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The Relationship between Thyroid Function and Depressive Symptoms—the FIN-D2D Population-Based Study

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ABSTRACT: The association between thyroid function and depression is controversial. Both conditions express many similar symptoms, but the studies done give conflicting results. This study draws on a random, population-based sample of 4500 subjects aged 45–75 years old from Finland. The basic clinical study was done in 2007 for 1396 men and 1500 women (64% participation rate). Thyroid stimulating hormone (TSH), free thyroxine (F-T4), and free triiodothyronine (F-T3) were measured in 2013 from frozen samples. The 21-item Beck Depression Inventory (BDI-21) was applied to assess depressive symptoms (score ≥10 points). The prevalence of depressive symptoms was 17.5% in women and 12.5% in men. In women, the mean levels of TSH, F-T4, and F-T3 without depressive symptoms vs. with the presence of depressive symptoms were 1.92/1.97 mU/L, 13.1/13.1 pmol/L, and 3.91/3.87 pmol/L (NS), respectively. In men, the levels were 1.87/1.94 mU/L, 13.5/13.7 pmol/L, and 4.18/4.12 pmol/L (NS), respectively. In multiple regression analysis, TSH had no relationship to BDI-21 total score. We found no association between depressive symptoms and thyroid values.

KEYWORDS: depressive symptoms, BDI-21, thyroid, population based

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Introduction

The association between depression and thyroid function, especially hypothyroidism, is controversial. The idea of association comes from similarity of symptoms between severely depressed and hypothyroid patients, the therapeutic use of thyroid hormones in the management of depression, and the apparent abnormalities in the hypothalamic–pituitary–thyroid axis of subjects with depression.[1]

The many studies in this area give conflicting results. The larger studies have shown either no effect or an inverse relationship between thyroid function and mood.[1] The largest study so far is the Norwegian HUNT study.[2] The investigators found no association between depression, self-reported using the Hospital Anxiety and Depression Scale (HADS), and thyroid dysfunction in 30,589 individuals aged 40–89 years. The same group also analyzed the connections between thyroid autoimmunity, depression, and anxiety, finding no associations.[3] A health database study from Taiwan of 1,000,000 random subjects found a higher prevalence (1.20% vs. 0.30%) and a higher annual incidence (0.40% vs. 0.13%) of hypothyroidism in patients with major depressive disorder than in the general population. The annual incidence of hyperthyroidism was also higher in patients with depression than in the general population (0.72% vs. 0.32%, risk ratio 2.06). The correlation was especially pronounced in the female subjects.[4]

Our aim was to study the relationship of thyroid function and depressive symptoms, measured with the 21-item Beck Depression Inventory (BDI-21),[5] in this rather large Finnish adult population, because the results of previous studies are conflicting in various populations.

Materials and Methods

Study population. The FIN-D2D survey was carried out in the hospital districts of Pirkanmaa, the Southern Ostrobothnia, and Central Finland between October and December 2007.

A random sample of 4500 subjects aged 45–74 years, which was stratified according to gender, 10-year age groups (45–54, 55–64, and 65–74 years), and three geographical areas, was selected from the National Population Register in August 2007. The study participants were invited to a clinical examination by mail. The overall participation rate was 64%. Thus, the main study included 2896 individuals, of which 1396 were men (62% of men invited) and 1500 were women (66.7% of women invited).

Thyroid values were measured in 2741 subjects (1434 women and 1307 men). Thyroxin hormone was used by 79 subjects, and they were excluded from the analysis. The final study population was 2662 (1358 women and 1304 men).

The study protocol was approved by the ethics committee of the Hospital District of Helsinki. All participants gave their written, informed consent prior to participation in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. The health examination was carried out according to the World Health Organization's (WHO's) MONICA project (Multinational MONItoring of trends and determinants in CArdiovascular disease) and the WHO's expert group for glucose assessments.

BDI-21 was applied to assess depressive symptoms.[5] Subjects were categorized as having depression when they scored ≥10 points in the BDI-21. The cut-off point of 10 in the BDI-21 has been shown to be a useful measurement for detecting depression in various adult populations.[6,7]

Subjects were asked to rate 21 items from 0 to 3 according to how they felt at that time. The items were summed as a total score with a range from 0 to 63. The BDI-21 data were missing for eight women and five men.

The participants reported their leisure-time physical activity (LTPA) according to three categories: (1) low—almost completely inactivate, (2) moderate—some physical activity more than four hours per week, and (3) high—vigorous physical activity many times a week. Current smoking and the use of alcohol were also queried. The participants were also asked whether they were using thyroid hormones or lipid-lowering, antihypertensive, antidepressive, or antihyperglycemic medications.

Height, weight, and waist circumference were measured by nurses who were specially trained for the survey procedures. Height was measured to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg in light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m^2). Blood pressure (BP) was measured twice, and the latter was used in the analysis, in a sitting position after a minimum of 15 minutes of acclimatization using a mercury sphygmomanometer.

Laboratory analysis. After an overnight fast, venous blood samples for serum lipid assays were drawn into a gel tube containing clot activator and samples for the plasma glucose assay into a fluoride citrate tube (Venosafe; Terumo Europe). The samples were immediately frozen after separating serum and plasma and transferred to the laboratory in dry ice once a week for analyses. The rest of samples were kept in −70°C.

All basic assays were performed at the Laboratory of Analytical Biochemistry at the National Public Health Institute, Helsinki (Disease Risk Unit, Institute for Health and Welfare since 2009), using an ARCHITECT ci8200 analyzer (Abbott Laboratories). High-sensitivity C-reactive protein (hs-CRP) was measured with an ultrasensitive immunoturbidimetric method using Abbott architect reagents.

Free thyroxine (F-T4), free triiodothyronine (F-T3), and thyroid stimulating hormone (TSH) were measured from frozen EDTA-plasma samples with Cobas e601 (Roche Diagnostics) automated analyzer in the Islab Laboratory of the University of Eastern Finland, Kuopio, in the year 2013. The reference values for free T4, free T3, and TSH were 11–22 pmol/L, 3.1–6.8 pmol/L, and 0.3–4.2 mU/L, respectively. Serum thyroid antiperoxidase antibodies were measured by Architect® (Abbott Laboratories) automated analyzer. Analytical sensitivity of the assay was 0.16 IU/mL. The upper reference limit was 6.0 IU/mL.

Statistical analysis. The comparisons between the groups in demographic, lifestyle, and biochemical characteristics and clinical and drug-treatment data were made by *t*-test, bootstrapped-type *t*-test, or chi-square test, as appropriate. The equality of distributions of the thyroid values was tested using the Epps–Singleton two-sample empirical characteristics function test and bootstrap-type analysis of covariance (ANCOVA) taking age, BMI, LTPA, current smoking, and alcohol use values as covariates. Linear regression analyses (bootstrap-type standard error) were used to identify the appropriate predictors of the BDI-21 total score, using standardized regression coefficient beta (β). Beta is measured in units of standard deviation, and value is a measure of how strongly each predictor variable influences the criterion (dependent) variable. Cohen's standard for beta values above 0.10, 0.30, and 0.50 represents small, moderate, and large relationships, respectively.

Results

The mean age of the study population was 59.7 years (women 59.2 years and men 60.0 years). The mean BMI of both men and women was 27.4 kg/m^2 (Table 1). Fasting plasma glucose values were 6.0 mmol/L in women and 6.5 mmol/L in men. The use of antihypertensive, lipid-lowering, and antidepressant medications was higher in men and women with depression. Hs-CRP was not statistically different in men or women with or without depression. LTPA was significantly higher both in men and women without depression. BP was the same in all groups.

Subclinical hypothyroidism (TSH over reference range and normal F-T4) was found in 4.2% of subjects. Subclinical hyperthyroidism (TSH under reference rate) was found in 1.1% of subjects. The prevalence of undiagnosed hypothyroidism (TSH over and F-T4 under the reference rate) was 1.3%. The prevalence of these groups was the same in BDI-21

Table 1. The basic demographic, lifestyle and biochemical characteristics of study population according to BDI-21 values <10 and ≥10.

	WOMEN			MEN		
	BDI-21			BDI-21		
	<10 N = 1114	≥10 N = 236	*P*-VALUE	<10 N = 1136	≥10 N = 163	*P*-VALUE
Demographic						
Age, years, mean (SD)	59 (8)	61 (9)	<0.001	60 (8)	62 (9)	<0.001
Waist, cm, mean (SD)	90 (13)	94 (14)	<0.001	99 (11)	104 (14)	<0.001
BMI, mean (SD)	27.2 (5.0)	28.4 (5.4)	0.001	27.3 (4.0)	28.7 (5.0)	<0.001
Clinical						
Blood pressure, mmHg, mean (SD)						
Systolic	135 (19)	135 (19)	0.96	138 (18)	138 (18)	0.98
Diastolic	80 (9)	80 (9)	0.99	83 (10)	83 (10)	0.64
Biochemical						
Total cholesterol, mmol/l	5.52 (0.96)	5.60 (0.96)	0.24	5.36 (1.01)	5.10 (0.96)	<0.001
HDL cholesterol, mmol/l	1.56 (0.34)	1.51 (0.32)	0.017	1.33 (0.32)	1.26 (0.28)	0.013
Total triglycerides, mmol/l	1.24 (0.58)	1.41 (0.72)	<0.001	1.49 (1.02)	1.53 (0.84)	0.56
Fasting plasma glucose, mmol/l	5.99 (0.93)	6.18 (1.34)	0.036	6.42 (1.26)	6.50 (1.26)	0.45
hs-CRP, mg/L	2.86 (8.24)	3.21 (5.64)	0.43	2.37 (6.26)	3.51 (11.64)	0.22
Medication						
Antihypertensive medication, n (%)	354 (32)	98 (42)	0.004	382 (34)	78 (48)	<0.001
Lipid lowering medication, n (%)	186 (17)	52 (22)	0.051	268 (24)	57 (35)	0.002
Use of antidepressants, n (%)	43 (4)	47 (20)	<0.001	22 (2)	28 (17)	<0.001
Lifestyle factors						
Current smoker, n (%)	208 (19)	59 (25)	0.027	279 (25)	44 (27)	0.50
Current use of alcohol, n (%)	558 (50)	111 (47)	0.39	843 (74)	102 (63)	0.002
LTPA			<0.001			<0.001
Low	164 (15)	73 (33)		191 (17)	58 (38)	
Moderate	668 (61)	122 (55)		649 (58)	81 (53)	
High	258 (24)	27 (12)		271 (24)	15 (10)	

Abbreviations: BDI-21, The 21-item Beck Depression Inventory; BMI, body mass index; LTPA, leisure-time physical activity; hs-CRP, high sensitivity C-reactive protein; SD, standard deviation.

over and under 10 points compared to subjects with normal thyroid values.

Table 2 shows that the prevalence of depressive symptoms (BDI-21 ≥10 points) was 17.5% in women and 12.5% in men. The mean thyroid values for women without depressive symptoms (BDI-21 <10 points) vs. with depressive symptoms (BDI-21 ≥10 points) were 1.92/1.97 mU/L (NS) for TSH, 13.1/13.1 pmol/L (NS) for F-T4, and 3.91/3.87 pmol/L (NS) for F-T3. For men, the values were 1.87/1.94 mU/L (NS) for TSH, 13.5/13.7 pmol/L (NS) for F-T4, and 4.18/4.12 pmol/L (NS) for F-T3.

Table 3 shows that in multiple regression analysis, TSH has no relationship to BDI-21 total score.

Discussion

This study found no association between depressive symptoms and TSH, F-T4, and F-T3 in this Finnish population-based cohort. The prevalence of depressive symptoms was 17.5% in women and 12.5% in men. This is in line with other studies assessing depressive symptoms in Finland.[8] The prevalence of hypothyroidism or subclinical hypothyroidism in this population, measured by s-TSH over the reference range 4.2 mU/L, was 5.5%. The calculated lifetime risk for developing overt hypothyroidism in Denmark was 2.3%, with a threefold excess in women (3.5% vs. 1.0% in men).[9]

We, like many others, excluded the persons ($N = 79$) who used thyroxine from the analysis. This may be an important bias because subjects with depressive symptoms and subclinical hypothyroidism are likely to have been on thyroxine therapy in countries like Finland where medical care and thyroid function tests are easily available. As these subjects are excluded, the remaining subjects with clinical hypothyroidism are likely to be less symptomatic.[1]

Several studies have investigated thyroid autoimmunity and depression.[3] The results are conflicting. Smaller studies, one with 583 women with TPO antibody levels >100 mU/L[10]

Table 2. The association between Beck Depression Inventory (BDI-21) scores <10 and ≥10 and thyroid values (TSH, F-T4, F-T3) in men and women.

	WOMEN				MEN			
	BDI-21		*P*-VALUE		BDI-21		*P*-VALUE	
	<10 N = 1114	≥10 N = 236	CRUDE	ADJUSTED*	<10 N = 1136	≥10 N = 163	CRUDE	ADJUSTED*
TSH								
Mean (SD)	1.92 (1.18)	1.97 (1.38)	0.61	0.63	1.87 (1.24)	1.94 (1.25)	0.54	0.85
Median (IQR)	1.68 (1.12, 2.48)	1.67 (1.01, 2.49)			1.58 (1.11, 2.25)	1.58 (1.06, 2.53)		
F-T4								
Mean (SD)	13.1 (2.0)	13.1 (2.1)	0.50	0.10	13.5 (2.0)	13.7 (2.4)	0.25	0.39
Median (IQR)	13.0 (11.9, 14.3)	12.7 (11.7, 14.3)			13.4 (12.2, 14.9)	13.7 (12.2, 15.2)		
F-T3								
Mean (SD)	3.91 (0.65)	3.87 (0.64)	0.38	0.18	4.18 (0.68)	4.12 (0.68)	0.32	0.13
Median (IQR)	3.88 (3.48, 4.30)	3.87 (3.46, 4.25)			4.17 (3.70, 4.63)	4.12 (3.66, 4.50)		

Notes: *Adjusted for age, BMI, current smoking, current alcohol use and LTPA.
Abbreviations: BDI-21, The 21 Item Beck Depression Inventory; F-T4, free thyroxine; F-T3, free triiodothyronine; TSH, thyroid-stimulating hormone; SD, standard deviation: IQR, interquartile range; LTPA, leisure-time physical activity.

and one with 201 subjects,[11] found an association with depressive scores and thyroid autoimmunity. However, the above-mentioned large Norwegian study found no relation.[3]

Both the symptoms of depression and biochemical subclinical hypothyroidism (slightly elevated TSH) are common, especially in the elderly female population. Thus, it is probable that they overlap, resulting in thyroxin therapy. Many studies have shown poor well-being in subjects on thyroxin, even if it was started with adequate biochemical values.[12,13] The Danish study found that hypothyroidism presented with a broad spectrum of symptoms. However, many of these symptoms were also experienced by volunteer control subjects with normal thyroid values.[9]

Interestingly, a study of a Dutch population-based cohort of elderly people (mean age 71 years) found that subjects with low-normal TSH levels had more concurrent depressive symptoms than those with normal levels as well as a substantially increased risk of developing a depressive syndrome in the subsequent years.[14]

Systemic inflammation increases the risk of depression, especially in people with type 2 diabetes.[15] The effect

Table 3. Multiple regression analysis for BDI-21 total score.

VARIABLE	BETA*	*P*-VALUE
TSH	0.02 (−0.02 to 0.05)	0.39
Male gender	−0.09 (−0.13 to −0.05)	<0.001
Age	0.10 (0.06 to 0.14)	>0.001
BMI	0.06 (0.01 to 0.10)	0.008
Current smoker	0.06 (0.02 to 0.10)	0.002
Current use of alcohol	−0.05 (−0.09 to −0.01)	0.012
LTPA		
Low	Reference	<0.001 (p for linearity)
Moderate	−0.18 (−0.23 to −0.13)	
High	−0.24 (−0.29 to −0.13)	
hs-CRP	0.03 (−0.01 to 0.06)	0.18
Fasting plasma glucose	0.01 (−0.03 to 0.05)	0.62
Lipid lowering medication	0.04 (0.01 to 0.08)	0.030
Antihypertensive medication	−0.01 (−0.04 to 0.08)	0.90

Note: *Standardized beta coefficients.

of low-grade inflammation in people with hypothyroidism is not known. In our study, we measured hs-CRP as a marker of systemic inflammation, but we did not find any differences between groups. On one hand, the depressive people had less LTPA than non-depressed people. On the other hand, people with depressive symptoms used more antihypertensive, lipid-lowering, and antidepressant medications.

The strength of this study is a rather large, randomly selected population, aged 45–74 years, with both men and women. The depressive symptoms were assessed by BDI-21, which is widely used and accepted in population-based studies.

The limitations of the study are that TPO-antibodies were measured only in 30% of subjects, and we do not have data about the subjects' disease and family history, factors that may have important influence on depression. In the beginning, the study population was randomly selected from the National Population Register database, but only 64% of invited subjects enrolled, and we excluded subjects receiving thyroxin-hormone therapy. So, the final study population is not randomly selected population based.

Conclusion

The association of depressive symptoms and the levels of thyroid hormones has been controversial. This study did not find any association between TSH, F-T4, and F-T3 values and depressive symptoms.

Author Contributions

Conceived and designed the experiments: JS, PM, MV. Analyzed the data: HK, JS, MV. Wrote the first draft of the manuscript: JS. Contributed to the writing of the manuscript: HK, PM, MV. Agree with manuscript results and conclusions. JS, HK, PM, AJ, SKK, EKH, HO, TS, MV. Jointly developed the structure and arguments for the paper: JS, HK, PM, AJ, MV. Made critical revisions and approved the final versions: JS, HK, PM, AJ, SKK, EKH, HO, TS, MV. All authors reviewed and approved of the final manuscript.

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