

Thyroid function in Exhaustion Disorder: Higher prevalence of
subclinical hypothyroidism



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subclinical hypothyroidism

Master thesis in Medicine

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ABSTRACT

Title: Thyroid function in Exhaustion Disorder: Higher prevalence of subclinical hypothyroidism

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Background: Exhaustion Disorder (ED) is a common illness characterized by reduced mental energy caused by stress. In order to increase understanding and improve treatments for the illness, research is needed to investigate its pathophysiology, including potential endocrine dysfunction.

Aims: The general aims were to investigate if thyroid function is associated with ED and if there is a difference in thyroid function between patients with only ED and patients with Major Depression (MD) co-morbid to ED.

Methods: The study was of a case-control, cross-sectional design. Thyroid function was assessed by measuring serum thyroid-stimulating hormone (TSH) and free thyroxine (fT4) in 350 ED patients and 200 controls.

Results: There was no difference in TSH and fT4 between ED patients and healthy controls. Neither were there any differences in TSH and fT4 between the three groups ED with MD, ED without MD and controls. However, the prevalence of subclinical hypothyroidism was

higher in ED patients compared to healthy controls. There was no difference between ED patients and controls in early thyroid failure defined as TSH above 2 mU/l.

Conclusions: ED does not seem to be associated with thyroid dysfunction in general.

However, subclinical hypothyroidism was more prevalent in ED patients compared with controls. ED patients with subclinical hypothyroidism may have started to develop thyroid failure prior or parallel to ED, which may have contributed to the symptoms seen in ED. Thus this could explain the higher prevalence of subclinical hypothyroidism found in ED patients. It is also possible that subclinical hypothyroidism is a negative prognostic factor for treatment of ED. Future randomised controlled studies on treatment outcome is needed to clarify if ED patients with subclinical hypothyroidism will benefit from thyroid hormone therapy.

Key words: Exhaustion Disorder, Psychosocial stress, Thyroid function, Subclinical hypothyroidism

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BACKGROUND

Exhaustion Disorder (ED) is an illness characterized by reduced mental energy caused by stress [1]. The prevalence of ED is unknown but in a report from the Institute of Stress Medicine in Gothenburg, 15% of women and 13% of men, among healthcare workers and social insurance officers in Region Västra Götaland in Sweden, reported symptoms of exhaustion [2]. ED is a relatively new diagnosis defined in 2003 by the National Board of Health and Welfare in Sweden. When the diagnostic criteria for Major Depression (MD), Generalized Anxiety Disorder or Dysthymic Disorder are fulfilled, ED is used as a supplementary specification to the diagnose in question, instead of being an independent diagnose [1]. It is logical to think that the syndrome existed before 2003 in Sweden but was then, as it still is in other western countries, sorted under diagnoses like depression or unspecific stress reactions [3]. As a consequence of the relatively short existence and the geographic narrowed area of the diagnosis the research concerning ED is limited. In order to reduce the individual suffering and society costs, including for sick leave, by prevention and effective treatment, research is needed to investigate the pathophysiology of ED. Important targets for research are among others, the endocrine system. In this thesis thyroid function in relation to ED was investigated.

Exhaustion Disorder

ED is caused by long term stress, almost always psychosocial stress, and insufficient rest [3]. One or more stressors causing the symptoms need to be identified and present for at least six months [3]. The most common stressor is job stress [4]. The main symptom is reduced mental energy but other physical and mental symptoms of exhaustion are also present [1]. At first there is the prodrome phase with physical and mental symptoms of overload e.g.,

gastrointestinal problems, neck and back pain, palpitations, insomnia or hypersomnia and irritability, often episodically occurring. If the overload is not reduced the acute phase can develop suddenly with alarming somatic and mental symptoms, for example sudden impaired memory. Pronounced mental and physical fatigue without the ability to recover despite sleep characterizes the acute phase. Often depression develops and anxiety disorders (AD) can be present. Following the acute phase, the recovery phase takes place with gradual reversion of the symptoms. Pronounced sensitiveness to stress and tendencies to relapse is also part of the recovery phase [3]. It can take one year sometimes longer before the patient can return to work, often part time in the beginning, and it can take several years to fully recover. Patients with depression and/or with pronounced concentration and memory impairment seem to have a longer remission [1].

Thyroid function

Thyroid hormones, mostly l-thyroxine (T4) are produced and secreted by the thyroid gland. The free form of T4 (fT4), that is not bound to serum binding protein, reflects the thyroid activity better than total serum T4. The thyroid hormone l-triiodothyronine (T3) is mainly produced from deiodination of T4 in tissues. T3 is generally not measured when assessing thyroid function because the deiodination of T4 to T3 is in part regulated by factors that do not reflect thyroid function [5]. The synthesis of thyroid hormones by the thyroid gland is stimulated by thyroid-stimulating hormone (TSH) released from the anterior pituitary. The synthesis and secretion of TSH is stimulated by thyreothropin-releasing hormone (TRH) from the hypothalamus. The thyroid hormones, in turn, exert a negative feedback mechanism on TSH and TRH [6]. The negative feedback system is sensitive. A relatively small increase or decrease in serum thyroid hormones may lead to a decrease respectively an increase in TSH. Because of the characteristic of the negative feedback system on TSH by serum thyroid

hormones, thyroid function is best assessed by simultaneous measurements of serum TSH and serum fT4 [5]. For the assays used in this thesis, the normal reference range of TSH is 0.3 – 4.2 mU/l and the normal reference range of fT4 is 12 – 22 pmol/l.

Thyroid Disease

Autoimmune thyroid diseases (ATD) affect about 1.5% of the population and more often women than men [7]. The two main ATD are Graves' disease (GD) and Hashimoto's thyroiditis (HT) [7]. HT is the most common cause of acquired hypothyroidism [8] and GD is the most common cause of hyperthyroidism [9].

Hypothyroidism

In hypothyroidism, thyroid hormone deficiency, symptoms and signs include fatigue, impaired memory, slowed mental processing and depression [8]. Lymphocytic infiltration in HT causes the destruction of the thyroid follicles and thus hypothyroidism [7]. Autoantibodies against thyroperoxidase (TPO) and thyroglobulin (Tg) are frequently measured in HT [7].

Overt hypothyroidism caused by diseases located to the thyroid gland is diagnosed by a decreased fT4 and a raised TSH. Subclinical hypothyroidism is characterized by normal fT4 and raised TSH [5]. Twenty percent to 50% of the patients with subclinical hypothyroidism develop overt hypothyroidism within four to eight years and subclinical hypothyroidism can be seen as the earliest detectable stage of hypothyroidism [5]. Population based prospective studies have found that even TSH elevation within the normal reference range is associated with the risk of developing hypothyroidism [10, 11]. One of the studies showed that particularly TSH > 2mU/l were associated with the risk of developing future hypothyroidism [11] while a study from Norway found a gradually increased risk from TSH values of 0.50-1.4mU/l to 4.0-4.5 mU/l [10]. Increasing TPO antibodies are seen with increasing TSH values

starting from as low as 1 mU/l. About half of the patients with TSH 3.0-4.0 mU/l had high or moderate concentrations of TPO antibodies [12]. Therefore it is possible that early thyroid failure is present despite of TSH being in the normal reference range. A reduction of the upper normal reference range for TSH may be indicated. Already the upper reference range for TSH has been lowered from 10 to 4.0 mU/l during the last decades much due to improvement of the TSH assays [13]. Presenting argument for a narrower TSH reference range, Wartofsky and Dickey [14] point out that when subjects with a family history of autoimmune thyroid disease or positive antithyroid antibodies are excluded, the normal reference range becomes 0.4-2.5 mU/l. They also bring up that studies has found a population mean TSH value of 1.5 mU/l [14] which seem to fit with a narrower reference range. Furthermore, a population based reference range for TSH does not seem to be optimal for the individual. Andersen et al [15] found that the normal individual reference range for TSH is approximately half the width of the population based reference range indicating that population based reference range can be unable to spot abnormal TSH for an individual.

Hyperthyroidism

In hyperthyroidism, elevated levels of systemic thyroid hormones causes symptoms including fatigue, nervousness or anxiety, weight loss and physical symptoms such as palpitations [9]. In GD, hyperthyroidism is caused by circulating antibodies directed against the TSH-receptor that stimulates thyroid growth and function [9]. In overt hyperthyroidism fT4 or/and fT3 are raised and TSH is decreased except in rare cases when the cause is excessive secretion of TSH often due to a pituitary tumour. Subclinical hyperthyroidism is characterized by normal fT4 and decreased TSH [5]. An increased risk of developing hyperthyroidism may exist for TSH values near the lower limit within the normal reference range [10]. In opposite to

autoimmune hypothyroidism that may take several years to develop, reflecting a gradual process, autoimmune hyperthyroidism seems to develop within a year [16].

Thyroid function in depression and anxiety

As mentioned above patients with ED frequently have depression [3] and depression is also associated with hypothyroidism [8], although contradicting data exists [17]. Studies investigating thyroid function in depression have shown inconsistent results. Some studies have found a higher fT4 in depressed patients [18, 19] compared to healthy controls while others found no difference [20, 21]. Results concerning TSH seem to be even more inconsistent than findings regarding fT4. Several studies have found lower [19, 22] or no difference [18, 23] in TSH in depression compared to healthy controls. A more recent study [21] found a slightly higher TSH in patients with MD compared to normal controls. Several factors may cause the inconsistent results, such as differences in subject characteristic, such as in/outpatient status, use of antidepressant medication, bipolar/unipolar disease and subtypes of depression. For example, when compared to controls only patients with melancholic depression showed higher fT4 and lower TSH in the study of Maes et al [19]. Also, in the same study patients with MD without melancholia had lower TSH compared to patients with minor depression [19]. Further, the oldest studies used a less sensitive TSH assay [18, 22]. A meta-analysis [24] of six studies on depression and thyroid function found that depression was associated with a lower TSH and a higher fT4. The authors of the meta-analysis mention that it is “classically taught” that low thyroid function may cause depression but point out that T4 levels in the blood do not necessarily reflect the levels in the brain. Eighty percent of T3 in the cerebral cortex comes from local deiodination of T4. T4 is transferred into the brain and then into glial cells by different transporters. In the glial cells T4 is converted to T3 by deiodinase enzyme type 2 (D2). T3 thereafter exerts its actions by binding to thyroid hormone

nuclear receptors [25]. Thus despite systemic euthyroidism brain hypothyroidism may exist in depression [24]. A recent review [25] concludes that thyroid hormone therapy appears to improve antidepressants effects on depression but more studies are needed to investigate their applicability for euthyroid patients. Furthermore, antidepressants, selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors have been shown to affect TSH and fT4 [26].

Because thyroid function has been shown to be associated with MD [18, 19, 24] it is possible that ED patients with MD differ from patients with only ED. It is, on the other hand, questionable if ED patients with MD still should be sorted under the MD diagnose. Research has shown that depressive symptoms due to chronic stress were characterized by exhaustion and less by the usual core depressive symptoms i.e. depressed mood and loss of interest [4]. Further, a study has found different dexamethasone/corticotrophin-releasing hormone test response in job-stress related depression compared to what has previously been found in MD [27].

Under the course of ED, Anxiety Disorder (AD) can develop [3]. There are fewer studies that have investigated anxiety than depression in relation to thyroid function. One study found that non-medicated patients with panic disorder with the highest severity of panic attacks had higher TSH than either the patients with mild or moderate severity of panic attacks [28]. Also the severity of anxiety in patients with panic disorder correlated negatively to fT4 in the non-medicated group [28].

Stress and the thyroid

Both Genetic and non-genetic factors are involved in the development of ATD [7]. Stress has been hypothesised to be a potential cause of the onset of ATD [29]. One possible mechanism by which stress can cause GD is through the stress-induced activation of the hypothalamic-pituitary-adrenal axis (HPA-axis) and the sympathoadrenal system which leads to elevations of systemic glucocorticoids and catecholamines [29]. The elevated level of glucocorticoids and catecholamines induced by stress may shift the balance between T helper subtype 1 (Th1) cells and T helper subtype 2 (Th2) cells, in the immune system, to Th2 by inhibiting type 1 cytokine secretion. In GD the T lymphocytes infiltrating the thyroid are predominantly Th2 leading to humoral immunity with production of TSH-receptor autoantibodies [29]. An association between increased susceptibility to Th1-mediated immune disorders and decreased stress system activity are shown in clinical situations and animal studies. This suggests that during recovery from stress, activation of Th1 may occur, leading to sporadic autoimmune thyroiditis [29].

Life events and thyroid disease

There are studies have attempted to investigate if stress is associated with ATD. The studies measured exposure to major life events and, because the exposure does not necessary lead to the experience of stress, the nature and/or the impact of the events was also characterized and measured. No association between autoimmune hypothyroidism and the exposure to major life events [30-32] and the perceived pleasantness/unpleasantness of these events [30, 31] have been found, except in one study where hypothyroid cases reported a lower amount of total unpleasantness at baseline compared to the controls [32]. Contradicting results exists regarding GD. Retrospective studies has found a positive association between the onset of GD and stressful major life events [33], exposure to negative stressful life events and the perceived impact of these [34]. However, a recent prospective study found no difference in

the number of life events or the total amount of perceived pleasantness/unpleasantness of these events between hyperthyroid cases and controls [32].

Job strain and thyroid function

A study [35] that investigated exposure to job strain and thyroid function, in workers in human service organizations, found no association between job strain and TSH. In the study, job strain was assessed by questions based on the demand-control model and also questions measuring emotional demands. It should be pointed out that being exposed to job strain is not the same as experiencing job stress.

Stress-related illness and thyroid function

Burnout is an American work psychological term and is often associated with ED [4]. As in many but not all cases of ED, burnout is caused by stressors on the job [36]. Furthermore, burnout is characterized by exhaustion, cynicism and inefficacy [36]. The emotional exhaustion is the same for burnout and ED but cynicism is often missing in the latter [4].

There is only one known study that has investigated burnout and stress-related illness in relation to thyroid function. The study [37] found no difference in TSH, total T4 and total T3 in women on long term sick leave for affective or stress-related mental disorder and women that scored high on professional burnout compared to healthy control workers.

There are no studies on stress-related illness that include simultaneous measurement of serum TSH and serum fT4, which, as mentioned above, is claimed to be the best way to assess thyroid function [5]. Moreover, having high score on professional burnout is not the same as having ED. In conclusion, there is no known study published that has investigated thyroid function in ED patients as a separate disorder.

Aim

The general aim of this thesis was to investigate if thyroid function assessed by TSH and fT4 is associated with ED. Furthermore, an additional aim was to investigate if there is a difference in thyroid function between ED patients with MD and patients with only ED. There is an overlap in symptoms between patients with ED and patients with thyroid disease and consequently a risk that the exhaustion seen in patients could be caused by thyroid dysfunction and not ED. Therefore the patients with thyroid disease were excluded from the study. Specifically, the aims of the thesis were to investigate:

1. If there is a difference in thyroid function between patients with ED compared to healthy controls.
2. If there is a difference in thyroid function between ED patients with MD compared to ED patients without MD and healthy controls.
3. If there are more ED patients than healthy controls with TSH outside the normal reference range indicating subclinical thyroid disease
4. If there are more ED patients than healthy controls with TSH above 2mU/l indicating early thyroid failure.

METHODS

Subjects

In this quantitative study, 350 patients and 200 healthy controls were compared using a case-control, cross-sectional design.

The patients were referred from primary care units or occupational health care centres to an outpatient clinic at the Institute of Stress Medicine (ISM) in Gothenburg. Referral criteria were 1) Most likely Exhaustion Disorder (ED) and no confirmed somatic disorder or abuse that could explain the condition. 2) Sick leave < 6months. None of the patients had been treated for their illness in an inpatient clinic and they continued to be ambulatory during the study.

Exclusion criteria for the patients were diseases that could explain the condition of exhaustion e.g. thyroid disease based on results of biochemical analyses and clinical symptoms assessed by a physician at ISM, vitamin B-12 deficiency, generalised pain, obesity, fibromyalgia or chronic fatigue syndrome. Medication with levothyroxine, severe or chronic psychiatric disease (except ED, MD and AD), alcohol abuse, pregnancy or breast-feeding and missing test results on TSH and fT4 were also used as exclusion criteria for the patients.

A senior physician assessed the patients regarding ED, anxiety disorders and mood disorder at their first visit to ISM. The diagnostic criteria for ED (Table 1) were also used as inclusion criteria for the patients.

Table 1. Diagnostic criteria for ED set by the National Insurance Board in Sweden.

A. Physical and mental symptoms of exhaustion with minimum two weeks duration. The symptoms have developed in response to one or more identifiable stressors which have been present for at least 6 months.
B. Markedly reduced mental energy, which is manifested by reduced initiative, lack of endurance, or increase time needed for recovery after mental efforts.
C. At least four of the following symptoms have been present most of the day, nearly every day, during the same 2-week period: <ol style="list-style-type: none">1. Persistent complaints of impaired memory.2. Markedly reduced capacity to tolerate demands or to work under time pressure.3. Emotional instability or irritability.4. Insomnia or hypersomnia5. Persistent complaints of physical weakness or fatigue.6. Physical symptoms such as muscular pain, chest pain, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sounds.
D. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
E. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism, diabetes, infectious disease)
F. If criteria for major depressive disorder, dysthymic disorder or generalized anxiety disorder are met, exhaustion disorder is set a co-morbid condition.

Mood and/or anxiety disorders were diagnosed in two steps. Firstly, the patients filled in the PRIME-MD questionnaire that is based on DSM-IV criteria and then a structured interview followed to confirm the diagnosis if the patient's results on the questionnaire indicated any mood and/or anxiety disorders.

From an ongoing longitudinal cohort study, healthy controls aged 25-50, mostly health care workers and social insurance officers, were recruited. The controls had to answer a question concerning stress and were subdivided into five different levels of experienced stress depending on their answer. From the five stress level groups a random sample was taken. The sampling assured that women and men as well as the five experienced stress levels were equally represented in the sample. 350 potential controls then underwent a screening

examination. Exclusion criteria for the healthy controls were: BMI <18,5 or >30 kg/m², over-consumption of alcohol, vitamin B₁₂ deficiency, known systemic or psychiatric disease, present infection, medication with systemic effects, oral contraceptives containing oestrogen, pregnancy or breast-feeding and missing test results on TSH and fT4.

Blood samples and Biochemical analyses

Blood samples from the patients were drawn in the morning on their first visit in the clinic before treatment onset. The same procedure was done for the healthy controls. All subjects were fasting when the blood samples were drawn and had been instructed not to do any intense physical activity the day before. The biochemical analyses of the blood samples were performed at the Laboratory for Clinical Chemistry, Sahlgrenska University Hospital. Serum concentrations of free thyroxine (fT4) and thyroid-stimulating hormone (TSH) were measured according to the standard protocol of the laboratory. Normal reference range for serum fT4 was 12-22 pmol/l and for serum TSH 0.30-4,2 mU/l. Vanderpump et al [11] found an increased risk in developing hypothyroidism at TSH value > 2mU/l compared to TSH ≤2mU/l, therefore a TSH value of 2 as well as a TSH value of 4,2 was used as upper cutoffs for TSH in this study.

Ethics Statement

The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden. All subjects in the study gave written informed consent.

Statistical Analysis

Age, sex, BMI, use of hormone containing substances, alcohol consumption and current nicotine use were considered to be potential confounders. Differences in the potential

confounders (except use of hormone containing substances) between patients and controls were tested for using Pearson's Chi square test and the independent samples t-test. The potential confounders were further investigated using the independent samples t-test and analysis of variance (ANOVA) and included as covariates in further analyses if they were associated with TSH or fT4. Analysis of covariance (ANCOVA) with TSH and fT4 as dependent variables was used to test for differences in TSH and fT4 between patients and controls. Firstly, all patients, men and women together and separately, were compared with controls for differences in TSH and fT4. Thereafter, the patient groups "patients with MD" and "patients without MD" and controls were tested for differences in TSH and fT4. Pearson's Chi square test was used to test for differences between the number of patients and controls with TSH outside the normal reference range and TSH above 2 mU/l. All analyses testing for differences in TSH or fT4 between patients and controls were done twice, first with and then without the patients taking antidepressants. The results when the patients taking antidepressants were left out from the analyses were only reported if it differed from the results when all patients were included in the analysis. The statistical analyses were done using SPSS (the Statistical Package for the Social Sciences) version 20. Statistical significance was set at $p < 0.05$.

RESULTS

Descriptive data of the subjects

Table 2 shows the characteristics of the patients (n=350) and controls (n=200). The patients were older, more often a woman, had a higher BMI, used less alcohol and used nicotine to the same extent as the healthy controls. Fifty-three of the 350 patients (15.1%), all women, were taking hormone containing substances. After investigation, only sex and age were considered as confounders. All 350 patients had ED, since fulfilment of the diagnostic criteria for ED was the inclusion criteria. 276 (78.9%) of the patients had MD and 286 (81.7%) had AD.

Table 3 shows the number and percentage of the patients with the different combinations of ED, MD and AD and the use of antidepressants.

Table 2. Subject characteristics

	Patients (n=350 [^])	Controls (n=200 [^])	p-value
Age (years), mean±SD [□]	42.2±9.2	39.3±8.1	<0.001
Sex (female), number of subjects (%) [#]	248 (70.9)	102 (51.0)	<0.001
BMI (kg/m ²), mean±SD [□]	24.3±3.3	23.7±2.6	0.020
Alcohol use (AUDIT), mean±SD [□]	3.5±2.9	4.2±2.5	0.008
Current nicotine use (yes) number of subjects (%) [#]	70 (20.6)	40 (21.1)	0.899

[^]AUDIT: Patients (n=325), Controls (n=199), Current nicotine use: Patients (n=340), Controls (n=190)

[□]Independent samples t-test

[#]Chi-square test

Table 3. Patient psychiatric characteristics

	Number of patients (%)
Diagnoses	
Only ED	28 (8.0%)
ED and only MD	36 (10.3%)
ED and only AD	46 (13.1%)
ED and both MD and AD	240 (68.6%)
Use of antidepressants	102 (29.1%)

Thyroid function in ED patients

Data and test results for TSH and fT4 in patients and controls when controlling for confounders are shown in table 4. The test results were essentially the same when confounders were controlled for compared to uncontrolled tests. There was no difference in TSH between patients and controls neither when women and men were compared together or separately. Figure 1 display the TSH means and 95% confidence interval for the patient and the control sample for women and men separately. The four TSH means for the women and men in the patient and the control sample, shown in figure 1 and table 4, are all close to 2 mU/l (1.93 mU/l to 2.14 mU/l). There was no difference in fT4 between patients and controls when women and men were analysed together. When women and men were analysed separately the women in the patient sample had a significantly higher fT4 compared to the women in the control sample whereas the men in the patient sample had a significant lower fT4 compared to the men in the control sample. When the patients taking antidepressants were left out from the analysis no significant difference in fT4 between the men in the patient sample and the men in the control sample was found. The rest of the test results did not change when the patients taking antidepressants were excluded from the analyses. Figure 2 shows the fT4 means and 95% confidence interval for the patient and the control sample for women and men separately. The descriptive data in figure 2 and table 4 show a bigger difference in fT4 between the women and men in the control sample compared to fT4 between the women and the men in the patient sample.

Table 4. TSH and fT4 data, mean±SD (number of subjects), for patients and controls.

		Patients	Controls	Test results
TSH, mU/l	W+M	2.07±1.16 (350)	1.99±0.88 (200)	F(1,546)=1.039, p=0.308 [‡]
	W	2.04±1.17 (248)	1.93±0.90 (102)	F(1,347)=0.749, p=0.387 [^]
	M	2.14±1.14 (102)	2.06±0.85 (98)	F(1,197)=0.343, p=0.559 [^]
fT4, pmol/l	W+M	14.95±2.27	15.08±2.21	F(1,546)=0.379, p=0.538 [‡]
	W	14.78±2.03	14.07±2.04	F(1,347)=8.662, p=0.003 , $\eta^2=0.024$ [^]
	M	15.37±2.72	16.13±1.86	F(1,197)=4.128, p=0.044 , $\eta^2=0.021$ [^]

W=women, M=Men [‡]adjusted for age and sex [^]adjusted for age

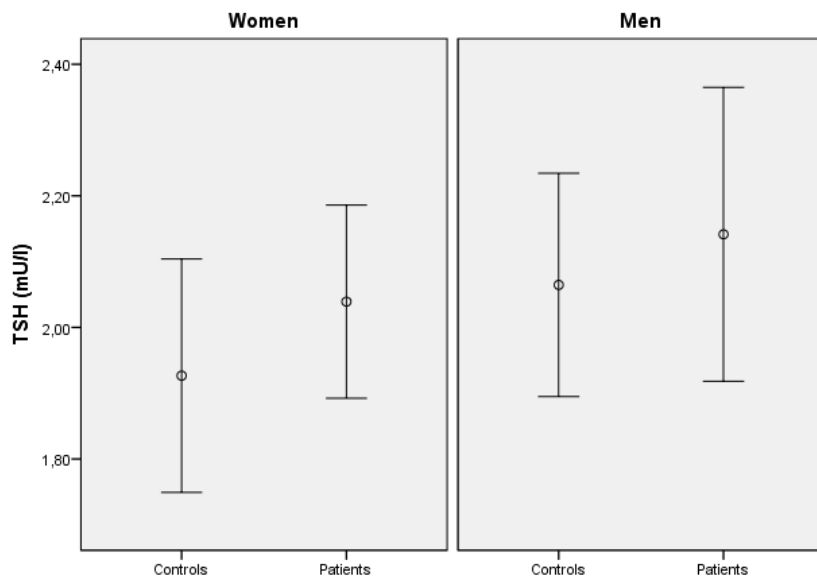


Figure 1. TSH (Mean and 95% CI) in patients and controls sample for women and men separately

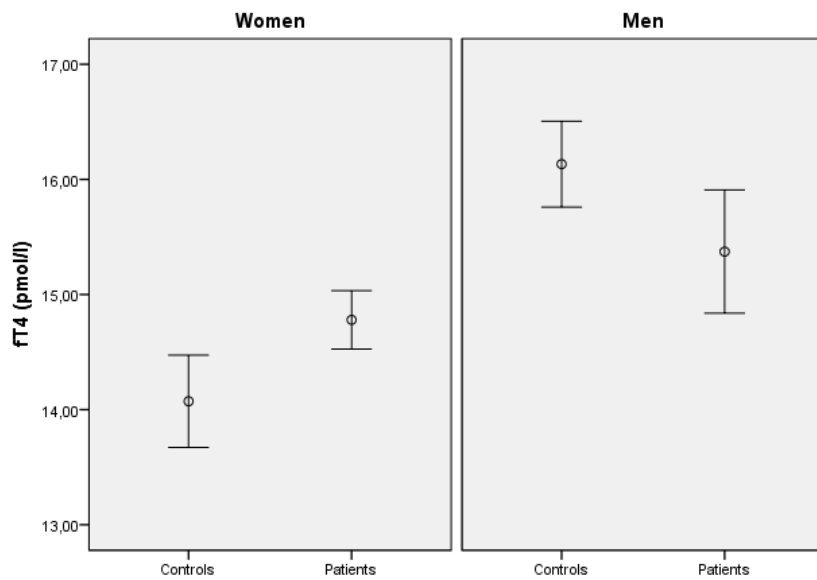


Figure 2. ft4 (Mean and 95% CI) in controls and patients divided by sex.

Thyroid function in ED patients with MD and without MD

There was no difference in TSH or fT4 between ED patients with MD, ED patients without MD and controls neither when confounders were controlled for (data and test results shown in table 5) or not. Also, the results did not change when patients taking antidepressants were excluded from the analyses.

Table 5. TSH and fT4 data, mean±SD (number of subjects), for ED patients with MD, ED patients without MD and controls.

	Controls	ED with MD	ED without MD	Test results
TSH, mU/l	1.99±0.88 (200)	2.08±1.17 (276)	2.02±1.14 (74)	F(2,545)=0.612, p=0.543 ^a
fT4, pmol/l	15.08±2.21	14.96±2.33	14.93±2.04	F(2,545)=0.193, p=0.824 ^a

^aadjusted for age and sex

Subclinical thyroid disease in ED patients

TSH for the patients (n=350) and the healthy controls (n=200) are shown in table 2. There was a significantly larger amount of patients (n=18) than controls (n=2) that had TSH outside the normal reference range ($\chi^2=6.234$, p=0.013). Two patients (n=2) and none of the controls (n=0) had TSH below the normal reference range which is not enough subjects for statistical analysis to be made. There was a significantly larger amount of patients (n=16, 4.6% of the total amount of patients) than controls (n=2, 1.0% of the total amount of controls) with TSH above the upper limit of the normal reference range ($\chi^2=5.128$, p=0.024). Two of the patients with TSH above the upper limit, 4.8mU/l and 6.10mU/l, respectively, had fT4 just below the normal reference range, both 11 pmol/l. Seven patients with TSH above the reference range and one below were taking antidepressants. When the patients taking antidepressants were excluded from the analyses there was still significantly more patients (n=10) compared to controls (n=2) that had TSH outside the normal reference range but there was no longer any significant difference between the number of patients (n=9) and controls (n=2) above the upper limit of the TSH reference range. There was no significant difference between the

numbers of patients and the number of controls that had a TSH value >2 mU/l as compared to TSH ≤ 2 mU/l ($\chi^2=0.039$, p=0.843).

Table 6. TSH for the patients and the healthy controls included in the study.

TSH mU/l	0.01	0.02	0.3-4.2	4.3	4.6	4.7	4.8	4.9	5.0	5.1	5.7	6.1	6.6	7.7	12.0
Controls, n=200	0	0	198 (7 ⁿ)	1	0	0	0	0	0	0	0	0	1	0	0
Patients, n=350	1	1	332 (14 ⁿ)	1	5	1	1 (1 ⁿ)	1	1	1	1	2 (1 ⁿ)	0	1	1

Normal reference range for TSH is 0.3-4.2 mU/l

ⁿNumber of subjects with fT4 outside the reference range.

DISCUSSION

Thyroid function in ED patients

The result showed no difference in TSH or fT4 between the ED patients and the healthy controls. In agreement with this study's results are the results from the two Swedish studies [35, 37] that showed no association in TSH with job strain and psychosocial stress, respectively.

Also in line with the result, studies investigating depression and thyroid function have found no difference between patients with depression and controls neither in TSH [18, 23] nor in fT4 [20, 21]. Contradicting results exist from studies that have found a higher [21] and lower [22] TSH and a higher fT4 [18, 19] in patients with depression compared to controls. The current study's result is also contradictory to the meta-analysis' result that a higher fT4 and a lower TSH are associated with depression [24].

There was no difference in TSH between the patient sample and the control sample when women and men were analysed separately. The women with ED had a higher fT4 than the women in the control sample and the men with ED had a lower fT4 than the men in the control sample. Although statistically significant it is questionable if the difference between the groups in fT4, 0.71 pmol/l for the women and 0.76 pmol/l for the men, is clinically significant. Difference in fT4 of 0.3 ng/dl [18], 3.86 pmol/l after transformation, and of 2.48 pmol/l [19] has been found between patients with depression and controls which are more than three times the difference that was found in this study. A study investigating depression and thyroid function [18] found no differences in TSH or in fT4 between healthy women and

depressed women and between healthy men and depressed men which is in agreement with the present study's findings regarding TSH but not fT4.

Similar TSH means were seen for women and men in the control sample and in the patient sample. For the women and men in the control sample the fT4 means were further apart compared to the fT4 means for the women and the men in the patient sample, although the women in both groups had the lower fT4 mean. Studies that have compared thyroid function in healthy women and men found no differences between the sexes neither in TSH nor in fT4 [18, 19]. This contradicts the observation made in this study, that women had lower fT4 compared to men in the control sample, but is in agreement with that no difference were seen in TSH. One possible explanation could be the use of different assays for TSH and fT4 analyses. A study examining the reference intervals for the assays that were used to measure TSH and fT4 in this study found significantly higher TSH and lower fT4 for women compared to men [38]. The result is not in agreement concerning TSH but in line with the results found in fT4 for the healthy controls in this study.

Thyroid function in ED patients with MD and without MD

Approximately 80% of the ED patients in the current study had MD. There was no difference in TSH and fT4 between ED patients with MD, ED patients without MD and healthy controls.

The results indicate that ED patients, whether or not they have MD, have similar thyroid function. Today, as mentioned before, ED patients with MD are sorted under the MD diagnose although research suggests that ED patients with MD differ from patients with only MD [4, 27]. To further support the statement of two separate diseases, future studies are

needed to investigate if there is a difference in thyroid function between ED patients with MD and patients with MD but no ED.

Subclinical thyroid disease in ED patients

A significantly larger amount of patients than controls had TSH outside the normal reference range. Of these subjects two patients and none of the controls had TSH below the reference range and normal fT4 indicating subclinical hyperthyroidism. Sixteen patients and two controls had TSH above the reference range. Fourteen patients and the two controls with TSH above the reference range had normal fT4 indicating subclinical hypothyroidism. Two of the patients with TSH above the reference range had fT4 just below the reference range.

Considering that none of the patients had been found to have thyroid disease by the physicians at ISM these two latter patients can be seen as having subclinical hypothyroidism and not overt hypothyroidism. By doing so, the prevalence of subclinical hypothyroidism in the current study was 4.6% for the patients and 1.0% for the controls which indicated that subclinical hypothyroidism was significantly more prevalent in patients than controls.

Previous studies have found a prevalence of approximately 4-8% of subclinical hypothyroidism in the U.S. population with no known thyroid disease and 15% in patients with depression [13]. The lower prevalence of subclinical hypothyroidism in the patient sample and the control sample found in this study may be a consequence of better general health of the subjects, due to more stringent exclusion criteria for thyroid disease and other diseases, compared to the studies made on the U.S population and patients with depression. Thus, in this study, it is even possible that some patients with subclinical hypothyroidism have been judged to have thyroid disease by the physicians and subsequently been excluded. This is probably because some patients with subclinical hypothyroidism report symptoms of thyroid dysfunction [39]. When the patients taking antidepressants were excluded from the

analysis there was no longer any significant difference between the number of patients and controls with subclinical hypothyroidism. In a study by Eker et al [26] investigating antidepressants effects on thyroid hormones, a selective noradrenaline reuptake inhibitor decreased TSH by 0.36 and a selective serotonin reuptake inhibitor increased TSH by 0.35. It is doubtful if the antidepressants' potential effect on TSH in this study were large enough to cause confounding effects on the difference found between ED patients and controls with subclinical hypothyroidism.

As mentioned above, some individuals with subclinical hypothyroidism experience symptoms of thyroid dysfunction [39]. Higher prevalence of symptoms of depression and anxiety has been found in patients with subclinical hypothyroidism compared to euthyroid patients [40]. Therefore, diagnostic uncertainties can potentially arise when patients have unspecific symptoms such as fatigue, depression and anxiety which all can be signs of ED, mood/anxiety disorders and thyroid dysfunction. Potential treatment problems can also occur. There is reason to recommend thyroxine treatment to patients that are found to have subclinical hypothyroidism if they seek medical attention with symptoms of the condition, including unspecific symptoms, or if they later can have complications due to the condition [39]. Before the onset of treatment, the patient should have had confirmed raised TSH at least at two occasions. Also the indication to treat is stronger if the patient also has TPO autoantibodies [39]. According to the recommendations it can be argued that because of the overlapping symptoms in ED and thyroid dysfunction, ED patients with subclinical hypothyroidism should be treated with thyroxine. A study that investigated thyroxine treatment outcome in subclinical hypothyroidism found positive effects on cardiovascular factors, endothelial function and reduction in symptom of tiredness [41]. In addition, functional magnetic resonance imaging studies have found abnormal function in frontal areas of the brain in

patients with subclinical hypothyroidism [42] and reduced activation of prefrontal cortex in females on work-stress related long-term sick leave [43] both findings indicate impaired working memory. The abnormal function of the frontal areas found in the patients with subclinical hypothyroidism was recovered after thyroxine treatment [42]. In the same study the hypothyroid patients performed worse than the patients with pre-treatment subclinical hypothyroidism in a 2 and 1-back task assessing working memory, which supports early intervention in patients with subclinical hypothyroidism before developing hypothyroidism [42]. To further complicate the matter, Andersen et al. [15] found that individual reference ranges for serum free T4 index, T4 and T3 (and TSH, see background) for men is approximately half of the width of the population-based reference range. Anderson et al [15] concludes that because minor changes in thyroid hormones give great responses in TSH, it means that when the thyroid hormones have left the individual's normal reference range it may cause TSH to be raised outside its normal population based reference range although the thyroid hormones might still be in the population based reference range. This means that subclinical hypothyroidism might in the reality be overt hypothyroidism for an individual [15]. But if all ED patients with subclinical hypothyroidism were to be treated with thyroxine, there would be a risk of overtreatment.

A lower frequency of response to antidepressants has been reported in depressed patients with subclinical hypothyroidism compared to depressed patients without subclinical hypothyroidism [44] although contradicting evidence exists [23]. ED patients with subclinical hypothyroidism in analogous with patients with depression might be a risk group for poorer treatment outcome compared to those without subclinical hypothyroidism. Co-administration of T3 with antidepressants, to potentiate the response to antidepressants, is a treatment option in treatment-resistant depression [45, 46] and possibly also for treatment-resistant ED. Future

randomized controlled studies are needed to investigate the outcome of thyroid hormone therapy in ED patients with subclinical hypothyroidism, and possibly even in co-administration with antidepressant therapy, in order to potentially support thyroid hormone treatment in ED patients with subclinical hypothyroidism.

Hypothetically, the stressors that caused ED could also have caused the onset of subclinical hypothyroidism in the ED patients. As mentioned before, recovering from stress may trigger the onset of sporadic autoimmune thyroiditis [29]. But considering that studies have found no association between autoimmune hypothyroidism and stress makes the hypothesis unlikely [30-32]. Autoimmune hypothyroidism may develop gradually during several years [16] and a TSH value above 2 mU/l has been found to be associated with the risk of developing future hypothyroidism [11]. In this study no significant difference in the amount of subjects with a TSH value above 2 mU/l between ED patients and controls were found. This suggests that the subclinical hypothyroidism found in the ED patients might have started to develop far back in time, maybe prior or parallel with the ED contributing to the symptoms seen in ED.

Strengths and weaknesses

The first step in the sampling process took place at the primary care units and occupational health care centres. This could introduce various types of selection bias. For example, individuals with ED are likely to differ whether they seek medical attention early or late during the course of the illness and may also differ regarding specific personality traits and severity of the illness. One selection bias was identified by Glise et al. [47], that used essentially the same patient sample as in this study, namely a higher education in the patient group compared to the general population. To the best of my knowledge, there are however no studies reporting an association between educational level and thyroid function. At the

patient's first visit to ISM a screening examination was undertaken to make sure that all the patients that were included met the diagnostic criteria for ED and did not have other diseases that could explain the symptoms nor conditions that could influence the result such as pregnancy (for a more complete description of exclusion and inclusion criteria see methods and measurements). By excluding ED patients with other diseases and conditions the results of the study on thyroid function in ED patients are less applicable on the whole population of individuals that meet the diagnostic criteria for ED. On the contrary, the results of the study are more likely to reflect true thyroid function in ED patients if the patients included did not have other conditions that could explain the exhaustion or additional conditions that could influence thyroid function. The controls also underwent a screening examination similar to the ED patients, thereby lowering the risk of underestimating differences between the groups. Thyroid function was assessed by measuring TSH and fT4, which has been described to be the most correct assessment [5]. However, additionally analyses of free T3 and TPO autoantibodies may have given a more comprehensive assessment of thyroid function. This should be taken into consideration when conducting future studies on ED and thyroid function. Age and sex were controlled for in the study as they were shown to be associated with thyroid function and therefore considered as confounders. BMI, AUDIT, current nicotine use and use of hormone containing substances were not associated with thyroid function and therefore not controlled for. Potential confounding effects of antidepressants, of which some have been shown to effect thyroid function [26], were handled by subgroup analyses. Addressing the potential confounding effects of AD, patients with AD were excluded when analysing ED patients with MD. It is possible that there were other potential confounders that were not controlled for in this study, for example sleep deprivation and weight reduction. The study had a cross-sectional design which did not allow investigation of any causal relationship between overt thyroid disease and ED. If the study had a longitudinal design it would have

been possible to investigate if ED patients are more prone to develop thyroid disease as compared to healthy controls. Instead, only normal and abnormal thyroid function that was not considered as thyroid disease was assessed in this study. Not only thyroid disease can cause an increase in TSH. A transient increase of TSH can for example be caused by systemic illness [14]. Therefore repeated measurements of TSH would have given a more accurate estimation of TSH. The large sample size in the study was a considerable strength. It helped addressing potential confounding effects accurately and also made the study results better applicable to the study population. Therefore, despite of being a minority, the sample size allowed men with ED to be investigated regarding thyroid function.

CONCLUSIONS AND IMPLICATIONS

As a group, ED patients did not differ from healthy controls in thyroid function and it seems that thyroid function in ED is not dependent of whether or not MD is present. Interestingly, the results suggest that more ED patients have subclinical hypothyroidism compared to healthy controls but no difference was found in early thyroid failure between the groups. ED patients with subclinical hypothyroidism may have started develop thyroid failure prior or parallel to the ED that may have contributed to the symptoms seen in ED. It is also possible that subclinical hypothyroidism is a prognostic negative factor for treatment outcome in ED which only future studies will reveal. Future randomized controlled studies are also needed to confirm if ED patients with subclinical hypothyroidism will favor from thyroid hormone therapy.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Utmattningssyndrom är en relativt ny diagnos formulerad av den svenska Socialstyrelsen 2003 då det fanns ett behov att samla utmattningstillstånd orsakade av långvarig stress under en diagnos. Det är okänt hur många som lider av utmattningssyndrom, dock rapporterade 15 % av kvinnorna och 13 % av männen som arbetar i hälso- och sjukvården och på försäkringskassan i Västra Götalandsregionen i Sverige, symtom på utmattning. För att minska kostnaderna i form av sjukskrivningar och lidande för individen behövs forskning inriktad på sjukdomens patofysiologi i syfte att bättre kunna förklara uppkomsten av sjukdomen och utveckla effektiva behandlingar. Tänkbart är att dessa patofysiologiska mekanismer utgörs av endokrina störningar häribland rubbningar i sköldkörtelfunktionen. Symtom på utmattningssyndrom presenterar sig bland annat i form av depression, ångest och trötthet vilka även är förknippade med störningar i sköldkörtelfunktionen. Hypofysen utsöndrar TSH (thyroid stimulating hormone) som stimulerar sköldkörteln (Glandula Thyreoidea) att producera och utsöndra sköldkörtelhormon, l-thyroxin (T4) och l-triiodothyronin (T3) som i sin tur utövar inhibitorisk effekt tillbaka på TSH-utsöndringen. Hypothyreos är ett tillstånd med brist på sköldkörtelhormon medans hyperthyreos innebär en ökad nivå av sköldkörtelhormon. Syftet med denna studie var att undersöka sköldkörtelfunktionen hos patienter med utmattningssyndrom i förhållande till friska kontroller. Många av patienterna med utmattningssyndrom uppfyller diagnoskriterierna för egentlig depression och får då diagnosen egentlig depression med utmattningssyndrom ("utmattningsdepression"). Ett ytterligare syfte var att undersöka om sköldkörtelfunktionen hos patienter med utmattningsdepression skiljer sig från patienter med enbart utmattningssyndrom. Serum koncentrationerna av TSH och fT4 som mått på sköldkörtelfunktionen uppmättes hos 350 patienter med utmattningssyndrom och 200 friska

kontroller. Patienter med utmattningssyndrom skiljde sig inte från de friska kontrollerna i sköldkörtelfunktion. Sköldkörtelfunktionen skiljde sig heller inte mellan patienter med enbart utmattningssyndrom, patienter med utmattningsdepression och friska kontroller. Fler patienter med utmattningssyndrom än friska kontroller hade subklinisk hypothyreos. Vid subklinisk hypothyreos är fT4 fortfarande normalt medan TSH-värdet har passerat den övre normala referensgränsen på 4.2 mU/l. Det förelåg ingen högre förekomst av tidig sköldkörtelsvikt definierat som ett TSH-värde över 2 mU/l hos patienterna jämfört med kontrollerna. Den vanligaste orsaken till förvärvad hypothyreos är autoimmun thyroideasjukdom och fynd tyder på att autoimmun hypothyreos utvecklas gradvis under flera år. En tänkbar förklaring till resultatet kan därför vara att patienterna med subklinisk hypothyreos börjat utveckla sköldkörtelsvikt före eller parallellt med utmattningssyndromet som sedan bidragit till syndromets utveckling. Det är även möjligt att subklinisk hypothyreos är en negativ prognostisk faktor för behandling av utmattningssyndrom. Framtida studier är indicerade för att avgöra om behandling med sköldkörtelhormon kan vara en effektiv behandling för utmattningssyndrom med subklinisk hypothyreos.

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