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RESEARCH ARTICLE
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ASSOCIATION BETWEEN FASTING THYROID STIMULATING HORMONE AND SUICIDAL IDEATION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER AT A TERTIARY CARE HOSPITAL- A CROSS-SECTIONAL STUDY

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Abstract:

Introduction: Major Depressive Disorder (MDD) is a leading cause of disability worldwide and poses significant risks for suicidal ideation and attempts. Despite extensive research on the biological underpinnings of MDD, the complex interactions between endocrine function and mental health outcomes remain incompletely understood. Elevated serum Thyroid stimulating hormone (TSH) levels, indicative of hypothyroidism, have been associated with depressive symptoms and increased risk of suicidal ideation. Understanding the relationship between fasting TSH levels and suicidal ideation in patients with MDD could offer new insights into the pathophysiology of depression and inform more effective screening and intervention strategies.

Aim: To investigate the role of serum Thyroid Stimulating Hormone (TSH) in depressive disorder and suicidality.

Materials and Methods: The study was carried out in Department of Psychiatry, S.V. Medical College, Tirupati, Andhra Pradesh from February to July 2024 for a duration of 6 months. A cross-sectional comparative study design was employed where the patients were divided into two groups, i.e., 30 subjects with Major Depressive Disorder (MDD) with suicidal ideation (SI) and 30 subjects with Major Depressive Disorder without suicidal ideation. Sociodemographic characteristics were recorded on a structured pro forma. DSM-V was used to diagnose MDD in the patients. Beck Depression Inventory (BDI-I) and Columbia- Suicide Severity Rating Scale (C-SSRS) were used on

subjects to determine the severity of depression and suicidal ideation respectively. ELISA method was used to measure serum values of fasting TSH in the collected samples.

Results: Most patients were between the ages of 31 and 40. Most of the participants received up to primary education and were married. 53.3% of the patients without suicidal ideation and 36.7% of patients with suicidal ideation had a past history of depressive illness with a chi-square value of 1.684. No significant association was found among the other sociodemographic parameters as p values were not significant. Compared with non-SI individuals, SI individuals had higher scores on BDI-I, 83.3% and 16.7% with severe and extreme depression respectively as well as higher TSH serum levels, 36.7% patients with TSH above 4.5 mIU/L. Elevated TSH levels (>4.5mIU/L) correlate with a higher incidence of severe depression, more severe ideation, and increased suicidal behavior with a p-value of 0.001. Extreme levels of depression are associated with higher severity of suicidal ideation and behavior, as well as greater intensity of suicidal ideation.

Conclusions: The study findings show that MDD patients with suicidal behavior had higher TSH levels compared to those without, though this difference wasn't statistically significant. The current study emphasizes the importance of regular assessment of thyroid function parameters for suicide prevention, along with possible treatment for impaired thyroid function for the suicide intervention in MDD patients. Such patients with abnormal TSH must undergo thorough screening for suicidal ideation.

Key words: Hypothyroidism, Hyperthyroidism, Suicidality, Biological psychiatry, Major depressive disorder

Introduction:

Suicide represents a significant global cause of death, responsible for approximately 800,000 fatalities annually.[1] It predominantly affects individuals diagnosed with psychiatric conditions like major depression and alcohol use disorder. The most critical risk factor for suicide is a history of previous attempts.[2] Thyroid dysfunction stands as the most prevalent endocrine disorder, with around one in eight women experiencing such issues in their lifetime.[3,4] Imbalances in thyroid hormones can significantly influence mental health, contributing to mood swings and cognitive impairment. Both excessive and inadequate levels of thyroid hormones can induce mood disorders such as depression, which often respond well to appropriate thyroid treatment. Additionally, certain cases of depression may be linked to subtle thyroid dysfunction, although overt thyroid disease seldom coincides with depression. Between 1% to 4% of patients diagnosed with mood disorders exhibit overt hypothyroidism, while subclinical hypothyroidism affects 4% to 40% of these individuals.[5] Research has noted a lack of nocturnal TSH surge in depression, with lower basal TSH levels reported in major depression compared to non-major depression.[6]Additionally, around 25-30% of depressed individuals exhibit a diminished TSH response to TRH compared to healthy controls. [7-9] The lower serum levels of thyroid hormones T3 and T4 in patients with Major depressive disorder with suicidality has been well documented. However, no significant association has been found between the levels of Thyroid stimulating hormone and suicidality in patients with Major depressive disorder. By examining this relationship in a clinical setting, we seek to contribute to the growing body of evidence on the endocrine aspects of depression and enhance our understanding of potential biomarkers for suicide risk assessment. This knowledge could ultimately aid in the development of targeted therapeutic approaches and improve outcomes for individuals suffering from this debilitating disorder. This study has been carried out to assess and explore the association between serum Thyroid Stimulating Hormone (TSH) levels and suicidal ideation in major depressive disorder.

Materials and Methods:

This cross-sectional study started on February 2024 and was carried out until June 2024. After receiving approval from the ethics committee (Lr.No.07/2024), participants who met the specified inclusion and exclusion criteria were selected using purposive and convenient sampling methods to

form the sample size. Subjects were recruited from those patients who attended Department of Psychiatry, S.V.Medical College, Tirupati, Andhra Pradesh from February to July 2024 for a duration of 6 months. The study subjects were divided into two groups – subjects with Major Depressive Disorder diagnosed using the Diagnostic and Statistical Manual of Mental Disorders V (DSM-5) with suicidal ideation and without suicidal ideation. [10]

Sample Size

One study conducted by Weiting Liu, et al., [11] Mean Group (m1) =4.65, Standard deviation Group (σ1) = 2.29, Mean Group (m2) =2.29, Standard deviation Group(σ2) = 2.90 for serum TSH. The formula used is as under:

$n = (\sigma 12 + \sigma 22)\ (Z\alpha + Z\beta)2/(\ m1 - m2)2$ where, Zα = Value of standard normal variate corresponding to α level of significance (1.96), Zβ = The standard normal deviate for desired power (0.842), m = Average, σ = Standard deviation. By substituting the values, the sample size for 95% confidence level & 80% power is 25 in each group. This number has been increased to 30 per group (a total of 60) to allow for a predicted dropout from treatment.

Inclusion Criteria:

1. Subjects between the age group of 18-60 years, who were willing to give written informed consent, with or without a past history of major depressive disorder and those who had suicidal ideation were included in this group.
2. Subjects between the age group of 18-60 years, who were willing to give written informed consent, with or without a past history of major depressive disorder and those who did not report suicidal ideation were included in this group.

Exclusion Criteria:

Subjects previously diagnosed with endocrinal disorders including thyroid dysfunction, chronic medical and surgical illness like cancer, epilepsy, significant head injury etc. or other psychiatric illnesses were excluded from the study.

Materials and methods:

During the study period, sixty patients, i.e., 30 from each group who met the inclusion criteria, were subjected to a detailed psychiatric interview, their sociodemographic characteristics including age, gender, educational status, marital status, economic status, past history and family history of psychiatric illness were noted on a structured pro forma. The socio-economic status was measured using modified kuppuswamy socioeconomic scale, and diagnosis of MDD in the patients was made using the Diagnostic and Statistical Manual of Mental Disorders V (DSM-5). [10]

The Beck Depression Inventory (BDI-I) was used on subjects to determine the severity of depression. BDI consists of 21 items, each corresponding to a specific symptom of depression such as sadness, guilt, fatigue, and changes in sleep and appetite. Each item is scored on a scale ranging from 0 to 3, with higher scores indicating more severe symptoms. The total score can range from 0 to 63 obtained by summing up the scores for all 21 items. The BDI categorizes the severity of depression symptoms into four levels, ranging from mild (11-16), borderline (17-20), moderate (21-30), severe (31-40) and extreme (41-63)**.** Higher scores on the Beck Depression Inventory generally indicate more significant depressive symptomatology. [12]

The Columbia- Suicide Severity Rating Scale (C-SSRS) consists of a series of questions that are administered by a trained clinician or researcher. It assesses the presence and intensity of suicidal ideation (e.g., frequency, duration, controllability), the intent and severity of suicidal attempts, and non-suicidal self-injurious behaviour. The Columbia-Suicide Severity Rating Scale (C-SSRS) is designed to differentiate between suicidal ideation and suicidal behavior. It evaluates four key

constructs. The first is the severity of ideation (severity subscale), assessed on a 5-point scale: 1—wish to be dead, 2—nonspecific active suicidal thoughts, 3—suicidal thoughts with a method, 4—suicidal intent, and 5—suicidal intent with a plan. The second is the intensity of ideation (intensity subscale). The third is the behavior subscale, categorized on a nominal scale that includes actual, aborted, and interrupted attempts, preparatory actions, and nonsuicidal self-injury. The fourth is the lethality subscale, which measures actual suicide attempts, rating lethality on a 6-point scale. If actual lethality is zero, the potential lethality of attempts is assessed on a 3-point scale. The scale categorizes responses into different levels of severity, ranging from "wish to be dead" to actual suicide attempts. [13]

Blood sample

After overnight fast, blood samples were collected between 6 am and 8 am. All samples were sent to the Multidisciplinary Research Unit of the hospital immediately, and measurements were taken before 11 am in the morning of the same day. The serum Thyroid Stimulating Hormone (TSH) level was measured using solid-phase enzyme-linked immunosorbent assay (ELISA). The normal range for TSH, as standardized in the laboratory, is 0.5-4.5 mIU/L. The diagnosis of hyperthyroidism was marked as positive if the serum TSH was < 0.5 mIU/L and hypothyroidism was considered if the serum TSH was > 4.5 mIU/L. [14]

Statistical Analysis: The statistical software SPSS 25.0 and Systat 8.0 were used for the analysis of the data. Descriptive statistics and chi square test were used. For comparing categorical data, Chi square ($\chi 2$) test was performed and fisher exact test was used when the expected frequency is less than 5. P value < 0.05 is considered statistically significant. Values are presented as mean ± standard deviation.

Results:

Table 1 displays the sociodemographic characteristics of the subjects. Most patients were between the ages of 31 and 40. The mean age of individuals with suicidal ideation was 40.77 ± 10.32 years, while those without suicidal ideation had an mean age of 41.53 ± 10.36 years. Most of the participants received up to primary education and were married. 53.3% of the patients without suicidal ideation and 36.7% of patients with suicidal ideation had a past history of depressive illness with a P value of 1.684. No significant association was found among the other sociodemographic parameters as p values were not significant.

Table 2 illustrates the relationship between the severity of depression, suicidal ideation, and serum TSH levels. Depression severity and ideation severity are both strongly and significantly associated with suicidal ideation with a significant-value of 0.001. Higher depression severity and ideation severity scores increase the likelihood of suicidal attempt.

Serum TSH levels, however, did not reveal a significant relationship with suicidal ideation. Even t there was a slight increase in elevated TSH levels among those with suicidal ideation, this difference is not statistically significant.

Table 3 illustrates the relationship between serum TSH levels and the different subscales of the Columbia Suicide Severity Rating Scale in patients who reported suicidal ideation. Elevated TSH levels (> 4.5 mIU/L) are significantly associated with more extreme depression (p-value 0.047), higher ideation severity (p –value 0.006), increased suicidal behavior (p-value 0.044), and greater intensity of suicidal ideation (p-value 0.041). eventhough potential lethality of suicide attempts does not show a significant relationship with TSH levels but among patients with TSH >4.5mIU/L, 45.5% of patients attempted suicide with potential lethality behavior which is likely to cause death despite availability of medical care.

Discussion:

The objective of this study was to assess the thyroid function status of major depressive disorder with suicidal ideation patients and compare it with that of major depressive disorder without suicidal ideation.

Depression results in a reduction of 5-HT, acetylcholine, norepinephrine, and other hormones in patients. In these circumstances, thyroid hormones might act as a compensatory mechanism to prevent further decline in neurotransmitter levels. However, in cases of prolonged depression, especially in patients with major depression, the thyroid gland may lose this compensatory ability, leading to hypothyroidism. [15]

Disturbances in the serotonin (5-HT) system are the most common biochemical abnormalities associated with suicide. [16] It is believed that thyroid hormones are part of a complex compensatory mechanism to address decreased central 5-HT activity. [17] If these compensatory mechanisms fail, the 5-HT deficiency persists. In depressed patients with a history of suicidal behavior, 5-HT dysfunction may signify a breakdown of these compensatory mechanisms.

A study by Pranje et al.[7] involved ten euthyroid women with unipolar depression, who received a single injection of thyrotropin-releasing hormone (T.R.H.) and a single saline injection in a double-blind crossover comparison study. The findings indicated that T.R.H. led to a rapid, temporary improvement in depression without significant side effects. Additionally, most patients showed a reduced thyrotropin (T.S.H.) response to the T.R.H. injection, with no abnormal thyroid function tests or clinical signs of pituitary or thyroid disease. If thyroid hormones are part of a complex compensatory mechanism to address decreased central serotonin activity, then the elevated serum TSH levels in these patients suggest the thyroid's compensatory role in serotonin secretion. Previous studies on TSH have considered T.R.H. hypersecretion as a compensatory mechanism to maintain normal thyroid hormone levels and normalize serotonin activity in depressed patients. [17-19]

Mann and Currier examined studies on the link between suicidal behavior and various neurotransmitter systems (serotonergic, noradrenergic, dopaminergic) as well as the HPA and HPT axes in mood disorders. [18] Previous research has explored the relationship between suicide and HPT activity. [17-21] Most studies have compared serum TSH levels in suicidal and depressive patients, yielding mixed results. Generally, it was found that depressed patients with suicidal tendencies showed a diminished TSH response to morning TRH administration, though some studies did not support this finding. [12-15]

In a cross-sectional study by Barbosa et al., hypothyroidism was more prevalent among 31 bipolar disorder patients with suicide attempts (25.8%) compared to 15.9% among 63 bipolar disorder patients without suicide attempts. [22] Sanna et al. found a 6.5% prevalence of thyroid disorders in males with suicidal ideation, versus 1.9% in males without suicidal ideation, though no significant correlation between sex and suicidality was observed. [23]

The current study revealed that 80% of patients without suicidal ideation were euthymic, while 36% of those with suicidal ideation were hypothyroid (TSH >4.5 IU/ml). This is consistent with Yanmei Shen et al.'s study of 1718 outpatients with M.D.D., which collected sociodemographic and clinical data along with thyroid function parameters. Using the PANSS, HAMA, and HAMD scales, they found that suicide attempts were associated with higher levels of TSH, TgAb, and TPOAb, suggesting these biomarkers could help assess suicide risk in M.D.D. patients. [24]

Huai Heng Loh et al. [25] conducted a meta-analysis to evaluate the relationship between subclinical hypothyroidism (S.C.H.) and depression. The study examined the prevalence of depression in S.C.H., the levels of thyroid-stimulating hormone (TSH) among patients with depression, and the effects of levothyroxine therapy on patients with S.C.H. and coexisting depression. The results indicated no differences in TSH, FT4, or TT3 levels among the groups. However, patients with suicidal behavior had significantly lower mean FT3 and FT4 levels compared to those without suicidal behavior. These findings partially align with the current study, where 36.7% of patients with suicidal ideation and 16.7% of patients without suicidal ideation had serum TSH levels above 4.5 mIU/L.

Heiberg-Brix et al. discovered in a Danish register-based study that patients with Hashimoto's thyroiditis had a higher rate of suicide compared to euthyroid controls. [26] In contrast, this increased frequency was not observed in patients with Graves' disease when compared to both controls without Graves' disease and euthyroid controls from the general population. [27, 28] These results imply that suicide may be more closely linked to hypothyroidism rather than hyperthyroidism. This is consistent with the current study's findings, which showed that 36.7% of patients with suicidal ideation had serum TSH levels above 4.5 IU/ml, while the remaining patients were euthymic.

The present study also highlighted a higher risk of suicidal thoughts and attempts among patients with severe depression. All 30 participants with suicidal thoughts exhibited severe to extreme levels of depression. Similar results have been documented in other studies, suggesting that the severity of depression is linked to the likelihood of suicidal thoughts. [28-31] Addressing the timing of suicide attempts in relation to depressive symptoms, reducing the duration of depressive episodes could be a key strategy in preventing suicide attempts. [32]

Poirier et al., [6] conducted a case-control study measuring serum TSH in 55 depressed individuals and 38 healthy controls finding that TSH levels were significantly lower in depressed patients compared to healthy controls, and lower in those with major depression compared to non-major depression. However, no differences in TSH levels were observed among the various subtypes of major depression. In contrast, the current study found that 20% of patients with mild to moderate depression and 36% of those with severe to extreme depression had TSH levels above 4.5 IU/ml, a statistically significant finding.

Among patients with suicidal ideation, 11 had serum TSH levels above 4.5 mIU/L. Of these, 36.4% had extreme depression, 54.5% experienced a high severity of ideation (level 5), 63.6% exhibited suicidal behavior, and 36.4% required hospitalization and intensive care due to their suicide attempts. Yongjie Zhou et al. conducted a large-scale cross-sectional study investigating the links between clinical factors, metabolic parameters, and thyroid hormones with suicide attempts in patients with major depressive disorder and anxiety. Their findings indicated that TSH levels were independently associated with suicide attempts in these patients. [33] Similarly, Ivan Berlin et al. found that higher TSH levels in MDD patients were positively correlated with an increased likelihood of suicide attempts. [34]

Limitations:

This research is a cross-sectional study aimed at exploring the causes of the disease but cannot establish a causal relationship due to its design. The study lacked a control group of healthy individuals and did not account for factors such as environment, income, stress, and other influences on suicidal behavior. Additionally, it did not address potential undiscovered comorbid factors that could contribute to suicidal behavior in patients with major depressive disorder, thus overlooking other possible triggers. The study participants were drawn from a tertiary care government hospital rather than the general community, and the small sample size limits its generalizability to the broader population.

Conclusion:

The study shows that Elevated TSH levels (> 4.5 mIU/L) were significantly associated with more extreme depression, higher ideation severity, increased suicidal behavior, and greater intensity of suicidal ideation. However, no strong association was found between thyroid function and suicidal ideation in this sample. The study highlights the crucial link between psychiatric issues and thyroid dysfunction, stressing its importance for public health and patient care. The study aims to increase awareness regarding the use of antidepressants and thyroid treatments alongside psychotherapy. In summary, thyroid hormonal dysfunction may exacerbate MDD and elevate suicidal behavior risk. We recommend regular thyroid function monitoring for MDD patients to identify abnormalities early and reduce suicide risk. Future, larger-scale, prospective studies could clarify the relationship

between thyroid hormone profiles and suicidality, and TSH levels may be useful as screening tools to assess suicidal tendencies and ensure timely treatment for depression.

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Conflict of interest: Nil

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TABLE 1: Demographic Characteristics

		Without suicidal ideation (n=30)		With suicidal ideation (n=30)		Total	Chi-square value	p-value
		No.	%	No.	%			
Age	< 30	1	3.3%	5	16.7%	6	4.267	0.234
	31-40	18	60.0%	12	40.0%	30		
	41-50	4	13.3%	6	20.0%	10		
	> 50	7	23.3%	7	23.3%	14		
Gender	Female	15	50.0%	20	66.7%	35	1.714	0.295
	Male	15	50.0%	10	33.3%	25		
Educational status	Illiterate	12	40.0%	7	23.3%	19	3.304	0.77
	Primary school	14	46.7%	11	36.7%	25		
	Secondary school	2	6.7%	4	13.3%	6		
	High school	2	6.7%	3	10.0%	5		

	Diploma	3	10.0%	3	10.0%	6		
	Graduate	3	10.0%	1	3.3%	4		
	Professional	0	0.0%	1	3.3%	1		
Marital status	Married	26	86.7%	25	83.3%	51	0.22	0.896
	Separated/Divorced/Widowed	2	6.7%	2	6.7%	4		
	Unmarried	2	6.7%	3	10.0%	5		
Economic status	Lower	7	23.3%	6	20.0%	13	0.517	0.972
	lower middle	10	33.3%	11	36.7%	21		
	upper class	1	3.3%	2	6.7%	3		
	upper lower	9	30.0%	8	26.7%	17		
	upper middle	3	10.0%	3	10.0%	6		
Past History of depressive illness	No	19	63.3%	14	46.7%	33	1.684	0.194
	Yes	11	36.7%	16	53.3%	27		
Family History	No	25	83.3%	23	76.7%	48	0.417	0.519
	Yes	5	16.7%	7	23.3%	12		

TABLE 2: Aassociation between the severity of depression, suicidal ideation, and serum TSH levels.

		Without suicidal ideation (n=30)		**With suicidal ideation (n=30)**		Total	**Chi-square**	**P-value**
Beck's Depression Inventory [13]	Mild	3	10.0%	0	0.0%	3	40.645	0.001
	Borderline	6	20.0%	0	0.0%	6		
	Moderate	15	50.0%	0	0.0%	15		
	Severe	6	20.0%	25	83.3%	31		
	Extreme	0	0.0%	5	16.7%	5		
Ideation severity subscale	1	27	90.0%	0	0.0%	27	60.000	0.001
	2	3	10.0%	0	0.0%	3		
	3	0	0.0%	9	30.0%	9		
	4	0	0.0%	14	46.7%	14		
	5	0	0.0%	7	23.3%	7		
TSH mIU/L	< 0.5	1	3.3%	0	0.0%	1	3.381	0.147
	0.5-4.5	24	80.0%	19	63.3%	43		
	> 4.5	5	16.7%	11	36.7%	16		
Total		30	100.0%	30	100.0%	60		

{TSH- Thyroid Stimulating Hormone}

TABLE 3: Association between serum TSH levels, severity of depression and the different subscales of the Columbia Suicide Severity Rating Scale.

		TSH mIU/L				Total	Chi-square value	p-value
		0.5-4.5		> 4.5				
Beck's Depression Inventory	Severe	18	94.7%	7	63.6%	25	4.852	0.047
	Extreme	1	5.3%	4	36.4%	5		
Ideation severity subscale	1	0	0%	0	0%	0	10.178	0.006
	2	0	0%	0	0%	0		
	3	8	42.1%	1	9.1%	9		
	4	10	52.6%	4	36.4%	14		
	5	1	5.3%	6	54.5%	7		
Suicidal behaviour subscale	No	14	73.7%	4	36.4%	18	4.043	0.044
	Yes	5	26.3%	7	63.6%	12		
Intensity of suicidal ideation subscale	1	9	47.4%	3	27.3%	12	8.254	0.041
	2	6	31.6%	3	27.3%	9		
	3	4	21.1%	1	9.1%	5		

	4	0	0.0%	4	36.4%	4		
Potential lethality	0	9	47.4%	3	27.3%	12	3.194	0.203
	1	7	36.8%	3	27.3%	10		
	2	3	15.8%	5	45.5%	8		
Total		19	100.0%	11	100.0%	30		