Associations between metabolic syndrome, serum thyrotropin, and thyroid antibodies status in postmenopausal women, and the role of interleukin-6

Powiązania między zespołem metabolicznym, subkliniczną niedoczynnością i autoimmunologicznym zapaleniem tarczycy u kobiet po menopauzie oraz rola interleukiny-6

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Abstract

Introduction: The prevalence of metabolic syndrome increases after menopause; however, the role of concomitant subclinical hypothyroidism has not been completely elucidated. The aim of the study was to identify associations between thyrotropin, immune status, inflammation, and metabolic syndrome in postmenopausal women.

The specific goals were: to assess thyrotropin (TSH) and interleukin-6 (IL-6) concentrations in the serum of subclinical hypothyroid postmenopausal women with and without metabolic syndrome and compare them with euthyroid controls; to test whether immune status is related to metabolic syndrome in postmenopausal women and determine the role of IL-6; to examine the relationships between TSH and different features of metabolic syndrome: insulin resistance, waist circumferences, waist-to-hip ratio (WHR), BMI, metabolic parameters (triglycerides, total cholesterol and high-density lipoprotein cholesterol), and inflammatory cytokines (IL-6).

Material and methods: Three hundred and seventy-two postmenopausal women were included in the study: 114 women had subclinical hypothyroidism (10.0 uIU/mL > TSH ≥ 4.5 uIU/mL, normal fT4), and 258 women were in euthyreosis (TSH 0.35–4.5 uIU/mL, normal fT4); both groups were matched by age. Anthropometric measurements were conducted (BMI, waist circumference, WHR) and blood pressure was measured. In all subjects the following were assessed in serum: lipid profile, glucose, insulin, TSH, fT4, thyroid antibodies (T-Abs) — TPO-Abs, TG-Abs, and IL-6 concentrations.

Results: The prevalence of metabolic syndrome was 49.12% in subclinical hypothyroid women and 46.89% in euthyroid women. However, the proportion of subjects with one or two abnormalities was significantly higher in the subclinical hypothyroid group (45.61%) than in the euthyroid group (32.17%). When we compared subclinical hypothyroid women with and without metabolic syndrome, subjects with metabolic syndrome had higher BMI, abdominal circumferences, WHR, and HOMA-I. They presented higher systolic and diastolic blood pressure. Serum concentrations of cholesterol, triglycerides, fasting glucose, IL-6, TSH, T-Abs were also higher and serum cHDL was lower. There were no significant differences in fT4 concentrations. A similar comparison was made for euthyroid women with and without metabolic syndrome. Higher BMI, waist circumference, WHR, HOMA-I, and systolic blood pressure were observed in subjects with metabolic syndrome. Serum concentrations of TSH, triglycerides, glucose, and IL-6 were also higher, but the concentration of cHDL was significantly lower. There were no significant differences in fT4, T-Abs, cholesterol levels, and diastolic pressure.

When we compared euthyroid women T-Abs (+) and T-Abs (–), the prevalence of metabolic syndrome was similar (48.68% *vs.* 46.15%). There were no differences in BMI, waist circumference, WHR, lipid profile, glucose, and HOMA-I, fT4. However, thyroid autoimmunity was associated with elevated TSH and IL-6 levels. When we analysed subclinical hypothyroid women with and without thyroid autoimmunity, there were no significant differences in glucose and lipid profile. However, Hashimoto`s subjects were more obese, had higher waist circumference, WHR, HOMA-I, and higher prevalence of metabolic syndrome. Serum concentrations of TSH and IL-6 were also higher and fT4 was lower.

Among all of the women, serum TSH concentration was significantly correlated with BMI, waist circumference, WHR, systolic blood pressure, cholesterol, triglycerides, and TPO-Abs. When the variables of subjects with upper quartile of TSH were compared with lower quartile of TSH, we found significantly higher BMI, waist circumference, WHR, increased concentration of IL-6, cholesterol, triglycerides, and T-Abs, and concentrations of cHDL and fT4 were lower. OR for metabolic syndrome in subjects with upper quartile TSH *vs.* lower quartile was 1.35 (95% confidence interval [CI] 1.10–1.60).

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Conclusions:

1. Our study confirms that metabolic syndrome in both euthyroid and subclinical hypothyroid women is connected with obesity, visceral fat accumulation, and higher TSH and IL-6 concentrations.
2. Immune thyroiditis is associated with higher TSH and IL-6 levels. Obese subclinical hypothyroid women with Hashimoto`s thyroditis have a higher prevalence of metabolic syndrome when compared with subclinical hypothyroid women without thyroid autoimmunity.
3. It is possible that in the crosstalking between subclinical hypothyroidism and metabolic syndrome, enhanced proinflammatory cytokine release in the course of immunological thyroiditis plays a role.

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Key words: metabolic syndrome; subclinical hypothyroidism; autoimmune thyroiditis; interleukin-6

Streszczenie

Wstęp: Nie jest do końca poznana rola subklinicznej niedoczynności tarczycy w patogenezie zespołu metabolicznego u kobiet po menopauzie. Celem pracy jest ocena powiązań pomiędzy zespołem metabolicznym, stanem tyreometabolicznym, autoimmunologicznym zapaleniem tarczycy i stanem zapalnym u kobiet po menopauzie.

Szczegółowe cele pracy to: ocena stężenia TSH, interleukiny-6 (IL-6) u kobiet po menopauzie z subkliniczną niedoczynnością tarczycy, z zespołem i bez zespołu metabolicznego oraz porównanie z grupą kontrolną w eutyreozie; określenie czy immunologiczne zapalenie tarczycy ma wpływ na rozwój zespołu metabolicznego oraz określenie roli IL-6; sprawdzenie zależności między TSH i składowymi zespołu metabolicznego: opornością insulinową, parametrami antropometrycznymi, metabolicznymi i cytokinami zapalnymi (IL-6).

Materiał i metody: Do badania włączono 372 kobiety po menopauzie: 114 kobiet z rozpoznaną subkliniczną niedoczynnością tarczycy (10,0 uIU/ml > TSH ≥ 4,5 uIU/ml, przy prawidłowym fT4) i 258 kobiet z eutyreozą (TSH 0,35–4,5 uIU/ml, prawidłowe fT4). Grupy nie różniły się wiekowo. Przeprowadzono pomiary antropometryczne (BMI, obwód w talii, WHR) oraz ciśnienia tętniczego. U wszystkich badanych oceniano we krwi: profil lipidowy, stężenie glukozy, insuliny, TSH, fT4, przeciwciał tarczycowych — TPO-Ab, TG-Ab oraz IL-6.

Wyniki: Częstość występowania zespołu metabolicznego wynosiła 49,12% u kobiet z subkliniczną niedoczynnością tarczycy i 46,89% u kobiet w eutyreozie. Jednakże w grupie z subkliniczną niedoczynnością, w porównaniu do kobiet w eutyreozie, u większego odsetka rozpoznano jedną lub też dwie składowe zespołu metabolicznego (45,61% *vs.* 32,17%). Gdy kobiety z subkliniczną niedoczynnością i zespołem metabolicznym porównano z kobietami bez zespołu, stwierdzono wyższe BMI, obwód w talii, WHR, HOMA-I, wyższe ciśnienie tętnicze skurczowe i rozkurczowe, wyższe stężenie cholesterolu, triglicerydów, glukozy, IL-6, TSH, przeciwciał przeciwtarczycowych i niższe stężenie cholesterolu frakcji HDL. Nie obserwowano różnic w stężeniu fT4. Gdy tą samą analizę przeprowadzono u kobiet w eutyreozie, również stwierdzono u osób z zespołem metabolicznym wyższe: BMI, obwód w talii, WHR, HOMA-I i skurczowe ciśnienie tętnicze. Stężenia TSH, triglicerydów, glukozy, IL-6 były znamiennie wyższe, a cholesterolu frakcji HDL niższe. Nie było różnic w stężeniu fT4, przeciwciał przeciwtarczycowych, cholesterolu i ciśnieniu rozkurczowym.

Gdy porównano kobiety w eutyreozie z immunologicznym zapaleniem i bez zapalenia, częstość występowania zespołu metabolicznego była podobna (48,68% *vs.* 46,15%). Nie było różnic w BMI, obwodzie talii, WHR, profilu lipidowym, glukozie, HOMA-I, fT4. Jednakże w przewlekłym zapaleniu tarczycy obserwowano podwyższone stężenia TSH i IL-6. Gdy analizowano kobiety z subkliniczną niedoczynnością oraz bez autoimmunologicznego zapalenia, nie stwierdzono różnic w stężeniu glukozy i profilu lipidowym. Jednakże kobiety z chorobą Hashimoto miały wyższe BMI, trzewne gromadzenie tkanki tłuszczowej, wyższy HOMA-I oraz częściej występował u nich zespół metaboliczny. Stężenie TSH, IL-6 były wyższe, a fT4 niższe.

Wśród wszystkich badanych kobiet stężenie TSH dodatnio korelowało z BMI, obwodem talii, WHR, ciśnieniem skurczowym, cholesterolem, triglicerydami, TPO-Ab. Gdy porównano analizowane parametry u kobiet z górnego i dolnego kwartyla TSH, stwierdzono wyższe BMI, obwód w talii, WHR, podwyższone stężenie IL-6, cholesterolu, triglicerydów i przeciwciał przeciwtarczycowych, natomiast stężenie cholesterolu frakcji HDL i fT4 było niższe. Iloraz szans (OR) wystąpienia zespołu metabolicznego u kobiet z TSH > 4,68 uIU/ml w porównaniu z osobami z TSH < 1,82 uIU/ml wynosiło 1,35.

Wnioski:

1. Zespół metaboliczny zarówno u kobiet w eutyreozie, jak i z subkliniczną niedoczynością, jest powiązany z otyłością, trzewnym gromadzeniem tkanki tłuszczowej oraz wyższym stężeniem TSH i IL-6.
2. W autoimmunologicznym zapaleniu tarczycy stężenia TSH i IL-6 są podwyższone.
3. Otyłe kobiety z subkliniczną niedoczynnością tarczycy w przebiegu choroby Hashimoto są bardziej narażone na ryzyko rozwoju zespołu metabolicznego.
4. Ogniwem łączącym subkliniczną niedoczynność tarczycy i zespół metaboliczny mogą być cytokiny zapalne.

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Słowa kluczowe: zespół metaboliczny; subkliniczna niedoczynność; autoimmunologiczne zapalenie tarczycy; interleukina-6

Introduction

The development of metabolic syndrome significantly increases in women after menopause. All its components including abdominal obesity, abnormal lipids, insulin resistance, and hypertension are the result mainly of ovarian failure. However, with age, increasing incidence of overt and subclinical hypothyroidism is observed, and this dysfunction also promotes weight gain, lipid disturbances, hypertension, and atherosclerosis. Metabolic changes in hypothyroidism are analogous to those observed in metabolic syndrome. The associations between overt hypothyroidism and metabolic syndrome are well described, but it remains controversial whether subclinical hypothyroidism also leads to higher cardiovascular risk and metabolic syndrome. The results of studies examining these connections are contradictory. A series of studies reported that subclinical hypothyroidism is associated with abnormal serum lipids, higher blood pressure, and markers of systemic inflammation [1, 2]. However, few studies have excluded the potential influence of subclinical hypothyroidism on metabolic syndrome [3].

The most common cause of hypothyroidism is autoimmune thyroiditis (AIT), a condition associated

with the infiltration of thyroid by lymphocytes and other immune cells. This may result in the development of thyroid dysfunction; however, the progression towards overt hypothyroidism is usually a gradual process, taking several years. In the early stage, thyroid stimulating hormone (TSH) levels may be within the reference range, and in the evolution from normal to abnormal thyroid function subclinical hypothyroidism may develop [4]. It is suggested that AIT is connected with higher cardiovascular risk independent of thyroid function. Chronic inflammation and endothelial dysfunction could be a link. Different cytokines and adhesion molecules are involved in the pathogenesis of AIT, working in both the immune system and the thyroid gland. They are known to modify epithelium integrity and allow the infiltration of thyroid by T cells and other immune cells. Interleukin-6 (IL-6) has been identified as one of the markers of systematic inflammation. Some researchers have found increased serum concentrations of IL-6 in Hashimoto`s thyroiditis [5, 6].

Because postmenopausal women with metabolic syndrome displayed higher serum IL-6 concentrations [7], we decided to investigate the relationships between IL-6, metabolic syndrome, AIT, and subclinical hypothyroidism. There are few studies regarding the prevalence of metabolic syndrome in postmenopausal women with subclinical hypothyroidism in the Polish population, and they do not explain whether thyroid failure and AIT have independent effects on metabolic syndrome in this population. Therefore, we undertook the present study to determine the association between thyroid function, autoantibodies to thyroid-specific antigens, and metabolic syndrome in Polish postmenopausal women. The study was conducted in the Silesian region.

The specific goals were:
— to assess TSH and IL-6 concentrations in the serum of subclinical hypothyroid postmenopausal women with and without metabolic syndrome and compare them with euthyroid controls;
— to test whether immune status is related to metabolic syndrome in postmenopausal women and determine the role of IL-6;
— to examine the relationships between TSH and different features of metabolic syndrome: insulin resistance, waist circumferences, waist-to-hip ratio (WHR), BMI, metabolic parameters (triglycerides, total cholesterol, and high density lipoprotein cholesterol), and inflammatory cytokines (IL-6).

Material and methods

Three hundred and seventy-two postmenopausal women were included into the study: 114 women had subclinical hypothyroidism and 258 women were in euthyreosis, both

groups were matched by age. We included women recruited from endocrinological and cardiological outpatient clinics, with age at least 55 years or without natural menses for at least five years. All the subjects who participated in the study gave their agreement in the written form. The study was approved by the Ethical Review.

The group of subclinical hypothyroidism included women with elevated serum TSH concentration above 4.5 uIU/mL but lower than 10 mIU/mL, whereas serum free thyroxine (fT4) was normal. At the moment of inclusion into the study no treatment of subclinical hypothyroidism was started. The mean age was 59.18 years (SD 5.64). The euthyroid group included participants with mean age 58.93 years (SD 5.78). The euthyroid status was confirmed by normal TSH (0.35–4.5 uIU/mL) and normal fT4.

Exclusion criteria of both groups were: diagnosis of coronary artery disease, diabetes mellitus, heart, renal, or liver failure. Women taking thyroxine, amiodarone, lipid-lowering, and antidiabetes drugs were excluded from the study. In all subjects medical history was evaluated, physical examination was performed, and blood pressure was measured. Anthropometric measurements were conducted. BMI was calculated as the ratio of weight to the square of height, and WHR was calculated by division of the circumferences of waist and hip. Blood samples were obtained in fasting condition and after centrifuging the serum were stored at $-70°C$ until assay. In all subjects lipid profile (total cholesterol, HDL cholesterol, triglycerides) and glucose concentrations were assessed using enzymatic method. Serum insulin, TSH, fT4, thyroid autoantibodies, and IL-6 were determined by ELISA methods using commercial assays. AIT was defined as the presence of elevation of at least one of the antithyroid antibodies (T-Abs) — thyreoperoxidase antibodies (TPO-Abs), thyroglobulin antibodies (TG-Abs), and the presence of typical thyroid sonography (heterogenous echotexture or hypoechogenicity). The homeostatic model assessment (HOMA) index was calculated (HOMA-IR = fasting serum glucose (mg/dL)/18.1 × fasting insulin levels (uIU/mL)/22.5). The diagnosis of metabolic syndrome was performed using the AHA/NHLBI criteria (it was defined as the presence of three or more of the following: waist circumference ≥ 88 cm, serum triglycerides ≥ 1.7 mmol/L, serum cHDL < 1.3 mmol/L, fasting glucose ≥ 5.6 mmol/L, elevated blood pressure $\geq 130/85$ mm Hg). Data were tested for normal distribution using W Shapiro-Wilk test. Results were given as mean and SD for normally distributed data or median plus (25th, 75th) percentiles for non-normal distribution. Groups were compared by Student`s test or U Manna-Whitney test. Correlations between variables were estimated by calculating the correlation coefficient R by Pearson`s method or Spearman`s method.

Table I. *Clinical and biochemical characteristics of subclinical hypothyroid and euthyroid postmenopausal women*

Tabela I. *Porównanie klinicznych i biochemicznych cech wśród kobiet po menopauzie z subkliniczną niedoczynnością tarczycy i eutyreozą*

	Euthyroid wome (n = 258)	Subclinical hypothyroid women (n = 114)	p
Age	58.93 ± 5.78	59.18 ± 5.64	NS
BMI [kg/m²]	28.77 ± 5.01	29.61 ± 5.07	0.10
Waist circumference [cm]	93.36 ± 12.41	95.76 ± 12.89	< 0.05
WHR	0.86 ± 0.06	0.87 ± 0.07	< 0.05
Cholesterol [mmol/L]	6.06 ± 1.20	6.35 ± 0.99	< 0.01
cHDL [mmol/L]	1.35 ± 0.37	1.30 ± 0.38	NS
Triglycerides [mmol/L]	1.63 ± 0.84	1.74 ± 0.80	< 0.05
Glucose [mg/dL]	90.80 ± 19.42	86.91 ± 14.88	NS
HOMA-IR	1.03 [0.64; 1.87]	1.10 [0.60; 2.12]	NS
IL-6 [pg/mL]	3.0 [2.37; 3.91]	2.95 [2.17; 4.25]	NS
TSH [mIU/mL]	2.15 ± 0.86	5.45 ± 0.90	< 0.001
fT4 [ng/dL]	1.32 ± 0.66 [1.22]	1.14 ± 0.58 [1.18]	< 0.01
TPOAb [IU/mL]	6.03 [2.36; 46.40]	65.29 [7.63; 145.0]	< 0.001
TGAb [IU/mL]	20.22 [16.35, 27.04]	53.86 [42.29, 156.04]	< 0.01
Systolic blood pressure [mm Hg]	128.48 ± 25.51	138.74 ± 34.29	< 0.01
Diastolic blood pressure [mm Hg]	80.56 ± 18.62	86.81 ± 22.92	< 0.05

Normally distributed data are given as mean ± SD, skewed data are given as median plus [25th, 75th] percentiles. The significance tests are the Mann-Whitney U test for normally distributed variables and unpaired t test for normally distributed variables.

Univariable logistic regression model (odds ratio, OR) was used to evaluate the association between metabolic syndrome and different metabolic and inflammatory variables. ANOVA trend analysis was used to evaluate means of metabolic and inflammatory factors according quartiles of TSH. The prevalence of metabolic syndrome and its components were compared using chi-squared test. Statistical analysis was performed using Statistica version 10, StatSoft Inc.

Results

In the first part of the study we analysed the data from all 372 postmenopausal women according to the thyroid status (hypothyroid, euthyroid). The characteristics of the subjects are summarised in Table I. The mean age of the postmenopausal subclinical hypothyroid subjects was approximately 59.18 ± 5.64 years and was similar to euthyroid women (58.93 ± 5.78 years). The mean BMI in subclinical hypothyroid group was 29.61 ± 5.07, being slightly higher in comparison to euthyroid women (28.77 ± 5.01), but the difference did not reach statistical difference (p = 0.10). However, waist circumference and WHR were significantly higher in the subclinical hypothyroid group, p < 0.05. As shown in Table I, the levels of total cholesterol, triglycerides, TSH, and T-Abs were higher and fT4 were lower in the subclinical hypothyroid group than in the euthyroid group. Mean systolic and diastolic blood pressures were higher in the subclinical hypothyroid group compared with the euthyroid group. Statistical analysis showed that there were no significant differences in glucose, HOMA-I, HDL cholesterol, and IL-6 concentrations between those groups.

In the next step we compared the frequencies of analysed risk factors among subclinical hypothyroid women and euthyroid women (Table II). Positive thyroid antibodies were detected in 73 (64.03%) subclinical hypothyroid postmenopausal women and in 76 (29.46%) euthyroid women. The prevalence of having at least three MS diagnostic criteria were met in 121 (46.89%) euthyroid and in 56 (49.12%) subclinical hypothyroid women, respectively, p = NS.

The proportion of subjects with one or two abnormalities was significantly higher in the subclinical hypothyroid group (45.61%) than in the euthyroid group (32.17%). The prevalence of subjects without risk factors was significantly higher in euthyroid women (20.93%) when compared with the subclinical hypothyroid group (5.26%) (Table II).

Assessment of analysed variables in euthyroid and subclinical hypothyroid women with and without metabolic syndrome

Then we compared subclinical hypothyroid women with and without metabolic syndrome (Table III).

Table II. *Comparison of risk factor frequencies in euthyroid and subclinical hypothyroid postmenopausal women*

Tabela II. *Porównanie częstości występowania czynnika ryzyka wśród kobiet po menopauzie w eutyreozie i z subkliniczną niedoczynnością tarczycy*

	Euthyroid women (n = 258)	Subclinical hypothyroid women (n = 114)	p
Without risk factors, n (%)	54 (20.93%)	6 (5.26%)	< 0.001
One or two risk factors, n (%)	83 (32.17%)	52 (45.61%)	< 0.01
Three or more risk factors = metabolic syndrome, n (%)	121 (46.89%)	56 (49.12%)	NS
antiTPO and/or antiTGAb positivity, n (%)	76 (29.46%)	73 (64.03%)	< 0.001

Table III. *Comparison of clinical and biochemical characteristics of euthyroid and subclinical hypothyroid postmenopausal women with and without metabolic syndrome*

Tabela III. *Porównanie klinicznych i biochemicznych cech wśród kobiet po menopauzie w eutyreozie i z subkliniczną niedoczynnością tarczycy z i bez zespołu metabolicznego*

	Euthyroid women (n = 258)			Subclinical hypothyroid women (n = 114)		
	Nonmetabolic women (n = 137)	Women with metabolic syndrome (n = 121)	p	Nonmetabolic women (n = 58)	Women with metabolic syndrome (n = 56)	p
BMI [kg/m²]	26.81 ± 4.5	30.99 ± 4.6	< 0.001	27.34 ± 3.88	31.95 ± 5.12	< 0.001
Waist circumference [cm]	88.1 ± 12.16	99.28 ± 9.7	< 0.001	89.33 ± 10.21	102.45 ± 12.02	< 0.001
WHR	0.83 ± 0.05	0.88 ± 0.05	< 0.001	0.84 ± 0.06	0.90 ± 0.06	< 0.001
Cholesterol [mmol/L]	5.99 ± 1.11	6.13 ± 1.30	NS	6.08 ± 0.77	6.63 ± 1.12	< 0.01
Cholesterol HDL [mmol/L]	1.52 ± 0.35	1.15 ± 0.29	< 0.001	1.47 ± 0.33	1.13 ± 0.35	< 0.001
Triglycerides [mmol/L]	1.26 ± 0.54	2.03 ± 0.93	< 0.001	1.32 ± 0.42	2.17 ± 0.86	< 0.001
Glucose [mg/dL]	84.72 ± 11.13	97.87 ± 23.93	< 0.001	81.64 ± 12.52	92.37 ± 15.26	< 0.001
HOMA-IR	0.79 [0.54; 1.14]	1.72 [0.94; 2.91]	< 0.001	0.67 [0.46; 1.11]	1.88 [1.08; 3.28]	< 0.001
IL-6 [pg/mL]	2.85 [2.17; 3.36]	3.15 [2.66; 4.50]	< 0.01	2.55 [2.04; 2.97]	3.69 [2.63; 5.01]	< 0.001
TSH [mIU/mL]	2.01 ± 0.77	2.38 ± 0.95	< 0.01	5.21 ± 0.74	5.68 ± 0.97	< 0.01
fT4 [ng/dL]	1.37 ± 0.59	1.32 ± 0.66	NS	1.14 ± 0.58	1.19 ± 0.68	NS
TPOAb [IU/mL]	5.65 [2.11; 46.58]	6.57 [2.47; 34.7]	NS	12.24 [2.01; 108.2]	125.84 [18.89; 191.69]	< 0.001
TGAb [IU/mL]	18.15 [12.79; 35.2]	20.22 [16.35; 27.04]	NS	42.75 [13.64; 56.04]	79.46 [27.34; 146.79]	< 0.01
Systolic blood pressure [mm Hg]	124.52 ± 26.74	131.17 ± 29.53	< 0.01	130.31 ± 20.86	139.55 ± 38.34	< 0.01
Diastolic blood pressure [mm Hg]	80.64 ± 13.70	82.44 ± 18.07	NS	85.44 ± 17.38	88.46 ± 18.97	< 0.01

Normally distributed data are given as mean ± SD, skewed data are given as median plus [25th, 75th] percentiles. The significance tests are the Mann-Whitney U test for normally distributed variables and unpaired t test for normally distributed variables.

Women with metabolic syndrome had higher BMI, abdominal circumferences, WHR, and HOMA-I. They presented higher systolic and diastolic blood pressure. Serum concentrations of cholesterol, triglycerides, fasting glucose, IL-6, TSH, and T-Abs were also higher and serum cHDL was lower. There were no significant differences in fT4 concentrations. A similar comparison was made for euthyroid women with and without metabolic syndrome. Higher BMI, waist circumference, WHR, HOMA-I, and systolic blood pressure were observed in subjects with metabolic syndrome. Serum concentrations of TSH, triglycerides, glucose, and IL-6 were also higher, but the concentration of cHDL was significantly lower. There were no significant differen-

ces in fT4, T-Abs, cholesterol levels, and diastolic pressure (Table III).

Effect of thyroid autoimmunity

To assess the potential effects of immunological thyroiditis, we performed a subgroup analysis according to the presence or absence of thyroid antibodies, after separating postmenopausal patients, just as subclinical hypothyroid and euthyroid (Table IV). The proportion of subjects with T-Abs (+) was higher in the subclinical hypothyroid group than in the euthyroid group (57.89% *vs.* 29.46%). When we compared euthyroid women's T-Abs (+) and T-Abs (–), the prevalence of metabolic syndrome was similar (48.68% *vs.* 46.15%). There were

Table IV. *Comparison of clinical and biochemical characteristics of euthyroid and subclinical hypothyroid postmenopausal women according to the presence or absence of thyroid antibodies*

Tabela IV. *Porównanie klinicznych i biochemicznych cech wśród kobiet w eutyreozie i z subkliniczną niedoczynnością tarczycy w zależności od obecności lub braku przeciwciał tarczycowych*

	Euthyroid women (n = 258)			Subclinical hypothyroid women (n = 114)		
	T-Abs (–) n = 182 (70.54%)	T-Abs (+) n = 76 (29.46%)	p	T-Abs (–) n = 48 (42.11%)	T-Abs (+) n = 66 (57.89%)	p
BMI [kg/m²]	28.93 ± 5.14	28.37 ± 4.68	NS	28.90 ± 5.62	30.12 ± 4.61	< 0.01
Waist circumference [cm]	93.73 ± 12.81	92.47 ± 11.43	NS	92.90 ± 13.58	97.84 ± 12.04	< 0.05
WHR	0.86 ± 0.06	92.47 ± 11.43	NS	0.84 ± 0.06	0.89 ± 0.06	< 0.01
Cholesterol [mmol/L]	6.09 ± 1.25	5.97 ± 1.07	NS	6.20 ± 0.95	6.46 ± 1.02	NS
Cholesterol HDL [mmol/L]	1.35 ± 0.36	1.33 ± 0.39	NS	1.34 ± 0.38	1.27 ± 0.38	NS
Triglycerides [mmol/L]	1.65 ± 0.90	1.54 ± 0.67	NS	1.61 ± 0.71	1.83 ± 0.85	NS
Glucose [mg/dL]	91.11 ± 21.10	89.55 ± 14.65	NS	84.48 ± 11.82	88.68 ± 16.63	NS
HOMA-IR	1.037 [0.65; 1.80]	1.00 [0.63; 1.96]	NS	0.85 [0.49; 1.75]	1.37 [0.75; 2.80]	< 0.01
IL-6 [pg/mL]	2.89 [2.29; 3.4]	3.34 [2.69; 5.35]	< 0.01	2.63 [2.12; 3.57]	3.16 [2.36; 4.47]	< 0.01
TSH [mIU/mL]	2.01 ± 0.79	2.58 ± 0.95	< 0.01	5.08 ± 0.79	5.70 ± 0.87	<0.01
fT4 [ng/dL]	1.34 ± 0.60	1.30 ± 0.71	NS	1.19 ± 0.67	1.12 ± 0.50	< 0.05
Systolic blood pressure [mm Hg]	125.43 ± 18.28	128.64 ± 29.48	NS	128.54 ± 35.86	138.03 ± 33.46	< 0.01
Diastolic blood pressure [mm Hg]	82.53 ± 11.53	83.32 ± 18.47	NS	85.21 ± 10.64	88.48 ± 12.49	NS
Metabolic syndrome, n (%)	84 (46.15%)	37 (48.68%)	NS	17 (35.4%)	39 (59.1%)	< 0.05

Normally distributed data are given as mean ± SD, skewed data are given as median plus [25th, 75th] percentiles. The significance tests are the Mann-Whitney U test for normally distributed variables and unpaired t test for normally distributed variables.

no differences in BMI, waist circumference, WHR, lipid profile, glucose, HOMA-I, fT4, and systolic and diastolic blood pressure. However, thyroid autoimmunity was associated with elevated TSH and IL-6 levels. When we analysed subclinical hypothyroid women with and without thyroid autoimmunity, there were no significant differences in glucose and lipid profile. However, Hashimoto`s subjects were more obese and had higher waist circumference, WHR, systolic blood pressure, and HOMA-I. The prevalence of metabolic syndrome was higher in the T-Abs (+) group. Serum concentrations of TSH and IL-6 were higher and fT4 was lower in T-Abs (+).

Correlations of TSH with variables in all postmenopausal women

Among all of the women, serum TSH concentration was significantly correlated with BMI, waist circumference, WHR, systolic blood pressure, cholesterol, triglycerides, and TPO-Abs (Table V). No associations were found between TSH and TG-Abs, cHDL, HOMA-I, IL-6 concentrations, and diastolic blood pressure.

In the last part of study all subjects were divided for quartiles of TSH. Ninety-three women had TSH below of 1.82 uIU/mL (lower quartile) and 93 women had TSH higher than 4.68 uIU/mL (upper quartile) (Table VI). Variables of subjects with upper quartile of TSH were compared with variables of lower quartile and we found significantly higher BMI, waist circumference, WHR, and increased concentration of IL-6, cholesterol, triglycerides, and T-Abs. Concentrations of cHDL and fT4 were lower. Systolic and diastolic blood pressures were also higher. In the lowest quartile 32 women (34.41%) had metabolic syndrome; in the highest quartile — 48 women (51.61%). Then logistic regression analysis was performed to calculate the odds ratio (OR) for metabolic syndrome. OR for subjects with TSH > 4.68 uIU/mL was 1.35 (95% confidence interval [CI] 1.10–1.60).

Discussion

Postmenopausal women are predisposed to metabolic syndrome. The decline in ovarian function, weight gain, body fat redistribution, and insulin resistance are considered as the main causes of this phenomenon. The prevalence of metabolic syndrome in women after menopause varies in different analyses. In a study conducted in Italy [8], metabolic syndrome was detected among 27% of postmenopausal women, but in the Korean population the prevalence was 58% [9].

Table V. *Correlations of serum TSH with selected anthropometric and biochemical parameters in all women*

Tabela V. *Zależności między TSH i wybranymi antropometrycznymi i biochemicznymi parametrami wśród wszystkich badanych kobiet*

Variables	Coefficient R Spearman	p
BMI	0.19	< 0.001
Waist circumference	0.16	< 0.001
WHR	0.12	< 0.01
Systolic blood pressure	0.24	< 0.05
Cholesterol	0.21	< 0.001
Triglycerides	0.12	< 0.05
TPOAbs	0.31	< 0.001

Genetic profile, eating habits, age, and social economic status influence the frequency of this syndrome. In our study 47% of euthyroid and 49% of subclinical hypothyroid women had metabolic syndrome. This is a high incidence but it should be noted that the study was conducted in the Silesian region, which is an area with a growing percentage of obesity in recent years [10], and it was carried out at the endocrinology and cardiology outpatient clinics, not among a random population.

It remains unclear if thyroid subclinical dysfunction accelerates the development of metabolic syndrome and whether menopause per se has an effect on the thyroid function regardless of aging. It has been estimated that 5–23% of postmenopausal women develop subclinical hypothyroidism, and this frequency increases with age [11]. Woeber reported that subclinical hypothyroidism occurs in at least 10% of women after the age of 60 years [12]. A higher prevalence was found in the LAVOS study performed in Puerto Rico in 2003 among 399 postmenopausal women; in this study the occurrence of subjects with TSH > 5.5 mIU/mL was 24.2% [13]. In the PolSenior Study 7.95% of women over 55 years had elevated serum TSH and 23.9% had elevated thyroid antibodies [14].

An exact comparison of the occurrence of metabolic syndrome in subclinical hypothyroidism is difficult because different authors use dissimilar definitions of subclinical hypothyroidism. Some authors defined subclinical hypothyroidism when concentrations of TSH are higher than 3.6 uIU/mL [15], others when it was higher than 4.0 uIU/mL [16] or 4.5 uIU/mL [17], and still others when it was higher than 5.7 uIU/mL [18]. It has recently been discussed whether the upper TSH range should be set around 2.5 mIU/L [19].

The next problem is that there is special, individual set point for pituitary-thyroid axis function, and the reference ranges of TSH are altered with age. Most cross-sectional and longitudinal studies have shown an age-related shift of TSH secretion [20]. Moreover, there is a lack of harmonisation of TSH examinations, and different methods of assays give analyses variations of around 1 mU/L.

Previous studies of the associations between thyroid function and metabolic syndrome have given contradictory results. In a study conducted in Mexico there was no difference in the prevalence of metabolic syndrome between euthyroid and subclinical hypothyroid sub-

Table VI. *Clinical and biochemical parameters of postmenopausal women, grouped for quartiles of TSH (upper quartile vs. lower quartile)*

Tabela VI. *Kliniczne i biochemiczne parametry wśród kobiet po menopauzie w zależności od kwartyla TSH (górny kwartyl vs. dolny kwartyl)*

	Lower quartile TSH TSH < 1.82 uIU/mL (n = 93)	Upper quartile TSH TSH > 4.68 uIU/mL (n = 93)	p
BMI [kg/m^2]	27.55 ± 4.50	30.55 ± 5.07	< 0.001
Waist circumference [cm]	90.72 ± 11.45	97.48 ± 13.17	< 0.001
WHR	0.84 ± 0.06	0.87 ± 0.06	< 0.01
Cholesterol [mmol/L]	5.84 ± 1.13	6.43 ± 1.05	< 0.001
cHDL [mmol/L]	1.38 ± 0.38	1.26 ± 0.37	< 0.05
Triglycerides [mmol/L]	1.56 ± 0.81	1.78 ± 0.81	< 0.05
Glucose [mg/dL]	89.377 ± 16.49	87.48 ± 15.39	NS
HOMA-IR	0.90 [0.65; 1.64]	1.33 [0.61; 2.51]	NS
IL-6 [pg/mL]	2.85 [2.24; 3.33]	2.97 [2.23; 4.29]	< 0.05
fT4 [ng/dL]	1.32 ± 0.66	1.14 ± 0.58	< 0.01
TPOAb [IU/mL]	3.42 [1.41; 8.44]	100.93 [12.00; 185.51]	< 0.01
TGAb [IU/mL]	15.85 [11.36; 29.54]	47.21 [20.03; 148.02]	< 0.001

jects [3]. However, in a study by Kim et al. TSH in the upper normal range (2.5–4.5 mIU/L) was connected with a 1.7-fold increased risk of metabolic syndrome when compared with TSH in the lower normal range (0.3–2.5 mIU/L) [1]. A significant association between serum THS and metabolic syndrome was also observed in almost 1200 Dutch persons. Subjects with serum TSH higher than 2.28 mU/L had significantly increased risk of metabolic syndrome compared with subjects with serum TSH lower than 1.04 mU/L (OR = 1.68) [2].

In our study the prevalence of metabolic syndrome was 47% in euthyroid women and 49% in subclinical hypothyroid subjects, and the difference did not reach any statistical significance. It should be noted that we used the definition of subclinical hypothyroidism according to NHANES III, with the upper limit for normal TSH at 4.5 mIU/mL [17]. Although the mean BMIs in subclinical hypothyroid and in euthyroid women were comparable, waist circumference, WHR, and triglycerides were significantly higher in the subclinical hypothyroid group. Moreover, 45.61% of subclinical hypothyroid individuals displayed one or two analysed abnormalities, and this frequency was higher when compared with the euthyroid group (32.17%). Since the AHA/NHLBI definition of metabolic syndrome is based on the presence of three or more risk factors, women with one or two disturbances were not recognised as having metabolic syndrome, but their metabolic profile was worse.

We found that TSH levels in the metabolic syndrome was higher than in the nonmetabolic group, both in the euthyroid and subclinical hypothyroid groups. Individual analysis revealed that there is a tendency towards an increase in metabolic disturbance rates across the quartiles of TSH, and this trend was evident in the highest compared with lowest quartile of TSH. Postmenopausal women with a serum TSH above 4.68 uIU/mL had a higher risk of metabolic syndrome than women with serum TSH below 1.82 uIU/mL (odds ratio 1.35). However, individuals with the upper quartile of TSH had significanlty higher BMI, waist circumference, and WHR, worse metabolic parameters, and higher concentrations of serum IL-6. Because obesity is potentially a casual pathway between thyroid function and metabolic syndrome, we assessed relations between TSH, BMI, WHR, and waist circumference, and we found positive correlations. Among metabolic syndrome components, serum TSH positively correlated also with systolic blood pressure, cholesterol, triglycerides, and TPOAbs.

Our observation about a positive correlation between BMI and TSH is in agreement with results by other researchers [21]. The associations between BMI and TSH are complex and include neuroendocrine regulation, mainly through leptin-hypothalamic-pituitary axis and different processes in adipose tissue such as adipogenesis, and lipogenesis/lipolysis. Adipocytes secrete leptin, which influences neurons in the hypothalamus, regulates appetite and energy expenditure, as well as thyreotropic axis and TSH secretion. Thyroid hormones and leptin regulate energy balance, thermogenesis, and resting metabolic rate and have an impact on the autonomous nervous system. Moreover, thyroid hormones and leptin regulate feeding [22]. Recently, Betry et al. hypothesised that the increase in TSH observed in obese subjects is the result of fat accumulation [23]. Subclinical hypothyroidism is associated with lower basal metabolic rate and heat production, which can lead to weight gain. Moreover, decreased concentrations of thyroid hormones can lead to reduced synthesis of sex hormone binding globuline and to slower conversion of androgens to estrone. In the result, amounts of biologically available androgens increase and this could be associated with central adiposity, higher blood pressure, and higher rates of lipids and glucose disturbances.

In our study we observed a positive association between TSH and waist circumference, WHR, and serum triglycerides concentrations; this finding is in agreement with other studies [24]. It is suggested that TSH is involved in the lipid metabolism and promotes accumulation of fat in the intraabdominal region, which is expressed as increasing WHR and waist circumference. In subjects with higher TSH, different processes in adipose tissue such as adipogenesis, lipogenesis, and lipolysis could be perturbed. Thyrotropin stimulates adipogenesis by activation of preadipocyte differentiation, and increases adipocyte hypertrophy by triglycerides synthesis in mature adipocytes via TSHR expressed in adipose tissue [25]. This might explain the pathogenesis of accumulation of visceral adipose tissue mass in subclinical hypothyroid women. In an in vivo experiment, in a mouse model, mice with elevated TSH exhibited a 25% increase in adipose tissue when compared to control animals with normal TSH [26]. On the other hand, TSH activates hormone-sensitive lipase and lipolysis; therefore, elevated levels of TSH are connected with raising serum free fatty acids [27]. Increased serum FFA concentrations have been observed in subclinical hypothyroid patients and could lead to insulin resistance [28]. Moreover, TSH promotes hepatic lipogenesis, which in turn may cause the development of non-alcoholic fatty liver [29]. Felske et al. have shown that elevated TSH directly inhibits insulin-stimulated intracellular signaling in human adipocytes and insulin modulates TSH-stimulated lipolysis [30].

Controversy persists as to whether insulin resistance is developing in subclinical hypothyroidism, and the

data about this subject are inconsistent. Some studies demonstrated that subclinical hypothyroidis leads to insulin resistance [31, 32], but other studies did not observe this effect [33, 34]. The reason for the differences in the obtained results may be due to different durations and degrees of subclinical hypothyroidism. In our analysis we did not find relationships between subclinical hypothyroid status and HOMA index; however, the subgroup of subclinical hypothyroid women with Hashimoto`s disease was more insulin resistant than both the subgroup of subclinical hypothyroid women without thyroid antibodies and all euthyroid women. However, in our analysis, subclinical hypothyroid women positive for thyroid Abs were more obese and had higher waist circumference/WHR; therefore, our results did not make clear whether autoimmune thyroidits has an independent impact on insulin resistance.

We found positive relationships between TSH and TPOAbs in all studied women. In chronic thyroiditis the mean TSH was higher when compared with subjects without thyroid antibodies, regardless of thyroid function. Radetti et al. demonstrated that the elevation of TSH levels during follow-up and the progressive increase in thyroid autoantibodies were the strongest predictive factors of future development of thyroid failure in autoimmune thyroiditis patients [35]. The evolution from normal stage to hypothyroidism is a long process, which consequently, after years, provides to hypothyroidism. As expected, the prevalence of Hashimoto's thyroditis was higher in the subclinical hypothyroid group than in the euthyroid group.

When we investigated the associations between thyroid antibodies status and metabolic syndrome, we observed higher prevalence of metabolic syndrome in Hashimoto's thyroiditis with subclinical hypothyroidism ($p < 0.05$), but we could not find such associations in euthyroid subjects. Since in our analysis Hashimoto`s women with subclinical hypothyroidism had greater visceral fat accumulation, our results did not clarify whether autoimmune thyroidits has an autonomous impact on the development of metabolic syndrome, or whether metabolic syndrome is the consequence of overweight. It may be that elevated TSH, immunological processes, and higher BMI commonly increase the risk of metabolic syndrome. Probably a combination of different risk factors observed in obese postmenopausal women with subclinical hypothyroidism and autoimmune thyroiditis generally increase the probability of metabolic syndrome development. The results of various studies on cardiovascular and metabolic risk in Hashimoto's thyroiditis are inconsistent. An increased prevalence of metabolic syndrome in Hashimoto's thyroiditis was reported by Waring et al. [36]. Tamer et al. reported that thyroid immunity is associated with

worsened lipid profile [37]. However, in the analysis by LeGrys et al. there was no connection between the presence of thyroid antibodies and the risk of myocardial infarction [38]. In a large epidemiological study conducted among more than 38 thousand participants the risk of CHD mortality and CHD events did not differ according to the TPOAb status [39].

Autoimmune thyroidits is not only an organ-specific disease but it is also a systemic disease with enhanced proinflammatory cytokine release. We observed that postmenopausal women with antithyroid antibodies exhibit elevated serum IL-6 concentrations when compared to women without antibodies, regardless of thyroid function. Our findings are in agreement with those obtained by Taddei et al. [6]. IL-6 is produced by adipocytes and adipose-tissue macrophages. Elevated concentration of this cytokine is the marker of endothelial dysfunction, which is an early step in the development of atherosclerosis. Impaired endothelial function and reduced nitric oxide availability have been shown in subjects with thyroid antibodies. We also found that IL-6 concentrations are elevated in subjects with higher TSH, and our results are in agreement with several studies that have reported low-grade chronic inflammation in subclinical hypothyroidism. It has been shown that TSH upregulates IL-6 and MCP-1 mRNA expression and release from adipose tissue. Serum concentrations of proinflammatory cytokines such as IL-6 and MCP-1 have been found to be elevated in chronic thyroidits with mild hypothyroidism; therefore, higher levels of TSH could be pro-inflammatory stimuli of adipocytes [40]. It has been shown that elevated TSH through TSHR is expressed in microvascular endothelial cells and attenuates NO and prostacyclin release [41].

In this work we have found that relationships between subclinical hypothyroid dysfunction and metabolic syndrome include the associations with obesity and different metabolic disturbances. Subclinical hypothyroidism, especially in the course of chronic thyroiditis, is associated with weight gain, dyslipidaemia, and insulin resistance, and combination of multiple factors can increase the risk of metabolic syndrome.

Our study has the following limitation: a relatively small number of subclinical hypothyroid women without antithyroid antibodies. Another limitation is the known fact that elevated levels of antibodies against thyroid peroxidase and/or thyroglobulin are not present in all patients with chronic thyroiditis. Although thyroid antibodies provide the most specific laboratory evidence of immunological thyroiditis, their occurrence is not mandatory. The next restraint is that in our study the diagnosis of Hashimoto's thyroiditis was made by elevated TPOAb and/or TGAb concentrations. However, some endocrinologists consider TPOAb concentrations

more specific for thyroiditis than TGAb, and they assume that TGAb is unnecessary for diagnosis of AIT. Therefore, our conclusion about the effect of autoimmune thyroiditis on metabolic syndrome only in subclinical hypothyroid women appears to be limited, and further studies are necessary.

Conclusions

1. Our study confirms that metabolic syndrome in both euthyroid and subclinical hypothyroid women is connected with obesity, visceral fat accumulation, and higher TSH and IL-6 concentrations.
2. Immune thyroiditis is associated with higher TSH and IL-6 levels. Obese subclinical hypothyroid women with Hashimoto's thyroditis have a higher prevalence of metabolic syndrome compared with subclinical hypothyroid women without thyroid autoimmunity.
3. It is possible that in the crosstalking between subclinical hypothyroidism and metabolic syndrome, enhanced proinflammatory cytokine release in the course of immunological thyroiditis plays a role.

References

1. Kim BJ, Kim TY, Koh JM et al. Relationship between serum free T4 (FT4) levels and metabolic syndrome (MS) and its components in healthy euthyroid subjects. Clin Endocrinol 2009; 70: 152–160.
2. Heima NE, Eekhoff EM, Oosterwerff MM et al. Thyroid function and the metabolic syndrome in older persons: a population-based study. Eur J Endocrinol 2012; 168: 59–65.
3. Garduno-Garcia Jde J, Alvirde-Garcia U, Lopez-Carrasco G et al. TSH and free thyroxine concentrations are associated with different metabolic markers in euthyroid subjects. Eur J Endocrinol 2010; 163: 273–278.
4. Caturegli P, Kimura H, Rocchi R et al. Autoimmune thyroid diseases. Curr Opin Rheumatol 2007; 19: 44–48.
5. Bai X, Sun J, Wang W et al. Increased differentiation of Th22 cells in Hashimoto`s thyroiditis. Endocr J 2014; 61: 1181–1190.
6. Taddei S, Caraccio N, Virdis A et al. Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto`s thyroiditis. J Clin Endocrinol Metab 2006; 91: 5076–5082.
7. Chedraui P, Escobar G, Faustino R et al. Angiogenesis, inflammation and endothelial function in postmenopausal women screened for the metabolic syndrome. Maturitas 2014; 77: 370–374.
8. Magi L, Stramenga C, Morosini P. Prevalence of the metabolic syndrome among Italian adults. Findings from the SIMAP study. Recenti Prog Med 2005; 96: 280–283.
9. Kim HM, Park J, Ryu SY, Kim J. The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey 2001. Diabetes Care 2007, 30: 701–706.
10. Webber L, Halicka E, Marsh T et al. Projected incidence of overweight and obesity and related disease incidence across Poland. Centr Eur J Public Health 2014; 22: 17–23.
11. Schindler AE. Thyroid function and postmenopause. Gynecol Endocrinol 2003; 17: 79–85.
12. Woeber KA. Subclinical thyroid dysfunction. Arch Intern Med 1997; 157: 1065–1068.
13. Gonzalez-Rodriguez LA, Felici-Giovanini ME, Haddock L. Thyroid dysfunction in an adult female population: a population-based study of Latin American Vertebral Osteoporosis Study (LAVOS) – Puerto Rico site. PR Health Sci J 2013; 32: 57–62.
14. Thyroid dysfunction and thyroid autoimmunity in a large unselected population of elderly subjects in Poland — the PolSenior multicentre crossover study. Endokrynol Pol 2012; 63: 346–355.
15. Monzani F, Caraccio N, Kozakowa M et al. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo-controlled study. J Clin Endocrinol Metab 2004; 89: 2099–2106.
16. Krysiak R, Okopien B. The effect of levothyroxine and selenomethionine on lymphocyte and monocyte cytokine release in women with Hashimoto`s thyroiditis. J Clin Endocrinol Metab 2011; 96: 2206–2215.
17. Hollowell JG, Staehling NW, Flanders WD et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Jealth and Nutrition Examination Survey (NHANES III) 2002; 87: 489–499.
18. Effraimidis G, Strieder TG, Tijssen JG et al. Natural history of the transition from euthyroidism to overt autoimmune hypo- or hyperthyroidism: a prospective study. Eur J Endocrinol 2011; 164: 107–113.
19. Kratzsch J, Fiedler GM, Leichtle A et al. New reference intervals for thyrotropin and thyroid hormones based on National Academy of Clinical Biochemistry criteria and regular ultrasonography of the thyroid. Clin Chem 2005; 51: 1480–1486.
20. Bremner A, Feddema P, Leedman P et al. Age-related changes in thyroid function: a longitudinal study of a community-based cohort. J Clin Endocrinol Metab 2012; 97: 1554–1562.
21. Nymes A, Jorde R, Sundsfjord J. Serum TSH is positively associated with BMI. Int J Obes (Lond) 2006; 30: 100–105.
22. Lopez M, Alvarez CV, Nogueiras R et al. Energy balance regulation by thyroid hormones at central level. Trends Mol Med 2013; 19: 418–427.
23. Betry C, Challan-Belval M, Berbard A et al. Increased TSH in obesity: Evidence for a BMI-independent association with leptin. Diabetes Metab 2014. doi: 10.1016/j.diabet.2014.11.009.
24. Wanjia X, Chenggang W, Aihong W et al. A high normal TSH levels is associated with an atherogenic lipid profile in euthyroid non-smokers with newly diagnosed asymptomatic coronary heart disease. Lipids Health Dis 2012; 27: 44–51.
25. Lu S, Guan Q, Liu Y et al. Role of extrathyroidal TSHR expression in adipocyte differentiation and its association with obesity. Lipids Health Dis 2012; 27: 17–28.
26. Ma S, Jing F, Xu C et al. Thyrotropin and obesity: increased adipose triglyceride content through glycerol-3-phosphate acyltransferase 3. Sci Rep 2015; 5: 7633.
27. Gagnon A, Antunes TT, Ly T et al. TSH-stimulates lipolysis in adipocytes in culture and raises serum free fatty acid levels in vivo. Metabolism 2010; 59: 547–53.
28. Carracio N, Natali A, Sironi A et al. Muscle metabolism and exercise tolerance in subclinical hypothyroidism: a controlled trial of levothyroxine. J Clin Endocrinol Metab 2005; 90: 4057–4062.
29. Yan F, Wang Q, Lu M et al. Thyrotropin increases hepatic triglyceride content through upregulation of SREBP-1c activity. J Hepatol 2014; 61: 1358–1364.
30. Felske D, Gagnon A, Sorisky A. Interacting effects of TSH and insulin on human differentiated adipocytes. Horm Metab Res 2014. doi: 10.1055/2-0034-1395673.
31. Dessein PH, Joffe BI, Stanwix AE. Subclinical hypothyroidism is associated with insulin resistance in rheumatoid arthritis. Thyroid 2004; 14: 443–446.
32. Handosurya A, Pacini G, Tura A et al. Effects of thyroxine replacement therapy on glucose metabolism in subjects with subclinical and overt hypothyroidism. Clin Endocrinol 2008; 69: 963–969.
33. Tuzcu A, Bahceci M, Gokalp D et al. Subclinical hypothyroidism may be associated with elevated high-sensitive C-reactive protein (low grade inflammation) and fasting hyperinsulinemia. Endocr J 2005; 52: 89–94.
34. Kowalska I, Borawski J, Nikołajuk A et al. Insulin sensitivity, plasma adiponectin and sICAM-1 concentrations in patients with subclinical hypothyroidism: response to levothyroxine therapy. Endocrine 2011; 40: 95–101.
35. Radetti G, Maselli M, Buzi F et al. The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto`s thyroiditis and isolated hyperthyrotropinemia: a three year follow-up. Clin Endocrinol 2011. doi. 10.1111/j.1365-2265.2011.04251.
36. Waring AC, Rodondi N, Harrison S et al. Thyroid function and prevalent and incident metabolic syndrome in older adults: the Health, Ageing and Body Composition Study. Clin Endocrinol 2012; 76: 911–918.
37. Tamer G, Mert M, Tamer I et al. Effects of thyroid autoimmunity on abdominal obesity and hyperlipidaemia. Endokrynol Pol 2011; 62: 421–428.
38. LeGrys VA, Funk MJ, Lorenz CE et al. Subclinical hypothyroidism and risk for incident myocardial infarction among postmenopausal women. J Clin Endocrinol Metab 2013; 98: 2308–2317.
39. Collet TH, Bauer DC, Cappola A et al. Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis. J Clin Endocrinol Metab 2014; 99: 3353–3362.
40. Gagnon A, Langille M, Chaker S et al. TSH signaling pathways that regulate MCP-1 in human differentiated adipocytes. Metabolism 2014; 63: 812–821.
41. Tian L, Zhang L, Liu J et al. Effects of TSH on function of human umbilical vein endothelial cells. J Mol Endocrinol 2014; 52: 215–222.