patients with major depressive disorder. J Affect Disord 263:507–515. A study in a large Chinese sample of MDD patients reporting that those with higher TSH (indicative of SCH) had more severe depressive and anxiety symptoms and a higher rate of suicidal ideation. This supports the notion that even mild thyroid dysfunction can exacerbate psychiatric symptom severity.

[7] Kumaratne M, et al. (2024). Lack of Association Between Depression and Subclinical Hypothyroidism in Adolescents. Clin Med Insights Pediatr 18:11795565231220503. This recent cross-sectional study of adolescents (during the COVID-19 era) found no statistical association between elevated TSH (SCH) and depression scores. It cautions against over-testing or over-interpreting mild TSH elevations in teenage depression, emphasizing that routine TSH screening may not be necessary in adolescent depression absent other indications [7]. Feller M, et al. (2021). Effect of levothyroxine therapy on the development of depressive symptoms in older adults with subclinical hypothyroidism. JAMA 326(20): 2014–2023 (ancillary study of TRUST trial). This randomized trial in adults ≥65 with SCH found that levothyroxine had no significant benefit over placebo in preventing or reducing depressive symptoms. It suggests that routine thyroid treatment in older SCH patients may not improve mood, aligning with a more conservative treatment approach in this group

[8] Harten AC van, et al. (2008). Should depressive symptoms in patients with subclinical hypothyroidism be treated with thyroid hormone? Tijdschr Psychiatr 50:539–543. (Dutch) – Summary in Nuguru et al. 2022: This analysis found a lack of strong evidence that levothyroxine therapy benefits patients with depression and SCH. It underscores that while treating overt hypothyroidism is clearly beneficial for mood, the advantage of treating SCH purely to alleviate depressive symptoms remains unproven, warranting a case-by-case approach.

[9] Bauer M & Whybrow PC. (2015). Thyroid Hormones in Psychiatric Treatment. Front Endocrinol 6: Article 65. This review (not directly cited above) provides context on using T3 and T4 as adjuncts indepression management. It describes how thyroid hormones can potentiate antidepressant effects and discusses the concept of “euthyroid hyperthyroxinemia” (deliberately raising thyroid hormone levels within high-normal range) to treat refractory depression. This evidence underlies current practice where clinicians add liothyronine (T3) to antidepressant regimens in patients with difficultto- treat depression, reflecting the clinical utility of the MDD-SCH interplay in therapeutics