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Original Research Article

Thyroid Dysfunction and Depression: Correlates of Thyroid Hormone Levels and Thyroid Status with Depression Severity as Measured by the Hamilton Depression Rating Scale

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Abstract:

Background: Thyroid dysfunction is widely recognized as a contributor to mood disorders, yet the precise relationship between circulating thyroid hormone concentrations and the severity of depressive symptoms remains incompletely characterized, particularly across the spectrum from euthyroidism to overt hypothyroidism.

Objectives: To evaluate the association between thyroid status (euthyroid, subclinical hypothyroidism, overt hypothyroidism) and depression severity measured by the Hamilton Depression Rating Scale (HDRS), and to examine the independent contribution of serum T3, T4, and TSH levels after controlling for age and sex.

Methods: A cross-sectional study was conducted among 144 adults (74 female, 70 male; mean age 42.7 ± 17.3 years) classified into three thyroid groups: euthyroid (n=64), subclinical hypothyroidism (n=43), and overt hypothyroidism (n=37). Serum T3, T4, and TSH were measured. Depression severity was assessed using the HDRS. Spearman correlations, partial correlations controlling for age and sex, Kruskal-Wallis and Mann-Whitney U tests, chi-square analysis, multiple linear regression, and ANCOVA were performed.

Results: T3 showed a statistically significant negative correlation with HDRS (Spearman $r = -0.19$, $p = 0.026$), which remained significant after controlling for age and sex (partial $r = -0.20$, $p = 0.017$). T4 and TSH did not reach significance. The HDRS did not differ significantly across thyroid status groups (Kruskal-Wallis $H = 4.93$, $p = 0.085$); however, overt hypothyroid patients had a higher proportion of severe depression (43.2%) compared to euthyroid patients (18.8%). ANCOVA revealed a borderline-significant elevation in HDRS among overt hypothyroid patients relative to euthyroid controls ($\beta = +1.46$, $p = 0.080$). Age and sex were not significant confounders.

Conclusions: Lower serum T3 is independently associated with greater depression severity, suggesting a role for T3-mediated central nervous system effects in the pathophysiology of hypothyroid-related depression. Overt hypothyroidism demonstrates a clinically meaningful trend toward more severe depressive symptomatology. These findings support routine thyroid screening in patients presenting with depression.

Keywords: thyroid dysfunction; hypothyroidism; depression; Hamilton Depression Rating Scale; T3; TSH; subclinical hypothyroidism.

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Introduction

The relationship between thyroid function and mood has been recognized for over a century. Hypothyroidism — both overt and subclinical — is frequently associated with depressive symptoms, and thyroid dysfunction is among the most commonly screened medical causes in patients presenting with a new depressive episode. [1] Despite this clinical awareness, the quantitative relationship between specific thyroid hormone levels and the degree of depressive severity, as measured by validated instruments, remains a subject of active investigation.

The hypothalamic-pituitary-thyroid (HPT) axis regulates circulating concentrations of triiodothyronine (T3) and thyroxine (T4) through a feedback loop governed by thyroid-stimulating hormone (TSH). T3 is the biologically active form, binding to nuclear thyroid hormone receptors in the brain and influencing serotonergic, noradrenergic, and GABAergic neurotransmission.[2] Reductions

in T3 availability — whether primary (thyroid origin) or from impaired peripheral conversion of T4 to T3 — may therefore directly affect the neurobiological substrates of mood regulation.

Subclinical hypothyroidism (SCH), defined by elevated TSH with normal free T4, is estimated to affect 4–10% of the general population and is even more prevalent among women and older adults.[3] Whether SCH carries a meaningful risk of depressive symptoms comparable to overt hypothyroidism remains contested.[4] Cross-sectional studies have yielded heterogeneous results, partly due to differences in depression measures, hormone assays, and patient populations.

The Hamilton Depression Rating Scale (HDRS) is a clinician-administered instrument widely used in research to quantify depression severity across categorical strata (mild, moderate, severe, very severe).[5] It provides a continuous outcome suitable for regression-based analyses, making it useful for detecting associations with biological variables such as hormone levels.

The present study aimed to: (i) determine whether serum T3, T4, and TSH levels are independently correlated with HDRS scores after accounting for age and sex; (ii) compare depression severity across euthyroid, subclinical hypothyroid, and overt hypothyroid groups; and (iii) assess whether differences in depression severity by thyroid status persist after covariate adjustment.

Materials and Methods

Study Design and Participants: This was a cross-sectional observational study. This study is approved from institutional ethical committee. A total of 144 adult participants were enrolled after providing written informed consent from September to October 2023. Participants were classified into three groups based on thyroid function tests: (i) euthyroid (normal TSH, T3, and T4; n = 64), (ii) subclinical hypothyroidism (elevated TSH with normal free T4; n = 43), and (iii) overt hypothyroidism (elevated TSH with low T4; n = 37). Exclusion criteria included current use of thyroid replacement therapy, antidepressants, antipsychotics, or lithium; active medical illness other than thyroid disease; and a history of bipolar disorder or psychosis.

Thyroid Hormone Assessment: Fasting venous blood samples were collected in the morning. Serum total T3 (ng/mL), total T4 (ng/mL), and TSH (μIU/mL) were measured using standard immunoassay techniques. Reference ranges applied were: T3 0.69–2.15 ng/mL, T4 52–127 ng/mL, and TSH 0.3–4.5 μIU/mL

Depression Assessment: Depression severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17), administered by a trained clinician.[5] Total scores were interpreted as: 8–13 mild, 14–18 moderate, 19–22 severe, and ≥23 very severe depression. All participants scored ≥8, indicating at least mild depression at the time of assessment.

Statistical Analysis: Continuous variables were described using means and standard deviations. Spearman rank-order correlation was used to evaluate bivariate associations between hormone levels and HDRS scores. Partial correlations controlling for age and sex were computed to assess the independence of each hormonal predictor. Between-group differences in HDRS scores were evaluated using the Kruskal-Wallis test, with post-hoc pairwise Mann-Whitney U tests and Bonferroni correction. Chi-square analysis with Cramer's V was used to examine the association between thyroid status and HDRS category. Multiple linear regression was performed with HDRS as the dependent variable: Model 1 included T3, T4, and TSH; Model 2 additionally included age and sex. ANCOVA examined HDRS by thyroid status while covarying for age and sex, with euthyroid as the reference group. Statistical significance was set at $p < 0.05$. All analyses were performed using Python (SciPy, NumPy, pandas).

Results

Participant Characteristics: The sample comprised 144 participants (74 female, 70 male) with a mean age of 42.7 ± 17.3 years (range 16–82). The three thyroid groups were broadly comparable in age and sex distribution. Descriptive statistics for clinical and hormonal variables are presented in Table 1.

Table 1: Participant characteristics by thyroid status

Variable	Euthyroid (n=64)	Subclinical Hypo (n=43)	Overt Hypo (n=37)
Age, years (mean ± SD)	43.2 ± 17.1	41.8 ± 18.2	43.5 ± 16.8
Female, n (%)	33 (51.6)	23 (53.5)	18 (48.6)
T3, ng/mL (mean ± SD)	1.46 ± 0.24	1.13 ± 0.31	0.78 ± 0.22
T4, ng/mL (mean ± SD)	88.4 ± 17.2	80.3 ± 21.4	63.5 ± 22.8
TSH, μIU/mL (mean ± SD)	2.6 ± 0.9	7.8 ± 2.4	22.1 ± 11.3
HDRS score (mean ± SD)	17.3 ± 3.8	17.5 ± 4.5	18.8 ± 3.6

Correlation Between Thyroid Hormones and HDRS: Spearman correlation analysis revealed a significant negative association between T3 and HDRS score ($r = -0.19$, $p = 0.026$), indicating that lower T3 levels corresponded to higher depression severity. T4 showed a trend toward negative correlation ($r = -0.14$, $p = 0.090$) that did not reach statistical significance. TSH demonstrated a weak positive but non-significant association with HDRS ($r = +0.12$, $p = 0.137$). After controlling for age and sex via partial correlation, T3 remained significantly associated with HDRS (partial $r = -0.20$, $p = 0.017$). T4 showed a borderline partial correlation ($r = -0.16$, $p = 0.056$), while TSH remained non-significant ($r = +0.11$, $p = 0.195$). These results are summarized in Table 2.

Table 2: Spearman and partial correlations between thyroid hormones and HDRS score

Hormone	Spearman r	p-value	Partial r (adj. age, sex)	p-value
T3	−0.19	0.026*	−0.20	0.017*
T4	−0.14	0.090	−0.16	0.056
TSH	+0.12	0.137	+0.11	0.195

* $p < 0.05$

HDRS Scores Across Thyroid Status Groups: Mean HDRS scores were 17.3 ± 3.8 for euthyroid, 17.5 ± 4.5 for subclinical hypothyroid, and 18.8 ± 3.6 for overt hypothyroid participants. The Kruskal-Wallis test indicated a trend but did not reach statistical significance ($H = 4.93$, $p = 0.085$). Pairwise Mann-Whitney U comparisons with Bonferroni correction showed a borderline difference between euthyroid and overt hypothyroid groups ($U = 862.5$, $p = 0.023$ uncorrected; $p = 0.069$ corrected), with no significant differences for the other pairs.

Examination of HDRS severity categories revealed clinically meaningful distributional differences. Among overt hypothyroid patients, 43.2% met criteria for severe depression compared to 18.8% of euthyroid participants. Chi-square analysis of the thyroid status × HDRS category contingency table yielded $\chi^2(6) = 9.65$, $p = 0.140$, with a Cramer's V of 0.18, indicating a small-to-moderate effect size. Categorical distributions are shown in Table 3.

Table 3: Distribution of HDRS severity categories by thyroid status (%)

Thyroid Status	Mild (%)	Moderate (%)	Severe (%)	Very Severe (%)
Euthyroid (n=64)	9.4	60.9	18.8	10.9
Subclinical Hypo (n=43)	14.0	44.2	34.9	7.0
Overt Hypo (n=37)	5.4	40.5	43.2	10.8

Multiple Regression and ANCOVA: Multiple linear regression with HDRS as the outcome and T3, T4, and TSH as predictors (Model 1) explained 3.9% of the variance in HDRS ($R^2 = 0.039$, Adjusted $R^2 = 0.019$, F p = 0.131). Addition of age and sex (Model 2) marginally increased explained variance ($R^2 = 0.048$, Adjusted $R^2 = 0.013$, F p = 0.237), but neither age nor sex reached significance. In both models, T3 carried the largest standardized effect ($\beta = -2.42$ in Model 2) but did not reach individual significance when entered alongside T4 and TSH, consistent with multicollinearity among hormonal predictors. Regression coefficients are presented in Table 4.

Table 4: Multiple linear regression results (dependent variable: HDRS score)

Predictor	Model 1 β (SE)	p	Model 2 β (SE)	p
Intercept	21.01 (1.98)	<0.001	20.55 (2.10)	<0.001
T3	−2.27 (1.55)	0.145	−2.42 (1.56)	0.122
T4	−0.005 (0.022)	0.805	−0.006 (0.022)	0.787
TSH	−0.017 (0.037)	0.641	−0.022 (0.037)	0.553
Age	—	—	+0.009 (0.019)	0.623
Sex (female)	—	—	+0.645 (0.668)	0.337
R^2 / Adj R^2	0.039 / 0.019		0.048 / 0.013	

ANCOVA with thyroid status, age, and sex as predictors confirmed a trend toward higher HDRS in overt hypothyroid patients relative to the euthyroid reference group ($\beta = +1.46$, SE = 0.83, $t = 1.77$, $p = 0.080$). Subclinical hypothyroidism did not differ significantly from euthyroidism ($\beta = +0.09$, $p = 0.908$). Neither age ($\beta = +0.006$, $p = 0.761$) nor sex ($\beta = +0.535$, $p = 0.425$) was a significant covariate.

Discussion

The principal findings of this study are threefold. First, serum T3 is negatively and independently correlated with depression severity as measured by

the HDRS, with the association persisting after adjustment for age and sex. Second, overt hypothyroidism is associated with a clinically meaningful shift toward more severe depressive symptomatology relative to euthyroid status, with a borderline-significant difference in mean HDRS score. Third, subclinical hypothyroidism does not appear to confer additional depression severity beyond that seen in euthyroid individuals in this sample.

The independent association between T3 and HDRS score is consistent with the established neurobiological role of T3 in the central nervous system. T3 modulates serotonin receptor sensitivity, enhances norepinephrine turnover, and influences BDNF expression in limbic regions. [2] These mechanisms provide a plausible substrate by which even modest reductions in T3 — potentially within the 'normal' range — could contribute to depressive phenomenology. Notably, T3 was a stronger correlate than TSH, which is perhaps counterintuitive given that TSH is the principal diagnostic marker of thyroid dysfunction. This finding aligns with observations that TSH may not accurately reflect intracellular thyroid hormone availability, particularly in the brain, where local deiodination and transport mechanisms partially decouple central T3 from peripheral TSH levels. [6,7]

The lack of statistically significant group differences in mean HDRS across thyroid status categories, despite a trend (Kruskal-Wallis $p = 0.085$), likely reflects limited statistical power. The relatively modest sample size ($n = 144$) and the heterogeneity of HDRS scores within each group reduce power to detect small-to-moderate differences. The observed effect size (Cramer's $V = 0.18$ for categorical analysis) and the ANCOVA beta coefficient of +1.46 for overt hypothyroidism are clinically meaningful and warrant investigation in a larger study. Similar findings have been reported by Bauer et al., who noted that subclinical hypothyroidism was not consistently associated with depression severity, while overt hypothyroidism showed a more reliable association.[8]

The absence of confounding by age and sex is noteworthy. While thyroid dysfunction is more prevalent in women and older adults, and depression prevalence similarly varies by sex and age, these demographic factors did not account for the T3-HDRS relationship in the present sample. This finding is consistent with Joffe and Marriott's observations in clinical populations that the thyroid-mood relationship holds independently of sex. [9]

The multicollinearity observed among thyroid hormones in the regression models is an important methodological consideration. T3, T4, and TSH are physiologically inter-related, and their simultaneous inclusion in a regression attenuates individual coefficient significance despite the robust partial correlation for T3. Future studies may benefit from computing composite thyroid indices or employing latent variable approaches to better capture overall thyroid axis activity. [10,11]

Several limitations should be acknowledged. The cross-sectional design precludes causal inference. Total rather than free T3 and T4 were measured, which may introduce confounding by binding protein variation. Severity of thyroid dysfunction was not formally graded within each category. The sample was drawn from a clinical population, limiting generalizability to community-based cohorts. Furthermore, comorbid anxiety, which commonly co-occurs with both hypothyroidism and depression, was not systematically assessed and may have influenced HDRS scores.

Conclusions

This study demonstrates that lower serum T3 is independently associated with greater depression severity as measured by the Hamilton Depression Rating Scale, even after controlling for age and sex. Overt hypothyroidism is associated with a trend toward higher HDRS scores and a markedly elevated proportion of patients meeting criteria for severe depression. These findings reinforce the clinical importance of thyroid hormone assessment in depressed patients and suggest that T3 — rather than TSH alone — may be a more sensitive marker of depression-relevant thyroid insufficiency. The sample size and study duration being a limiting factor in this study, further prospective studies examining the effect of thyroid hormone normalization on HDRS outcomes, as well as studies incorporating free T3 and central thyroid indices, are warranted.

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