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Depressive Symptoms in Different Ranges of TSH in Patients with Subclinical Hypothyroidism

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Abstract

Objectives: Depressive symptoms are a prevalent issue associated with subclinical hypothyroidism (SCH). Despite receiving levothyroxine (LT-4), many patients continue to exhibit neuropsychological symptoms even after achieving a euthyroid state (<4.0 mIU/L). The aim of this study was to evaluate the association between thyroid stimulating hormone (TSH) levels and depressive symptoms in SCH in different TSH ranges.

Methods: 144 participants were recruited and biochemical measurements done for thyroid profile and they were divided into four groups: 1) Individuals with no history of thyroid issues (TSH < 2.5mIU/L), 2) Newly diagnosed patients (TSH range ≥2.5mIU/L); 3) Patients with TSH levels ≥4.0mIU/L (ongoing LT-4), 4) Euthyroids with TSH levels <4.0mIU/L (ongoing LT-4). Depressive symptoms were evaluated with Hamilton depression rating scale.

Results: A positive association with a significant value ($p = 0.009$) was found in Group 2, with a correlation coefficient value of $r = 0.43$.

Conclusion: The present study concluded that early and regular screening for hypothyroidism appears warranted for patients stating neuropsychological complaints. Patients with SCH presenting with distressing neuropsychological symptoms (especially depressive symptoms), clinicians may possibly consider the initiation of LT4 at a TSH level of ≥ 2.5 mIU/L.

Keywords: Depression, hypothyroidism, thyroxine, thyrotropin

Main Points

1. Positive correlation between TSH levels and HDRS scores in newly diagnosed patients with SCH with TSH value ≥2.5 mIU/L: This correlation suggests that TSH ≥2.5 mIU/L is an optimal cut-off value for expecting depressive symptoms.

2. Effects of LT-4 treatment on depressive symptoms: The findings of the current study suggest LT-4 may be effectively improving depressive symptoms. Therefore, in patients with SCH presenting with distressing neuropsychological symptoms, physicians may possibly consider the initiation LT-4 treatment for patients with SCH at a TSH level of ≥ 2.5 mIU/L.

3. Association between Hypothyroidism and neuropsychological symptoms: Early and regular screening for hypothyroidism appears warranted for individuals experiencing neuropsychological complaints such as fatigue, depressive symptoms, lack of memory and insomnia.

INTRODUCTION

The hypothalamic-pituitary-thyroid axis (HPT) is an intricate chemistry between several factors, such as deiodinase enzymes, thyroid stimulating hormone (TSH), transporter proteins, and receptors. The interactions of these factors may contribute to better explicating the pathophysiology of depression. Thyroid hormone (TH) secretion is delimited by TSH, which itself is stimulated by hypothalamic thyrotropin-releasing hormone (TRH), and it is downregulated by TH (Duval *et al.*, 2021).

The thyroid secretes 20% of triidothyronine (T3) in the cerebral cortex, whereas the other 80% comes from the local conversion of thyroxine (T4) via deiodination. The majority of T4 enters the brain via a number of transporters, including transthyretin (TTR). TH transports a protein produced by the choroid plexus and released into cerebrospinal fluid. Deiodination occurs at intracellular level, mostly in glial cells, and T4 must reach these cells via specialised plasma membrane carrier proteins such as organic anion transporter polypeptide 1 (OATP1C1) and monocarboxylase transporter. The former preferentially transports T4 and rT3, whereas the latter is more selective to T3 transport. In glial cells, the deiodinase enzyme type 2 converts T4 to T3 when it is inactivated. The latter also deiodinates T3, converting it into inactive T2. T3's activities are refereed via requisite to thyroid hormone nuclear receptors (THR). The adult brain has the highest expression of THR-α, accounting for 70-80% of THR distribution. Thus, the HPT axis involves numerous paths, and impairment in certain of its components has been associated with behavioural abnormalities such as depressive symptoms(Ma, Wang and Zhang, 2024). Based on this, many scholars have used the term “brain hypothyroidism”(Nuguru *et al.*, no date).

TH together with TSH plays an extensive role in brain development. In 1786, the association between brain and thyroid was first reported. In 1873, Gull first demonstrated the connection between myxedema and psychosis, which was later confirmed by the Committee of the Clinical Society in 1888. In 1949, Asher coined the term “myxedema madness” to describe the mental state in hypothyroidism. Depression is associated with endocrine disorders such as thyroid dysfunctions. In the guidelines of 2002, the American Association of Endocrinologists stated that depression must be measured in subclinical hypothyroidism (SCH) population. Depressive symptoms are a prevalent issue(Demartini *et al.*, 2014), with potential risk factors such as SCH and thyroid autoimmunity(Almeida *et al.*, 2007).

SCH is characterized by elevated TSH levels above the reference range while maintaining normal levels of free triiodothyronine (fT3) and free thyroxine (fT4). In the general population, it has a prevalence rate of 3% to 8.5% (Kumar *et al.*, 2025).

TSH levels between 4.5 and 9 mIU/L are referred to mild SCH, whereas severe SCH is referred as when TSH levels reach 10 mIU/L or higher, both with normal free T4 levels (Fatourechi, 2009). However, clinical controversy exists concerning the upper limit of the normal TSH reference range in SCH. Some review studies suggest a value of 4.5–5.0 mIU/L for the TSH upper limit. In previous review study, it is documented that most laboratories express 4 mIU/L as the upper limit, but some experts and proficient organizations recommend values of 2.5-3 mIU/L as the appropriate upper threshold(Raza and Mahmood, 2013). The study of the National Health and Nutrition Examination Survey (NHANES-III) has stated euthyroid status with a value between 0.45mIU/L and 4.12mIU/L, irrespective of symptoms present (Dhir, Jain and Merritt, 2024).

Despite receiving levothyroxine (LT-4), many patients with SCH continue to exhibit neuropsychological symptoms (such as fatigue, depressive symptoms, lack of memory and insomnia) even after achieving a euthyroid state (<4.0 mIU/L), leading clinicians to suggest that elevated TSH levels may have persistent long-term consequences for these symptoms(Samuels *et al.*, 2008). A clinical consensus has emerged supporting a symptom-based approach to diagnosis and treatment. Based on this perception, asymptomatic individuals with TSH levels ≤4.0 mIU/L should be considered euthyroids; however, when patients with SCH present with depressive symptoms, a TSH cut-off value of 2.5 mIU/L may permit the initiation of LT-4 (Talaei *et al.*, 2017).

Considering the role of THs in sustaining mood or behavior constancy in SCH. A connection between SCH and depressive symptoms has been assumed for many years. However, the true nature of this connection and recovery from these symptoms has not been fully determined. Therefore, we hypothesized that this may be related to the TSH range. There was a need to establish a potential link between depressive symptoms in SCH across different TSH ranges. Additionally, to strengthen the therapeutic guidelines for the initiation of LT-4 in patients having neuropsychological symptoms.

Aim of the study: To evaluate the association between TSH levels and depressive symptoms in patients with SCH in varying ranges of TSH. It was hypothesised that newly diagnosed patients with SCH (TSH ≥ 2.5 mIU/L) would show more depressive symptoms than euthyroid patients (TSH <4.0 mIU/L), as well as those patients who were on LT-4 treatment might have recovered from these symptoms.

MATERIALS AND METHODS

Study design and participants: This was a cross-sectional observational type of study, conducted on patients with SCH along with individuals with no thyroid issues. Patients with SCH were recruited from the multiple health centers of the city. Individuals with no thyroid issues were recruited from the local community of the city. The study was conducted between May 2022 to May 2025.

This observational study used the guidelines of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE). Ethical approval was taken from the Institutional Ethics Committee (dated: 07/04/2022) and the study is also recorded under Clinical Trial Registry of India (CTRI/2022/04/042319). The study was conducted in accordance with the Declaration of Helsinki 2013. Informed consent in written form was obtained from the participants.

The sample size was determined by $n= (Z_{1-\alpha/2})^2 + Z_1 - \beta)^2/ES$, taking into account the following variables: n= designed sample size; ES= 0.27(Demartini *et al.*, 2014), effect size; $\alpha = 0.05$, significance level; $1-\beta = 0.90$, statistical power (type II error); $Z_{1-\alpha/2} = 1.96$ for 5% of α, a standard and critical value for the corresponding level of confidence (type-I error); $Z_1-\beta = 1.282$ for 90% power i.e., 1-β;$n = (1.96 = 1.282)^2 / 0.27 = (3.24)^2 / 0.0729 = 10.4976/0.0729 \approx 143.5$ (n= 144).

Eligibility criteria: Participants from the general population of the local community: individuals with no thyroid issues and diagnosed patients with SCH:

1. Newly diagnosed patients reported neuropsychological symptoms (such as fatigue, depressive symptoms, lack of memory and insomnia) and no past history of thyroid issues.
2. Patients already on LT-4 treatment, presented with hypothyroidism symptoms (such as fatigue, weight increase, constipation, cold intolerance, insomnia, dry skin, and hearing loss) or elevated and uncontrolled TSH values.
3. Euthyroid patients (ongoing LT-4 treatment)

Exclusion Criteria were individuals with other psychiatric disorders and with drug history for psychiatric disorders; a diagnosis of mental retardation (intelligence quotient < 70) or dementia.

Thyroid function test and study groups: Biochemical measurements were taken for the thyroid function tests. The blood sample was taken in the morning (8:00 am to 10:00 am) with fasting status of the participants. The estimation of serum TSH level in mIU/L, free T3 (fT3) in ng/mL and fT4 in µg/dL was done with mini VIDAS (automated immunoassay system) by the certified laboratory technologist. Report of the thyroid profile was verified by the pathologist.

Categorization of the participants based on thyroid profile:

Group 1: Individuals with no history of thyroid issues (TSH range < 2.5mIU/L)

Group 2: Newly diagnosed patients with TSH range ≥2.5mIU/L

Group 3: Patients with TSH levels ≥4.0mIU/L (ongoing LT-4 treatment)

Group 4: Euthyroid patients with TSH levels <4.0mIU/L (ongoing LT-4 treatment)

Clinical interview - assessment of depressive symptoms: Depressive symptoms were assessed by using HDRS. It consists of 17 questions. Nine questions were asked regarding depressive mood, feelings of guilt,

suicide, work & activities, retardation, agitation, anxiety psychic, anxiety somatic, and hypochondriasis, where each question is recorded on a 0 to 4 point scale. Single question was asked concerning loss of weight, which is scored on a 0 to 3 point scale. Seven questions concerning insomnia (early in the night), insomnia (middle of the night), insomnia (early hours of the morning), somatic symptoms gastro-intestinal, general somatic symptoms, genital symptoms, and insight were asked, where each question is recorded on a 0 to 2 point scale. Total scores were recorded according to their responses. Participants were assessed according to their scores: absence of depressive symptoms or no depression (score, 0-7), mild depressive symptoms or mild depression (score, 8-17), moderate depressive symptoms or moderate depression (score, 18-24), and severe depressive symptoms or severe depression (score, ≥25).

Statistical analysis: Statistical analysis was done with SPPS version 27.0 (IBM SPSS Statistics for Windows- IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was utilized for the analysis of the normal distribution of demographic and clinical data. Descriptive statistics were taken into account for the analysis of the demographic data and clinical symptoms. Non-parametric test- the Spearman's rank correlation analytic test was used to inspect the association between TSH levels and HDRS scores. The detailed descriptive values were taken for each component of the HDRS across study groups.

RESULTS

108 patients with SCH and 36 individuals with no thyroid issues were recruited, and the data were analysed for results. Descriptive values were used to demonstrate the demographic data and clinical symptoms, as shown in Table 1. Further analysis was done for correlation results between TSH levels and HDRS scores. A positive association with a statistically significant value ($p = 0.009$) was found in Group 2 (newly diagnosed patients), with a correlation coefficient value of $r = 0.43$, as shown in Figure 1. The frequency values were used to demonstrate the results for each component of HDRS across all study groups (Supplementary File).

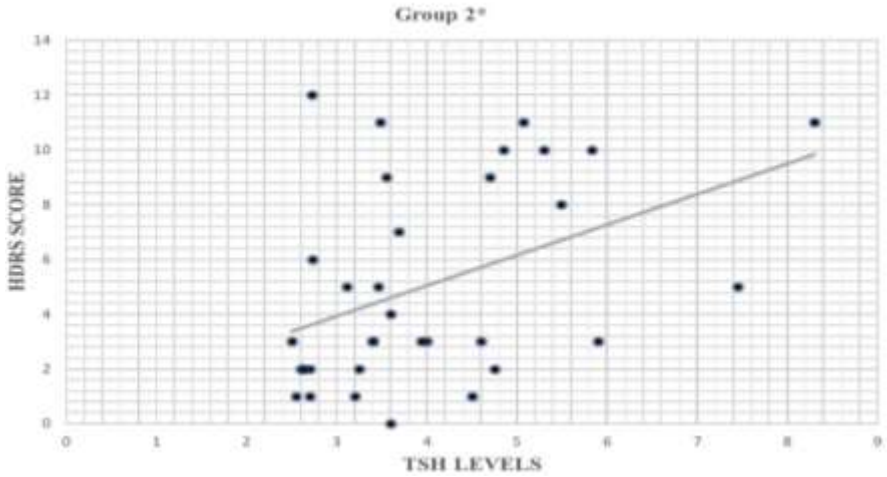

Fig 1: shows the positive correlation between the TSH levels and HDRS scores in Group 2 (newly diagnosed patients with TSH range > 2.5 ml U/L). The correlation was moderate, where correlation coefficient r=0.43 and p=0.009, indicating that significant depressive symptoms were observed in newly diagnosed patients with SCH

Table 1: Descriptive results of demographic and clinical symptoms (n=144)

Variables	Group 1 (n=36)	Group 2 (n=36)	Group 3 (n=36)	Group 4 (n=36)
Age (years)	36.22±8.85	36.72±7.98	38.22±9.7	39.27±9.24
Gender	F=30; M=6	F= 31; M=4	F= 35; M=1	F= 34; M=3
HDRS	1.97±1.62	4.72±3.76	4.25±3.12	2.47±2.03
TSH (mIU/L)	1.69±0.72	3.99±1.36	13.30±19.85	2.44±0.92
T3 (pmol/L)	1.57±1.43	1.17±0.58	1.05±0.54	1.07±0.50

Free T4 index (ug/dl)	7.71±2.42	8.43±1.70	8.88±1.70	8.98±1.43
Duration of LT-4 treatment (years)	-	-	3.75±3.33	4.19±3.56
Fatigue	52.8%	80.6%	91.7%	58.3%
Weight Gain	16.7%	38.9%	72.2%	13.9%
Insomnia	22.2%	47.2%	63.9%	47.2%
Lack of memory	08.3%	83.3%	86.1%	44.4%
Depressive symptoms	13.9%	86.1%	77.8%	58.3%
Cold intolerance	05.6%	33.3%	36.1%	27.8%

Abbreviations: M-Male; F-Female; HDRS- Hamilton Depression Rating Scale; TSH - Thyroid Stimulating Hormone; T3-thyroxine; T4-Triiodothyronine Group 1 = Individuals with no history of thyroid issues; Group 2= Newly diagnosed patients with TSH levels ≥ 2.5 mIU/L; Group 3=Patients with TSH levels ≥4.0mIU/L (ongoing LT-4 treatment); Group 4=Euthyroid patients with TSH levels < 4.0mIU/L (ongoing LT-4 treatment).

Table 1. shows the mean and the standard deviation for the continuous variables (age, HDRS, TSH, T3, T4) and the frequency (%) for the categorical variables (fatigue, weight gain, insomnia, lack of memory, depressive symptoms and cold intolerance). Mean age was near to similar in all groups. Frequency of fatigue, weight gain, insomnia, cold intolerance, dry skin, and hearing loss was higher in Group 3, indicating that patients with elevated TSH levels had higher hypothyroidism symptoms. The frequency of lack of memory and depressive symptoms was greater in all 3 patient groups, indicating that these clinical symptoms were present in the spectrum of SCH. Remarkably, depressive symptoms are present with the highest frequency in newly diagnosed patients with SCH having neuropsychological complaints.

DISCUSSION

The present study examined the depressive symptoms in patients with SCH across different TSH ranges as well as the effect of LT-4 on the reversibility of these symptoms. Our results revealed a significant positive correlation between TSH levels and HDRS scores in newly diagnosed patients with SCH (≥2.5 mIU/L). This is endorsed with the suggestion of the previous study that TSH ≥2.5 mIU/L is an optimal cut-off value for expecting depressive symptoms. Our results are consistent with previous research (Chueire *et al.*, 2003; Davis, Stern and Flashman, 2003; Gulseren *et al.*, 2006; Almeida *et al.*, 2007; Demartini *et al.*, 2014), but the findings of these studies have the limitation of a pre-set TSH range.

A significant positive correlation between TSH levels and HDRS scores in Group 2 (patients with TSH levels of ≥2.5 mIU/L) was seen in the current study. The correlation is moderate but it is suggesting important clinical implications. Although the mean HDRS score in Group 2 was 4.72±3.96, indicating subclinical depression levels, 86.1% of these patients exhibited depressive symptoms, higher than other groups in the current study. This finding supports previous research, which suggests that TSH levels ≥2.5 mIU/L are an optimal cut-off point for predicting depressive symptoms in patients with SCH(Talaei *et al.*, 2017).

However, in Group 4 (euthyroid patients with TSH <4.0 mIU/L), there was no significant association between TSH levels and HDRS scores, indicating that TSH normalization following LT-4 treatment relates to reduced depressive symptoms. This aligns with previous research(Vishnoi *et al.,* 2014), who demonstrated a positive connection between scores of HDRS and TSH levels, with significant improvements in both measures after two months of LT-4 treatment. Despite receiving LT-4 treatment, Group 3 continues to experience depressive symptoms, although to a lesser extent than Group 2. This could be attributed to the elevated levels of TSH in Group 3.

The findings of the current study suggest LT-4 may be effective for improving depressive symptoms, supporting previous studies(Rack and Makela, 2000; Bauer *et al.*, 2008). Therefore, screening and managing hypothyroidism are recommended in depression population.

Additionally, results suggest in patients with SCH presenting with distressing neuropsychological symptoms, physicians may possibly consider the commencement of LT-4 in SCH at a TSH value of ≥ 2.5

mIU/L. The relation between elevated TSH and the depressive symptoms likely reflects thyroid hormones' complex influence on the HPT and neurotransmitter systems. Elevated levels of TSH have been linked to depressive symptoms, indicating that an increase in TSH may disrupt the stability of the 5-HT (serotonin) system. Additionally, may contributing to development of depression in patients with SCH (Pasqualetti *et al.*, 2015).

The present study was not without limitations. The inherent nature of the cross-sectional study did not allow the longitudinal follow up of patients. Subjects were not evaluated for their dosage of LT-4, which could potentially impact their depressive symptoms.

CONCLUSION

Based on the findings of the present study, early and regular screening for hypothyroidism appears warranted for individuals experiencing neuropsychological complaints. Additionally, results suggest in patients with subclinical hypothyroidism presenting with distressing neuropsychological symptoms (especially depressive symptoms), clinicians may possibly consider the initiation levothyroxine for patients with subclinical hypothyroidism at a TSH level of ≥ 2.5 mIU/L.

Prospects for further research: Randomized clinical controlled trials with longitudinal follow-up of patients are essential for understanding the natural progression of depressive symptoms in the course of hypothyroidism and evaluating efficacy of LT-4 in recovering these symptoms.

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