ORIGINAL RESEARCH PAPER

Psychiatry

KEY WORDS: first episode depression, free T3, Free T4, thyroid stimulating hormone(TSH)

THE CORRELATION BETWEEN SERUM THYROID HORMONE LEVELS AND FIRST EPISODE OF MAJOR DEPRESSIVE DISORDER

Pal V. S — Professor, Department of Psychiatry, M.G.M. Medical college Indore

Chauhan Beema* — Resident doctor, Department of Psychiatry, M.G.M. Medical College Indore *Corresponding Author

Rastogi Pali — Associate Professor, Department of Psychiatry, M.G.M. Medical college Indore

Razdan R — Professor, Department of Psychiatry, M.G.M. Medical college Indore

ABSTRACT

Background: Hypothalamus-pituitary-thyroid (HPT) axis dysfunction has been connected with pathophysiology of depression. The object of this study was to determine serum level of free 3,5,3'-triiodothyronine (T3), free thyroxine (T4) and thyroid-stimulating-hormone (TSH) in drug naive patients with unipolar depression and healthy controls. **Methodology:** The study included 100 medication-free patients with unipolar depression and 100 healthy controls. **Results:** A higher FT4, lower FT3 and lower TSH mean values which were statistically significant as compared to healthy controls however the means were still in the euthyroid range. **Conclusion:** The results showing altered levels of thyroid hormones in depression advisable that further research on thyroid hormone activity can contribute to the greater understanding of the biological basis of depression.

INTRODUCTION

The possibility of a relationship between thyroid gland, brain and behaviour has sought the attention of clinicians and researchers. Although, a relationship between clinical disorders of the thyroid gland and psychiatric comorbidity has been well established but the significance of the relation between thyroid functioning and primary psychiatric disorder is much less clear.

Psychiatric manifestations are frequently noticed during the course of endocrine disorders. Psychiatric symptoms often related with endocrine dysfunction include mood dysregulation, anxiety, psychosis, cognitive dysfunction, dementia, delirium. Endocrine diseases may lead to psychiatric symptoms as one of the initial presenting signs. Patients who have thyroid disorders are more prone to develop depressive symptoms and conversely depression may be associated by subtle thyroid abnormalities .it seems that thyroid hormone supplements accelerate and enhance the clinical response to antidepressant drugs. Studies have revealed that although a majority of the cases of depression are associated with **euthyroidism**, **thyroid dysfunction** has commonly been seen associated with **depression**.[1]

The **most commonly** seen thyroid abnormality in the thyroid patients are **raised** levothyroxine (FREE T4), **decreased** triiodothyronine (FREE T3), and **raised** thyrotropin release hormone (TRH) levels, and a blunted thyroid stimulating hormone (TSH) response. 1 to 4% of patients with affective disorders are found to have overt hypothyroidism while subclinical hypothyroidism occurs in 4% to 40% of these patients.[1] Hypothyroidism either clinical or subclinical must be considered in every patient of depression as per the American Association of Clinical Endocrinologists.**[2]**.

The effects of thyroid dysfunction on depression are well documented and understood however there is a lacuna of research on the effects of depression on thyroid hormones in absence of pre-existing thyroid dysfunction. There are few studies which define the changes in thyroid hormones as per severity of depression and duration of illness. There is a dire need to assess thyroid dysfunction in first episode of depression as it may be a predictor of treatment response in future episodes.

Methodology-

The present study is cross sectional in design where we included 100 (52 females,48 males) drug naïve first episode of depression patients in the age range of 18 to 65 years as cases and 100 healthy controls. The study was conducted in department of Psychiatry, M.G.M. Medical College, Indore between January 2018 to December 2018. The study was approved by institutional scientific and ethics committee. The Hamilton Depression Rating Scale (HAM-D 17)[3], General Health Questionnaire (GHQ-12)[4], ICD-10 DCR [5]were used for assessment of the subjects. After complete description of the study to the subjects, written informed consent was obtained from all participants. The diagnosis of major depression was made using structured clinical interview based on ICD 10(DCR) criteria. Socio-demographic data was collected using a semi-structured proforma. After that clinical assessment of patient group was done using HAM-D to ascertain severity. Morning blood samples were withdrawn in clot activator (red top tube). Estimation of the parameters of the study–quantitative serum TSH, FREE T4, FREE T3 was done by using in vitro competitive ELISA (Enzyme- Linked Immunosorbent Assay) kit is designed for the accurate quantitative measurement of Thyroxine in serum at M.Y. Hospital. After all the samples were collected ELISA kit was used to determine the values of FT3, FT4, TSH. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS for Windows, Version 23, SPSS Inc.).

Results

Table-1: Comparison of basal TFT between first episode depression and healthy controls

Variables	depressive patients (mean)	healthy controls (mean)	t-value	p-value
Free T4 (pg/l)	1.91	1.78	2.00	0.04
Free T3(pmol/l)	1.85	2.42	7.55	0.001
TSH (mIU/l)	2.13	2.73	2.49	0.01

Table 1 shows the comparison of mean values of free thyroxin (T4), free triiodothyronine (T3) and thyroid stimulating hormone (TSH) between the depressive and the control groups. In depression group FT4 was slightly higher than control group which was statistically significant however the range was within normal limits. In control group FT3 and TSH was slightly higher than case group which was statistically significant however the range was within normal limits.

Table -2

	Correlation with Free T4	
Variables	r	p
HAM-D	0.084	0.40
Age of onset	0.04	0.67
Duration of illness	-0.079	0.45

- Table 2 shows the correlation of free FT4 with HAM-D, age of onset and duration of illness. No significant correlation was found between them.

Table -3

	Correlation with Free T3	
Variables	r	p
HAM-D	0.09	0.33
Age of onset	0.09	0.36
Duration of illness	0.019	0.85

- Table 3 shows the correlation of free T3 with HAM-D,age of onset and duration of illness. No significant correlation was found.

Table -4

	Correlation with TSH	
Variables	r	p
HAM-D	0.09	0.33
Age of onset	0.01	0.89
Duration of illness	0.018	0.73

Table 4 shows the correlation of TSH with HAM-D,age of onset and duration of illness. No significant correlation was found.

DISCUSSION

Comparison of FT4 levels between first episode depression patient and healthy controls (**table 1**) revealed that the mean FT4 for first episode depression was 1.91± 0.48 while for healthy controls was 1.78 ± 0.40 . Depression patients showed slightly higher mean value for FT4 than healthy controls which was statistically significant but within normal limits which were in agreement with the previous studies like **Saxena et al.2000[6], Hage and Azar et al. 2012[7], Kassaee et al.2016[8], Talukdar B et al.2018 [9]** who also found T4 levels to be elevated. But normal levels of T4 were reported by **Maes et al (1993)[10] and Fava et al. (1995) [11].** The effect on the HPT axis in depressive patients seems to be weaker than in healthy subjects. 80% of T3 is derived from local conversion of T4 by deiodination. It has been hypothesized that activation of hypothalamic TRH producing neurons and subsequent increase in thyroid function secondary to depression which is associated with the rise in cortisol, which inhibit the type-2 deiodinase (D2) enzyme liable for conversion of T4 into T3 **(Nemeroff, 1989)[12],(Baskin et al., 2002[1] Bahls and De Carvalho, 2004,[13].**

The mean FT3 for first episode depression was 1.85 ± 0.37 while for healthy controls was 2.42 ± 0.64 .Depression patients showed lower mean FT3 value than healthy controls which was statistically significant. **Bauer et al. (1994)[14] and Fava et al. (1995)[11], Premachandra et al.2006)[15], Jinxue et al., 2014[16]** have also reported low T3 levels in their study. However, all the above studies concluded that although the T3 levels were lower in the depression group the value was still euthyroid as per cut off. In **2000 Saxena et al.** conducted a study on FT3 levels in depression patients and found them to be within normal range which is in concordance with our study. The literature regarding total T3 in first episode depression is less accordant. Many other studies have reported either normal or decreased total T3 during acute depression when compared to the healthy controls like **Baumgartner et al. (1992)[17] and Orsulak et al. (1995)[18].** found marginally elevated T3 during acute depression. **Muller and Boning (1988)[19], Chopra et al,2001[20]** found elevated thyroxin (T4) and decreased triiodothyronine (T3) during acute depression and concluded that this finding may indicate that there is some defect in the conversion of thyroxin (T4) to triiodothyronine (T3).

The mean TSH for first episode depression was 2.13 ± 1.51 while for healthy controls was 2.73± 1.84. Depression patients showed lower mean value of TSH than healthy controls which was statistically significant. **Yanbin jia et al.2015 [21]** found that the levels of TSH were significantly decreased in MDD group when compared to the healthy controls, similar findings were found by **Stipcevic et al., 2008[22] Russell T Joffe et al.,2008[23]** found that the lower normal range of TSH when compared with the higher normal range of TSH were significantly more depressed. A new cohort study identified low-normal TSH as an important risk factor for depression, especially in the elderly **(Marco et al., 2014)[24] and females, (Wenjiao et al., 2012)[25].** Another possible explanation for decreased TSH in depression is due to chronic stress factors. It was seen that HPT axis impairment which do not match the endocrine pattern usually was causal towards major depressive disorder. Still very little is known about the impact of acute stress on the HPT axis and almost nothing about that of chronic stress. We must highlight that the results for thyroid hormones are ambivalent and that TSH levels appear to be rise in acute stress and fall in chronic stress **(Bschor et al., 2003[26], Michael Bauer et al., 1993[14]).** FT3, FT4, TSH of depressive patients didn't show any significant correlation with HAM-D score. This finding is in concordance with **Joffe et al.,2008[23]**.

As per our findings the basal TFT (FT3, FT4, TSH) did not correlate significantly with age of onset of depressive disorder, duration of illness and HAM-D scores. **Jia et al., 2015[21**] also replicated similar findings. Since, the mean age of onset our sample population was 32.6 years in the case group with a standard deviation of about 12 years it is unlikely that the basal TFT would raise or fall significantly as per the age of onset. Hence, we conclude that basal TFT variations are independent of the age of onset of the depressive disorder.

CONCLUSION:

Depression patients showed higher FT4, lower FT3 and lower TSH mean values which were statistically significant as compared to healthy controls however the means were still in the euthyroid range. As per our current findings and previous studies we can implicate that augmenting thyroid along with conventional antidepressants may help in better treatment outcome and prevent against clinical hypothyroidism.

FT3, FT4, TSH didn't show any significant correlation with HAM-D score, onset of illness and duration of illness of depression. Hence, we conclude that depression may affect thyroid levels leading primarily towards hypothyroid spectrum, so any drug which is anti-thyroid must be used with caution.

REFERENCES

1. H. J. Baskin, R. H. Cobin, and D. S. Duick, "American association of clinical endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism," Endocrine Practice, vol. 8, no. 6, :457-69
2. Hage, Mirella & Azar, Sami. (2012). The Link between Thyroid Function and Depression. Journal of thyroid research. 2012. 590648. 10.1155/2012/590648.
3. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
4. Goldberg,D.,& Williams,P.(1988).A user's guide to the General Health Questionnaire.Windsor, UK:NFER-Nelson
5. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. Geneva: World Health Organization;1993.p.89-103
6. Saxena J, Singh PN, Srivastava U, Siddiqui AQ. A study of thyroid hormones (t(3), t(4) &tsh) in patients of depression. Indian J Psychiatry. 2000;42(3):243–246
7. Hage, Mirella & Azar, Sami. (2012). The Link between Thyroid Function and Depression. Journal of thyroid research. 2012. 590648. 10.1155/2012/590648.
8. Kassaee, Seyed Mehrdad & Ahmadi, Rahim &Seif, Asghar &Molaei, Sedigheh. (2016). Assessment of Serum Tri-Iodothyronine (T3), Thyroxin (T4) and Thyroid-Stimulating Hormone (TSH) Levels Among Patients with Major Depressive Disorder (MDD) in Hamedan, Northwestern Iran. Jentashapir Journal of Health Research. In Press. 10.17795/jjhr-23066.

9. Goswami H., Talukdar B Thyroid Profile in Drug Naive Cases of Depression. Journal of Depression and Anxiety. 07. 10.4172/2167-1044.1000300.
10. Maes M, Scharp S, Cosyns P, Meltzer H. Relationships Between Basal Hypothalamicpituitary-Thyroid-Axis Activity And Plasma Haptoglobin Levels In Depression (20 December 1993) .I. Psychmr. Rss., Vol. 28, No. 2, Pp 1235134. 1994 Copyright3' 1994elsevicrscccncc Ltd Printed In Grealbritain, Pergamon
11. Fava M, Labbate LA, Abraham ME, Rosenbaum JF. Hypothyroidism and hyperthyroidism in major depression revisited. J. Clin. Psychiatry. 1995;56:186–192.
12. Nemeroff CB, Simon JS, Haggerty JJ Jr, Evans DL.Antithyroid antibodies in depressed patients Am J Psychiatry. 1985 Jul;142(7):840-3.
13. Bahlsa SC, Carvalhob GA (2004) The relation between thyroid function and depression: A review. Rev Bras Psiquiatr 26:40-48
14. Bauer M1, Priebe S, Kürten I, Gräf KJ, Baumgartner A. Psychological and endocrine abnormalities in refugees from East Germany: Part I. Prolonged stress, psychopathology, and hypothalamic-pituitary-thyroid axis activity Psychiatry Res. 1994 Jan;51(1):61-73. DOI:10.1016/0165-1781(94)90047-7
15. B. N. Premachandra, H. T. Blumenthal, Abnormal Binding of Thyroid Hormone in Sera from Patients with Hashimoto's Disease, The Journal of Clinical Endocrinology & Metabolism, Volume 27, Issue 7, 1 July 1967, Pages 931–936, https://doi.org/10.1210/jcem-27-7-931
16. Wei, Jinxue & Sun, Guizhi& Zhao, Liansheng& Liu, Xiang & Lin, Dongtao& Li, Tao & Ma, Xiaohong. (2014). Hair thyroid hormones concentration in patients with depression changes with disease episodes in female Chinese. Psychiatry research. 220. 10.1016/j.psychres.2014.07.029.
17. Baumgartner A1, Gräf KJ, Kürten I, Meinhold H. The hypothalamic-pituitary-thyroid axis in psychiatric patients and healthy subjects: Parts 1-4. Psychiatry Res. 1988 Jun;24(3):271-332.
18. Orsulak, Paul J. et al. Free triiodothyronine (T3) and thyroxine (T4) in a group of unipolar depressed patients and normal subjects Biological Psychiatry, Volume 20, Issue 10, 1047 – 1054.
19. Muller B, Boning J. Changes in the pituitary – thyroid –axis accompanying major affective disorder. Acta PsychiatricaScandinavica 1988;77:143–50.
20. Chopra VK, Ram D. Basal thyroid functions in first episode depressive illness : a controlled study. Indian J Psychiatry. 2001;43(1):61–66.
21. Jia, Yanbin& Zhong, Shuming& Wang, Ying & Liu, Tao & Liao, Xiaoxiao& Huang, Li. (2015). The correlation between biochemical abnormalities in frontal white matter, hippocampus and serum thyroid hormone levels in first-episode patients with major depressive disorder. Journal of Affective Disorders. 180. 10.1016/j.jad.2015.04.005.
22. Stip evi , Tamara &Pivac, Nela&Kozari -Kova i , Dragica& Muck-Šeler, Dorotea. (2008). Thyroid activity in patients with major depression. Collegium antropologicum. 32. 973-6.
23. Joffe, R. T., & Levitt, A. J. (2008). Basal Thyrotropin and Major Depression: Relation to Clinical Variables and Treatment Outcome. The Canadian Journal of Psychiatry, 53(12), 833–838. https://doi.org/10.1177/070674370805301209.
24. Medici, Marco &Direk, Nese& Visser, W &Korevaar, Tim &Hofman, Albert & Visser, Theo &Tiemeier, Henning &Peeters, Robin. (2014). Thyroid Function Within the Normal Range and the Risk of Depression: A Population-Based Cohort Study. The Journal of clinical endocrinology and metabolism. 99. jc20133589. 10.1210/jc.2013-3589.
25. Min, Wenjiao& Liu, Chuanxin& Yang, Yanchun& Sun, Xiao & Zhang, Bo & Xu, Li & Sun, Xueli. (2012). Alterations in hypothalamic-pituitary-adrenal/thyroid (HPA/HPT) axes correlated with the clinical manifestations of depression. Progress in neuro-psychopharmacology & biological psychiatry. 39. 206-11. 10.1016/j.pnpbp.2012.06.017.
26. Bschor T, Baethge C, Adli M, Lewitzka U, Eichmann U, Bauer M. Hypothalamic-pituitary-thyroid system activity during lithium augmentation therapy in patients with unipolar major depression. J Psychiatry Neurosci. 2003;28(3):210–216.