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Low mood and response to Levothyroxine treatment in Indian patients with subclinical hypothyroidism

Gaurav Vishnoi [a,*], Baidarbhi Chakraborty [b], Hormaz Garda [c], Srinivas H. Gowda [d], Binita Goswami [e]

[a] Department of Pharmacology, Maulana Azad Medical College, New Delhi, India
[b] Department of Biochemistry, Dr. D.Y. Patil Medical College, Navi Mumbai, India
[c] Department of Psychiatry, Dr. D.Y. Patil Medical College, Navi Mumbai, India
[d] Department of Biochemistry, AIIMS, New Delhi, India
[e] Department of Biochemistry, Lady Hardinge Medical College, New Delhi, India

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ABSTRACT

Background and aim: There is considerable controversy regarding the association of subclinical hypothyrodism (SCH) and depression. We studied the association of SCH with low mood and also investigated the effects of L-thyroxine (LT_4) therapy on improvement of symptoms.
Methods: Three hundred patients with SCH and 300 age and sex-matched healthy controls were studied. Serum levels of TSH, FT3, FT4 were measured by chemi-illuminescence. Hamilton Depression Rating Scale (HAM-D) was used to evaluate baseline depression in all participants and subsequently, in 133 patients who had undergone LT_4 therapy for 2 months.
Results: The HAM-D scores were significantly higher for cases (10.0 ± 4.7) as compared to controls (2.4 ± 1.5). A positive correlation ($r^2 = 0.87$, $p = 0.00$) was found, between the Hamilton scores and serum TSH levels. No such association was seen between serum FT3, FT4 levels and HAM-D scores. Levothyroxine treatment resulted in a significant decrease in TSH levels and Hamilton scores.
Conclusions: SCH is associated with low mood and there is a positive correlation between serum TSH levels and HAM-D scores. The administration of Levothyroxine therapy is associated with significant improvement in HAM-D scores. This underlines the importance of thyroid screening in cases of low mood and also asserts the role of Levothyroxine therapy.

1. Introduction

The association between altered thyroid function and mood impairment is well documented (Whybrow et al., 1969; Rack and Makela, 2003; Gussekloo et al., 2000; Teixeira et al., 2006) with overt hypothyroidism often being recognized as an established risk factor for depression (Patten et al., 2006). Many investigators suggest that thyroid tests should be an integral part of evaluation related to depression (Farmer et al., 2008; Baldwin, 2008; Blazer, 2003; Helfand, 2004).

Subclinical hypothyroidism (SCH) is defined as elevated serum TSH in the presence of normal circulating levels of free thyroxine (T4) and triiodothyronine (T3) (Vanderpump et al., 1995; Wenzel et al., 1974). SCH affects about 5% of the general population worldwide (Tunbridge et al., 1977). Studies from different parts of India have also reported very high incidence of SCH ranging from 9.4% in Southern India (UshaMenon et al., 2009) to 21.56% in Northern part (Bashir et al., 2013). Although overt thyroid disorders negatively influence physical and cognitive function; association of subclinical thyroid disorder with such outcome measures are less clear and studies demonstrate contradictory results (Simonsick et al., 2009; Begin et al., 2008; Park et al., 2010). There is considerable controversy on whether Levothyroxine (LT_4) replacement is warranted in these patients who are otherwise apparently healthy with only mildly elevated TSH levels (Gussekloo et al., 2000; Parle et al., 2010; Surks et al., 2004; Gharib et al., 2005; Jorde et al., 2006; Biondi and Cooper, 2008). Also the association between the TSH levels and severity of depression has not been clearly described and there is disagreement if administration of LT_4 reverts the symptoms of low mood.

The aim of this study was to determine if biochemical markers of subclinical hypothyroidism are associated with clinically significant low mood and also to investigate the effects of LT4 therapy on level of mood.

* Corresponding author at: Flat No. E-801, Army CHS, Sector-9, Nerul, Navi Mumbai 400706, India. Tel.: +91 9833981979.
E-mail addresses: gvishnoi@gmail.com, dr.baidarbhi@gmail.com (G. Vishnoi).

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2. Material and methods

The study was conducted in the Department of Pharmacology and Department of Biochemistry Maulana Azad Medical College in collaboration with the Department of Psychiatry, G.B. Pant Hospital. It was a hospital based case control study which was completed in 3 years (June 2009 to May 2012). Within this period a total of 5500 patients attended the Endocrinology lab for hormonal assessment after being referred by various clinical departments. We recruited 440 cases of SCH after conducting tests on thyroid profile. The TSH level in this group was more than 5.0 mIU/L and the peripheral thyroid hormones were in the normal range (FT_3: 3.1–6.8 pmol/l; FT_4: 12–22 pmol/l). Patients were freshly diagnosed cases of SCH with no history of any prior medication for any pathology pertaining to thyroid disease. Subjects with previously diagnosed major depressive disorder, neurological disorders such as stroke and Parkinson's disease or chronic medical disorders that might affect mood and thyroid status were excluded from the study. Also patients were screened for any major stressors in life in recent past like bereavement, unemployment/loss of job, job stressor and relationship issues which could confound the results by causing stress related changes to thyroid hormone levels. A standard questionnaire was used in all cases and controls. Finally 300 cases of newly diagnosed subclinical hypothyroidism were recruited.

Three hundred age and sex-matched healthy control subjects were also enrolled. The control subjects were selected from volunteers and healthy persons accompanying the patients in general OPD. They had euthyroid status with their TSH levels in the range of 0.5–5.0 mIU/L. The peripheral thyroid hormones, free thyroxine (FT_4) and free tri-iodothyronine (FT_3) were in the normal range (FT_3: 3.1–6.8 pmol/l; FT_4: 12–22 pmol/l). Written informed consent was obtained from all the participants enrolled in the study; the study protocol was approved by the Ethics Committee of the hospital.

2.1. Clinical examination

A detailed history and clinical evaluation was carried out. The patients were interviewed to rule out personal history of past or present mental disorder, ischemic cardiac disease, stroke, any other chronic disease or major life stressors. Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) which uses a multiple item questionnaire was used to evaluate baseline depression in all participants and in patients after they attained euthyroid status with LT_4 therapy. The scale was assessed by an experienced clinician. Score of 0–7 was taken as normal, 8–13 as mild depression, 14–18 as moderate depression, 19–22 as severe depression and values greater than 23 as very severe depression. This scale was chosen for its large and established use in psychiatric literature. Out of these 300 cases, 133 patients were started with Levothyroxine (LT_4) treatment (25 mcg/day) in view of deranged lipid profile, menstrual irregularities, symptoms of hypothyroidism and presence of anti-thyroid antibodies. These patients were followed up for two months. Repeat clinical evaluation and TSH assay at 2 month interval was performed in these 133 patients to study the effect of LT4 on low mood. Patients with severe forms of depression as assessed by HAM-D were excluded in the second clinical assessment as they were started on anti depressant medications and could confound our results.

2.2. Laboratory investigations

Fasting blood samples were taken from patients on two occasions. Initial sample was drawn on the day when the patient first arrived at Endocrinology lab for hormonal evaluation (henceforth called day 1) from all patients ($n = 300$). A second blood sample was drawn after a period of two months after Levothyroxine treatment had been initiated for 133 patients. 5 ml of whole blood was drawn and the serum was separated by centrifuging at $1000 \times g$ for 15 min. Thyroid hormones including TSH, FT3 and FT4 were done by Chemiluminescence technique on Elecsys 2010 (Roche Diagnostics).

2.3. Statistical analysis

Statistical analysis was done with Statistical Package for the Social Science 17.0 (SPSS Inc., Chicago, IL). Continuous data were presented as average (minimum, maximum). Student's t test was used to compare means. Paired t test was used to assess the level of depression before and after LT_4 treatment. Spearman's correlation was used to assess level of correlation between TSH and HAM-D scores. The level of significance was chosen to be $p < 0.05$.

3. Results

The clinical characteristics of the study group are shown in Tables 1 and 2. The study groups are age and sex matched. Risk factor analysis showed prevalence of smoking and alcohol in 24% and 15% of the cases respectively. In comparison with control subjects, patients with SCH had higher BMIs ($p = 0.0002$).

The age range of the study group was 23–80 years, with mean age of 52.5 ± 11.5 years and the group consisted of 92 males and 208 females. In the control group, ages ranged from 23 to 78 years, with mean age of 52.4 ± 11.5 years. This group included 87 males and 213 females. There was no statistical difference between the ages of cases and controls ($p > 0.05$) (Table 2).

Significantly elevated levels of serum TSH were observed in patients with SCH, as compared to healthy control subjects (Table 3). The patients with SCH also exhibited lower FT4 and FT3 levels, as compared with controls. Though the serum levels of these peripheral hormones were within normal range, FT4 levels were

Table 1
Demographic features of the study population.

	Subclinical hypothyroid patients ($n = 300$)	Controls ($n = 300$)
BMI (kg/m^2)	26.6 ± 3.7*	21.5 ± 2.11
Systolic BP (mm Hg)	130 ± 9	124 ± 10
Diastolic BP (mm Hg)	89 ± 5	82 ± 5
Past history of CAD	–	–
Family history of CAD (%)	5	–
Smoking (%)	24	–
Alcohol (%)	15	–
Diabetes mellitus (%)	8	–
Hypertension (%)	5	–
Cholesterol (mg/dl)	288.6 ± 40.1*	145.5 ± 29.7
Triglycerides (mg/dl)	243.3 ± 64.8*	123.2 ± 41.9
HDL (mg/dl)	38.18 ± 6.3*	43.16 ± 5.6
LDL (mg/dl)	171.3 ± 40.4*	77.7 ± 27

* Significantly high compared with control group ($p < 0.05$).

Table 2
Age and gender distribution in study population.

	Cases, $n = 300$		Control, $n = 300$		p Value (Mann–Whitney)
	Mean	Range	Mean	Range	
Age	52.5 ± 11.5	23–80	52.4 ± 11.5	23–78	0.9
Males	52.1 ± 10.7	23–80	48.8 ± 13.8	23–78	0.06
Females	52.7 ± 11.9	24–76	54.0 ± 10.0	24–77	0.19