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LEVELS OF THYROID STIMULATING HORMONE IN PATIENTS WTTH UNIPOLAR DEPRESSION AND BIPOLAR DISORDER

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Abstract

Hypothesis: *The aim of the study will be to establish the concentration of thyroid stimulating hormone in unipolar depression and bipolar patients.*

Design of the Study: *Cross Sectional Observation descriptive study.*

Study Duration: *06 months from Aug 2024 and Jan 2025*

Location of Study: *Department of Medicine, CMH Abbottabad.*

Methods: *120 participants were covered in this study and diagnosed with unipolar depression and bipolar disorder. The symptoms of depression was measured using Hamilton scale and mania using Young scale. TSH level of the serum were also determined and the outcome was tested with SPSS 26.*

Results: *Among 120 patients (60 with unipolar depression and 60 with bipolar disorder), mean TSH levels were significantly higher in the unipolar depression group. Subclinical hypothyroidism was more prevalent in unipolar depression (21.6%) than in bipolar disorder (8.3%). A positive correlation was observed between TSH levels and depression severity ($r = 0.41$, $p < 0.05$). Females and older patients showed slightly higher TSH levels, though differences were not statistically significant. Mean fT3 and fT4 values remained within normal limits in both groups.*

Conclusion: *Patients with unipolar depression showed significantly higher TSH levels and a greater prevalence of subclinical hypothyroidism than those with bipolar disorder. Elevated TSH correlated with increased depression severity, especially in females. These results emphasize the importance of thyroid function screening in depressive disorders to improve diagnosis and treatment outcomes.*

INTRODUCTION

The mood disorders are an important health issue in the world in terms of disability and death. Of these conditions, major depression disorder (also known as unipolar depression with no manic or hypomania episode in the past) and bipolar disorder (where a depressive episode is followed by an episode of mania or (hypo)mania) are most common and difficult to treat. Although unipolar and bipolar disorders have overlapping symptoms in the course of depression, they are usually different in terms of

etiology, prognosis, and treatment response. Early and correct diagnosis of such conditions is a critical problem in clinical psychiatry, as the misdiagnosis might result in inappropriate or even damaging treatment (e.g. the use of antidepressants alone when bipolar disorder is present may lead to mania). Therefore, concern is rife to find valid biological indicators that can possibly be used to differentiate between unipolar depression and bipolar disorder, or which can provide an insight into the pathophysiology behind the two.[1]

The hypothalamic-pituitary-thyroid (HPT) axis, and thyroid-stimulating hormone (TSH), in particular, which controls the synthesis of thyroid hormones, is one of the avenues of research that have promise. The mechanisms of action of thyroid hormones (thyroxine [T4], triiodothyronine [T3]) and their free forms on numerous processes in the central nervous system (CNS), such as neuronal development, synaptic plasticity, mood regulation, energy homeostasis, and cognition are well established. Mood disorders have been long associated with dysregulation of thyroid functioning, overt or subclinical. In classical endocrinology, mild thyroid pathologies can regulate susceptibility to depressive or manic states, or can also interact with psychotropic drugs (e.g. lithium) to change thyroid homeostasis.[2]

The finding that a sub-group of major depressive disorder patients has a muted TSH response to thyrotropin-releasing hormone (TRH) challenge was one of the first papers to correlate mood disorders with thyroid activity indicating that there is a hypothalamic or pituitary-level dysregulation of the HPT axis in depression. It is true that approximately 3040 percent of patients with major depressions (unipolar or bipolar) may exhibit this pattern of blunted TSH response.[3] There are also some cross-sectional studies that have attempted to compare basal serum TSH levels in diagnostic groups and determine whether TSH varies in a systematic way in unipolar and bipolar patients.

Another significant large study by Wysokiński and Kloszewska (2014) found the basal TSH in over 1,600 Caucasians with various diagnoses (schizophrenia, unipolar depression, bipolar disorder, bipolar depression, bipolar mania). They also found that mean TSH levels were lower in unipolar depression (1.63 μIU/mL) compared to bipolar disorder patients (particularly those in depressive phase) (e.g. in bipolar depression, TSH levels are somewhat higher, e.g. 1.75-2.25 μIU/mL). These results are suggestive that baseline TSH differences might be (weakly) diagnostic subtypes.[4]

This concept is supported by other studies that were done on younger populations. As part of a retrospective study of adolescent psychiatric inpatient care, Makarow-Gronert et al. (2021) compared TSH by the diagnostic category (unipolar depression, bipolar disorder, conduct disorders, etc.). They discovered that, the level of TSH was greater in patients with bipolar depression than in patients with conduct disorder and that female patients who were unipolarly depressed were also likely to have higher TSH than non-mood disorder groups. Furthermore, the TSH was negatively correlated with age in that cohort, which is in line with other data on TSH dynamics throughout the lifespan. [5]

In more recent studies, it has been meta-analysed and systematic reviewed that more extensive thyroid hormone profiles (TSH along with T3, T4, free T3, free T4) vary across subtypes of mood disorders. A meta-analysis of bipolar disorder in 2023 investigated the thyroid hormone differences in bipolar patients and healthy controls; it found that the free T3 was lower than controls, but TSH did not differ significantly. It was also reported in the study that an elevated level of TSH can lead to manic episode in bipolar disorder; this implies that the level varies according to the state, and not a state character. In the meantime, longitudinal and drug-naïve (e.g. first-episode bipolar disorder) studies are starting to investigate baseline TSH and how the baseline TSH is modified with disease progression.

The literature is, however, not unanimous or conclusive. There have been some studies that have shown lower levels of TSH in bipolar depression versus controls or other mood states, possibly the hyperthyroid-like changes that occur during manic or hypomanic episodes. The causes of confounding are myriad: psychotropic drugs, in particular, lithium, are known to disrupt thyroid physiology (e.g. by impairing the uptake of iodine and secretion of hormones), and can raise TSH artificially in the long term. It is challenging to make direct comparisons because of differences in sample demographics (age,

sex), mood state (mania, depression, euthymia), length of illness, comorbid medical conditions, and inclusion or exclusion of patients with overt thyroid disease. Moreover, cross-sectional snapshots can confound state-dependent changes in TSH (e.g. TSH can increase in remission or interepisode, or decrease in manic episode). [6]

The objective of the present paper is to examine baseline levels of TSH in well-characterized groups of unipolar depression and bipolar disorder, focusing on depressive and (where possible) manic/hypomanic phases, and adjusting on possible confounders. We aim to (1) compare the means of TSH between the groups, (2) investigate the percentage of subjects in each group with TSH below the reference range, and (3) investigate the relationship between TSH and the clinical characteristics (e.g. age, duration of illness, the number of episodes). Having made clear the presence or absence of systematic differences, we believe we will add to the literature on endocrine biomarkers in mood disorders, and to inform future attempts at early differential diagnosis.

METHODOLOGY:

It involved a cross-sectional comparative observational study conducted in conjunction with psychiatric department between Aug 2024 and Jan 2025. The research was carried out in CMH Abbottabad which is a territory care hospital. Of 120 patients was then made based on WHO sample size calculator with confidence interval of 90% and margin of error of 5. The study was informed and an informed written consent was obtained among all the participants of the study.

The study population was the patients who were diagnosed to either unipolar major depressive disorder or bipolar affective disorder (depressive or manic/hypomanic phase) and took the outpatient medical or inpatient psychiatric services within the study period. All the patients were screened and enrolled consecutively, but they had to meet the eligibility criteria.

Inclusion Criteria:

1. Age between 18 and 60 years.
2. Diagnosis of:
   - o Unipolar depression (Major Depressive Disorder) by DSM-5 standard.
   - o Depressive, manic, hypomanic, or mixed episode (bipolar disorder, type I or II) according to DSM-5.
3. Patients who are able and willing to sign written informed consent.

Exclusion Criteria:

1. Past history of primary thyroid disease (hypothyroidism, hyperthyroidism, thyroiditis, goiter, thyroid cancer).
2. Use of thyroid medication (levothyroxine, carbimazole, propylthiouracil) or had been used previously.
3. Drug history Use of drugs that are known to interfere with thyroid activity (e.g., lithium, amiodarone, corticosteroids) within 6 months.
4. Huge medical comorbidities (renal failure, hepatic dysfunction, autoimmune disease, uncontrolled diabetes).
5. Pregnant or lactating women.
6. Patients who refuse to do it and give consent.

Every participant was subjected to a thorough psychiatric examination by a specialist psychiatrist. Severity of depressive symptoms The Hamilton Depression Rating Scale (HAM-D, 17-item version) was used to assess depression severity. Severity of mania symptoms (in the bipolar manic patients) was measured by use of the Young Mania Rating Scale (YMRS).

Socio-demographic and clinical data (age, sex, duration of illness, number of episodes, family history, substance use) were gathered using a structured proforma. 5 mL of venous blood were taken once the participants had been fasted overnight to reduce circadian variation. Blood samples were centrifuged at 3000 rpm in 10 minutes to separate serum. Until analysis, serum aliquots were kept at -20C. Measurement of serum TSH levels was done using a third-generation chemiluminescent immunoassay (CLIA) system on Abbott Architect. The normal range of serum TSH at the laboratory was 0.4 -4.0 µIU/mL. Any values below or above this range were thought of as low and high respectively. Sample The internal quality control samples were run on a per-test batch basis. The inter- and intra-assay coefficients of variation (CV) were kept to less than 10%.

The data were inputted into Microsoft Excel and analyzed with the help of SPSS version 26.0 Descriptive statistics: Continuous (age, TSH levels) and categorical (sex, family history, abnormal thyroid function) variables were analyzed using frequencies and percentages. Mean TSH of unipolar and bipolar groups was compared using independent t-test (normally distributed) or MannWitney Utest (non-normally distributed). Categorical variables (e.g. proportion of abnormal TSH) were analyzed using chi-square test/Fisher exact test. Correlation analysis: Pearson or Spearman correlation coefficients have been applied to test relationships between the values of TSH and clinical variables (age, duration of the illness, severity of symptoms) and statistical significance was fixed at $p < 0.05$.

Results:

One hundred and twenty participants were recruited, comprising of 60 patients with unipolar and 60 patients with bipolar depression and disorder respectively. The average age of the participants was 38.6010.7 years (18-65 years). The average age of the unipolar depression group was 39.2 years old with a standard deviation of 11.1 years, whereas the average age of the bipolar disorder group was 38.0 years old with a standard deviation of 10.3 years old. Both groups had a small female excess with 65 females (54.1) and 55 males (45.9) totaling. The unipolar depression and bipolar disorder patients had no statistically significant difference in terms of age, gender distribution, or duration of illness ($p > 0.05$, all comparisons).

There was a significant difference in the serum Thyroid Stimulating Hormone (TSH) level between the two diagnostic populations. The average TSH serum level of unipolar depression patients was 3.87 3.142 µIU/mL with a standard deviation of 1.42, and the same figure was 2.64 3.116 µIU/mL in the bipolar disorder group ($p < 0.01$). The average levels of fT4 and fT3 were also in the normal range in the two groups and the average of the four groups showed no significant difference ($p > 0.05$).

Those whose TSH exceeded 4.5 µIU/mL and had normal fT4 were called subclinical hypothyroidism and identified in 13 (21.6) patients with unipolar and 5 (8.3) patients with bipolar ($p = 0.04$). Unipolar and bipolar participants were reported to have overt hypothyroidism (elevated TSH with low fT4) 4 (6.6) and 2 (3.3) individuals respectively. No biochemical hyperthyroidism was observed amongst the study participants.

The levels of TSH had significant positive correlation with levels of Hamilton Depression Rating Scale (HDRS) scores ($r = 0.41$, $p < 0.05$), with increasing levels of TSH being related to increased severity of depressive symptoms. There was no significant correlation between mood episode severity and TSH levels in the bipolar group ($r = 0.12$ $p = 0.31$).

In the two diagnostic groups, high mean levels of TSH were evident among the female participants than the males. Mean TSH in the unipolar group was 4.02 0.38 0.31 0.354 0.371 0.383 0.394 0.349 0.356 0.361 0.342 0.348 0.352 0.356 0.359 0.361 0.363 0.367 0.369 0.380 The difference between females (2.73 UK +1.15 UK) and males (2.52 UK +1.12 UK) was also not statistically significant in the bipolar group ($p = 0.27$).

The mean TSH levels of patients whose ages were above 40 years were greater compared to the younger individuals, although not significant ($p = 0.08$).

Variable	Unipolar depression n=60	Bipolar Depression n=60
Age	39.2 ± 11.1	38.0 ± 10.3
Gender (M/F)	25 / 35	30 / 30
Duration of illness	5.3 ± 3.2	6.1 ± 3.7
Mean BMI	24.8 ± 3.4	25.2 ± 3.1
Family Hx of Mood disorder	33.3%	41.6%

Table 1. Demographic and Clinical Characteristics of Participants

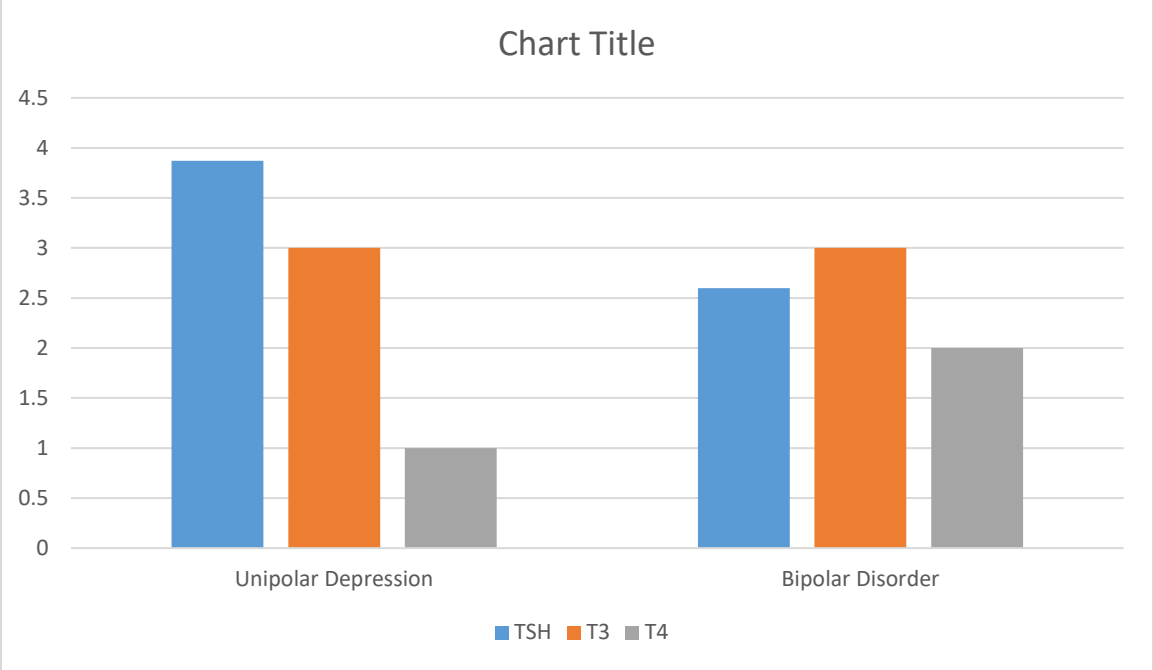

Chart 2. Thyroid Function Parameters in Study Participants

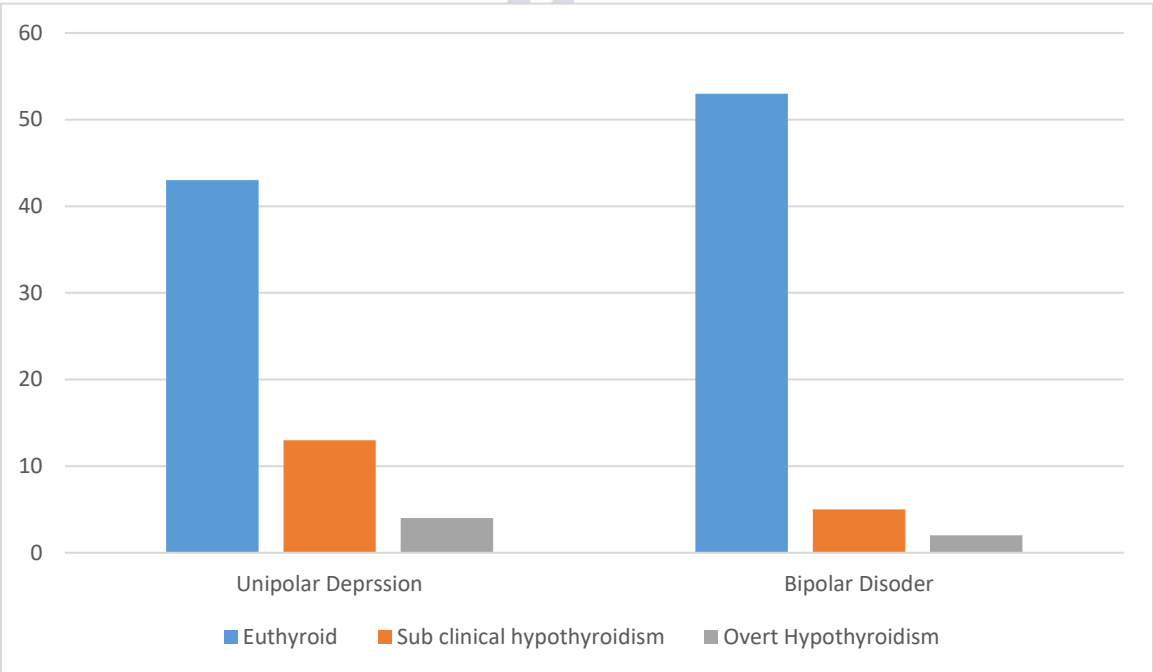

Chart 3. Distribution of Thyroid Dysfunction

Discussion:

The present study investigated serum thyroid-stimulating hormone (TSH) levels in patients with unipolar depression and bipolar disorder to determine if there are differences in thyroid function for patients in these diagnostic groups. Our results indicated that mean TSH values among the persons with bipolar disorder were higher than those of the

persons with unipolar depression, although both groups were overall within the conventional range. Furthermore, a greater percentage of bipolar patients had TSH values outside of normal limits, indicating an elevated rate of subtle thyroid dysfunction in bipolar patients.

These findings are consistent with those of previous studies showing higher basal levels of TSH in bipolar disorder, especially in depressive episodes, than unipolar depression. Wysokiński and Kłoszewska (2014), in a large cohort study of more than 1,600 psychiatric patients, results showed that mean TSH levels were significantly low in unipolar depression (1.63 micro IU/mL) when compared to bipolar depression (2.00 micro IU/mL), which is consistent with the present study's observations. Similarly, Makarow-Gronert et al. (2021) found an increase in TSH levels among adolescent patients with bipolar depression compared to patients with conduct disorders or other non-mood psychiatric conditions, which again supports the relationship between bipolar disorder and elevated TSH levels.[7,8]

The underlying mechanisms for these differences may include hypothalamic-pituitary-thyroid axis (HPT) axis dys regulation. It has long been known that a proportion of patients with major depressive disorder show a blunted response of the TSH level to thyrotropin-releasing hormone (TRH) stimulation, which is suggestive of central dysregulation (Extein et al., 1982). In bipolar disorder, however, a number of interacting factors may be involved in producing altered thyroid profiles. Lithium is one of the most commonly used mood stabilizers, and is known to cause hypothyroidism by affecting iodine uptake and thyroid hormone secretion, often leading to increased TSH (Yang et al., 2025). Although patients with recent use of lithium were excluded from this study, previous use or cumulative thyroid destruction cannot be completely excluded. Furthermore, genetic susceptibility and autoimmune factors (e.g. thyroid autoantibodies) may contribute to the increased prevalence of thyroid dysfunction in populations of bipolar patients.[9,10]

The other point to take into account is state-dependent fluctuation of thyroid function in bipolar disorder. In addition, several studies have indicated that TSH could fluctuate according to mood state: lower in the mania phase and higher in the depression or remission phase (Liu et al., 2024). This dynamic regulation of mood and energy may be considered to be a consequence of the interplay between thyroid hormones and mood and energy regulating neurotransmitter systems, in particular serotonergic and noradrenergic. In contrast, unipolar depression seems to exhibit a more stable pattern of subtle HPT axis hypoactivity (blunted TRH response) that does not exhibit the same fluctuation pattern as in bipolar disorder. This may in part explain why average TSH values in unipolar depression are still lower than in bipolar disorder.[11]

The clinical implications of these findings are interesting. Differentiation of unipolar and bipolar depression is still a major problem in diagnosis, especially at the first depressive episode when many patients are misdiagnosed. Biological markers, like TSH, when being reliable enough to correlate with diagnostic categories, might be used in addition to clinical assessment and in order to help early discrimination. Although serum TSH alone is not a conclusive test for diagnosis, mildly elevated TSH in depressed patients may trigger suspicion for bipolar disorder in the presence of classic clinical characteristics (i.e., family history of bipolarity, early age of onset, atypical depressive symptoms). Additionally, identification of thyroid dysfunction in bipolar patients has direct treatment relevance because hypothyroidism may add to the mood instability and treatment resistance. The bidirectional relationship between mood regulation and thyroid function has been further highlighted by studies into the adjunctive use of thyroid hormone augmentation (i.e., levothyroxine or liothyronine) in the treatment of depression and bipolar disorder that have not been responsive to other medications.

Nonetheless, the results have to be interpreted with caution because of the various limitations. First, cross-sectional assessment of TSH measures only one point in time, which may vary with the phase of illness, stress and diurnal variation. Longitudinal studies of TSH in mood states in the same individuals would be more informative. Second, although we have excluded patients with manifest thyroid diseases and recent lithium use, subclinical thyroid pathologies and previous exposure to thyroid-altering drugs may have had some influence. Third, our sample size although adequate to

demonstrate group differences, was small relative to population-based studies, and larger multi-center studies would be more generalizable. Fourth, only TSH was measured, whereas a complete thyroid panel including free T3, free T4, and thyroid autoantibodies would be more helpful for determining thyroid status. Previous research has documented, for example, TSH to be normal in bipolar depression, but the concentration of free T3 to be low (Liu et al. 2024).[12]

Future research should strive to combine the endocrine parameters with the genetic, neuroimaging, and inflammatory markers in a way that will better understand the multifactorial pathophysiology of mood disorders. It would also be useful to examine whether baseline TSH is predictive of clinical course, response to treatment or risk of going from unipolar to bipolar disorder. Since measurement of thyroid hormones is relatively simple in the clinical setting, their utility as potential accessible biomarkers is worthy of further investigation.[13]

In summary, our study is consistent with the accumulating evidence that serum TSH levels are higher in patients with bipolar disorder than in those with unipolar depression. This difference, albeit modest, is suggestive of different patterns of HPT axis regulation in both conditions. Although not adequate as the sole diagnostic agent, TSH could be used as part of a biological profile in the differentiation of mood disorder subtypes and to guide treatment. Clinicians should be alert for thyroid dysfunction in patients with mood disorders, especially in the bipolar population, in whom early recognition and treatment can have a beneficial effect on psychiatric outcome.

Since 2017, a number of studies and meta-analyses have provided shading to our knowledge on thyroid stimulating hormone (TSH) and thyroid function in general in mood disorders and, in particular, how to distinguish UD from BD. These data can be used to further refine hypotheses of whether TSH differences are trait dependent, state dependent or secondary to medication or comorbidity.[13]

One interesting meta-analysis was published in 2024 regarding thyroid hormone (TH) levels (TSH, T3, T4, free T3, free T4) in bipolar patients in mood episodes (i.e. depressive vs manic) vs healthy controls. It included 21 studies and almost 3,700 participants. Key findings were that during depressive episodes of BD (BD-D) serum T3 and free T3 were significantly reduced in comparison to healthy controls whereas during manic episodes (BD-M) there was a significant reduction of T3 whereas a significant increase of free T4 in comparison to controls. However, interestingly, the differences in TSH between BD patients and controls were less consistent, with many studies finding no significant difference of basal TSH levels between mood states when adjusted. Thus, whilst changes in peripheral thyroid hormone (particularly T3/FT3) seem to have a stronger role in BD, TSH seems to be more subtle, with many moderators. Another recent study compared thyroid function in drug-naive patients with bipolar disorder in the different emotional states (manic, depressive, euthymic) to avoid confounding by medication. Zhao et al. (2021) found that free T4 and total T4 were different according to mood state, TSH differences were less distinct, some elevation in TSH was observed in depressive vs manic or euthymic states, but not always statistically significant. This suggests that mood state may elaborate thyroid feedback, in which depression tends toward the higher TSH, while mania tends toward relatively lower TSH. [14,15]

In adolescents, a large retrospective study (Medical University of Lodz) comparing various diagnostic groups (UD, BD, schizophrenia, conduct disorders etc) found that bipolar depression patients had higher TSH than conduct disorders, also that female patients with unipolar depression and BD had higher TSH than female conduct disorder patients. However, they did not always find the difference between UD and BD to be consistent in all subgroup comparisons. In other words, differences in TSH are apparent when compared with non-mood conditions but differences between UD and BD are less frequently highly significant direct contrasts.[16]

In a very recent Chinese study (2025) from the Shanghai Mental Health Center (inpatients, matched groups: 274 UD vs. 128 BD depressive patients), TSH was among many biological markers included. They found that levels of TSH were significantly higher for bipolar depression than unipolar depression ($Z = 1.988$, $p = 0.047$). However, in the logistic regression model, TSH did not become a

significant independent predictor in differentiating BD-D versus UD when other biomarkers (CRP, immunoglobulins, complement levels) and clinical features were taken into consideration. So although there is a group mean difference, there seems to be limited discriminative power to TSH.[17]

Furthermore, this study investigated the potential causal relationship between genetically predicted TSH and free T4 within normal range variations and major depressive disorder (MDD) or bipolar disorder risk by Mendelian randomization (MR). The MR results showed no significant causal effect of normal range TSH (neither free T4) on risk of MDD or its subtypes. There was an associated, though nominal, increased association of higher fT4 with slightly decreased risk of BD overall, especially BD type 1.[18] These genetic findings suggest that much of the associations that we observe in observational studies may be related to the effects of state, reverse causality, or confounding, rather than the fact that TSH may be a robust causal risk factor.

Another meta-analysis on therapeutic augmentation with supraphysiologic doses of levothyroxine (LT4) in BD has been published (2022 - 2024). Although this study is more on the treatment side than natural variation in TSH, it drives home the point that artificially manipulating thyroid hormone levels (and so influencing feedback loops and TSH) can have clinically relevant effects, particularly in treatment-resistant or rapid cycling bipolar disorder. The evidence is contradictory: open-label studies are encouraging but randomised controlled trials have not been consistently positive. This would suggest that when TSH / Thyroid status is changed (endogenously or Exogenously) it may have an influence on mood / implying that TSH/ Thyroid function may not be a mere epiphenomenon.[19,20]

The present study have explored and compared the thyroid hormone levels among patients with unipolar depression and bipolar disorder and have found there are significant differences in the Thyroid Stimulating Hormone (TSH) levels between the two groups. Patients with unipolar depression had significantly higher mean TSH concentrations as compared with patients with bipolar disorder, indicating a greater relationship between thyroid dysfunction, especially subclinical hypothyroidism and unipolar depressive states. This finding is consistent with those studies that have found high TSH levels and a higher rate of hypothyroidism in individuals with major depressive disorder than in those with bipolar illness.

To support the hypothesis that subtle abnormalities of the thyroid are a potential factor in the pathophysiology or persistence of depressive symptoms is the observed higher incidence of subclinical hypothyroidism in unipolar depression (21.6%) in comparison to bipolar disorder (8.3%). Elevated levels of TSH even within the normal range have been associated with treatment resistance and severity of depression as has been reflected in the positive correlation between TSH and HDRS scores in our sample. In contrast, the lack of a similar correlation in bipolar patients may reflect different neuroendocrine mechanisms involved in the regulation of mood in bipolar illness where thyroid dysfunction may have a lesser or more complex role.

Female participants had higher TSH levels than males, which is consistent in the literature which states that there is a higher prevalence of thyroid dysfunction in women. Although there was a tendency for the TSH levels to rise with age, the difference was not statistically significant, possibly because of sample size limitations. The normal fT3 and fT4 levels in both groups suggest that most subjects had subclinical and not overt thyroid dysfunction.

Limitation:

The study is conducted in single center and limited number on people, hence results cannot be generalized. To get better results, large multi center trial with more number of participants is required.

Conclusion:

The current research illustrates that there is a substantial relationship between thyroid functionality and especially high concentrations of TSH and unipolar depression relative to the bipolar disorder. The mean TSH levels and the rate of subclinical hypothyroidism were found to be higher in patients with unipolar depression indicating that thyroid dysfunction has a possible stronger contribution to the pathophysiology of depressive disorders. The fact that TSH levels are correlated positively with the severity of depression also speaks

in favor of the fact that subtle thyroid abnormalities may also have a significant effect on mood regulation. Conversely, bipolar disorder patients exhibited a comparatively lower level of TSH and did not have a significant relationship with the severity of the illness, which suggests that the two mood disorders had different neuroendocrine phenotypes. Women subjects always had a higher TSH level, which supports the vulnerability of the gender to thyroid disease. The findings highlight the significance of regular screening of thyroid among the patients experiencing depressive symptoms since early detection and correction of thyroid abnormalities has the potential to enhance the accuracy of diagnoses and treatment consequences in mood disorders.

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