



## Depression in Hypothyroidism: Can hypothyroids have low mood?

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### I. INTRODUCTION:

Hypothyroidism is caused by deficiency of circulating thyroid hormone. There are various causes of hypothyroidism. These can be classified as congenital or acquired; primary, secondary and tertiary; subclinical and overt hypothyroidism. The disease is diagnosed by estimating the circulating hormone levels (Free T<sub>3</sub>, Free T<sub>4</sub> and TSH) in blood. The incidence of clinical hypothyroidism is 0.5-1.9% in women and <1% in men whereas the incidence of subclinical hypothyroidism is 3-13.6% in women and 0.7-5.7% in men.<sup>[1]</sup>

Hypothyroidism effects every organ system of the body for e.g. musculoskeletal, skin, cardiovascular, reproductive, gastrointestinal, blood and bone marrow, etc. Neuropsychiatric manifestations are of utmost importance in this disease due to the fact that there are complex neuro-endocrine and psycho-endocrine interactions between these systems in patients with hypothyroidism. There is dysregulation of hypothalamic-pituitary-thyroid axis in patients of depression.<sup>[2]</sup> Depression is mood disorder which is one of the most common causes of suicide and death due to mental disorders globally. Hence, detecting depression and early replacement of thyroxine in patients with hypothyroidism can decrease progression of the psychiatric manifestation of latter.

### II. REVIEW OF LITERATURE:

Grabe et al. in 2005 analyzed mental and physical complaints in thyroid disorders among 3790 participants. Females with overt hypothyroidism and autoimmune thyroiditis (AIT) were found to have a tendency of higher scores for tachycardia and anxiety.<sup>[3]</sup> In 2006, Patten et al. investigated Canadian community health survey 1.2 data and found that the prevalence of mental disorder being higher in individuals with thyroid disease compared to other chronic diseases. Major depressive disorder, bipolar disorder,

panic/agoraphobia disorder and social phobia etc. were studied and it was concluded that only social phobia was found to be associated with thyroid illness.<sup>[4]</sup>

In a cross-sectional study published in 2006 by Schreckenberger et al, the hospital anxiety and depression scale (HADS scale) was applied to seven patients and the results were 9.08 for anxiety and 7.08 for depression. It was noticed that a metabolic decline in glucose occurred in both the groups, with a significant correlation for the regulation of anxiety and depression ( $p < 0.0001$ ).<sup>[5]</sup> In 2007, Krausz et al. compared cerebral perfusion deficits on brain SPECT scans in patients with major depressive disorder and patients with hypothyroidism. It was found that after treatment, levels of TSH normalized in the hypothyroidism group and were practically unaltered in depressed patients. These findings suggested that depressive symptoms in hypothyroidism may be mediated by neural circuitry different from that of major depression. The average Hamilton depression rating scale (HAMD scale) scores decreased significantly in depressed patients ( $p = 0.00001$ ), but not significantly in patients with hypothyroidism ( $p = 0.4$ ) that were within the normal limits, and were similar for both groups. Mini-Mental State Exam scores (MMSE) already within the normal range before treatment did not increase significantly in either group.<sup>[6]</sup>

Gupta, Saha, and Mukhopadhyay in 2008 studied the prevalence of hypothyroidism in major depressive disorder on a total of 78 patients in India with age group ranging between 19-67 years. The prevalence was found to be 20.5%. Out of total patients, 16 patients with hypothyroidism the mean serum cholesterol was significantly higher than the euthyroid group ( $p < 0.01$ ).<sup>[7]</sup> On 75 patients, Mowla et al. in 2011 studied the difference in patients with major depressive disorder with and without hypothyroidism, using the HAMD



depression scale. The patients with the major depressive disorder without hypothyroidism had worse results on item 1 (depressed mood), item 2 (feelings of guilt), item 3 (suicidality), item 6 (insomnia), and score 16 (loss of weight). In contrast, depressed patients with hypothyroidism presented with more severe symptoms of anxiety and greater levels of agitation (items 9, 10, and 11).<sup>[8]</sup>

In 2013, Radhakrishnan et al. analyzed the results of 468 patients presenting a diagnosis of abnormal hormone status, with hypothyroidism or hyperthyroidism. 37 of 147 (25.17%) hypothyroid patients had schizophrenia-spectrum disorders. Of the 185 patients with mood spectrum disorders, 40 (21.62%) (bipolar disorder=28/122, major depressive disorder =12/63) had hypothyroidism. Three subjects with schizophrenia and two with the major depressive disorder had clinically significant hypothyroidism. Anti-TPO antibodies were positive in 18 patients. Out of these 18 anti-TPO positive patients, 11 had schizophrenia-spectrum disorders, while mood disorder was found in 7 patients. The rate of anti-TPO positivity in the schizophrenia spectrum disorder group was higher 13.58% as compared to 5.6% in the mood disorder group.<sup>[9]</sup>

In 2013, Ayhan et al. studied the prevalence of depression and anxiety disorders in patients with euthyroid Hashimoto's thyroiditis. Statistically significant difference was found between euthyroid Hashimoto's thyroiditis group, goiter and control groups in terms of major depression ( $p=0.001$ ), any mood or anxiety disorder ( $p=0.000$ ), any depressive disorder ( $p=0.020$ ), any anxiety disorder ( $p=0.016$ ), and obsessive-compulsive disorder (OCD) ( $p=0.013$ ). In the Hashimoto thyroid group (HT), the prevalence of depression ( $p=0.000$ ), obsessive-compulsive disorder ( $p=0.005$ ), and panic disorders ( $p=0.041$ ) were significantly higher than the control group. In the goiter group, depression ( $p=0.006$ ), any depressive disorder ( $p=0.03$ ), and any mood or anxiety disorder ( $p=0.000$ ) were significantly more common in comparison to the control group. No significant difference was found between the goiter group and the Hashimoto thyroid group.<sup>[10]</sup>

### III. MATERIALS AND METHODS:

This hospital based observational study was conducted in the Department of Internal Medicine, Guru Gobind Singh Medical College and Hospital, Faridkot, a tertiary care hospital in Malwa region of Punjab, India. A total of 120 patients newly detected hypothyroidism were included in the study.

Inclusion criteria: Patients with age  $\geq 18$  years, newly detected cases of hypothyroidism who were not yet started on treatment were included in the study.

Exclusion criteria: Patients known case of depression or on treatment, cases of hyperthyroidism, pregnancy and patients with age  $< 18$  years were excluded from the study.

Hamilton depression (HAMD) rating scale was used to assess the depression severity in these patients. The patients were divided into 4 categories on the basis of total HAMD score as no, mild, moderate, and very severe depression. The individual characteristics of HAMD scale were also studied and were correlated with thyroid profile of patients and anti-thyroid peroxidase and anti-thyroglobulin antibodies (Anti-TPO and Anti-Tg antibodies).

### IV. RESULTS:

In present study, out of 120 total patients studied, 23.33% of patients belonged to age group 41-50 and 20.83% of patients belonged to 21-30 years, 31-40 years and 51-60 years each. However, 10.83% of patients belonged to  $>60$  years. Age group was 18-20 years of only 4 out of 120 patients. Mean value of age(years) of study subjects was  $43.37 \pm 14.6$  with median(IQR) of 44.5(32-54.25). In present study, 102 (85.00%) of patients were females and 18 (15%) of patients were males. In present study, majority 98 (81.67%) of patients had primary hypothyroidism followed by subclinical hypothyroidism 20 (16.67%). Secondary hypothyroidism was present in only 2 out of 120 patients.

Table 1:-Distribution of thyroid profile of study subjects.

Thyroid profile	Frequency
<b>FT3(pg/mL)</b>	
Mean $\pm$ SD	1.98 $\pm$ 0.9
Median(IQR)	2(1.12-2.49)
Range	0.1-3.9
<b>FT4(ng/dL)</b>	
Mean $\pm$ SD	0.57 $\pm$ 0.23
Median(IQR)	0.56(0.41-0.755)
Range	0.11-1.08
<b>TSH(IU/mL)</b>	
Mean $\pm$ SD	17.07 $\pm$ 31.34
Median(IQR)	8.38(6.445-14.002)
Range	0.05-238
<b>Anti-TPO antibodies(IU/mL)</b>	
Mean $\pm$ SD	142.95 $\pm$ 308.89
Median(IQR)	24(12.248-101.5)
Range	4-1544



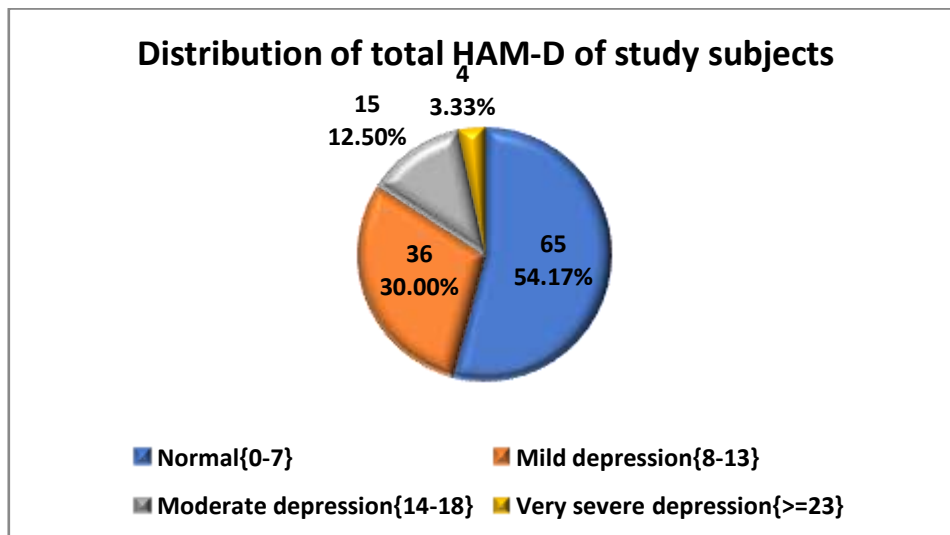
Anti-Tgantibody(IU/mL)	
Mean ± SD	54.46 ± 119.79
Median(IQR)	24(14-36)
Range	4-908

In present study (Table 1.), in majority (75.00%) of patients, FT3(pg/mL) was <2.5[low FT3]. Mean value of FT3(pg/mL) of study subjects was 1.98 ± 0.9 with median(IQR) of 2(1.12-2.49). In majority (61.67%) of patients, FT4(ng/dL) was <0.61[low FT4]. Mean value of FT4(ng/dL) of study subjects was 0.57 ± 0.23 with median(IQR) of 0.56(0.41-0.755). In 95.00% of patients, TSH(IU/mL) was >5.50 [high TSH]. Mean value of TSH(IU/mL) of study subjects was 17.07 ± 31.34 with median(IQR) of 8.38(6.445-14.002). In

60.00%) of patients, anti TPO antibodies(IU/mL) was negative. Mean value of anti TPO antibodies(IU/mL) of study subjects was 142.95 ± 308.89 with median(IQR) of 24(12.248-101.5). In 90.00% of patients, anti-Tgantibody(IU/mL) was negative. Mean value of anti-Tgantibody(IU/mL) of study subjects was 54.46 ± 119.79 with median(IQR) of 24(14-36). In present study, HAM-D was normal in 54.17% of patients, mild depression (HAMD score 8-13) was seen in 30% of patients, moderate depression (HAMD score 14-18) was seen in 12.50% of patients, very severe depression (HAMD score ≥23) was seen in 3.33% of patients. Mean value of HAM-D was 7.99 ± 5.34 with median (IQR) of 7(5-10). It is shown in Table 2 and Figure 1.

**Table 2:-Distribution of total HAM-D of study subjects.**

Total HAM-D	Frequency	Percentage
Normal{0-7}	65	54.17%
Mild depression{8-13}	36	30.00%
Moderate depression{14-18}	15	12.50%
Very severe depression{>=23}	4	3.33%
Mean ± Stdev	7.99 ± 5.34	
Median(IQR)	7(5-10)	
Range	0-30	



**Figure 1:-Distribution of total HAM-D of study subjects.**



**Table 3:-Correlation of TSH, anti-TPO antibodies and anti-Tg antibody with HAMD scale components.**

<b>Variables</b>	<b>TSH(IU/mL)</b>	<b>Anti-TPO antibodies(IU/mL)</b>	<b>Anti-Tg antibody(IU/mL)</b>
<b>Depressed mood</b>			
Correlation coefficient	0.340	0.401	0.291
P value	0.0002	<0.0001	0.001
<b>Feelings of guilt</b>			
Correlation coefficient	0.007	0.002	-0.084
P value	0.937	0.987	0.362
<b>Suicide</b>			
Correlation coefficient	-0.091	-0.041	-0.006
P value	0.323	0.659	0.952
<b>Insomnia-initial</b>			
Correlation coefficient	0.191	0.155	0.179
P value	0.037	0.091	0.051
<b>Insomnia-middle</b>			
Correlation coefficient	0.141	-0.010	0.062
P value	0.126	0.915	0.503
<b>Insomnia-delayed</b>			
Correlation coefficient	-0.016	-0.026	0.097
P value	0.863	0.780	0.293
<b>Work and interests</b>			
Correlation coefficient	0.209	0.210	0.134
P value	0.022	0.022	0.144
<b>Retardation</b>			
Correlation coefficient	0.168	0.174	0.152
P value	0.067	0.058	0.098
<b>Agitation</b>			
Correlation coefficient	0.207	0.202	0.220
P value	0.024	0.027	0.016
<b>Anxiety psychic</b>			



Correlation coefficient	0.068	0.095	0.093
P value	0.462	0.301	0.311
<b>Anxiety somatic</b>			
Correlation coefficient	0.029	0.117	0.153
P value	0.753	0.204	0.096
<b>Somatic symptoms-gastrointestinal</b>			
Correlation coefficient	-0.086	0.025	-0.005
P value	0.349	0.790	0.959
<b>Somatic symptoms-general</b>			
Correlation coefficient	0.033	0.159	0.108
P value	0.718	0.083	0.240
<b>Genital symptoms</b>			
Correlation coefficient	0.002	-0.043	0.046
P value	0.981	0.642	0.618
<b>Hypochondriasis</b>			
Correlation coefficient	0.108	0.132	0.007
P value	0.240	0.149	0.941
<b>Weight loss</b>			
Correlation coefficient	0.004	0.054	-0.103
P value	0.963	0.555	0.263
<b>Insight</b>			
Correlation coefficient	0.071	0.077	0.041
P value	0.438	0.405	0.656
<b>Diurnal variation</b>			
Correlation coefficient	-0.003	-0.090	0.104
P value	0.976	0.327	0.257
<b>Depersonalization and derealization</b>			
Correlation coefficient	0.024	0.112	0.083
P value	0.794	0.224	0.369
<b>Paranoid symptoms</b>			
Correlation coefficient	-0.001	-0.093	0.024
P value	0.991	0.313	0.792
<b>Obsessional symptoms</b>			



Correlation coefficient	-0.018	0.051	0.076
P value	0.849	0.583	0.411
<b>Total HAM-D</b>			
Correlation coefficient	0.164	0.192	0.172
P value	0.074	0.036	0.060

Spearman rank correlation coefficient

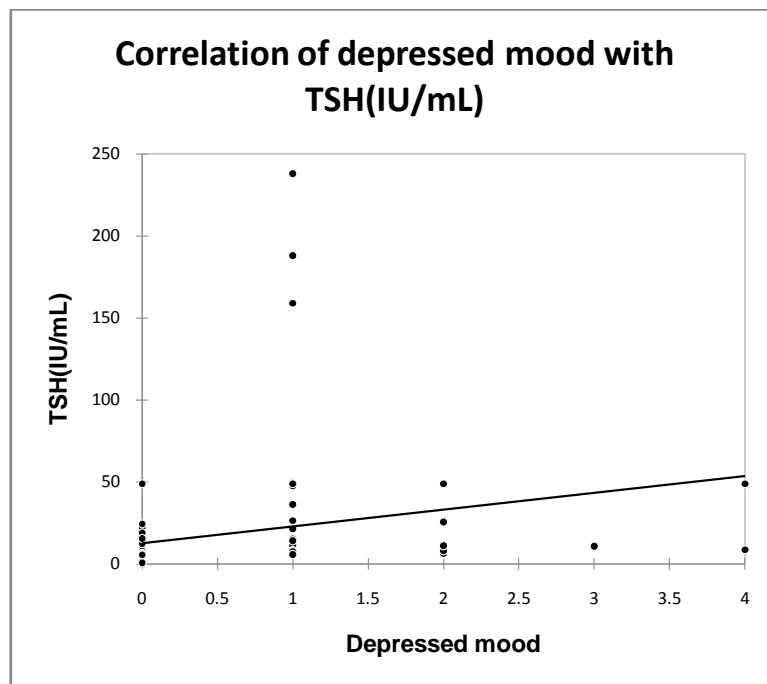


Figure 2.1:-Correlation of depressed mood with TSH(IU/mL).

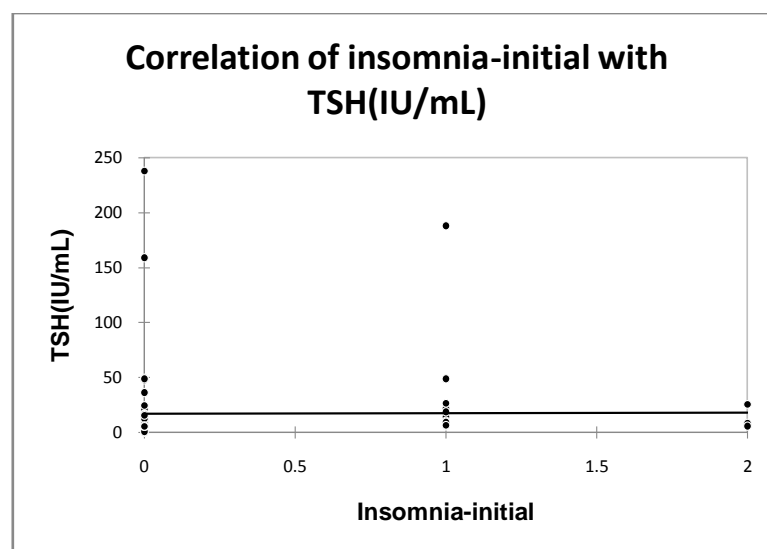


Figure 2.2:-Correlation of insomnia-initial with TSH(IU/mL).

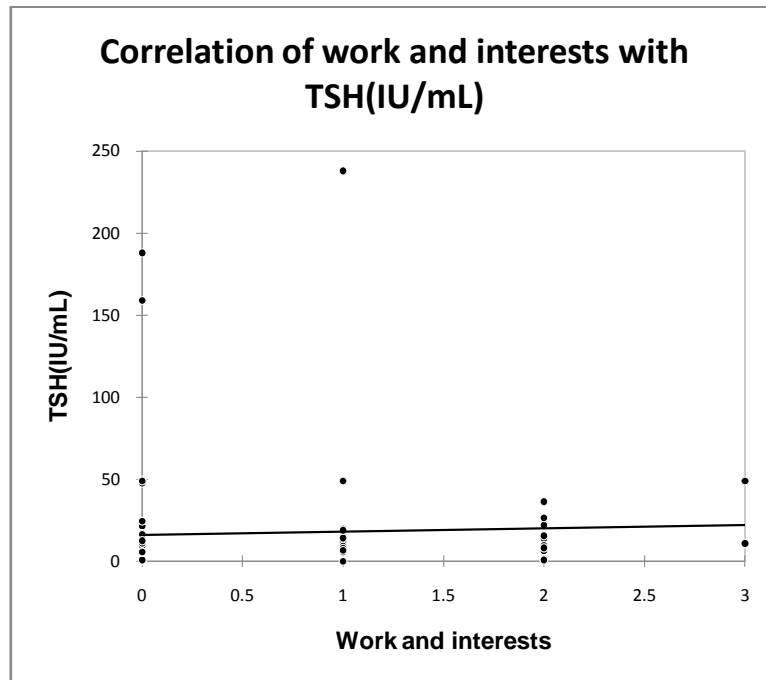


Figure 2.3:-Correlation of work and interests with TSH(IU/mL).

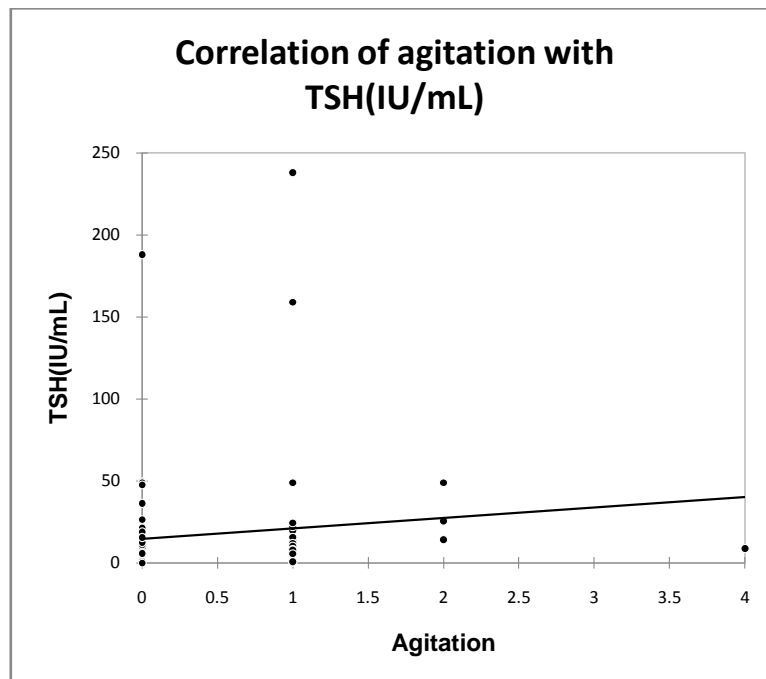


Figure 2.4:-Correlation of agitation with TSH(IU/mL).

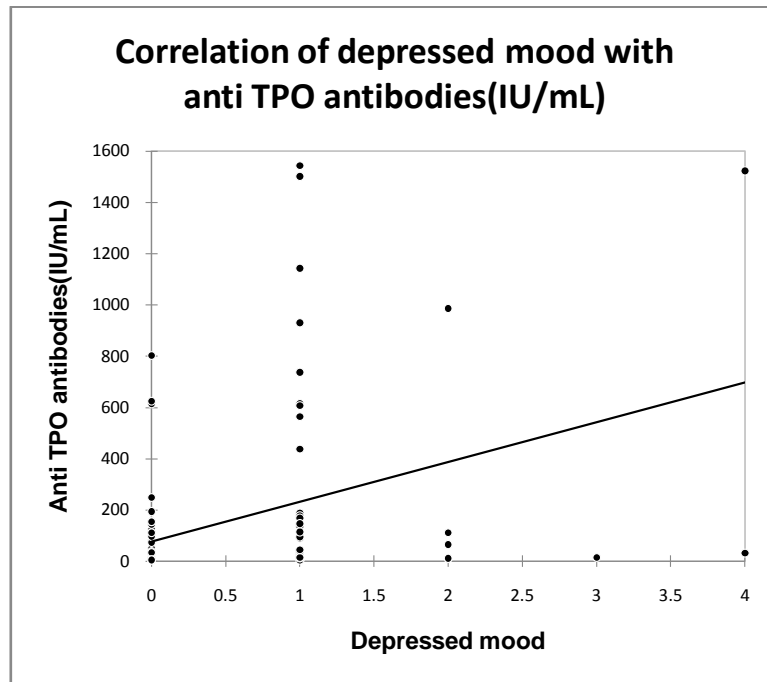


Figure 2.5:-Correlation of depressed mood with anti TPO antibodies(IU/mL).

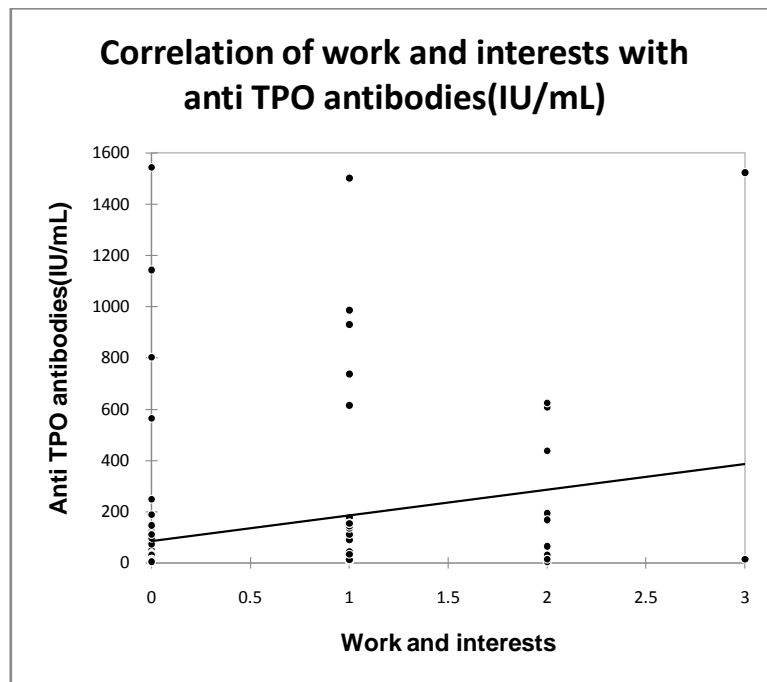


Figure 2.6:-Correlation of work and interests with anti TPO antibodies(IU/mL).



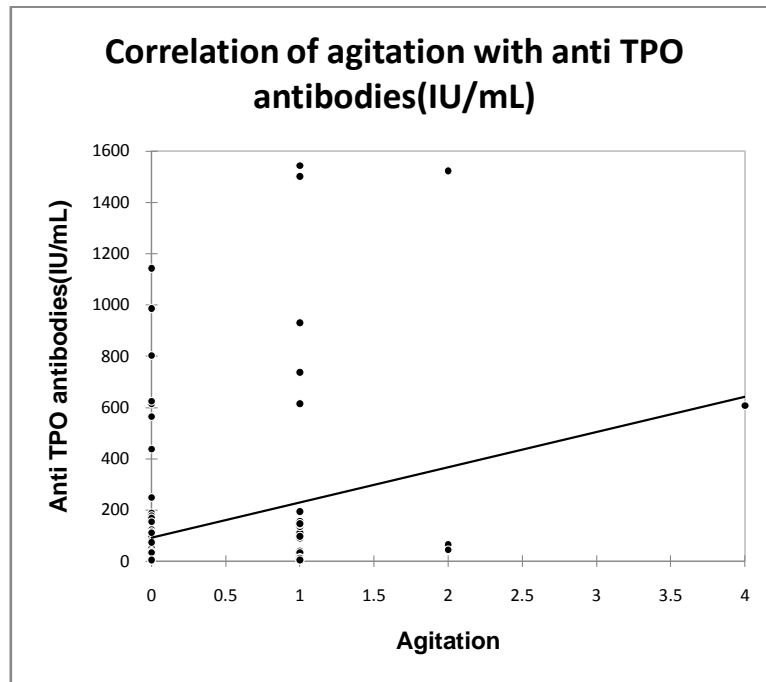


Figure 2.7:-Correlation of agitation with anti TPO antibodies(IU/mL).

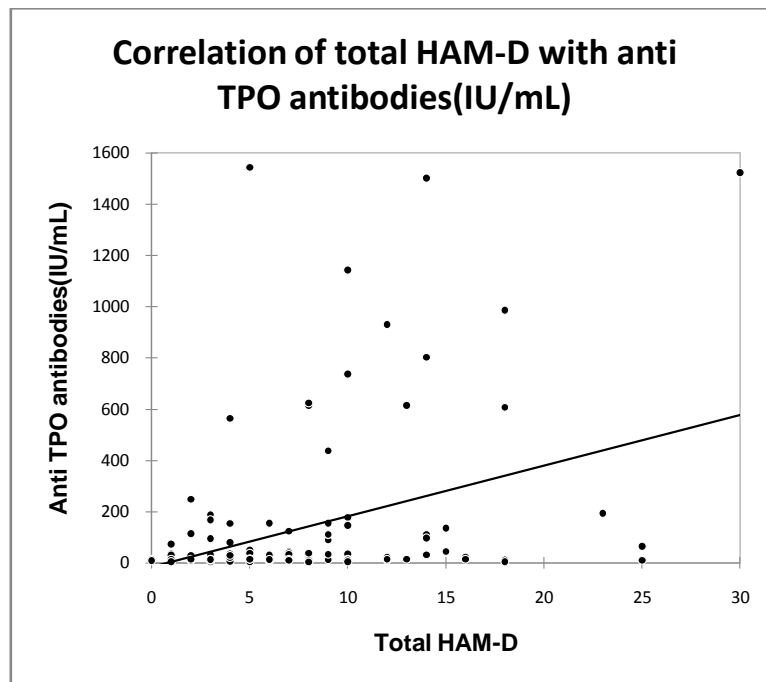


Figure 2.8:-Correlation of total HAM-D with anti TPO antibodies(IU/mL).

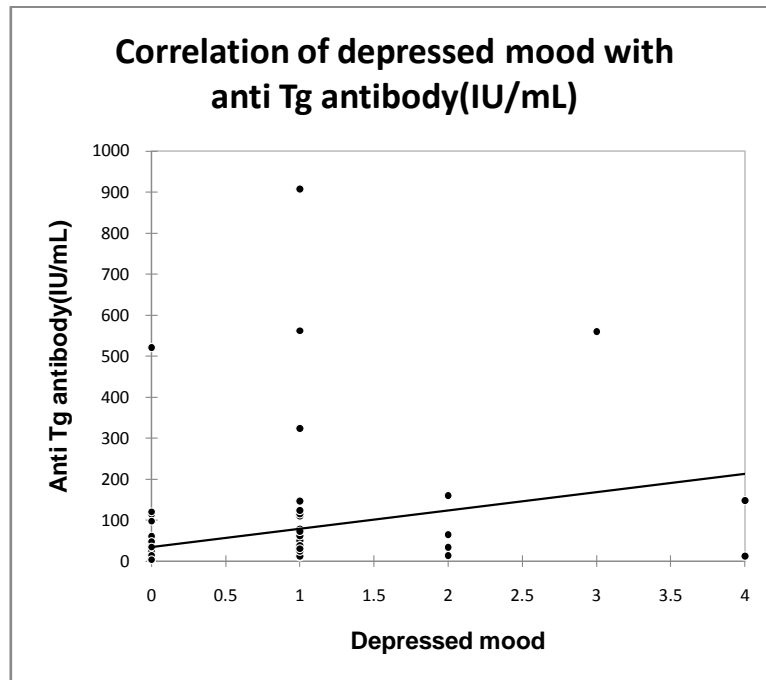


Figure 2.9:-Correlation of depressed mood with anti Tgantibody(IU/mL).

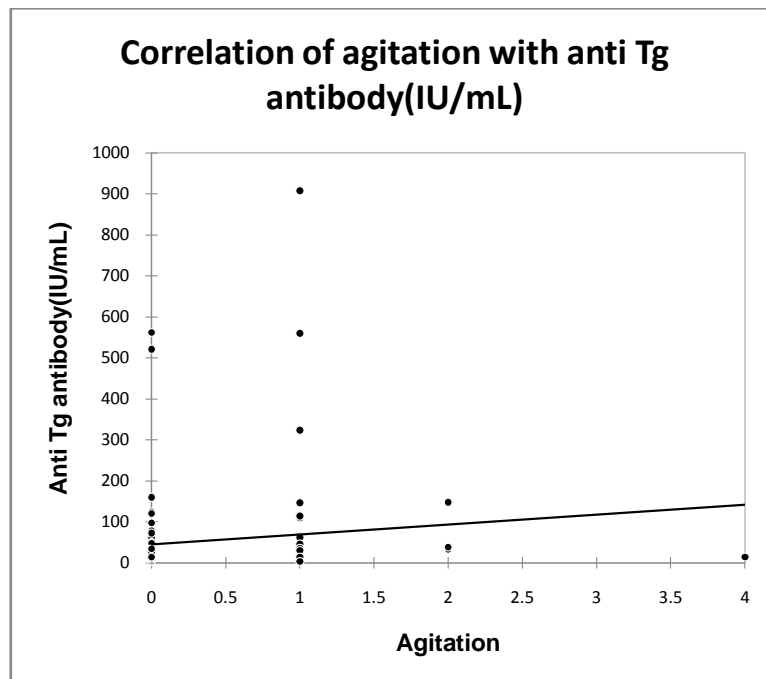


Figure 2.10:-Correlation of agitation with anti Tgantibody(IU/mL).

Significant positive correlation was seen between depressed mood with TSH(IU/mL), anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.34, 0.401, 0.291 respectively. No correlation was seen between feelings of guilt with TSH(IU/mL), anti TPO antibodies(IU/mL) with correlation coefficient of

0.007, 0.002 respectively. Non significant mild negative correlation was seen between feelings of guilt with anti Tgantibody(IU/mL) with correlation coefficient of -0.084. No correlation was seen between suicide with anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of -0.041, -0.006 respectively. Non



significant mild negative correlation was seen between suicide with TSH(IU/mL) with correlation coefficient of -0.091. Significant positive correlation was seen between insomnia-initial with TSH(IU/mL) with correlation coefficient of 0.191. Non significant mild positive correlation was seen between insomnia-initial with anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.155, 0.179 respectively. No correlation was seen between insomnia-middle with anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of -0.01, 0.062 respectively. Non significant mild positive correlation was seen between insomnia-middle with TSH(IU/mL) with correlation coefficient of 0.141.

No correlation was seen between insomnia-delayed with TSH(IU/mL), anti TPO antibodies(IU/mL) with correlation coefficient of -0.016, -0.026 respectively. Non significant mild positive correlation was seen between insomnia-delayed with anti Tgantibody(IU/mL) with correlation coefficient of 0.097. Significant positive correlation was seen between work and interests with TSH(IU/mL), anti TPO antibodies(IU/mL) with correlation coefficient of 0.209, 0.21 respectively. Non significant mild positive correlation was seen between work and interests with anti Tgantibody(IU/mL) with correlation coefficient of 0.134.

Non significant mild positive correlation was seen between retardation with TSH(IU/mL), anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.168, 0.174, 0.152 respectively. Significant positive correlation was seen between agitation with TSH(IU/mL), anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.207, 0.202, 0.22 respectively.

No correlation was seen between anxiety psychic with TSH(IU/mL) with correlation coefficient of 0.068. Non significant mild positive correlation was seen between anxiety psychic with anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.095, 0.093 respectively. No correlation was seen between anxiety somatic with TSH(IU/mL) with correlation coefficient of 0.029. Non significant mild positive correlation was seen between anxiety somatic with anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.117, 0.153 respectively.

No correlation was seen between somatic symptoms-gastrointestinal with anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.025, -0.005

respectively. Non significant mild negative correlation was seen between somatic symptoms-gastrointestinal with TSH(IU/mL) with correlation coefficient of -0.086. No correlation was seen between somatic symptoms-general with TSH(IU/mL) with correlation coefficient of 0.033. Non significant mild positive correlation was seen between somatic symptoms-general with anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.159, 0.108 respectively.

No correlation was seen between genital symptoms with TSH(IU/mL), anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.002, -0.043, 0.046 respectively. No correlation was seen between hypochondriasis with anti Tgantibody(IU/mL) with correlation coefficient of 0.007. Non significant mild positive correlation was seen between hypochondriasis with TSH(IU/mL), anti TPO antibodies(IU/mL) with correlation coefficient of 0.108, 0.132 respectively.

No correlation was seen between weight loss with TSH (IU/mL), anti TPO antibodies (IU/mL) with correlation coefficient of 0.004, 0.054 respectively. Non significant mild negative correlation was seen between weight loss with anti Tgantibody(IU/mL) with correlation coefficient of -0.103. No correlation was seen between insight with TSH(IU/mL), anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.071, 0.077, 0.041 respectively.

No correlation was seen between diurnal variation with TSH(IU/mL) with correlation coefficient of -0.003. Non significant mild positive correlation was seen between diurnal variation with anti Tgantibody(IU/mL) with correlation coefficient of 0.104. Non significant mild negative correlation was seen between diurnal variation with anti TPO antibodies(IU/mL) with correlation coefficient of -0.09. No correlation was seen between depersonalization and derealization with TSH(IU/mL) with correlation coefficient of 0.024. Non significant mild positive correlation was seen between depersonalization and derealization with anti TPO antibodies(IU/mL), anti Tg antibody(IU/mL) with correlation coefficient of 0.112, 0.083 respectively.

No correlation was seen between paranoid symptoms with TSH(IU/mL), anti Tgantibody (IU/mL) with correlation coefficient of -0.001, 0.024 respectively. Non significant mild negative correlation was seen between paranoid symptoms with anti TPO antibodies(IU/mL) with correlation coefficient of -0.093. No correlation was seen between obsessional symptoms with TSH(IU/mL), anti TPO antibodies(IU/mL), anti Tg



antibody(IU/mL) with correlation coefficient of -0.018, 0.051, 0.076 respectively.

Significant positive correlation was seen between total HAM-D with anti TPO antibodies (IU/mL) with correlation coefficient of 0.192. Non significant mild positive correlation was seen between total HAM-D with TSH (IU/mL), anti Tgantibody (IU/mL) with correlation coefficient of 0.164, 0.172 respectively.

It is shown in table 3, figure 2.1 to 2.10.

## V. DISCUSSION:

Overall HAMD score was used to calculate the severity of depression in the patients. In the present study, a non-significant mild positive correlation was seen between total HAMD with TSH (IU/mL) with a correlation coefficient of 0.164. Previous studies also showed that there are significantly deranged levels of T<sub>3</sub>, T<sub>4</sub>, and thyroid-stimulating hormone (TSH) in patients with depression (91,92). Gupta, Saha, and Mukhopadhyay reported a 20.5% prevalence of depression in patients with hypothyroidism.<sup>[7]</sup> A statistically significant correlation was found with TSH and HAMD (p=0.027) was found in the study by Mani K and co-workers.<sup>[13]</sup>

In the present study, it was found that anti-TPO was significantly correlated with total HAMD scores (r=0.192, p=0.036) but TSH (r=0.164, p=0.074) and anti-Tg (r=0.172, p=0.06) showed no significant correlation with it. This may suggest the autoimmune link with depression and its symptoms whereby the autoantibodies may affect the dopamine and other neurotransmitters in the brain in patients with hypothyroidism.<sup>[7,11,12]</sup>

Among the various symptoms studied in the present study, depressed mood and agitation were positively correlated with TSH, anti-TPO, and anti-Tg antibodies. It was noted that the more the values of TSH, anti-TPO, and anti-Tg antibodies, the more were the patients depressed (p=0.0002,<0.0001,0.001) and agitated (p=0.024,0.027,0.016). Such findings have been noted previously in the study by Mowla et al. where it was found that depressed patients with hypothyroidism presented more severe symptoms of anxiety and greater levels of agitation.<sup>[8]</sup>

Even in the study by, Ayhan et al. it was observed that patients with hypothyroidism were more depressed as compared to controls and the difference was statistically significant (P=0.001).<sup>[10]</sup> Pop VJ et al. in 1998 concluded that patients (especially females) with elevated anti-TPO antibody levels ( $\geq 100$  IU/ml) were found to be at risk for depression.<sup>[14]</sup> Ayhan MG et al. found a higher prevalence of major depression among

Hashimoto's thyroiditis patients.<sup>[10]</sup> Yalcin et al. indicated that Hashimoto's thyroiditis may increase predisposition to depression.<sup>[15]</sup>

It was also noted that the work and interests of the patients were decreased in correlation with increasing TSH values (p=0.022). Also, the patients had insomnia or difficulty in falling asleep with the increasing TSH values (p=0.03). This may be because of deregulated thyroid function in these individuals. This leads to symptoms of depression like disinterest, constant sensations of tiredness, lack of motivation to do many things, possible feelings of restlessness and agitation or lethargy, loss of appetite or overeating, sleeping too much or too little, feelings of uselessness and guilt, and even loss of concentration. Moreover, a normal sleep cycle requires an adequate hypothalamic-pituitary-thyroid axis. Dysregulation of this axis in hypothyroidism can lead to insomnia.<sup>[16]</sup> The strengths of the study include a comprehensive assessment of depression and its components was done in patients with hypothyroidism and correlated with thyroid profile. There is dearth of studies on anti-thyroid antibodies' and their correlation with depression in hypothyroidism. This study can act as a stepping stone to add to literature on depression in hypothyroidism. The only limitations being a single centred study and we did not follow up hypothyroid patients with depression for treatment outcomes with thyroxine replacement.

## VI. CONCLUSION:

Hypothyroidism showed a female predominance, with most of them occurring in an age group of 30-50 years. The thyroid profile (FT<sub>3</sub>, FT<sub>4</sub>, and TSH) is a useful investigation for diagnosing and differentiating cases of primary and secondary hypothyroidism. Hypothyroidism patients should get a psychological consultation for ascertaining the presence of mood, anxiety, or depressive disorder. Thyroid profile along with antibody levels may be considered an important diagnostic tool for testing autoimmunity as a cause of hypothyroidism especially in female patients to guide for therapy.

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