Assessment of Anxiety in Subclinical Thyroid Disorders

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Abstract. It is well known that manifest thyroid dysfunction causes mood disorders. In the literature there are few studies related with subclinical thyroid dysfunction and anxiety. We aimed to determine if there exists a relation between the anxiety and subclinical thyroid dysfunction. This study was carried out in the Meram Medical Faculty of Selçuk University, Department of Endocrinology and Metabolism. Eighty-five outpatients were enrolled into the study. In the presence of normal fT3 and fT4, patients were grouped as subclinical hyperthyroid with TSH lower than 0.1 mU/L (n = 24), subclinical hypothyroid with TSH higher than 4.5 mU/L (n = 32) and euthyroid subjects (n = 29). Beck’s Anxiety Inventory (BAI) was administered to all patients. There was no any statistically significant difference between euthyroid and study groups in terms of age, gender, weight and height (p<0.05). One-way ANOVA showed that both of the subclinical hypothyroid and subclinical hyperthyroid groups had significantly higher anxiety scores than euthyroid group (F: 11.4, p<0.001). Manifest hypothyroidism and hyperthyroidism, as causes of mental and neurological dysfunction have been known for a long time, but the relation between subclinical thyroid dysfunction and anxiety is less well studied. We have found that subclinical thyroid dysfunction increases the anxiety of patients whether hyperthyroid or hypothyroid. Overlap of symptoms common to both thyroid dysfunction and anxiety is an important limitation in this study. Mood changes especially anxiety due to subclinical thyroid dysfunction may have an important impact on the patient’s quality of life. Negative effect on quality of life may be an indication of treatment in these patients. It is the first study evaluating anxiety in subclinical hypothyroidism in the literature.

Key words: Subclinical hypothyroidism, Subclinical hyperthyroidism, Anxiety, Beck’s anxiety questionnaire

THE presence of a chronically suppressed serum TSH level with peripheral thyroid hormone levels within the normal range has been defined as mild “subclinical” hyperthyroidism [1]. It is not a rare finding with rates between 0.2% and 11.8% having been reported in different groups, according to age and sex [2]. The term subclinical hypothyroidism designates a situation in which an asymptomatic patient has a low to normal fT4-I but elevated serum TSH level [3]. The overall prevalence has been reported to range from 4–10% in large general population screening surveys [4]. Important complications of the subclinical thyroid dysfunction include those of cardiac, bone metabolism and neuro-psychiatric disorders [5]. Two-thirds of patients with thyroid disease are reported to have psychiatric disorders [6]. Panic attacks, anxiety, depression, phobia and obsessive compulsion disorders are more commonly encountered in thyroid diseases [7]. Rodewig stated that psychological symptoms in hyperthyroidism are similar to neurotic anxiety symptoms and anxious depressive syndrome [8]. In the differential diagnosis, this should be considered.

Subclinical hypothyroidism is the most commonly encountered organic cause of depression and subclinical hyperthyroidism may cause irritability, nervousness and palpitations [9]. Hendrick et al. reported that
even mild thyroid dysfunction was associated with changes in mood and cognitive functions [10]. There are few studies on the topic of association of anxiety disorders with subclinical thyroid dysfunction [5, 11, 12]. Consequently, we decided to determine if there is a relation between the subclinical thyroid dysfunction and anxiety.

**Material And Methods**

This study was carried out in the Selçuk University Meram Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism. Eighty-five consecutive outpatients were enrolled into the research after informed consent was obtained. Thirty-two subclinical hypothyroid and 24 subclinical hyperthyroid and 29 euthyroid subjects were studied. Subjects with previously known psychiatric disorders, lactation, pregnancy, alcohol or substance abuse within the 6–12 months and comorbid disorders such as diabetes mellitus (DM) and cancer were excluded from the study. Patients had serum TSH levels as follows: a subclinical hyperthyroid group with normal fT₃ and fT₄ levels and serum TSH lower than 0.1 mU/L, and a subclinical hypothyroid group who had serum TSH higher than 4.5 mU/L and normal fT₃ and fT₄ levels. Sex- and age-matched control group had normal TSH levels between 0.4–4 mU/L. Euthyroid subjects have no previously known disease except for thyroid disease history. Serum samples were taken and the 21-question Beck Anxiety Inventory (BAI) was administered at the same time to measure the level of anxiety.

BAI obtains information about the physical (feeling shaky, butterflies in the stomach), cognitive (being afraid that something terrible will happen, fear of losing control) and emotional aspects (being tense, angry). Subjects are asked how much they experienced each symptom during the previous week on a four-point preference type scale ranging from 0 to 3. Higher total scores indicate higher level of anxiety. This anxiety inventory was developed by Beck et al. and adopted to Turkish by Ulusoy et al. [13, 14].

**Laboratory**

fT₃ (n: 1.8–4.2 pg/ml), fT₄ (n: 0.8–1.9 ng/dl), TSH (n: 0.4–4 mU/L) were measured using commercially available kits (DPC, Diagnostics Products Corporation, Los Angeles, CA, USA).

**Data analysis**

Anxiety scores and age, weight and height of three groups were compared using one way ANOVA, post hoc comparisons was performed using Tukey’s honest significant difference test. Chi-square test was performed to compare the sex distribution of the groups. Level of significance was set at p<0.05. Computer software for statistical analysis was SPSS 9.05 for Windows.

**Results**

We studied three groups, namely, euthyroid group (n = 29; 5 males, 24 females) (39.97 ± 14.66 yrs), subclinical hypothyroid group (n = 32; 3 males, 29 females) (39.84 ± 12.67 yrs), and subclinical hyperthyroid group (n = 24; 5 males, 19 females) (46.25 ± 18.06 yrs) (Table 1). There was not any statistically significant difference between euthyroid and study groups in terms of age, gender, height and weight (p>0.05). Subclinical hypothyroid and hyperthyroid

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subjects had significantly different fT₄ levels than euthyroid subjects (1.7 ± 0.8, 1.1 ± 0.3 and 1.4 ± 0.2 ng/dl, respectively; F = 11.9, p<0.001). One-way ANOVA showed that both of the subclinical hypo- and subclinical hyperthyroid groups had significantly higher anxiety scores than euthyroid group (F = 11.4, p<0.001) (Table 2).

### Discussion

For a long time, the relation between anxiety and thyroid dysfunction was studied in detail [7, 15–19]. Some of these studies examined thyroid dysfunction in mood disorders, especially anxiety. Lesser et al. did not demonstrate any relation between anxiety measures in patients and present thyroid dysfunction. However, increased thyroid disease history in mood disorders was detected in the same study, probably due to complex effect of thyroid hormones on adrenergic receptors [17]. Munjack et al. studied the thyroid hormones on the generalized anxiety disorders and could not find any significant difference for thyroid functions between subgroups of general anxiety disorder and controls [16]. According to Simon et al., thyroid abnormalities were not etiologically inherent to generalized anxiety disorder, because of absence of even mild thyroid abnormalities in these groups of patients [18].

We found that both the subclinical hyperthyroid and hypothyroid subjects had higher anxiety scores than euthyroid subjects, as assessed by BAI (p<0.05). According to our results, subclinical thyroid disorders may cause anxiety. The central nervous system function is sensitive to thyroid hormones. Denicoff et al. have shown that total thyroidectomized patients experience increased sadness and anxiety when thyroid hormone substitution was stopped [15]. Monzani et al. found increased anxiety in subclinical hypothyroid patients [5]. Monzani claimed that the cause of higher anxiety scores in subclinical hypothyroid subjects might be the minor neurobehavioral disturbances. Monzani has shown that free-floating anxiety, obsessi- onality and depression seem to characterize these patients’ behavior. Although normal in range, mean thyroid hormone profile of subclinical hypothyroid group is lower than control group in Monzani research. Our subclinical hypothyroid and hyperthyroid subjects also had different fT₄ levels than euthyroid subjects. In normal range, but significant difference between these groups in mean fT₄ hormone serum level may be the cause of mood disturbances. Monzani found that hormone replacement therapy had favorable effect on patient’s performance and proposed L-thyroxine (L-T₄) replacement therapy for subclinical hypothyroid patients. The other study related with subclinical hypothyroidism and anxiety was reported by Baldini et al. [11] who evaluated the effect of subclinical hypothyroidism on psychopathological functions including anxiety in female patients and euthyroid female goiter controls. No significant difference in anxious symptomatology was detected between groups. The result of Baldini’s study is inconsistent with ours. This inconsistency can be explained by the differences in study designs and characteristics of patients and controls selected in both studies. Although in some as- pects, Baldini’s study is consistent with Monzani’s study and ours as it revealed statistically significant difference of fT₄ between subclinical hypothyroid and control group. Baldini showed that, L-T₄ treatment does not improve anxiety, which is dissimilar with Monzani’s study. Engum et al. performed a field re- search study in Norway as a component of the Hunt study [12]. They reported that there is not any sig- nificant increased risk of anxiety in subclinical hypo- thyroidism and hyperthyroidism. The result of Engum’s study is consistent with Baldini’s study, although inconsistent with Monzani and our study. Different results between Engum’s study and ours derive from lack of international standardization of hormone as- says and better generalizability in Engum’s study (field research is always better for generalizability) and high statistical power in Engum’s study due to the large number of subjects included. Anxiety in hyper- thyroidism is an expected finding, but not in hypo- thyroidism. Our study and related studies by Manzoni et al., Denicoff et al. revealed that, hypothyroidism may cause anxiety [5, 15]. Although the exact mecha- nism of this relation is not known, probably increased sensitivity of catecholamine receptors is involved.
Also the other explanation may be the increased sensitivity of CNS to T4 due to mild thyroid deficient state. Manifest hyperthyroidism is one of the most common medical causes of anxiety. Demet et al. state that anxiety disorder is more frequent in the hyperthyroid patients than euthyroid ones, but overlap of the symptoms common to both hyperthyroidism and anxiety disorder is another problem related with this study [19]. Kathol and Delahunt used DSM-III criteria in newly diagnosed hyperthyroid patients so as to see whether if there is any difference of anxiety disorder frequency compared with general population [20]. When compared with general population, 3–4 times more frequent anxiety disorder was detected in this study. Kathol and Delahunt pointed out that overlap of thyroid symptoms and anxiety disorder artificially inflates the frequency of anxiety disorder. They concluded that DSM-III criteria, in the presence of symptoms common to both psychiatric and medical illness, is not a good choice [20]. These studies were made in manifest hyperthyroidism. Their results are consistent with our results. There is not any study in the literature that shows increased anxiety in subclinical hyperthyroidism.

Overlap of symptoms common to both thyroid hormone abnormalities and mood disorders is an important limitation in this study. The second limitation, although statistically sufficient, was the low number of subjects included in the study. Different results in studies related with ours are probably related with different anxiety questionnaires used. This is the first study with Beck’s anxiety questionnaire performed for subclinical thyroid disorders. BAI, a good psychometric test for differentiating anxiety from the symptoms of the physical illness with proven high sensitivity and specificity for this purpose, was used in this study [21]. According to results of citation analysis of database from psycINFO for the years 1991–1998, BAI presently ranks third following State Trait Anxiety Inventory and Fear Survey in terms of research [21]. It is designed to measure the level of anxiety.

The probable theories related with pathogenesis of the mood changes in thyroid dysfunction are related with HLA-Bw35 and HLA-B8 genes (common to Graves, mood disorders), hypothalamic abnormalities manifested by blunted TSH response to TRH, globally reduced brain activity [22, 23]. The direct influence of thyroid hormones on brain functions stems from the presence of wide distribution of T3 receptors throughout the brain [11]. A minor change in iodocompound economy and fT4 serum concentration may result in neuropsychiatric consequences and significant behavioral effects [11]. Relation between thyroid hormones and central neurotransmitters is the target of many studies considering mood disorders [11]. Thyroid hormones probably affect the neuropsychiatry function through increasing the effect of catecholamine. Several studies have demonstrated that thyroid hormones increase the number and activity of beta catecholamine receptors at different areas [24, 25]. The causal relation in between thyroid disorder and anxiety remains unclear. Mood changes especially anxiety due to subclinical thyroid dysfunction may have an important impact on the patient’s quality of life. There is not any study, which evaluates the effect of anxiety caused by subclinical hypothyroidism, on patient’s quality of life. The impact of anxiety could be evaluated with quality of life questionnaire. Negative effect of anxiety on quality of life may be an indication of treatment in these patients. As a result, replacement treatment in subclinical hypothyroidism or an antithyroidal treatment in subclinical hyperthyroidism is still a matter of debate.

References