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Original Research Article

An Observational Cross Sectional Study to Evaluate the Impact of Thyroid Hypo Function on Anxiety and Depression among Hypothyroid Females of Reproductive Age Group in Eastern India

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ABSTRACT

Background: Thyroid hormone affects the central nervous system during developmental phase and also throughout life and thyroid dysfunction may result in significant changes in mental health.
Aims: To evaluate the impact of thyroid hypofunction on anxiety and depression in females of reproductive age group in Eastern region of India**.**
Materials & methods: The present observational cross sectional epidemiological study was conducted on 175 hypothyroid subjects in Burdwan Medical College for a time span of 12 months after taking Institutional ethical clearance. 75 controls were also enrolled for the study. The two groups were age matched. Serum TSH and FT4 levels were estimated. Patients were assessed for anxiety and depression using Hospital Anxiety and Depression Scale (HADS). The computer software SPSS, version 16.0 was used for analyzing data.
Results: Among hypothyroid subjects 28% was with anxiety and 22.28% was with depression whereas 8% anxiety and 5.33% depression found out of 75 controls. Significant difference was noticed between control and hypothyroid subjects for mean TSH (P<0.0001), mean FT4(P<0.0001), mean HADS-A score(P:0.0001) and mean HADS-D score(P<0.0001). No significant difference was found for mean age (Age in years: 30.85±6.43 vs. 31.66 ±6.86; P value: 0.384) between control and hypothyroid subjects. HADS-A score for anxiety was positively correlated with serum TSH (R: 0.174, P:0.0213) and was negatively correlated with Sr. FT4 (R: - 0.288, P:0.00011) Also HADS-D score for depression was positively correlated with serum TSH (R:0.636, P<0.00001) and was negatively correlated with Sr. FT4 (R: - 0.291, P:0.000093).
Conclusion: Occurrence of anxiety and depression was significantly more in hypothyroid subjects as compared to controls. A positive correlation was observed between anxiety, depression scores and TSH levels. So, it maybe concluded that subjects with hypothyroidism are at higher risk of developing anxiety and depression and screening tests needs to be administered for early detection of such mental disorders in hypothyroid subjects.

Keywords: Hypothyroidism, Anxiety, Depression, FT4, TSH. HADS

INTRODUCTION

Hypothyroidism is a common condition in clinical practice with women being more commonly affected than men. [1] Thyroid gland secretes two related hormones and they include thyroxine (T4)

and triiodothyronine(T3). Synthesis of thyroid hormone starts at 11thweeks of gestation.T3 is generated specifically in peripheral tissue by deiodination of T4 and is much biologically active than T4. [2] Thyroid hormone affects the central nervous system during developmental phase and also throughout life. [3] Many neuropsychiatric and cognitive complications are found in hypothyroid patients. These include comorbid depression to depressive features with or without anxiety, memory impairment and defect in executive function. [1,3]

Thyroid hormones influence the central nervous system by various mechanisms: [3,4]

1. Control of gene expression in myelination, neuronal function and differentiation of neural and glial cells
2. Modulation of gene expression of many proteins, some of them are having implications in mood disorders
3. Effect on serotonin (5HT-5hydroxy tryptamine) by desensitization of 5 HT1A autoreceptor in raphe nucleus
4. Effect on noradrenergic neurotransmitter having antidepressant action.

Organic anion transporting polypeptide (OATPs) transport thyroid hormones in to the cell and OATP1C1 plays a key role to deliver serum T4 to brain. Severe hypothyroidism may manifest with depressive psychosis. [5] HLA-Bw 35 and HLA-B8 genes, hypothalamic abnormalities and globally decreased brain activity are related with pathogenesis of mood changes in thyroid dysfunction. [6] Thyroid dysfunction causes significant manifestation in mental health and causes reduction in health related quality of life. Increased prevalence of moderate to severe depression, anxiety causes increased stress response producing changes in cardiorespiratory functions. [7]

An increased incidence of depression is found in Thyroid disorders with immune and autoimmune background and immune dysregulation is one of known pathophysiological mechanisms for the development of depression. [8,9]

Placidi et al. [10] in 1998 in their study found higher prevalence of mood and anxiety disorders in thyroid dysfunction. A study in 2017 observedhigh prevalence of depression in patients with hypothyroidism. [9] Clinical features and serum TSH were noted and Anti TPO antibody was estimated. Patients were administered the Hospital anxiety and depression score (HADS). Patients were classified as normal, those with borderline depression and those with depression. One hundred and forty-four patients were included in the analysis. Eighteen out of 144 patients had depression and another 20 had borderline depression. Higher serum thyroid stimulating hormone, anti-thyroid peroxidase antibody levels and body mass index were found to have a significant relation to presence of depression. The independent association of TPO antibody to depression when adjusted for TSH could not be proven.

There are limited studies on depression in hypothyroid females using current diagnostic tools in eastern India. The present study was conducted to evaluate the impact of thyroid hypo function on anxiety and depression in females of reproductive age group in Eastern region of India.

MATERIALS AND METHODS

This observational cross sectional epidemiological study was conducted on 175 newly diagnosed hypothyroid female subjects of reproductive age group in Burdwan Medical College within a time span of 12 months after taking approval from institutional ethics committee and informed consent from the participating subjects.75 control subjects(normal thyroid status) were also enrolled. The study protocol was explained to all subjects. Patients were assessed for anxiety and depression using Hospital Anxiety and Depression Scale (HADS). The formula used for the calculation of the size of the required sample was $n=(z)^2p(1-p)/d^2$, n= sample size, z= z statistic for a level of confidence (95% level of confidence used, so z value is 1.96),p= expected prevalence

of proportion, d= desired precision taken as 6% and previous studies were taken into consideration. [12,13]

Inclusion criteria:

175 newly diagnosed hypothyroid female subjects of reproductive age group attending in the Department of Biochemistry, Burdwan Medical College and 75 control subjects were taken for the present study.

Exclusion criteria:

- History of substance dependence like drug and alcohol dependence
- History of major psychotic disorders
- History of depressive or anxiety disorder before diagnosis as hypothyroid
- Associated with comorbid chronic illness
- Cognitive impairment
- Organic disorders like delirium or dementia
- Taking psychotropic drugs
- Patients already on thyroxine supplementation
- Neurological problems like seizure
- History of thyroid surgery

Parameters studied:

- Age
- TSH
- FT4
- HADS-A for anxiety
- HADS-D for depression

Methods:

We had taken approval from the Institutional ethics committee before conduction of the study and Informed consent was taken from each participant. Subjects were recruited by random sampling using an online randomizer. Detailed history was taken from each subject as per case record format. Participants were also screened on the basis of inclusion and exclusion criteria.

Fasting Blood samples (5 ml) were drawn from subjects using sterile needle and syringes and sent to biochemical laboratory in sterile vials for analysis.

Estimation of Serum TSH was done by Quantitative determination of TSH concentration by Microplate immunoenzymometric assay using Monobind Inc. USA manufactured TSH AccuBind ELISA Kit (Normal value:0.39-6.16 micro IU/ml).

Estimation of Serum FT4 level was done by Quantitative determination of FT4 concentration by Microplate Enzyme Immuno assay using Monobind Inc. USA manufactured FreeT4 AccuBind ELISA Kit (Normal value:0.8-2.0 ng/dl)

Biochemical methods:

Estimation of TSH:

Measurement of serum TSH is generally regarded as the most sensitive indicator for the diagnosis of Hypothyroidism.

Test principle: (Method-Immunoenzymometric assay)

The immobilization occurs at the surface of microplate well between the interaction of streptavidin coated on the well and biotinyted monoclonal anti-TSH antibody. By mixing the monoclonal biotinyted antibody, the enzyme labelled antibody and a serum containing native antigen, reaction occurs between native antigen and the antibodies to form a soluble sandwich complex. Then the complex is deposited to the well. After equilibrium is achieved, the antibody bound fraction is separated from unbound antigen by aspiration or decantation. The enzymatic activity of the antibody bound fraction which is directly proportional to the native free antigen concentration is measured by adding substrate. By utilizing calibrators of known antigen concentrations, a dose response curve can be generated from which the antigen concentration of an unknown sample can be ascertained

Kit content:

1. Streptavidin Coated Microplates-96 wells coated with streptavidin and packaged in an aluminium bag with a drying agent.
2. TSH Enzyme Reagent- 13 ml/vial containing enzyme labelled polyclonal antibody, biotinylated monoclonal IgG in buffer, dye and preservative.

3. Thyrotropin Calibrators-seven vials(0.5ml/vial) of references for TSH Antigen at levels of 0,0.5,2.5,5.0,10,20 and 40 μIU/ml
4. Substrate A(7ml/vial) -one bottle containing tetramethylbenzidine (TMB) in buffer.
5. Substrate B(7ml/vial)-one bottle containing hydrogen peroxide (H2O2) in buffer.
6. Stop Solution (8ml/vial)- one bottle containing a strong acid (1 N HCL)
7. Wash Solution Concentrate (20 ml)-one vial containing a surfactant in buffered saline. A preservative has been added.

Calculation of results:
(I) Calculation of the mean absorbance value of calibrator and samples was done at 450 nm.
(2) A point to point curve was plotted by plotting the absorbance of each calibrator on the vertical Y-axis against concentration of each calibrator on the horizontal or X-axis.
(3) Using the absorbance value for each sample the corresponding concentration of TSH was determined in microIU/ml. and standard curve used

QUALITY CONTROL:

Controls were assayed at levels in the low, normal, and high range for monitoring assay performance. These controls were regarded as unknowns and values determined in every test procedure performed. Quality control charts were maintained to follow the performance of the supplied reagents. Pertinent statistical methods were employed to get trends. Acceptable assay performance limits were set. Other parameters monitored included the 80, 50 and 20% intercepts of the dose response curve for run-to-run reproducibility. Maximum absorbance was consistent with previous experience. Marked deviation from established performance might indicate degradation of kit reagents or unobserved change in experimental conditions. Fresh reagents were used to determine the cause for the variations

Estimation of FT4: -

Thyroxine circulates in blood almost bound to carrier proteins. Thyroxine binding globulin (TBG) is the main carrier protein. Only the free (unbound) fraction of thyroxine is biologically active. Concentrations of the carrier proteins are altered in different clinical conditions. So the free thyroxine (FT4) concentration remains constant. The measurement of FT4 concentration correlates better than total thyroxine level.
Test principle: (Competitive Enzyme Immunoassay-EIA)
In competitive EIA, a competitive reaction results between the native free antigen and enzyme-antigen conjugate for limited number of insolubilized binding sites on antibody coated on the micro well. After the equilibrium is attained the antibody-bound fraction is separated from unbound antigen by aspiration or decantation. The enzymatic activity of the antibody bound fraction which is inversely proportional to the native free antigen concentration is measured by adding substrate. By utilizing calibrators of known antigen concentrations, a dose response curve can be generated from which the antigen concentration of an unknown sample can be found out.

Kit contents: -
1.FT4 Antibody coated microplate(96 wells)-one96 well microplate coated with anti-thyroxine serum.
2.Enzyme reagent(13ml/vial)-one vial of thyroxine-horseradish peroxidase(HRP) conjugate in a protein stabilized matrix.
3.FT4 calibrators(0.5 ml/vial)- six vials of human serum based reference calibrators for free thyroxine.
4.Substrate A (7 ml/vial)-one bottle containing tetramethylbenzidine(TMB) in acetate buffer.
5.Substrate B (7 ml/vial)-one bottle containing hydrogen peroxide(H2O2) in acetate buffer.

6.Wash solution concentrate(20 ml)-one vial containing a surfactant in buffered saline.
7.Stop solution(8 ml/vial)-one bottle containing a strong acid (1 N HCL).
Calculation: -
1.Calculation of absorbance value was done at 450 nm.
2.A point to point curve was plotted by plotting the absorbance of each calibrator on Y axis against concentration of each calibrator on X axis.
3.Using the absorbance value for each sample the corresponding concentration of FT4 was determined in ng/dl.
QUALITY CONTROL:
Controls were assayed at levels in the hypothyroid, Euthyroid and hyperthyroid range for monitoring assay performance. These controls were treated as unknowns and values determined in every test procedure performed. Quality control charts were maintained to follow the performance of the supplied reagents. Pertinent statistical methods were employed to ascertain trends. Marked deviation from established performance might indicate degradation of kit reagents or unobserved change in experimental conditions. Fresh reagents were used to determine the reason for the variation

Hypothyroidism was defined as an elevated TSH (>6.16micro IU/ml) with a decreased(<0.8ng/dl) or normal serum FT4 level (range:0.8-2.0 ng/dl) as per kit values.

Hospital Anxiety and Depression Scale (HADS):
HADS is a 14 items self-report likert scale and is widely used to assess and screen anxiety and depression symptoms [14] in non-psychiatric patients. [15,16] This scale was developed by Zigmond and Snaith in 1987 and divided into anxiety subscale (HADS-A) and a depression subscale(HADS-D) consisting of 7 items each. [17] Each item is rated from '0 to 3' on a 4-point scale. [16]

We assessed the anxiety and depression level of our study subjects according to HADS scale.
Each subject was given considerable time and asked as per item of the HADS scale. Then total score was calculated separately for anxiety and depression.
HADS Score: [16]
7 or less- normal
8 to 10- presence of disorder
11 to 21-significant case
We used a score of 8 or more as the cut off score in HADS scale.
The HADS questionnaire has been validated in many countries, languages and settings. The National Institute for Health and Care Excellence (NICE) recommended this tool for diagnosis of depression and anxiety [18]
The Hospital Anxiety and Depression Scale (HADS) is having good sensitivity and specificity for mental disorders. [19]

Statistical analysis:

Data was analyzed using the computer software "Statistical Package for the Social Sciences (SPSS) version 16 (SPSS Inc. Released 2007.SPSS for Windows, Version 16.0. Chicago, SPSS Inc.)". A p-value of less than 0.05 was considered as statistically significant and p-value of less than 0.01 was considered as highly significant.

RESULTS

Newly diagnosed 175 hypothyroid female subjects and 75 controls were taken for the present study. Among hypothyroid subjects 28 % was with anxiety and 22.28% was with depression whereas 8% anxiety and 5.33% depression found out of 75 controls. Significant difference was noticed between control and hypothyroid subjects for mean TSH (P<0.0001), mean FT4 (P<0.0001), mean HADS-A score (P:0.0001) and mean HADS-D score (P<0.0001). No significant difference was found for mean age (Age in years: 30.85±6.43 vs. 31.66 ±6.86; P value: 0.384) between control and hypothyroid subjects. (Table 1; Figure 1)

A significant difference of prevalence for anxiety (P:0.0004) and depression (P:0.0011) was observed between control and hypothyroid subjects (Table 2).

HADS-A score for anxiety was positively correlated with serum TSH (R: 0.174, P:0.0213) and was negatively correlated with Sr. FT4 (R: - 0.288, P:0.00011) (Figure 2). Also HADS-D score for depression was positively correlated with serum TSH (R:0.636, P<0.00001) and was negatively correlated with Sr. FT4 (R: - 0.291, P:0.000093) (Figure 3).

Table 1: Shows Age, TSH, FT4, HADS-A score and HADS-D score of control and hypothyroid subjects

Parameter	Control (Mean±SD)	Hypothyroidism (Mean±SD)	P value
Age (years)	30.85 ± 6.43	31.66 ± 6.86	0.384
TSH(micro IU/ml)	1.99 ± 0.97	19.39± 9.71	<0.0001**
FT4(ng/dl)	1.31 ± 0.24	0.78± 0.37	<0.0001**
HADS-A score	6.44 ± 1.74	8.56±4.45	0.0001**
HADS-D score	5.85± 1.54	8.31±4.35	<0.0001**

P<0.05*significant, <0.01 highly significant**

Table 1: shows that the difference of TSH, FT4, HADS-A score and HADS-D score were highly significant.

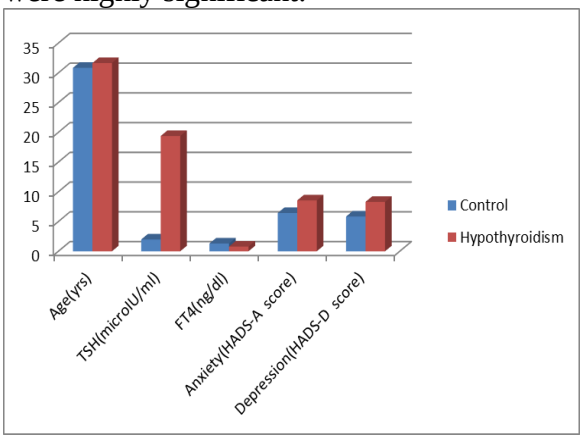

Figure 1: Shows the difference of Age, TSH, FT4, HADS-A score and HADS-D score between control and hypothyroid subjects

Table 2: Shows comparison of Anxiety and Depression between Control subjects and Hypothyroid subjects

Parameter	Controls (n=75)	Hypothyroid (n=175)	P value
Anxiety	6(8%)	49(28%)	0.0004**
Depression	4(5.33%)	39(22.28%)	0.0011**

P<0.05*significant, <0.01 highly significant.**

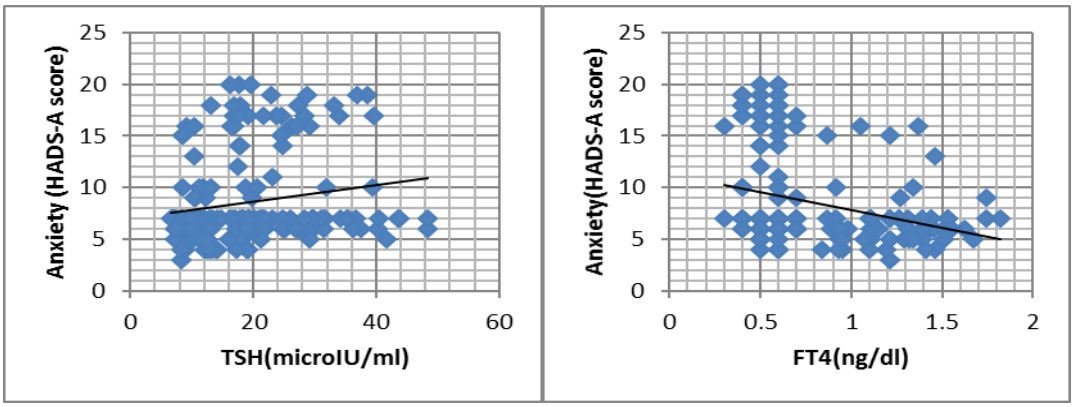

Figure 2: Shows HADS-A score was positively correlated with serum TSH and was negatively correlated with Sr. FT4

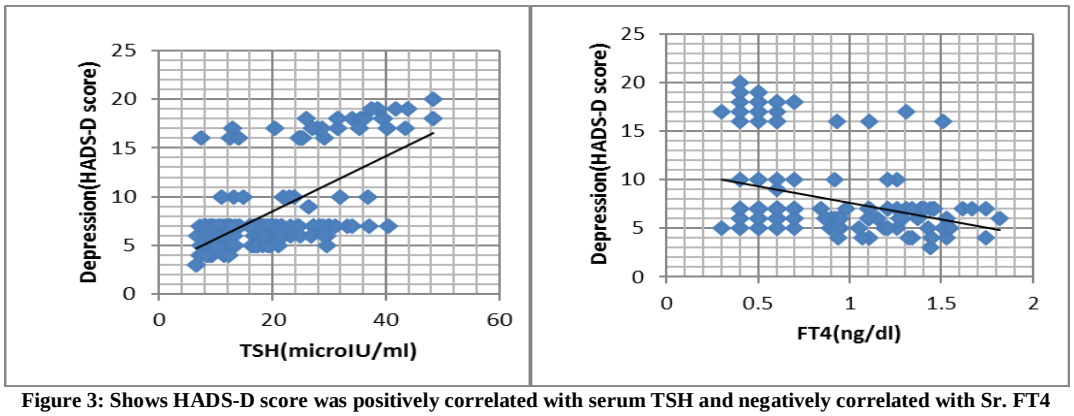

Figure 3: Shows HADS-D score was positively correlated with serum TSH and negatively correlated with Sr. FT4

DISCUSSIONS

Significance of thyroid hormone regarding cerebral development and functioning is emphasized by catastrophic neurological outcome of increased deficiency of iodine, untreated congenital

hypothyroidism and MCT8 mutations. Thyroid hormones affect serotonergic and noradrenergic neurotransmission which carry a major role in pathogenesis of depression. [20]

Spencer et al. [21] addressed the psychological abnormalities in hypothyroidism and other endocrine abnormalities like hyperthyroidism, diabetes, Cushing's syndrome, hyperpara-thyroidism and androgen disorders.

Brain is the major target organ for thyroid hormone [22] and in adults, hypothyroidism causes depressive symptoms, behavioral problems, anxiety and memory impairment. [3] Patients with hypothyroidism may be expected improvement of their depressive symptoms with levothyroxine therapy. [22]

The present study was conducted to evaluate the impact of thyroid hypofunction on anxiety and depression in hypothyroid female subjects of reproductive age group in Eastern region India We had enrolled 175 newly diagnosed hypothyroid female subjects and 75 controls for our present study. Factors interfering our present study were excluded from our study. Patients were assessed and screened for anxiety and depression using Hospital Anxiety and Depression Scale (HADS).

Significant difference was noticed between control and hypothyroid subjects for mean TSH (P<0.0001), mean FT4 (P<0.0001), mean HADS-A score (P:0.0001) and mean HADS-D score (P<0.0001). No significant difference was found for mean age (Age in years: 30.85±6.43 vs. 31.66 ±6.86; P value: 0.384) between control and hypothyroid subjects.

It is well known that thyroid dysfunction may significantly affect mental status. [11] Recently, much attention has been given for the diagnostic assessment of mental abnormalities associated with thyroid diseases. [10]

A study by Bathla et al. [3] in 2016 observed 60% depression and 63% anxiety in hypothyroidism out of the total patients screened. Chaudhary et al. [23] in2014 in their study found that 63% hypothyroid patients were with co morbid depression and 47.29 % females were with mild anxiety. Another study by Jain et al. [24] in 2013 noticed 36.67% depression in hypothyroid subjects and a highly significant correlation (p:0.001) between depression and hypothyroidism.

In the present study, among hypothyroid subjects 28 % were having with anxiety disorders and 22.28% was had depression; whereas 8% anxiety disorder and 5.33% depression was observed among controls.

Anxiety (HADS-A score) was positively correlated with serum TSH (R:0.174,P:0.0213) and was negatively correlated with Sr. FT4 (R:-0.288,P:0.00011). Also depression (HADS-D score) was positively correlated with serum TSH (R:0.636, P<0.00001) and was negatively correlated with Sr. FT4 (R:-0.291,P:0.000093).Similar results have also been observed in previous studies. [25-43]

CONCLUSION

Occurrence of anxiety and depression was significantly more in hypothyroid subjects as compared to controls. A positive correlation was observed between anxiety, depression scores and TSH levels. So, it may be concluded that subjects with hypothyroidism are at higher risk of developing anxiety and depression and screening tests needs to be administered for early detection of such mental disorders in hypothyroid subjects. Further longitudinal studies are needed to validate the findings.

Conflict of interest: Declared none.
Source of funding: Nil

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