



Depression in Hypothyroidism and Risk Factors

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Abstract

Background: *There are limited studies on depression in medically ill using current diagnostic tools in India. The present study aims to find the prevalence of depression in patients with hypothyroidism and its association with clinical parameters and thyroid autoantibody levels.*

Materials and Methods: *Patients fulfilling clinical and biochemical criteria suggesting hypothyroidism of either gender or age between 18 and 65 years were included in the study. Clinical features and serum TSH were noted, Anti TPO antibody test was done. Patients were administered the validated local language version of the Hospital anxiety and depression score (HADS). Patients were classified as normal, those with borderline depression and those with depression.*

Results and Discussion: *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. Symptoms such as, cold intolerance, memory loss and clinical assessments like BMI as an association to depression in hypothyroid patients is a novel finding when compared to older studies.*

Conclusion: *There is a high prevalence of depression in patients with hypothyroidism which can be diagnosed only if systematic screening using validated tools is used for the same. Depression needs to be actively screened and managed appropriately in hypothyroid patients so as to avoid the devastating consequences of untreated depression. Some clinical indicators like obesity, cold intolerance and memory loss may signal the presence of depression in hypothyroid patients.*

Keyword: *Hypothyroidism, Thyroiditis, Depression, TPO, BMI.*

Introduction

Thyroid disorders are the most common among all the endocrine diseases in India.¹ It is known that decreased thyroid function has effect on mood and there is similarity of symptoms in both hypothyroidism and depression. Depression produces number of functional limitations, including poorer physical, psychosocial, and role functioning, increased number of disability days and if untreated can lead to life-threatening complications such as suicide². Treatment of depression improves the quality of life in physically ill and has positive effect on course of illness³. General depression criteria carry risk of false-positive diagnosis by including certain features which may be secondary to the medical illness rather than reflecting depression per se⁴. Hashimoto's thyroiditis is a common cause of hypothyroidism. Autoimmune thyroid disease may be linked to depression⁵ and anxiety⁶. There are limited studies on depression in medically ill using current diagnostic tools in India. The present study aims to find the prevalence of depression in patients with hypothyroidism and its association with thyroid autoantibody.

Materials and Methods

The study was conducted in the Department of General Medicine, Government Medical College Hospital Trivandrum which is a tertiary care teaching hospital in South India. The study period was six months and it was conducted in a cross sectional design. Cases were patients diagnosed with hypothyroidism. Ethical clearance for the study was obtained from Institutional Ethics Committee of Govt. Medical College, Thiruvananthapuram. The research protocol was explained to all participants and written consent was obtained from all subjects. Patients fulfilling clinical and biochemical criteria suggesting hypothyroidism of either gender and an age between 18 and 65 years were included in the study. Patients having TSH more than 5 μ IU/ml attending the Thyroid outpatient clinic of General Medicine Department were included in to the

study after considering exclusion criteria. Specifically, patients with substance dependence, known acute or chronic psychosis or affective disorder, gross cognitive deficits, major or chronic medical illness, those on treatment with antipsychotic medications, patients within 6 weeks post-partum period and those with post-thyroidectomy hypothyroidism were excluded from the study. All consecutive cases fulfilling the inclusion criteria were included. A detailed history and a thorough clinical examination were done. The demographic details and clinical assessment of thyroid function was noted on a predesigned proforma.

Hospital Anxiety and Depression Scale (HADS): The HADS is a self-reported scale developed by Snaith and Zigmond⁷. This instrument was designed to screen for the presence of a mood disorder in medically ill patients. The scale consists of 7 questions which assesses the mental status of the patient with regard to presence of depression and anxiety, the response to each question being graded from 0-3. A score of 11 or more is diagnostic for the presence of depression. A score 8-10 is termed borderline depression and a score upto 7 is normal. HADS has sensitivity estimates ranging from 56% to 100% and specificity 73% to 94%. Thomas et al⁸ have translated and validated the hospital anxiety and depression scale (HADS) in to Malayalam which is the local language which was used in this study. It is also recommended for use by various professional bodies^{9, 10, and 11}. All participants were administered the HADS.

The anti-thyroid peroxidase antibody levels were estimated using ECLIA (electro-chemiluminescence Elecsys 2010, Roche Diagnostics Germany) test kits.

Data was analyzed using Microsoft Excel and SPSS version 22.0. Mean and Standard deviation were used for description of continuous variables and percentages for categorical variables. Between groups comparison of quantitative variables was analyzed by Independent sample t-test and Mann Whitney test as appropriate and between

group comparisons of categorical variables was analyzed by Chi square test. Strength of association is described using odds ratio with 95 % confidence interval. Variables found to have significant association in univariate analysis were subjected to multivariate analysis using Binary logistic regression. A p-value of less than 0.05 was considered as statistically significant.

Results

A total of 144 patients could be enrolled in the study. The basic demographic and clinical details of the subjects are presented in table 1. In short the mean age (\pm SD) of the study subjects was 33.68 (11.54) years. Most of the patients (93.8 %) were females. All patients were educated but only 21 (14.6 %) were graduates. About half of the patients (46.5%) of the population were poor as assessed by the "below poverty line (BPL)" status and 86.8 % of them resided in rural areas. 14.6 % patients gave history of stress at home, and 14.6 % patients had history of thyroid diseases in the family and 0.7% had that of mental illness. None of the study subjects was a smoker, only 6 % were vegetarians. All patients were consumers of iodine fortified salt. The mean body mass index (BMI) of the study subjects was 24.5 (4.1) kg/m^2 , 38 patients (26.38%) were obese ($\text{BMI} \geq 27 \text{ kg/ m}^2$) and 52 patients (36.11%) patients were overweight ($\text{BMI} 23- 26.99 \text{ kg/ m}^2$).The clinical profile of patients showed that 99.5% patients had some form of typical hypothyroid symptoms on detailed questioning whereas only one patient reported as having none of the classic hypothyroid symptoms. General tiredness followed by loss of hair were the most common complaint (91 % and 83.3% respectively). Clinically goiter was present in 11.1 % patients. The mean serum thyroid stimulating hormone (TSH) was 14.1 $\mu\text{IU/ml}$ and Anti thyroid peroxidase (TPO) antibody was positive in 108 patients. The Median HADS score was 5 with an inter quartile range of 2 to 8. Out of the 144 patients screened for depression 102 were normal, 24 patients had borderline depression (HADS of 8-10) and 18 were depressed

(moderate- severe). If patients with stressors at home are excluded, 15 out of 123 patients show definite evidence of depression. When a comparison of cases with depression and those without depression is done with respect to various variables (Table 2) it is seen that the patients with depression had a higher prevalence of TPO antibody positivity and the mean TSH level was significantly higher in them (42.8 ± 25.8 vs $10.0 \pm 6.2 \mu\text{IU/ml}$ p value < 0.001). On adjusting for Serum TSH levels (multivariate analysis using binary logistic regression) elevated TPO was not found to be associated independently with depression. Patients who were married, had overweight or obesity, or had cold intolerance or memory loss as symptoms were at higher risk for depression. No association could be found between serum TSH levels and serum TPO antibody levels which may be attributed to alteration in TSH values due to treatment of hypothyroidism.

Table 1. Demographic and clinical parameters of study subjects with hypothyroidism

Parameter	Expressed as	Value (n=144)
Age in years	mean \pm sd	33.68 \pm 11.54
Female Gender	n (%)	135 (93.8%)
Occupation	n (%)	26 (18.1%)
Education	Below SSLC	38(26.4%)
	SSLC	51(35.4%)
	Pre degree	34(23.6%)
	Degree & above	21(14.6%)
Socio economic status	BPL	67(46.5%)
Place of residence	Rural	125(86.8%)
Marital status	Married	122(84.7%)
Grief or stress in the family	n (%)	21(14.6%)
Diet	Vegetarian	6(4.2%)
Family history	Thyroid disease	21(14.6%)
	Mental illness	1(0.7%)
	Others	1(0.7%)
Clinical profile	Cold intolerance	30(20.8%)
	Dryness of skin	54(37.5%)
	Hoarse voice	45(31.3%)
	Constipation	31(21.5%)
	Weight gain	45(31.3%)
	Increased sleep	100(69.4%)
	Memory loss	86(59.7%)
	Impaired hearing	9(6.3%)
	Tiredness & weakness	131(91%)
	Goiter (neck swelling)	16(11.1%)
	Loss of hair	120(83.3%)
	Menstrual irregularity	51(35.4%)
	Miscarriage	2(1.4%)
Pulse rate	mean \pm sd	80.4 \pm 6.2
BMI	mean \pm sd	24.5 \pm 4.1
TSH(μ iu/ml)	mean \pm sd	14.1 \pm 15.2
Anti TPO(iu/ml)	mean \pm sd	172.5 \pm 131.7
HADS score	median \pm IQR	5 (2-8)
Depression	No depression	102(70.8%)
	Borderline	28(16.7%)
	Definite	18(12.5%)

Table 2. Comparison between clinical and demographic variables among patients with or without definite depression

Variables	No or border line depression (N=126)	Depression (N=18)	p
Age in years †	34.2±11.6	30.2±11.2	0.175
Female gender ‡	118(93.7%)	17(94.4%)	0.896
No Occupation ‡	102(81%)	16(88.9%)	0.413
Unmarried ‡	13(10.3%)	9(50%)	<0.001
Grief or stress in the family ‡	18(14.3%)	3(16.7%)	0.789
Diet- vegetarian ‡	4(3.2%)	2(11.1%)	0.115
Cold intolerance ‡	23 (18.3%)	7(38.9%)	0.044
Dryness of skin ‡	46(36.5%)	8(44.4%)	0.515
Hoarse voice ‡	37(29.4%)	8(44.4%)	0.197
Constipation ‡	28(22.2%)	3(16.7%)	0.592
Weight gain ‡	38(30.2%)	7(38.9%)	0.455
Increased sleep ‡	88(69.8%)	12(66.7%)	0.784
Memory loss ‡	71(56.3%)	15(83.3%)	0.029
Goiter ‡	13(10.3%)	3(16.7%)	0.423
Loss of hair ‡	104(82.5%)	16(88.9%)	0.499
Menorrhagia ‡	24(19%)	5(27.8%)	0.388
Pulse rate †	80.1±5.9	82.3±8.0	.154
BMI †	24.7±4.3	23.0±2.6	.087
TSH †	10.0±6.2	42.8±25.8	<0.001
Anti TPO †	162.3±132.1	243.8±107.0	.014
Blood glucose Random (mg/dl) †	100.0±22.7	102.6±25.3	.658
Creatinine (mg/dl) †	0.88±0.51	0.85±0.15	.793

†- Quantitative variables expressed in mean± sd, ‡ Categorical variables expressed in n (%)

Discussion

The present study was a descriptive study conducted in the Medical outpatient clinics of a tertiary care hospital in south India. Most of the patients studied were females. Patients with hypothyroidism were administered the hospital anxiety and depression scale after noting the symptom profile and conducting a physical examination, serum TPO antibody levels were also measured. The study finds a prevalence of depression in 12.5 % of hypothyroid patients. Another 13.8% patients had borderline depression. Also a significant association between higher TSH levels and prevalence of depression was observed. Higher thyroid peroxidase antibody levels also increased the risk of depression but when adjusted for TSH levels there was no such increased risk observed. Overweight and obesity married status, overweight or obesity, a history of cold

intolerance or memory loss predisposed the patients for developing depression which are novel findings.

In a study by Pies et al approximately 40% of clinically hypothyroid patients had significant signs and symptoms of depression¹² whereas our study shows a combined prevalence of depression and borderline depression to be present in 26% patients. Suxena et al¹³ and Boral et al¹⁴ have found that significantly higher number of patients with unipolar depression have subnormal T3 and T4 levels and a corresponding increase in thyroid stimulating hormone (TSH) levels. Another study found that 20.5% subjects of major depressive disorders have hypothyroidism.¹⁵

The finding that higher TSH is associated with higher risk of depression is consistent with the study performed by Das BKL et al¹⁶ to assess serum level of Thyroxine (T4), Triiodothyronine

(T3) and thyroid stimulating hormone (TSH) in patient with depression. The TSH level was significantly increased in severe depression.

Our results are in agreement with Pop et al that women with elevated TPO antibody levels are especially vulnerable to depression, whereas post-menopausal status does not increase the risk of depression.¹⁷ But our study results are in distinction to the above in the fact that when adjusted for TSH levels there was no significant association of depression with TPO antibody levels.

Chopra et al¹⁵ studied subtle abnormalities in the thyroid functions in depressive patients. Total tri-iodo-thyroxine (T3) was lower in depressive patients but the difference was not significant. The mean value of thyroid stimulating hormone (TSH) was comparable in the two groups. But depressive patients with psychotic features had significantly higher mean value of TSH as compared to those without them.

In this study by Bente et al¹⁸ on endocrine parameters in 113 depressed outpatients and in 113 sex and age matched controls were assessed. It found that the serum concentration of TSH was slightly higher in depressed patients as compared with controls ($P < 0.001$), independent of the presence of subclinical hypothyroidism and/or TPO antibodies.

Eller et al¹⁹ studied the role of thyroid peroxidase autoantibodies (anti-TPO) in depressive patients with respect to clinical status and treatment outcome in depression. Although there were no significant differences in the measurements between treatment responders and non-responders, the last group showed a trend for a higher prevalence of anti-TPO compared with responders and they concluded that thyroid autoimmunity might be a factor predicting treatment response to antidepressants in depressive patients.

Conclusion

Depression is an important comorbidity of hypothyroidism for which bidirectional associations have been demonstrated in numerous studies.

Serum TSH levels and BMI are contributors to the risk of depression in hypothyroid patients. Thyroid autoimmunity measured by TPO antibody levels are associated with higher prevalence of depression but seem to be affecting through a higher TSH levels only. Depression needs to be actively screened and managed in hypothyroid patients and so as to avoid its devastating consequences. Clinical indicators like history of cold intolerance memory loss and a married status should prompt the clinician to screen the patient for depression. Further studies may evaluate the effect of lowering BMI in these patients with respect to depression.

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Author contributions: Authors MYN and AKS conceived the study, CJK and MYN designed the project. MYN conducted the data collection. SBM supervised the biochemical investigations involved in the study. AN conducted data analysis and manuscript preparation.

References

1. Kochupillai N. Clinical Endocrinology in India. 2 Current Science 2000, 8: 1061-7.
2. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA. 1990;264: 2524-2528.
3. Linda H, Maren K, et al. Improving depression outcomes in older adults with comorbid medical illness. 2005;27:4-12
4. Clark DA, Cook A, Snow D. Depressive symptom differences in hospitalised, medically ill, depressed psychiatric

- patients and nonmedical controls. *J Abnorm Psychol* .1998;107:38-48.
5. Fountoulakis KN, Iacovides A, Grammaticos P: Thyroid function in clinical subtypes of major depression. *BMC Psychiatry* 2004., 4(6):
 6. Carta MG, Hardoy MC, Boi MF, Mariotti S, Carpiniello B, Usai P: Association between panic disorder, major depressive disorder and celiac disease. A possible role of thyroid autoimmunity. *Journal of Psychosomatic Research* 2002, 53:789-7937.
 7. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;61:361-370.
 8. Thomas BC, Devi N, Sarita GP, Rita K, Ramdas K, Hussain B.M., Rejnish R & Pandey M. Reliability & validity of the Malayalam hospital anxiety & depression scale (HADS) in cancer patients *Indian J Med Res* 122, November 2005, pp 395-399.
 9. Ladenson PW, Singer PA, Aink B, et al. American Thyroid Association Guidelines for Detection of Thyroid Dysfunction. *Arch Intern Med* 2000; 160:1573-5.
 10. Wilson GR, Curry RW Jr. Subclinical thyroid disease. *Am Fam Physician* 2005;72(8):1517.
 11. Col NF, Surks MI, Daniels GH. Subclinical thyroid disease clinical applications. *JAMA* 2004;291:239-43
 12. Pies RW. Women, mood, and the thyroid. *Women Psychiatr Health*. 1995;4:4-10.
 13. Saxena J, Singh PN, Srivastava U, Siddiqui AQ. A study of thyroid hormones (T3, T4 and TSH) in patients of depression. *Indian J Psychiatry* 2000;42:243-6.
 14. Boral GG, Ghosh AB, Pal SK, Ghosh KK, Nandi DN. Thyroid function in depression. *Indian J Psychiatry* 1980;22:353-5.
 15. Chopra VK, Basal DR Thyroid Functions In First Episode Depressive Illness: A Controlled Study. *Indian J Psychiatry* 2001;43:61-6.
 16. DasBKL, BaralN, ShyangwaPM, Toora BD, Lamsal M .Altered serum levels of thyroxine, triiodothyronine and thyroid stimulating hormone in patients with depression ; *Kathmandu Univ Med J (KUMJ)*. 2007 Jul-Sep;5(3):330-4.
 17. Pop et al. Are Autoimmune Thyroid Dysfunction and Depression Related? *The Journal of Clinical Endocrinology & Metabolism*. September 1, 1998 21.
 18. Appelh of BC, Hoogendijk WJG, Huyser J, Endert E. Thyroid and adrenal axis in major depression: a controlled study in outpatients *Eur J Endocrinol* February 1, 2005 152 185-191
 19. Eller T, Metsküla K, Talja I, Maron E, Uibo R, VasarV. Thyroid autoimmunity and treatment response to escitalopram in major depression *Nord J Psychiatry*. 2010 Aug; 64(4):253-7.