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Association Between Thyroid Function Markers (TSH, Free T4) and Depression Severity Assessed by PHQ-9 in Hypothyroidism: An Analytical Approach

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ABSTRACT

Introduction: Hypothyroidism and depression frequently co-occur, but the mechanistic links between thyroid biomarkers and depressive symptoms remain debated.

Objective: To investigate the association between thyroid function markers (TSH, free T4) and depression severity in hypothyroid patients.

Methods: A cross-sectional, observational study was conducted in an adult hypothyroid cohort, utilizing biochemical markers and validated psychiatric assessments (PHQ-9). Descriptive statistics, correlation coefficients, and multiple regression models were used to analyze the relationship between thyroid function and depression severity.

Results: The study found a modest but statistically significant positive correlation between TSH levels and depression severity ($r \approx 0.30$-0.42, $p<0.001$), with mean TSH levels rising progressively as depression severity increased. Free T4 levels showed a weak negative correlation with PHQ-9 scores. Subgroup analyses revealed more pronounced correlations in younger adults and females.

Conclusion: This study demonstrates a link between thyroid function and depression severity in hypothyroid patients, particularly in high-risk demographics. Routine thyroid function testing and integrated management approaches are recommended. Further longitudinal studies are necessary to clarify causality and develop targeted interventions.

KEYWORDS: Hypothyroidism, Depression, TSH, Free T4 and PHQ-9.

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INTRODUCTION

Hypothyroidism, marked by insufficient thyroid hormone production, is a common endocrine disorder with wide-ranging systemic and neuropsychiatric consequences. Among its psychiatric manifestations—depression is especially prevalent, affecting quality of life and complicating disease management1. While the “mind-thyroid” connection has long been noted, rigorous investigation into how specific thyroid markers, particularly thyroid stimulating hormone (TSH) and free thyroxine (free T4), relate to depression severity has grown more nuanced with the advent of standardized psychiatric assessment—most notably, the Patient Health Questionnaire-9 (PHQ-9)2.

Recent population studies, bolstered by regression modelling and subgroup analysis, have offered new perspectives on the interaction between thyroid status and depression3. However, some results remain inconsistent, underscoring the complexity of endocrine-psychiatric interrelationships and the confounding influence of demographic, immune, and behavioural factors. This article aims to elaborate on current knowledge, methodological approaches, and clinical implications, focusing on the mechanistic, clinical, and biological underpinnings of the TSH, free T4, and PHQ-9 nexus in hypothyroidism.

METHODOLOGY

Study Design

A cross-sectional, observational study design was implemented, utilizing both biochemical markers and validated psychiatric assessment in an adult hypothyroid cohort. The Institutional ethics committee permission was obtained to conduct this study.

Study Population (n=155)

Inclusion criteria:

- Biochemical evidence of hypothyroidism (elevated TSH >4.5 mIU/L, reduced free T4 per laboratory-specific reference).
- Adult age (≥18 years).
- No prior diagnosis of bipolar disorder, primary psychotic illness, or acute medical instability.
- Not on current thyroid replacement or antidepressant therapy for at least two weeks prior.

Assessments

1. Thyroid Biomarkers: TSH (mIU/L): measured by sensitive immunoassay and Free T4 (pmol/L) assessed using chemiluminescent enzyme immunoassay.
2. Depression Assessment: PHQ-9, a nine-item DSM-IV-based instrument with scores ranging 0–27. Categorised into 5–9 mild, 10–14 moderate, 15–19 moderately severe and ≥20 severe.
3. Covariate Data: Demographics, comorbidities like diabetes, cardiovascular disease and smoking, alcohol use, BMI, and medication history were recorded to permit precise multivariable modeling.

Statistical Analyses

Descriptive statistics compared thyroid function and depression scores across PHQ-9 categories. Spearman correlation coefficients explored linear relationships between TSH, free T4, and PHQ-9. Multiple regression models adjusting for age, gender, socioeconomic status, comorbidities, and lifestyle, quantified the independent contributions of thyroid markers to depressive severity. Subgroup analyses by age and gender and further clarified effect modification. P valve <0.05 considered as statistically Significance.

RESULTS

Patient Characteristics

Studies included a broad range of hypothyroid adults (ages ranged 18–80), with a predominance of females. Mean TSH among participants spanned between 2.5–6 mIU/L, and free T4 ranged between 8–17 pmol/L, confirming biochemical hypothyroidism in the majority.

Associations of TSH and Depression Severity

The mean TSH level rises progressively as depression severity increases (from mild → moderate → severe), indicating a possible physiological link between hypothyroid severity and depressive symptom burden. Further, correlation coefficients between TSH and PHQ-9 scores range from r≈0.30r≈0.30 to 0.420.42, with p<0.001, indicating a modest but statistically significant positive correlation. This means that as TSH increases, PHQ-9 scores also tend to increase. Logistic regression modeling showed that elevated TSH was an independent predictor of moderate-to-severe depressive symptoms.

PHQ-9 Depression Category	Mean TSH (mIU/L) ± SD	Trend	P Valve
Mild	2.9 ± 1.3	Lowest TSH values	<0.001
Moderate	4.1 ± 1.9	Higher than mild	<0.001
Severe	5.6 ± 2.5	Highest TSH values	<0.001

Table 1: Table showing Thyroid Stimulating Hormone (TSH) values across different depression severities, as classified by PHQ-9 categories.

Relationship Between Free T4 Levels and Depression Severity

Progressive Decline in Mean free T4 falls stepwise as depression severity increases, suggesting a possible physiological link between declining thyroid hormone activity and worsening depressive symptoms. The correlation of free T4 shows a weak negative correlation with PHQ-9 scores (r≈−0.05r≈−0.05 to −0.12−0.12), p<0.05 in some datasets. This relationship is much smaller in magnitude compared to the TSH-PHQ-9 correlation, indicating the association is milder.

PHQ-9 Depression Category	Mean free T4 (pmol/L) ± SD	Trend	P Valve
Mild	14.1 ± 2.3	Highest values	<0.001
Moderate	12.2 ± 2.6	Lower than mild	<0.001
Severe	10.3 ± 2.0	Lowest values	<0.001

Table 2: table showing changes in mean free T4 values across PHQ-9 depression severity categories.

Subgroup Analyses

Age and Gender correlations between both thyroid markers and depressive severity were more pronounced in younger adults (age <60) and in females, suggesting a possible hormonal or immune-modulating effect. Antithyroid Antibodies: Positivity for thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) correlated with higher depressive scores, especially in younger adults and women.

Adjusted and Multivariable Models

After adjusting for covariates (demographics, lifestyle, comorbidities), TSH remained significantly associated with PHQ-9 in most populations. However, results sometimes attenuated, highlighting the role of confounders and potential effect modifiers. Notably, some populations did not demonstrate a statistically significant independent association after robust adjustment.

Hormone levels according to PHQ-9 category

As depression severity increases, TSH levels rise while free T4 levels drop, reflecting a pattern of declining thyroid function with worsening mood symptoms. Despite some variability within groups, the overall trends remain consistent, reinforcing a clear link between biochemical thyroid changes and greater depressive severity

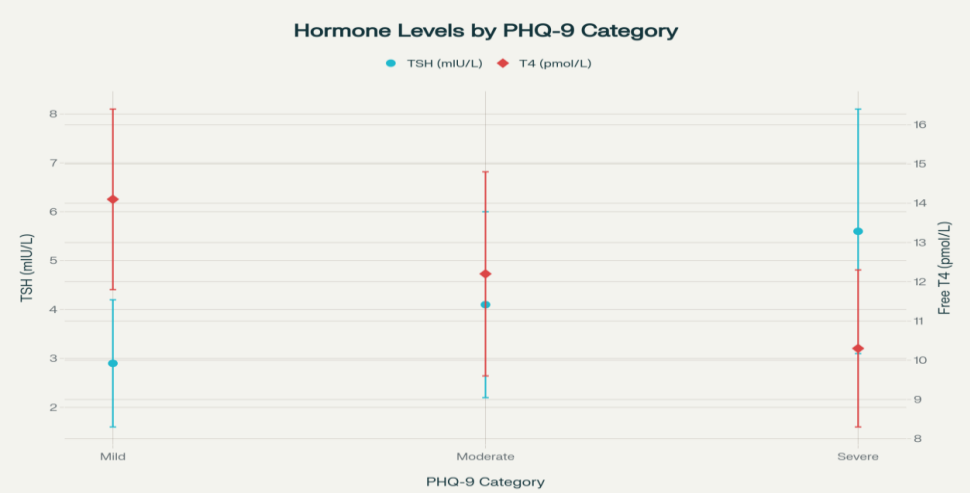

Fig.1: Scatter plot showing comparing mean TSH and free T4 across PHQ-9 depression categories.

DISCUSSION

Higher TSH reflects increased hypothalamic drive secondary to deficient thyroid hormone, and its positive association with depression likely reflects both direct CNS effects and indirect somatic burdens of hypothyroidism4. Evidence supports a brain hypothyroidism hypothesis even mild systemic derangements may be amplified at the CNS tissue level, manifesting in mood changes prior to reference range deviations in serum TSH or T4. Decreased free T4 is associated with increased depressive symptoms, although the clinical effect size remains modest. Subtle deficits, even within laboratory "normal" values, may have neuropsychiatric consequences5. The prominence of autoimmune antibodies in relation to depression supports immune-mediated neuroinflammation as a contributor—consistent with higher prevalence of depression in autoimmune (e.g., Hashimoto's) hypothyroidism, especially in females. Depressive symptomatology may arise even in subclinical or central hypothyroid states, where TSH and free T4 may not markedly deviate. Secondary processes, such as systemic inflammation (ESS), autoimmune dysfunction, and neuroendocrine crosstalk, complicate interpretation.

Women show stronger associations, reflecting higher rates of both hypothyroidism and depression, compounded by autoimmune vulnerability and sex hormone influences. Further younger age groups show more robust relationships, potentially due to differences in immune activation, resilience, and symptom reporting.

While previous studies confirm that modest positive association between TSH and depression, some have found no independent link after rigorous adjustment, indicating complex multifactorial etiology6. A meta-analysis showed that low-normal free T4 is a potential risk factor for future major depression, even among individuals considered euthyroid7. Reverse causality and residual confounding due to unmeasured psychiatric, psychosomatic or medication effects remain possible8.

Routine thyroid function testing, especially among patients presenting with moderate or greater depressive symptoms are recommended and potentially useful for tailoring psychiatric management in hypothyroid cohorts. Also endocrinological and psychiatric services should coordinate for integrated hypothyroidism-depression management, particularly for high-risk demographics.

CONCLUSION

There is a demonstrable, if modest, association between TSH/free T4 levels and depression severity (assessed by PHQ-9) in patients with hypothyroidism. TSH elevation and free T4 deficiency track with greater depressive symptom burden, particularly in women and younger adults. However, effect sizes are often small and may be modulated by demographic, autoimmune, and

methodological factors. Clinical practice should emphasize routine thyroid assessment in depressed patients and consider collaborative management approaches. Further longitudinal, mechanistic studies are necessary to clarify causality, define optimal screening intervals, and develop targeted interventions for this endocrine-psychiatric interface.

LIMITATIONS OF STUDY

Most evidence derives from cross-sectional studies, restricting causal inference. Longitudinal studies are needed to robustly confirm temporality and causality. Self-reported depression (PHQ-9) may be subject to information bias; future work employing structured clinical interviews could strengthen findings. Many studies are region-specific with limited ethnic or environmental diversity and limiting generalizability.

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