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The relationship between serum thyroid-stimulating hormone, insulin resistance, and cardiovascular risk factors in obese patients with subclinical hypothyroidism

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Abstract. Background. The epidemic of overweight and obesity presents a major challenge to chronic disease prevention and health across the life course around the world. The putative relationships between thyroid hormones, body weight, and adipose tissue homeostasis have been the focus of several studies in recent years, but the causal relationships between these parameters have not been well established. The purpose of the study: to investigate the relationship between serum thyroid-stimulating hormone (TSH), insulin resistance (IR), and cardiovascular risk factors in a sample of obese people with subclinical hypothyroidism. **Materials and methods.** A retrospective, longitudinal analysis of 145 obese patients was performed. The TSH and free thyroxine (fT₄) levels, anthropometric measurements, and laboratory test results were analyzed. **Results.** Twenty-three individuals presented with TSH levels above the normal level (subclinical hypothyroidism). Their waist circumference (WC) was significantly higher than that of euthyroid individuals. Serum TSH positively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR) index, triglycerides, and high-density lipoprotein cholesterol (HDL-C). Using TSH and body mass index as independent variables, TSH levels were shown to be independently related to HOMA-IR ($p = 0.002$) and triglycerides ($p = 0.006$). Among euthyroid subjects, individuals with TSH values < 2.5 mIU/ml exhibited statistically significant decreases in waist-to-hip ratio, HDL-C levels, and HOMA-IR scores and a tendency toward lower WC values. **Conclusions.** Subclinical hypothyroidism in overweight and obese people appears to be associated with excess weight, especially visceral weight. In the present sample of obese patients, TSH levels appear to be associated with insulin resistance.

Keywords: subclinical hypothyroidism; obesity; cardiovascular risk factors

Introduction

The incidence of obesity is increasing in developing and developed countries [1]. In Ukraine, a developing country, the incidence of childhood obesity until recently was much lower but has shown a significant rise over the last decade, increasing from 0.083 % among age groups 0–18 years in 2003 to 1.23 % in 2009 and 1.34 in 2016 [2, 3].

The well-established association between obesity and lipid metabolism disorders, hypertension and increased cardiovascular risk is frequently referred to as metabolic syndrome [4].

Thyroid hormones play a key role in regulating metabolism through the modulation of thermogenesis and energy expenditure. The putative relationships between thyroid

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hormones, body weight, and adipose tissue homeostasis have been the focus of several studies in recent years, but the causal relationships between these parameters have not been well established [5–7]. One review [8] included several population-based studies that revealed a correlation between increased serum thyrotropin (TSH) levels and increased body mass index (BMI).

Thyroid diseases have been associated with atherosclerotic cardiovascular disease [9, 10]. Although this association has been documented conclusively for overt hypothyroidism, it remains controversial whether it is also present in subclinical hypothyroidism [11, 12]. The association of thyroid diseases with atherosclerotic cardiovascular disease may be partially explained by the roles of thyroid hormones in the regulation of lipid metabolism and blood pressure (BP). Indeed, several recent population-based studies have observed positive correlations between TSH and lipid parameters and between TSH and BP, even in euthyroid populations [13–15].

The purpose of this study was to investigate the relationship between obesity, thyroid function, lipids, insulin resistance in a sample of overweight patients. The study also aimed to assess the metabolic and anthropometric differences of euthyroid patients with TSH in the upper limit of normality ($\geq 2.5 \mu\text{IU/mL}$) in comparison to patients with the lower levels.

Materials and methods

This study evaluated a total of 145 obese individuals of both genders aged from 19 to 59 years, from May 2018 to February 2019. The protocol was approved by the Ethics Committee of I. Horbachevsky Ternopil National Medical University (protocol 4, 23.04.2018) and a written informed consent was obtained from the participants.

The exclusion criteria were as follows: previous diagnosis of either type 1 or type 2 diabetes mellitus; patients who were receiving anti-diabetic and/or anti-obesity medications; those who had an endocrine disease diagnosis; diagnosed thyroid disease (the use of levothyroxine or thionamides); creatinine and urea levels above normal values; aspartate aminotransferase (AST) and/or alanine aminotransferase

(ALT) levels three times above the upper limit of normality; alcohol or drug abuse; chronic and constant-dose concomitant use of beta-blockers, diuretics, antidepressants, neuroleptics, bromocriptine, systemic steroids, appetite suppressants, or drugs that interfere with amine activity or are used to treat psychiatric disorders within the past three months; pregnant and lactating females; or a history of neoplasia in the past five years.

All participants underwent a complete medical history-taking and physical exam. The following parameters were evaluated: weight (kg), height (m), body mass index (kg/m^2), waist circumference (WC), waist-to-hip ratio (WHR), BP (mmHg), and demographic factors (gender and age). WC was measured at the midpoint between the iliac crest and the costal margin. Hip circumference (HC) was obtained by measuring the largest diameter over the great trochanters. The WHR was calculated by determining the ratio between WC and HC. BMI was calculated by dividing the weight (kg) by the height squared (m^2).

Blood samples were collected after a 12-h fasting period, and the results from the following blood tests were evaluated: fasting glucose, 2-h glucose following glucose overload with 75 g glucose, complete blood count, urea, creatinine, sodium, potassium, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, ALT, AST, TSH, free T₄ (fT_4), and basal insulin.

Using the results of fasting glucose and basal insulin, the homeostasis model assessment — insulin resistance (HOMA-IR) index for each patient was calculated using the following formula: $\text{HOMA-IR} = [\text{glucose (mmol)} \times \text{insulin (}\mu\text{U/ml)}] / 22.5$. To evaluate TSH levels, an electrochemiluminescence method was employed. Electrochemiluminescence consists of an immunoassay that quantitatively determines TSH levels from human serum and plasma samples. The normal range of values that have been reported using this kit is $0.27\text{--}4.2 \mu\text{IU/ml}$. The fT_4 levels of the patients were also evaluated by electrochemiluminescence, and the reference values ranged between 0.93 and 1.7 ng/ml . The fT_4 values were only used to exclude patients if the values outside of the normal range were obtained.

Table 1. Anthropometric and metabolic data of the studied sample

Anthropometric and laboratory data	Median	Variation (minimum to maximum)
Age	42	19–59
BMI, kg/m^2	34.9	30.9–42.3
WC, cm	109	91–137
SBP, mmHg	130	90–160
DBP, mmHg	85	60–100
Glucose, mmol/l	5.3	3.7–11.2
2-h glucose, mmol/l	6.9	3.9–14.8
HOMA-IR	4.7	3.1–24.2

Notes: here and in Table 2: BMI — body mass index; WC — waist circumference; SBP — systolic blood pressure; DBP — diastolic blood pressure; HOMA-IR — homeostasis model assessment — insulin resistance.

Table 2. A comparison of metabolic and anthropometric parameters between patients with subclinical hypothyroidism and those with normal thyroid function

Parameter	Normal (n = 122)	Subclinical hypothyroidism (n = 23)	p
Age, years	41.0 (19–59)	44.0 (19–59)	0.33
BMI, kg/m ²	33.9 (30.9–41.4)	37.8 (32.3–43.9)	0.043
WC, cm	101 (92–137)	114 (94–139)	0.0018
WHR	0.92 ± 0.07	0.94 ± 0.06	0.23
SBP, mmHg	125 (90–160)	130 (90–160)	0.46
DBP, mmHg	80 (60–100)	85 (65–105)	0.37
Glucose, mmol/l	5.3 (3.7–11.1)	5.9 (3.8–11.7)	0.081
2-h glucose, mmol/l	6.8 (3.9–13.7)	7.1 (3.8–11.9)	0.39
HOMA-IR	4.6 (3.1–23.8)	4.9 (3.6–24.2)	0.17

Notes: WHR — waist-to-hip ratio. Data are presented as median (minimum — maximum).

The diagnosis of subclinical hypothyroidism was based on the recommendation 14.1 of the Clinical Practice Guidelines for Hypothyroidism in Adults, cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association [16]: the reference range of a given laboratory exam should determine the upper limit of normal for a third-generation TSH assay. Therefore, the diagnosis of subclinical hypothyroidism was defined as normal fT₄ associated with TSH above 5.0 µIU/ml.

Euthyroid patients were also divided into two groups according to TSH levels. There has been some discussion about lowering the upper value of TSH to 2.5 µIU/ml. This

Table 3. Correlations between serum TSH levels and various anthropometric and metabolic parameters in 122 patients with normal thyroid function

Parameter	Correlation	p
Age, years	–0.14	0.11
BMI, kg/m ²	0.16	0.063
WC, cm	0.11	0.14
WHR	0.06	0.47
Glucose, mmol/l	0.11	0.081
2-h glucose, mmol/l	0.07	0.46
HOMA-IR	0.15	0.02
TG, mmol/l	0.17	0.034
HDL-C, mmol/l	–0.15	0.052
LDL-C, mmol/l	0.04	0.62

Notes: BMI — body mass index; WC — waist circumference; WHR — waist-to-hip ratio; HOMA-IR — homeostasis model assessment — insulin resistance; TG — triglycerides; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol.

discussion is based on some data that indicated that patients with TSH ≥ 2.5 may have different profiles than those with TSH < 2.5 µIU/ml [17].

Data were analyzed using Social Sciences Statistical Data Processing Package, version 20 (software for statistical analysis SPSS, version 20.0; SPSS Inc., Chicago, Illinois, USA). The different groups were compared using Student’s t-tests for parametric variables and Mann-Whitney tests for nonparametric variables. For parametric variables, the data are presented as means ± standard deviations. For nonparametric variables, the data are presented as medians with maximum and minimum values. Correlational analyses were performed with Pearson’s test for parametric variables and Spearman’s test for nonparametric variables. All tests were two-tailed, and the level of significance was set at p = 0.05 for all analyses.

Results

A total of 145 patients with obesity examined at I. Horbachevsky Ternopil National Medical University Hospital were consecutively evaluated. Table 1 shows the anthropometric and metabolic data of the studied population.

Regarding glucose metabolism, 15.2 % of the sample (22 out of 145) had abnormal fasting glucose levels (between 5.5 and 6.9 mmol/l). Also, 11.7 % (17 out of 145) had a 2-h glucose level following a load with 75 g glucose between 7.2 and 11.1 mmol/l and thus were classified as having impaired glucose tolerance. Finally, three individuals (2.1 %) were diagnosed with type 2 diabetes mellitus. Having HOMA-IR value above 2.7, 87.6 % (127 out of 145) of the patients presented insulin resistance.

Thyroid function was evaluated by measuring TSH levels. There were no individuals exhibited TSH levels below the normal range (subclinical hyperthyroidism), and 23 individuals (15.9 %) presented with TSH levels above the normal level (subclinical hypothyroidism). All these patients had fT₄ within normal limits. No patient was diagnosed with overt hypothyroidism (low fT₄ and TSH above 5.0 µIU/ml).

Table 2 shows a comparison of the anthropometric and metabolic parameters of individuals diagnosed with subclinical hypothyroidism and euthyroid patients. Patients with subclinical hypothyroidism exhibited a significantly higher WC than those with normal thyroid function. No significant differences were observed between the groups in any of the metabolic parameters examined.

After excluding patients with subclinical hypothyroidism, the rest 122 patients (TSH levels within the normal range) were analyzed separately. Table 3 shows the correlations between TSH levels and various anthropometric and metabolic parameters in individuals with normal thyroid function.

Multiple linear regression analysis was used to assess the relationship between TSH and metabolic parameters. In this first model, TSH and BMI were used as independent variables, and each metabolic parameter as the dependent variable. After regression, TSH levels remained independently associated with HOMA-IR ($p = 0.002$), HDL ($p = 0.042$), and TG levels ($p = 0.006$). The same analysis was also used to assess whether the relationship between TSH and metabolic parameters would remain statistically significant independent of age and gender. In this second model, age, gender, and TSH levels were used as independent variables, and each metabolic parameter as the dependent variable. After regression, TSH remained independently related to HOMA-IR ($p = 0.002$) and triglycerides ($p = 0.006$). A trend toward significance was still found for HDL cholesterol ($p = 0.051$) and fasting glucose ($p = 0.07$).

Individuals with TSH levels > 2.5 had higher WHR and HOMA-IR and a trend toward higher WC.

Discussion

In this sample of obese people, 84.1 % of patients exhibited normal thyroid function and 15.9 % exhibited subclinical hypothyroidism. The frequency of subclinical hypothyroidism observed in this sample was higher than that reported in the literature, even using a cutoff value of $5.0 \mu\text{IU/ml}$ [17]. In the population in general, the prevalence of subclinical hypothyroidism is less than 2 %, but it is important to note that epidemiological studies in this age group are scarce [18].

Several studies have indicated a positive correlation between weight and TSH levels. These studies have also demonstrated that 10–23 % of obese persons have moderately high levels of TSH ($4\text{--}10 \mu\text{IU/ml}$), which are associated with normal levels of fT_4 or slightly elevated fT_4 and/or fT_3 levels. The levels of TSH in obese adults have been consistently reported to be elevated when compared with normal-weight individuals [19]. Prior research has revealed not only a positive correlation between BMI and TSH but also between five-year weight gain and a gradual increase in serum TSH levels [20].

This is the first study to evaluate TSH levels in the Ukrainian population of obese persons. Further studies are necessary to investigate whether the prevalence of subclinical hypothyroidism is higher in Ukraine and/or other European countries.

When patients with subclinical hypothyroidism were compared with euthyroid individuals, it was observed that patients with subclinical hypothyroidism had higher WC.

This finding is extremely important, as WC provides information regarding fat distribution. Central or abdominal obesity, which is characterized by increased WC, has been shown to be correlated with SBP, DBP, total cholesterol, TG, LDL-C, and HDL-C [21].

In the euthyroid individuals, a weak, but statistically significant correlation was observed between TSH and HOMA-IR, HDL, and TG. Using TSH and BMI as independent variables, TSH was found to be independently related to HOMA-IR and TG.

Even when examining only euthyroid patients, individuals with higher TSH levels ($> 2.5 \mu\text{IU/mL}$) had higher HOMA-IR and WHR, lower levels of HDL-C, and a tendency toward lower WC. There have been relatively few studies investigating euthyroid obese patients, but the correlation of HOMA-IR with TSH has been reported in several studies [22].

The present study has several limitations. First, the fact that it was a cross-sectional study prevented the establishment of temporal relationships between the variables under investigation. Also, because this study was performed retrospectively, the authors were unable to analyze other parameters, including the levels of fT_3 and leptin. More importantly, thyroid antibodies were also not evaluated. Therefore, it was not possible to determine whether this increased frequency of subclinical hypothyroidism was related to Hashimoto's thyroiditis or another etiology.

Conclusions

The frequency of subclinical hypothyroidism is 15.9 % in a sample of obese persons. These individuals, despite exhibiting a metabolic condition similar to that of patients with normal thyroid function, have a higher WC, suggesting that subclinical hypothyroidism may be associated with excess body weight, especially visceral weight. In persons with normal thyroid function, there also appears to be a direct relationship between TSH and some of the primary markers of insulin resistance.

Multiple linear regression analysis was used to assess the relationship between TSH and metabolic parameters. After regression, TSH levels remained independently associated with HOMA-IR ($p = 0.002$), HDL ($p = 0.042$), and TG levels ($p = 0.006$).

The clinical significance of these findings needs to be determined in prospective studies.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Взаємозв'язок між рівнем тиреотропного гормону, інсулінорезистентністю та серцево-судинними факторами ризику в пацієнтів з ожирінням та субклінічним гіпотиреозом

Резюме. *Актуальність.* Епідемія надмірної ваги та ожиріння розглядається як головний виклик системі охорони здоров'я і потребує проведення профілактики. Взаємозв'язок між функціональним станом щитоподібної залози, масою тіла та гомеостазом жирової тканини перебуває в центрі уваги декількох досліджень протягом останніх років, але причинно-наслідковий зв'язок між цими параметрами чітко не встановлений. **Мета:** дослідити взаємозв'язок між вмістом тиреотропно-

го гормону (ТТГ), інсулінорезистентністю (ІР) та факторами серцево-судинного ризику у вибірці людей із ожирінням та субклінічним гіпотиреозом. **Матеріали та методи.** Проведено ретроспективний аналіз 145 осіб з ожирінням. Проаналізовано рівні ТТГ та вільного тироксину (вТ₄), антропометричні показники та результати лабораторних досліджень. **Результати.** У 23 осіб рівень ТТГ перевищував нормальний рівень (субклінічний гіпотиреоз). Обвід талії (ОТ) у цих осіб

був вірогідно вищим, ніж в осіб у стані еутиреозу. Рівень ТТГ у сироватці крові позитивно корелював з індексом НОМА-IR, вмістом тригліцеридів та ліпопротеїнів високої щільності (ЛПВЩ). З використанням ТТГ та індексу маси тіла як незалежних змінних було показано, що рівні ТТГ незалежно пов'язані з НОМА-IR ($p = 0,002$) та вмістом тригліцеридів ($p = 0,006$). Серед еутиреоїдних пацієнтів в осіб зі значеннями ТТГ $< 2,5$ мМО/мл спостерігалися статистично значуще

зниження співвідношення ОТ і обводу стегон, рівня ЛПВЩ та показників НОМА-IR, а також тенденція до зниження значень ОТ. **Висновки.** Субклінічний гіпотиреоз у людей з ожирінням асоціюється зі збільшенням маси висцерального жиру. У цій вибірці людей з ожирінням рівні ТТГ вірогідно пов'язані з наявністю інсулінорезистентності.

Ключові слова: субклінічний гіпотиреоз; ожиріння; серцево-судинні фактори ризику

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Взаимосвязь между уровнем тиреотропного гормона, инсулинорезистентностью и сердечно-сосудистыми факторами риска у пациентов с ожирением и субклиническим гипотиреозом

Резюме. Актуальность. Эпидемия избыточного веса и ожирения представляет собой серьезную проблему для системы здравоохранения во всем мире и требует проведения профилактических мероприятий. Предполагаемые взаимосвязи между гормонами щитовидной железы, массой тела и гомеостазом жировой ткани находятся в центре внимания нескольких исследований в последние годы, однако причинно-следственные связи между этими параметрами четко не установлены. **Цель:** изучить взаимосвязь между уровнем тиреотропного гормона (ТТГ), инсулинорезистентностью (ИР) и факторами риска сердечно-сосудистых заболеваний в выборке лиц с ожирением и субклиническим гипотиреозом. **Материалы и методы.** Проведен ретроспективный продольный анализ 145 лиц с ожирением. Проанализированы уровни ТТГ и свободного тироксина (свТ₄), антропометрические измерения и результаты лабораторных тестов. **Результаты.** У 23 человек уровень ТТГ был выше нормы (субклинический гипотиреоз). Окружность талии (ОТ) у

них была достоверно выше, чем у людей в состоянии эутиреоза. Уровень ТТГ в сыворотке положительно коррелировал с индексом инсулинорезистентности (НОМА-IR), содержанием триглицеридов и холестерина липопротеинов высокой плотности (ЛПВП). С использованием ТТГ и индекса массы тела в качестве независимых переменных было показано, что уровни ТТГ независимо связаны с НОМА-IR ($p = 0,002$) и содержанием триглицеридов ($p = 0,006$). Среди эутиреоидных пациентов лица со значениями ТТГ $< 2,5$ мМЕ/мл демонстрировали статистически значимое снижение соотношения ОТ и охвата бедер, уровня ЛПВП и показателей НОМА-IR, а также тенденцию к более низким значениям ОТ. **Выводы.** Субклинический гипотиреоз у людей с ожирением связан с избыточным наличием висцеральной жировой ткани. В настоящей выборке людей с ожирением уровни ТТГ связаны с инсулинорезистентностью.

Ключевые слова: субклинический гипотиреоз; ожирение; факторы риска сердечно-сосудистых заболеваний