Original Paper

TSH and T4 Levels in a Cohort of Depressive Patients

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ABSTRACT: Depression is a significant contributor to the overall burden of disease on a global scale. Thyroid hormones thyroxine (T4) and triiodothyronine (T3) have been shown to play a critical role in the development and normal function of the brain. It has been suggested that dysregulation of thyroid function could be associated with depression, especially hypothyroidism, but not all studies support this hypothesis. We enrolled a cohort of 96 subjects with major depressive disorder and tested TSH and FT4 levels for 80 of them in order to assess the status of the hypothalamic-pituitary-thyroid axis (HPT). We found 7 cases (8.75% of the tested) of subclinical hyperthyroidism and 1 case (1.25%) of overt hyperthyroidism. While we did not find supporting evidence for association between TSH and FT4 levels and depression, our findings question whether screening depressive patients for HPT axis anomalies could be clinically relevant, if anything, in a regional context.

KEYWORDS: *TSH, FT4, depression.*

Introduction

Depression is considered a chronic disabling disorder that leads to a decrease in the quality of life on an individual scale [1,2] while at the same time accounting for a significant portion of the global burden of neuropsychiatric disease [2,3].

Thyroid hormones, thyroxine (T4) and triiodothyronine (T3) play a critical role in brain development.

They have a significant impact on numerous processes such as myelination, neurogenesis, synapse generation and glial development.

It stands then that their presence and action would be critically important for normal brain function [4-6].

A complex set of mechanisms regulates the hypothalamic-pituitary-thyroid (HPT) axis and several factors other than the hormones themselves such as: transport proteins, receptors and deiodinase enzymes play essential roles.

Secretion of thyroid hormones is regulated by the pituitary hormone thyrotropin (TSH) whose secretion is in turn stimulated by the thyrotropin-releasing hormone (TRH) which is produced at a hypothalamic level and inhibited by the serum concentrations of circulating thyroid hormones.

The majority of T3 in the cerebral cortex is derived from local conversion of T4 with only one fifth of the total T3 level being secreted by the thyroid [7,8].

T4 is transported at a cerebral level through numerous transporters, the most numerous being transthyretin (TTR) [8-10].

Conversion of T4 to T3 mostly takes place inside glial cells and following this the resulting T3 hormones exercise their action by binding to the thyroid hormone nuclear receptors (THR) [8,11].

Some studies have reported a high prevalence of symptoms specific to depression in clinically hypothyroid patients [12] and a correlation with clinically overt hypothyroidism [13] while others have attempted to establish a link between subclinical hypothyroidism and depression [14-16].

Subclinical hypothyroidism as quantified by normal circulating FT4 and FT3 levels but elevated circulating TSH levels has been reported to affect 8.5% of the general population with some authors reporting values as high as 17% [16] and with a higher rate amongst the elderly [2,17].

Several authors have demonstrated a link between subclinical hypothyroidism while others have failed to report such an association [15,16].

Currently it is recommended that patients that have subclinical hypothyroidism undergo levothyroxine replacement therapy only if their TSH levels are above 10mIU/L [2,18,19].

However the benefits on mental health outcome are unclear with a lack of solid evidence due to a small number of randomized controlled trials focused on L-T4 supplementation therapy and its effects on patients with depressive symptoms [2,16,20].

We aimed to assess the status of the hypothalamic-pituitary-thyroid axis in a cohort of patients that had been diagnosed with major depressive disorder (MDD) by evaluating their serum TSH and FT4 levels.

Materials and Method

After receiving the approvals of the Medical Ethics Committees of the University of Medicine and Pharmacy of Craiova (UMFCV), and of the hospital involved, we enrolled 96 patients, 34 men and 62 women, with ages ranging from 28 to 74, mean age 54.07±8.67 from the number I and number II clinics of the Clinical Neuropsychiatry Hospital in Craiova.

After explaining the purpose of our study and obtaining a written consent form from each of the patients we proceeded to harvest a 2ml sample of whole blood which was then used for the subsequent laboratory analysis.

We were able to obtain plasma values for FT4 levels for 80 subjects due to conditions pertaining to sample collection circumstances or sample quantity or quality.

Interviewing our enrolled subjects, we obtained self-reported information regarding a history of previous depressive episodes, the presence of feelings of anxiety, treatment administration, suicidal ideas and/or suicidal gestures.

TSH levels were assessed using the NovaTec Immundiagnostica ELISA assay, having an analytical sensitivity of 0.07µUI/ml, a range of 0.07µUI/ml-20µUI/ml and normal range values between 0.3-4.5µUI/ml.

According to the specifications of this assay, it does not produce an observable Hook effect even after applying 5000µUI/ml TSH.

FT4 levels were assessed using the same NovaTec Immundiagnostica ELISA Assay with the lowest concentration that was detectable of free T4 that can be measured being 0.5ng/l at a 95% confidence limit. Normal reference values were 8-20ng/l.

Both assays were analyzed using the CLARIOstar® high performance microplate reader at the Human Genomics Laboratory (UMFCV).

We performed statistical analysis using BMG Labtech's proprietary Mars Data Analysis Software and GraphPad Prism 8.0.1.

Results

All patients had been admitted to the clinic following a major depressive episode, quantified using the Hamilton Rating Scale for Depression (HAM-D).

Out of the 96 patients enrolled 79 (83.68%) had a history of at least one previous depressive episode with 21 patients (20.16%) having experienced three or more such episodes.

Although our enrollment criteria did not include or exclude thyroid pathology, all of the enrollees had no known previous history of thyroid disorders.

The enrolled cohort is in line in both age and sex for the profile for the patients with depression in the collaborating clinics (unpublished data).

We identified one case of a 61 years old male with hyperthyroidism, with TSH lower than the detection threshold of the ELISA test of 0.07µUI/ml and fT4 20.937ng/l.

The patient did not have any clinical complaints and was unaware of this condition.

Further 7 subjects had low TSH levels, 3 of them below detection limit, but all had normal T4 levels, indicating the possibility of subclinical hyperthyroidism.

T4 levels were also within normal ranges for the majority of the tested subjects with only one outlier, one female with levels of 21.05ng/l and TSH of 3.32µUI/ml.

Table 1 summarizes mean values and standard deviations for the two evaluated hormone levels for the subjects in the normal range.

TSH ranges per age decade are also visually displayed in Figure 1.

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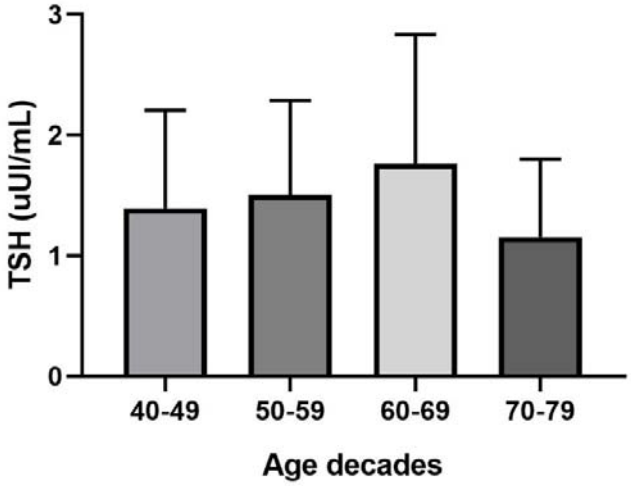

Figure 1. TSH mean levels and standard deviation (shown by vertical bars) by age decades. Y axis represents TSH levels expressed in µUI/ml. X axis represents age decades. One-way ANOVA (p=0. 0.6364) shows no significant association despite the apparent trend.

Table 1. Subjects with normal TSH and FT4 values distributed by sex and age.

Age group	Percentage	TSH mean value (µUI/ml)	FT4 mean value (ng/ml)
Females	**61.1% (n=44)**	**1.55±0.87**	**11.59±2.56**
21-30	1.4% (n=1)	0.72	10.64
31-40	1.4% (n=1)	2.19	9.27
41-50	12.5% (n=9)	1.47±0.94	10.39±1.12
51-60	25.0% (n=18)	1.36±0.71	12.42±3.26
61-70	19.4% (n=14)	1.86±1.02	11.64±2.12
71-80	1.4% (n=1)	1.60	10.31
Males	**38.9% (n=28)**	**1.51±0.86**	**12.08±2.29**
41-50	5.6% (n=4)	1.23±0.51	10.77±0.58
51-60	25.0% (n=18)	1.65±0.84	11.68±1.72
61-70	5.6% (n=4)	1.43±1.33	13.75±2.86
71-80	2.8% (n=2)	0.93±0.73	14.95±5.32
Total	**100% (n=72)**	**1.53±0.86**	**11.78±2.46**

We applied t-student parametrical testing after checking for normal distribution.

We could not identify any correlations between thyroid function and sex (p=0.65), anxiety (p=0.72), or suicidal thoughts (p=0.36), and/or gestures (p=0.87) as illustrated in Figure 2.

We did identify a correlation of TSH with age (p<0.00010), which is validated by known physiology of aging.

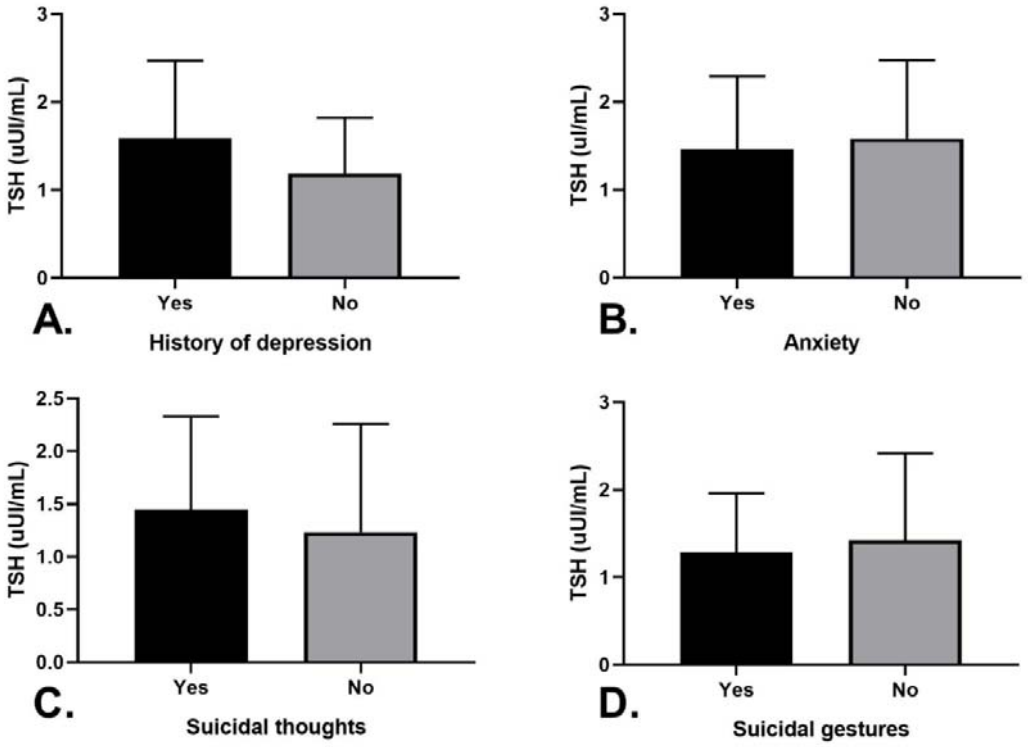

Figure 2. TSH breakdown by studied variables. Y axis represents plasma TSH levels expressed in µUI/ml. X axis represent A. history of depression B. self-reported anxiety C. presence of suicidal thoughts D. previous manifestation(s) of suicidal gestures. Overhanging bars represent standard deviation. No significant correlations found.

Discussion

Our findings place undiagnosed overt hyperthyroidism in depressive patients at 1.25%, which is consistent with other findings, reporting comorbid hyperthyroidism at 1.6% in depressive patients [21] in larger cohorts.

The clinical presentation of a hyperthyroid patient can be missed in a nonspecialized clinical environment, all the more if the patients do not recognize and report symptoms that may lead the clinician to the suspicion.

Especially in elderly patients, like the case of the 61 years old male we identified, symptoms are more subtle and often attributed to normal aging.

On the other hand, we are also showing TSH levels increase per decade in both sexes (see Table 1), described as part of physiological aging.

The questions that rises is whether we should be using age-specific reference TSH ranges to reduce the number of patients unnecessarily treated with thyroid hormone replacement [22].

Overall, we found 7 further subjects out of 80 patients enrolled in our study (8.75%) had a quantifiable thyroid disorder.

This reported value of subclinical and clinical hyperthyroidism is higher than reported elsewhere, with some studies claiming that as much as 11.5% of depressed patients had subclinical hypothyroidism [24,25].

As shown, most studies in the field concur on a relatively higher incidence of hypothyroidism, which in our case was not found.

This disagreement between our data and literature data may be a limitation of our cohort size.

Otherwise, having no reliable data for comparison, we are unable to support or discharge the hypothesis that our findings reflect the undiagnosed thyroid dysfunction profile of our region [22].

The results of our study found no significant association between depressive symptoms and a patient's TSH and T4 levels.

This could be, as some have suggested, because there is no significant association

10.12865/CHSJ.46.02.03

between them [14,26], although other studies pick it up [27].

It has been suggested that screening for thyroid function in patients that have been admitted in a hospital setting for major depression could be beneficial as it might add significantly to the overall evaluation of the patient [23].

Some studies have shown an association between lower FT3 and FT4 levels and clinical outcomes for depressed patients with higher FT3 levels being associated with a better clinical outcome for male patients [28].

Other studies have reported similar results with a significant improvement in response rate for depressed patients whose treatment included T3 supplementation [29,30].

Overall, there seems to be little consensus about whether or not there exists a significant association between thyroid disorders and depression, or its treatment outcome.

Conclusions

Currently screening patients with major depression for thyroid function anomalies is not routine practice, as is not treating subclinical thyroid dysfunction.

Based on the prevalence of thyroid dysfunction found by our limited study we question whether or not implementing such a measure could benefit patients and improve the quality of clinical practice.

Further studies must be carried out to clarify the intricacies between thyroid dysfunction and depression looking for benefit for the health service providers and patients alike.

Acknowledgments

AC, IU, MP, MI developed the study design. ALR performed sample processing, laboratory testing and ALR and MI performed the preliminary data analysis. AC, IU were responsible for data collection.

AC, ALR, MP, MD, MV wrote the first draft of the manuscript.

All authors read and approved the final manuscript.

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Conflict of interests

None to declare.

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