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Level of thyroid-stimulating hormone in elderly patients with unipolar depression – case–control analysis

Poziom hormonu tyreotropowego u osób starszych z depresją jednobiegunową – analiza typu *case–control*

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Abstract

Aim: Thyroid-stimulating hormone (thyrotropin, TSH) stimulates the thyroid gland to produce metabolism-stimulating hormones (thyroxine and triiodothyronine). Changes in thyroid function can affect mood and trigger mood swings, anxiety or depressive symptoms. The aim of the study was to determine the differences in serum TSH level between elderly patients with unipolar depression and non-depressed elderly patients based on a case–control analysis. **Methods:** Serum level of TSH was measured in depressed Caucasian in-patients aged ≥60 and age- and sex-matched healthy controls. **Results:** In depressed patients mean serum TSH levels in the study groups were higher (1.44 ± 1.23 vs. 2.00 ± 1.70 μIU/mL, $p < 0.001$). TSH levels were lower in depressed than non-depressed women (1.45 ± 1.19 vs. 2.06 ± 1.70 μIU/mL, $p < 0.001$). The overall rate of being below the low level of TSH (set at 0.8 μIU/mL) was 12.0% for depressed patients and 8.8% for healthy controls. No correlations were found between TSH level and age. **Conclusions:** Elderly patients (especially women) with depression have decreased TSH levels, and hyperthyroidism may be more frequent in this clinical subpopulation.

Keywords: TSH, thyroid-stimulating hormone, depression, elderly, old age psychiatry

Streszczenie

Cel: Hormon tyreotropowy (TSH) stymuluje tarczycę do produkcji hormonów stymulujących metabolizm (tyroksyna i trijodotyronina). Zmiany czynności tarczycy mogą wpływać na nastrój i wywoływać jego wahania, lęki lub objawy depresyjne. Celem pracy było porównanie stężenia TSH w surowicy osób starszych z depresją jednobiegunową ze zdrowymi osobami starszymi, w oparciu o analizę typu *case–control*. **Metody:** Stężenie TSH w surowicy mierzono u pacjentów z depresją w wieku ≥60 lat oraz u zdrowych osób w wieku ≥60 lat, dopasowanych pod względem wieku i płci do grupy pacjentów. **Wyniki:** U pacjentów z depresją średnie stężenia TSH były wyższe (1,44 ± 1,23 *vs* 2,00 ± 1,70 μIU/ml, $p < 0,001$). Stężenie TSH było niższe u kobiet z depresją niż u kobiet bez depresji (1,45 ± 1,19 *vs* 2,06 ± 1,70 μIU/ml, $p < 0,001$). Ogólna częstość występowania obniżonego stężenia TSH (ustalonego na poziomie 0,8 μIU/ml) wynosiła 12,0% dla pacjentów z depresją i 8,8% dla grupy kontrolnej. Nie stwierdzono korelacji pomiędzy poziomem TSH a wiekiem. **Wnioski:** Pacjenci w podeszłym wieku (zwłaszcza kobiety) z depresją mają obniżone stężenie TSH, a nadczynność tarczycy może być częstsza w tej subpopulacji klinicznej.

Słowa kluczowe: TSH, hormony tarczycy, depresja, starość, psychiatria wieku podeszłego

INTRODUCTION

Depression is the leading cause of disability worldwide and is a significant contributor to the global burden of disease. It affects millions of people worldwide and is associated with great human and economic costs (stigma, limited activity, decreased life expectancy, raised health care costs). The World Health Organization (WHO) estimates that depression is responsible for 6% of total DALYs (disability-adjusted life years) caused by all diseases in Europe. The total annual cost of depression in Europe was estimated to be 118 billion Euros in 2004 (Sobocki et al., 2006), which makes depression the most costly mental disorder in this region of the world.

Thyroid-stimulating hormone, also known as thyrotropin (TSH), is synthesised and secreted by thyrotrope cells in the anterior pituitary gland and regulates the endocrine function of the thyroid gland by stimulating it to produce the metabolism-stimulating hormones thyroxine (T_4) and triiodothyronine (T_3). The production and secretion of TSH is stimulated by the hypothalamus, which produces thyrotropin-releasing hormone (TRH). TSH production is inhibited by somatostatin, which is also produced by the hypothalamus, and by T_3 and T_4 via a negative feedback loop (Larsen et al., 1981).

The relation between thyroid function and mental disorders has long been recognised but the precise relationship between the hypothalamus–pituitary–thyroid axis and the brain remains obscure (Bahls and de Carvalho, 2004). Thyroid disorders, including both hypothyroidism and hyperthyroidism, may be accompanied by various neuropsychiatric manifestations, ranging from depression (Trzepacz et al., 1988) and anxiety (Kathol and Delahunt, 1986) to psychosis (Snabboon et al., 2009) and bipolar disorders (Hu et al., 2013). The clinical symptoms of hypothyroidism may mimic melancholic depression and dementia, while in elderly patients, those of hyperthyroidism may mimic depression (Hage and Azar, 2012) and affect cognitive functioning (Wahlin et al., 2005, 1998). In addition, TSH levels are correlated with depression severity (Bauer et al., 2008). Placidi et al. (1998) report higher rates of panic disorder, simple phobia, obsessive-compulsive disorder, major depressive disorder, bipolar disorder and cyclothymia in thyroid patients than in the general population. These findings would suggest that the co-occurrence of psychiatric and thyroid diseases may be the result of common biochemical abnormalities.

The relationship between thyroid function and mood disorders is particularly important in elderly patients. Chueire et al. (2007) report that depression was observed more frequently among individuals with subclinical (49.7%) hypothyroidism than among individuals with overt hypothyroidism (16.8%) ($p < 0.001$), and subclinical hypothyroidism increased the risk of a patient presenting with depression by more than four times (odds ratio, OR = 4.9). The above findings would suggest that the co-occurrence of psychiatric and thyroid diseases may be the result of common biochemical abnormalities.

Studies investigating TSH levels in elderly patients with depression are limited. Therefore, the aim of this study was to identify any differences in TSH level between groups of elderly patients with and without depression using a case–control design.

METHODS

This was a retrospective, cross-sectional, case–control study. The databases of two hospital clinical units (psychiatry of old age and geriatrics) were searched for identified serum TSH levels: this is a routine blood test done for every patient admitted. Data for all patients with depression admitted to the hospital from 2012 to 2015 was included into the analysis. Only the first entry for each patient was used. As these initial blood tests are performed the day following admission, it is assumed that most patients included in the study were in the acute phase of depression.

The database search was focused on patients aged ≥60 years with unipolar depression (all severities). For the diagnosis of depression, the following codes were used: International Statistical Classification of Diseases and Related Health Problems, ICD-10: F32/F33.

To form the control group, each patient was assigned an age- and sex-matched subject without depression. The control group consisted of 274 patients admitted to the hospital unit of geriatrics from 2012 to 2015, who were aged ≥60 years with excluded mental disorders. In both groups, patients with previously diagnosed thyroid dysfunctions and/or TSH ≥10 μIU/mL were excluded from the analysis. Also, only non-demented patients with a score ≥24 on the Mini-Mental State Examination (MMSE) (Crum et al., 1993) were included in the analysis. Therefore, from the initial group of 823 Caucasian patients (364 subjects with depression, 459 subjects without depression), only 548 were finally included in the study.

Depression severity was assessed using a 15-item version of the Geriatric Depression Scale (GDS-15) (scores of 0–4 are considered normal; 5–8 indicate mild depression; 9–11 indicate moderate depression; and 12–15 indicate severe depression), assuming that higher scores indicate higher depression severity (Marc et al., 2008). The protocol for the research project was approved by the Medical University of Lodz Ethics Committee and it conforms to the provisions of the Declaration of Helsinki of 1995 (as revised in Tokyo, 2004).

Blood samples were drawn from all patients between 8 and 9 a.m. after a 12-hour overnight fast. Immediately after collecting the blood samples, serum TSH level was determined using a Dirui CS-400 automatic analyser (Dirui, China). A range of 0.4 to 5.8 μIU/mL was assumed to be the normal TSH range for subjects aged 60+ (Fontes et al., 2013).

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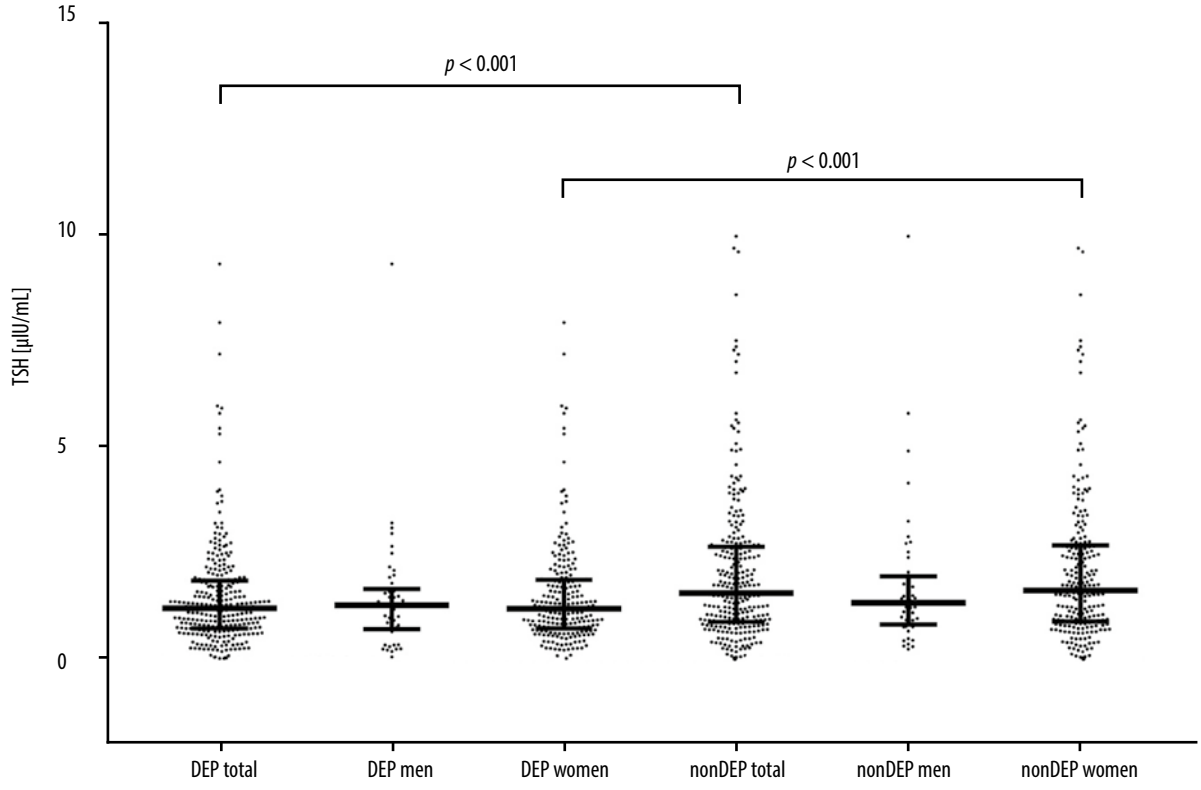

DEP – elderly patients with unipolar depression; **nonDEP** – non-depressed elderly patients.
Horizontal bars represent medians and 25th–75th centiles.

Fig. 1. TSH in the study groups

Statistical procedures were performed with STATA 14.1 (StataCorp, USA) and GraphPad Prism 7.00 (GraphPad Software, USA). Simple descriptive statistics (means, standard deviation, median) were generated for continuous variables. For discrete variables, the number of patients and percentages are given. The normality of the distribution was tested with the Shapiro–Wilk test. As TSH levels did not follow a normal distribution, even after transformation, any differences were subsequently analysed using the Kruskal–Wallis and the Mann–Whitney tests. The difference between proportions was analysed with the chi-square test. Associations were tested by Spearman's correlation coefficients. The level of significance was set at $p < 0.05$ (two-tailed).

RESULTS

The number of subjects in both study groups was equal [$n = 274$ in in the depression (DEP) and $n = 274$ in the non-depressed (nonDEP) group]. In each group there were 228 women. The mean age of the whole study group and of both subgroups was 77.1 ± 8.2 years.

The mean serum TSH level in the study groups was found to be 1.44 ± 1.23 μIU/mL in the DEP group (median: 1.17), and 2.00 ± 1.70 μIU/mL in the nonDEP group (median: 1.52). This difference was significant ($p < 0.001$). The TSH levels in men with and without depression were 1.39 ± 1.42 and 1.72 ± 1.69 μIU/mL, respectively ($p = 0.27$).

Group	TSH category [μIU/mL], *n* (%)			*p*†
	Low (<0.4)	Normal (0.4–5.8)	High (>5.8)	
Depression: • Men • Women	33 (12.0) 10 (21.7) 23 (10.1)	236 (86.1) 35 (76.1) 201 (88.2)	5 (1.9) 1 (2.2) 4 (1.7)	$X^2 = 4.99$ $p = 0.08$
Non-depressed: • Men • Women	24 (8.8) 4 (8.7) 20 (8.8)	240 (87.6) 41 (89.1) 199 (87.3)	10 (3.6) 1 (2.2) 9 (3.9)	$X^2 = 0.34$ $p = 0.84$

Data shown as *n* (%).
† Chi-square test for sex vs. TSH-categories, performed separately in the DEP and the nonDEP groups.

Tab. 1. Distribution of TSH ranges in the study groups

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Group	Total	Age category			$p^{\dagger}$
		60–70 (DEP: $n = 57$, nonDEP: $n = 57$)	70–80 (DEP: $n = 111$, nonDEP: $n = 111$)	>80 (DEP: $n = 106$, nonDEP: $n = 106$)	
Depression (all): • Men • Women • $p^{\ddagger}$	1.44 ± 1.23 1.39 ± 2.02 1.45 ± 1.19 $z = 0.49$ $p = 0.62$	1.38 ± 0.93 1.06 ± 0.98 1.46 ± 0.90 $z = 1.66$ $p = 0.10$	1.49 ± 1.37 1.05 ± 0.66 1.59 ± 1.46 $z = 1.29$ $p = 0.20$	1.41 ± 1.22 2.02 ± 2.06 1.31 ± 0.98 $z = -1.84$ $p = 0.07$	$H = 0.08, p = 0.95$ $H = 5.40, p = 0.07$ $H = 1.82, p = 0.40$
Non-depressed (all) • Men • Women • $p^{\ddagger}$	2.00 ± 1.70 1.72 ± 1.69 2.06 ± 1.82 $z = 1.59$ $p = 0.11$	1.71 ± 1.59 1.15 ± 0.59 1.85 ± 1.72 $z = 0.91$ $p = 0.36$	2.01 ± 1.68 1.83 ± 2.13 2.05 ± 1.58 $z = 1.51$ $p = 0.13$	2.14 ± 1.78 1.99 ± 1.58 2.17 ± 1.82 $z = 0.27$ $p = 0.79$	$H = 3.09, p = 0.21$ $H = 1.88, p = 0.39$ $H = 1.77, p = 0.41$

Data shown as mean ± standard deviation.
† Kruskal–Wallis test for age subgroups, performed separately in DEP and nonDEP groups.
‡ Mann–Whitney test for men vs. women within a given age category, performed separately in the DEP and the nonDEP groups.

Tab. 2. Mean TSH [mg/L] levels in age groups

TSH levels in women with and without depression were 1.45 ± 1.19 and 2.06 ± 1.70 μIU/mL, respectively ($p < 0.001$). No difference in TSH level was observed between men and women in the DEP group ($p = 0.62$), in the nonDEP group ($p = 0.11$) and in the whole study group ($p = 0.15$). A summary of TSH levels in the study groups is shown in Fig. 1. As expected, depressed patients had a significantly higher score on GDS-15 (8.5 ± 3.6 vs. 3.9 ± 3.0, $p < 0.001$).

Tab. 1 presents the distribution of TSH ranges in two study groups. The overall rate of being in the low range (<0.4 μIU/mL) was 12.0% for patients with depression and 8.8% for non-depressed patients, while the overall rate of being in the high range (>5.8 μIU/mL) was 1.8% for patients with depression and 3.6% for non-depressed patients. The evaluation of the low, moderate and high TSH ranges revealed no significant differences between the two groups with regard to serum TSH categories ($X^2 = 3.12$, $p = 0.21$). No differences were found in the distribution of TSH categories with regard to sex, either for the DEP or the nonDEP groups (Tab. 1).

The association between age and TSH level was found to be non-significant for the DEP group ($r = -0.01$, $p = 0.81$), the nonDEP group ($r = 0.08$, $p = 0.17$) and the whole study group ($r = 0.03$, $p = 0.47$). A significant correlation was found between TSH level and age in men in the DEP group ($r = 0.33$, $p = 0.03$), but not in women in the DEP group ($r = -0.09$, $p = 0.19$) or in the nonDEP group (men: $r = 0.12$, $p = 0.44$; women: $r = 0.07$, $p = 0.27$). Also, a significant correlation was found between TSH level and age in men in the whole study group ($r = 0.22$, $p = 0.03$), but not in women ($r = -0.01$, $p = 0.90$). In addition, no differences in TSH level were found with regard to three age categories (<70 years, 70–80 and >80 years), either between depressed and non-depressed patients, or between male and female subjects; the mean TSH levels are shown in Tab. 2.

DISCUSSION

The aim of this retrospective, case–control, cross-sectional, naturalistic study was to investigate the differences in TSH level between elderly patients with unipolar depression and non-depressed elderly patients. The depressed elderly patients were found to have lower TSH levels; this difference was also significant in the subgroup of women, but not for men. The elderly patients with depression presented with comparable TSH levels to those identified in our previous study of adult patients with unipolar depression ($n = 651$, mean TSH 1.63 μIU/mL, $p = 0.13$) (Wysokiński and Kłoszewska, 2014). In the large National Health and Nutrition Examination Survey (NHANES), the mean serum TSH was found to be 1.50 μIU/mL, and was higher in females than males (Hollowell et al., 2002); a similar tendency was also observed in the present study. While the non-depressed older patients in the present study were found to have higher mean TSH scores (2.00 μIU/mL) than the NHANES data, the TSH level was found to be comparable in depressed patients (1.44 μIU/mL).

A meta-analysis of thyroid dysfunctions in Europe found the prevalence of undiagnosed thyroid dysfunctions to be 6.71%, with the prevalence of hypothyroidism being 4.94% and hyperthyroidism 1.72% (Garmendia Madariaga et al., 2014). The prevalence of clinical and subclinical hyperthyroidism in the present study sample may be as high as 12.0% in the DEP subjects and 8.8% in the nonDEP subjects; however, as no data was obtained on free T_4 level, our estimation of the TSH level might be inaccurate.

It should be noted that a state of "brain hypothyroidism" has also been reported in patients with depression (Hatterer et al., 1993); it is believed to occur in systemic euthyroidism and may result from a defect of thyroid hormone receptor or impaired thyroid hormone transporter (Hennemann et al., 2001). Also, thyroid hormone replacement therapy is associated with a restoration of metabolic activity in

brain areas that are integral to the regulation of affect and cognition, which indicates that thyroid hormones modulate regional glucose metabolism and psychiatric symptoms in the mature brain (Bauer et al., 2009). As a result, many studies have noted that thyroid hormone supplementation has good efficacy in treating depression (Łojko and Rybakowski, 2007).

Our observation that depression may be associated with increased TSH levels is reflected in some previous studies. A cohort study of 1,503 elderly men and women (mean age 70.6 years) found that low-normal TSH levels were associated with more severe concurrent depressive symptoms and a substantially increased risk of developing a depressive syndrome in subsequent years (Medici et al., 2014). Similarly, in a sample of 183,647 patients with the diagnosis of hyperthyroidism, Thomsen et al. (2005) reported that patients hospitalised with hyperthyroidism are at a greater risk of re-admission with depressive disorder or bipolar disorder than control patients, which suggests that hyperthyroidism is associated with long-term mood disturbances. Larisch et al. (2004) report that hypothyroidism increases age and gender-adjusted risk for critical mood deterioration by seven times. The results of a population-based (n = 14,787) study found a slight association between suppressed TSH (subclinical hyperthyroidism) and the risk of subclinical depression (Kvetny et al., 2015).

However, the opposite relationships have also been reported by numerous authors. For example, in a retrospective cohort study of 13,017 subjects, Kim et al. (2015) found that the risk of depressive symptoms was increased among women with the highest tertile TSH level [adjusted hazard ratio (HR): 2.236; 95% confidence interval (CI): 1.443–3.466; $p < 0.001$] compared with those with the lowest tertile; no such relationship was found in men. Similarly, another study based on 1500 middle-aged women from the general population found higher levels of TSH to be associated with an increased chance of developing depression (Guimarães et al., 2009).

Also, de Jongh et al. (2011) report no association between TSH level and cognitive function, depression and mortality in 1,219 individuals aged 65 years or older, van de Ven et al. (2012) note no association between TSH levels, FT_4 levels and severity of depressive symptoms, current depression or lifetime diagnosis of depression in 1,125 adult subjects, and Engum et al. (2002) report no significant relationship between thyroid dysfunction and the presence of depression or anxiety disorder in a large (n = 30,589) sample of individuals aged 40–89 years from the general population. In addition, Sabeen et al. (2010) found no significant association between elevated TSH and depression in elderly patients, where 11.5% (n = 70) of depressed cases and 8.8% (n = 24) of non-depressed cases displayed elevated TSH ($p < 0.122$). Finally, Almeida et al. (2011) found subclinical thyroid disease not to be associated with prevalent or incident depression in a community-dwelling sample of 3,932 men aged 69 to 87 free of overt thyroid disease.

The results of the population-based NHANES (Hollowell et al., 2002) indicated a positive correlation between age and TSH level in a large (n = 17,353) sample. However, our present findings indicate that TSH levels correlated with age only in men. This observation might be explained by the fact that our study sample was much older and had various potential risk factors of thyroid dysfunction because of multiple chronic concomitant diseases.

Our study has some limitations, which result mainly from its retrospective and naturalistic design. No detailed thyroid assessment, including T_3, T_4 or antithyroid autoantibody assay, or ultrasonography examination was performed. The number of men was much smaller in both study groups. Also, antidepressants may have a range of effects on thyroid hormone levels, and this could be attributed to their various mechanisms of action (Eker et al., 2008). Despite these limitations, the large sample size is a strength of the study, together with its case–control design.

In conclusion, our findings show that elderly patients with unipolar depression have lower TSH levels than non-depressed elderly subjects, and that the TSH level of patients with mood disorders should be regularly monitored. This is particularly important in the light of the recommendations of the American Association of Clinical Endocrinologists, which state that "The diagnosis of subclinical […] hypothyroidism must be considered in every patient with depression" (Baskin et al., 2002). Also, as recommended by Livner et al. (2009), the previously identified "normal-range" interval for TSH should be moved upwards in old age, at least when cognitive functioning is considered. Our findings also suggest that elderly patients with depression should also be monitored for subclinical hyperthyroidism, which may be more prevalent in this population.

Conflict of interest

All authors have no conflict of interest.

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