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The effect of hypothyroidism occurring in patients with metabolic syndrome

Niedoczynność tarczycy u pacjentów z zespołem metabolicznym

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Abstract

Introduction: Metabolic syndrome involves abdominal obesity, arterial hypertension, type 2 diabetes and lipid disorders manifested as atherogenic dyslipidaemia. Abnormal thyroid function affects the severity of MetS components, since regulating metabolism is one of the most important functions of thyroid hormones. In this study, we present the influence of hypothyroidism on lipid and carbohydrate disorders in patients with MetS.

Material and methods: The described study was a prospective, two-centre screening study of 24-month duration. The study participants were 441 patients (350 women, 91 men, aged 28–82) with metabolic syndrome diagnosed according to the 2005 IDF.

Results: By comparing the study and the control group, statistically significant differences were observed in the mean triglyceride levels (respectively 161,5 *vs.* 134,8 mg/dL, p = 0.047), mean fasting glycaemia (respectively 111,8 *vs.* 126,1 mg/dL, p = 0.044) and TG/HDL ratio (4,74 *vs.* 3,71, p = 0.043).

Hypothyroidism shows a positive correlation with the TG levels and TG/HDL-C ratio and a negative correlation with the mean fasting glycaemia in people with MetS. A significantly higher TG/HDL-C ratio and lower mean insulin sensitivity ratio observed in men with hypothyroidism, indicated higher insulin resistance in men.

Conclusions: In view of the above, it may be hypothesized that in patients with both MetS and hypothyroidism, especially of male gender, the risk of death of cardiovascular causes is greater due to the severity of MetS components.

Moreover, we suggest that in patients recently diagnosed with MetS, active detection of hypothyroidism should be performed by determining the TSH levels, while patients diagnosed with hypothyroidism (apart from replacement therapy) should be monitored for the possible occurrence of MetS in the future. **(Endokrynol Pol 2015; 66 (4): 288–294)**

Key words: *metabolic syndrome; hypothyroidism; hyperinsulinemic euglycemic clamp*

Streszczenie

Wstęp: W skład zespołu metabolicznego wchodzą: otyłość brzuszna, nadciśnienie tętnicze, cukrzyca typu 2 oraz zaburzenia gospodarki lipidowej pod postacią aterogennej dyslipidemii. Nieprawidłowa funkcja tarczycy wpływa na poszczególne składowe zespołu metabolicznego, z uwagi na różne mechanizmy regulowanie metabolizmu przez hormony tarczycy.

W niniejszym badaniu przedstawiono wpływ niedoczynności tarczycy na zaburzenia gospodarki lipidowej i węglowodanowej u pacjentów z rozpoznanym zespołem metabolicznym.

Materiał i metody: Badanie prospektywne, 2-ośrodkowe z grupą badaną obserwowaną przez okres 24 miesięcy. Do badania włączono 441 pacjentów (350 kobiet oraz 91 mężczyzn w wieku 28–82 lata) z rozpoznanym na podstawie kryteriów IDF zespołem metabolicznym.

Wyniki: Porównując grupę badaną z grupą kontrolną stwierdzono istotne statystycznie różnice w poziomie TG (odpowiednio 161,5 *vs.* 134,8 mg/dl, p = 0,047), średnim poziomie glikemii na czczo (odpowiednio 111,8 *vs.* 126,1 mg/dl, p = 0,044) oraz współczynniku TG/HDL (4,74 *vs.* 3,71, p = 0,043).

Niedoczynność tarczycy występująca u pacjentów z zespołem metabolicznym wykazywała dodatnią korelację ze stężeniem TG oraz wskaźnikiem TG/HDL-C oraz ujemną korelację ze średnim poziomem glikemii na czczo. Istotnie wyższy wskaźnik TG/HDL-C, większa insulinooporność oraz niższy poziom wskaźnika insulinowrażliwości obserwowano głównie u mężczyzn z niedoczynnością tarczycy.

Wnioski: W świetle powyższych danych, hipotetycznie można założyć, że u pacjentów z niedoczynnością tarczycy oraz zespołem metabolicznym, szczególnie u mężczyzn, ryzyko zgonu z przyczyn sercowo-naczyniowych jest większe w zależności od występowania poszczególnych składowych zespołu metabolicznego.

Autorzy sugerują, aby u wszystkich pacjentów ze stwierdzonym zespołem metabolicznym oznaczyć stężenie TSH w celu wykluczenia ewentualnej niedoczynności tarczycy, która pogarsza rokowanie oraz pacjentów z rozpoznaną niedoczynnością tarczycy monitorować w kierunku wczesnego rozpoznania zespołu metabolicznego. **(Endokrynol Pol 2015; 66 (4): 288–294)**

Słowa kluczowe: *zespół metaboliczny; niedoczynność tarczycy; euglikemiczna klamra metaboliczna*

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Introduction

Metabolic syndrome (MetS) involves abdominal obesity, arterial hypertension, type 2 diabetes, and lipid disorders manifested as atherogenic dyslipidaemia (hypertriglyceridaemia and hypoHDLaemia) [1, 2].

MetS is an important social problem concerning a growing number of people. In different countries across Europe, its incidence is estimated at 17.4–28% [3, 4]; however, in the United States of America about 24% of males and 23.4% of females are affected [5]. The occurrence of metabolic syndrome has increased mainly because of abdominal obesity [6].

Abnormal thyroid function affects the severity of MetS components, since metabolism regulation is one of the most important functions of thyroid hormones [7]. In hypothyroidism, the basal metabolism rate is lower, the blood lipid profile is disturbed, and body mass and insulin resistance are increased [8].

In this study, we present the influence of hypothyroidism on lipid and carbohydrate disorders in patients with MetS.

Material and methods

The described study was a prospective, two-centre (University Hospital No. 1 in Bydgoszcz, District Hospital in Wąbrzezno, Poland) screening study of 24-month duration. The study participants were 441 patients (350 females [F], 91 males [M], aged 28–82 years) with metabolic syndrome diagnosed according to the 2005 IDF (International Diabetes Federation) criteria (meeting at least three criteria). The criteria are presented in Table I.

Anthropometric measurements (height, weight, and waist circumference) and blood pressure were measured in all subjects. Body mass index (BMI) was calculated as body weight (in kilograms) divided by the square of body height (in metres). Demographic factors (age, sex, obesity) were determined.

Fasting total plasma cholesterol (TC), triglycerides (TG), high-density-lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG) were determined in all patients. Low-density-lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Non-high-density-lipoprotein cholesterol (non-HDL-C) was figured on the base of the following formula: TC–HDL-C. The ratio of triglycerides to HDL-cholesterol (TG/HDL-C), as an indirect marker of insulin resistance, was also evaluated. Insulin resistance was measured with the use of a hyperinsulinaemic euglycaemic clamp [8], as the gold-standard method. Also the glucose assimilation ratio (M) — glucose infusion rate adjusted accordingly to glucose level changes in time — as an insulin resistance was measured.

Table I. *IDF criteria of metabolic syndrome*

Tabela I. *Kryteria zespołu metabolicznego według IDF*

Abdominal obesity [cm]	F ≥ 80, M ≥ 94
Arterial hypertension (HT) [mm Hg]	≥ 130/85 or treated for arterial hypertension
Triglycerides (TG) [mg/dL]	≥ 150 [1.7 mmol/L] or treated for dyslipidaemia
HDL-C [mg/dL]	< 50 [1.3 mmol/L] in women and < 40 [1.0 mmol/L] in men
Fasting glycaemia [mg/dL]	≥ 100 [5.6 mmol/L] or treated for diabetes

Table II. *The hormonal profile of the study group with hypothyreosis (mean value ± standard deviation)*

Tabela II. *Profil hormonalny badanej grupy z niedoczynnością tarczycy*

	TSH (0.27–4.2 mIU/L) ± SD	fT_4 (0.93–1.7 ng/dL) ± SD
Female n = 140	6.57 ± 1.26	0.68 ± 0.22
Male n = 37	6.24 ± 1.72	0.76 ± 0.14
Total n = 177	6.48 ± 1.43	0.71 ± 0.20

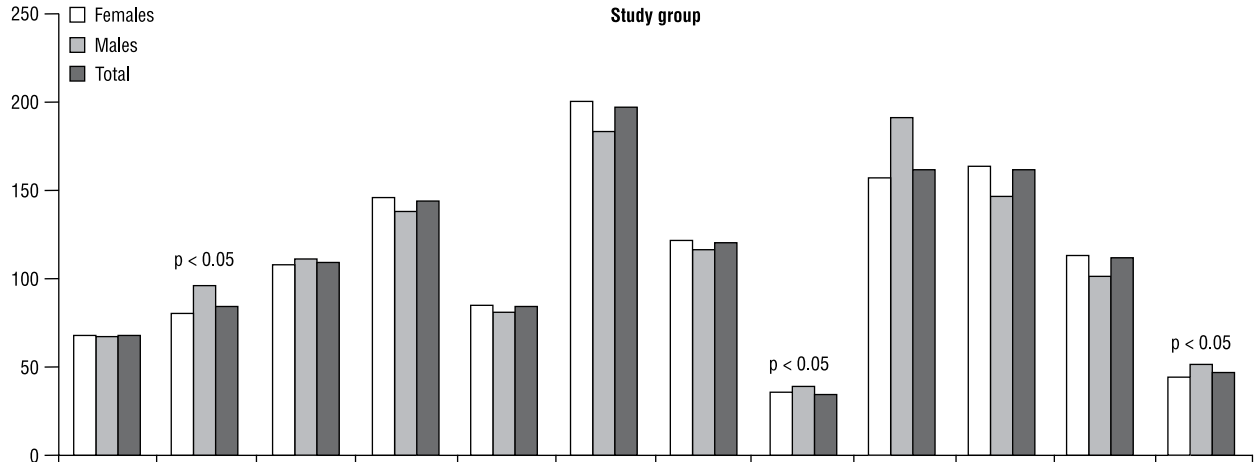
Exclusion criteria:

— a history of heart surgery or other cardiovascular interventions,
— congenital defects of the heart,
— cardiac rhythm disorders,
— pregnancy,
— chronic kidney disease,
— electrolyte disorders,
— inflammation,
— anaemia,
— prostate disease,
— Cushing's syndrome.

The group was divided into two subgroups: the study group with hypothyreosis (n = 177) and control group with euthyreosis (n = 264). The diagnosis of hypothyroidism was established on the basis of elevated level of TSH and decreased level of fT_4 in fasting venous blood taken on the day after admission. The hormonal profile of the study group is presented in Table II.

The study protocol was approved by the Ethics Committee at the University Hospital in Bydgoszcz. All subjects granted their informed consent for participation in the study.

All statistical analyses were performed using Statistica 10.0 software (Statsoft Poland, Bydgoszcz). The Mann-Whitney test, a nonparametric version of the Student's t-test for independent variables, was used for the compari-



	Age	Weight [kg]	WC [cm]	SYS [mm Hg]	DIA [mm Hg]	TC [mg/dL]	LDL [mg/dL]	HDL [mg/dL]	TG [mg/dL]	non-HDL [mg/dL]	Fasting glucose [mg/dL]	TG/HDL [mg/dL] × 10
Females	67,8	80,2	108,8	145,4	85,5	200,1	122,4	35,3	156,1	164,8	113,2	44,2
Males	66,9	95,7	111,4	138,8	81,2	183,2	116,2	37,5	191,1	145,7	101,8	50,9
Total	67,5	83,1	109,2	143,2	84,2	196,2	120,2	34,1	161,5	162,1	111,8	47,4

Figure 1. *Comparison of each parameter according to patient sex in patients with hypothyroidism*
Rycina 1. *Porównanie poszczególnych parametrów u pacjentów z niedoczynnością tarczycy w zależności od płci*

son. No parametric tests were used in the analyses because for some variables the assumptions of the Student's *t*-test regarding normal distribution and variance were not met. The value of Pearson's linear correlation coefficient was determined in the analysis. The results were considered as statistically significant at $p < 0.05$. The bilateral test was used to determine the significance of the differences between correlation coefficients.

Results

The characteristics of the study and control groups (age, sex, waist circumference, and other parameters) are presented in Figures 1 and 2.

In the study group, the levels of HDL-C in men were higher in a statistically significant manner than in women (37.5 *vs.* 35.3 mg/dL, $p = 0.032$). The remaining MetS parameters did not differ significantly between the two groups: mean waist circumference ($p = 0.762$), mean systolic (SYS), and diastolic (DIA) blood pressure – ($p = 0.102$ and $p = 0.108$), mean triglyceride levels ($p = 0.183$), and mean fasting glycaemia ($p = 0.446$).

Apart from the MetS components, statistically significant differences were observed in body mass (80.2 kg in women *vs.* 95.7 kg in men, $p = 0.046$) and the mean TG/HDL-C ratio (4.42 in women *vs.* 5.09 in men, $p = 0.033$).

In the control group the levels of HDL-C in men were lower in a statistically significant manner than in women (34.3 *vs.* 45.1 mg/dL, $p = 0.001$), similarly to the mean systolic pressure (135.8 *vs.* 148.8 mm Hg, $p = 0.013$). The remaining MetS parameters did not differ significantly between the two groups: mean waist circumference ($p = 0.908$), mean diastolic (DIA) blood pressure ($p = 0.128$), mean triglyceride levels ($p = 0.098$), and mean fasting glycaemia ($p = 0.824$).

Apart from the MetS components, statistically significant differences were observed in the mean TG/HDL-C ratio between women and men (3.08 *vs.* 6.14; $p = 0.0007$) (Fig. 3).

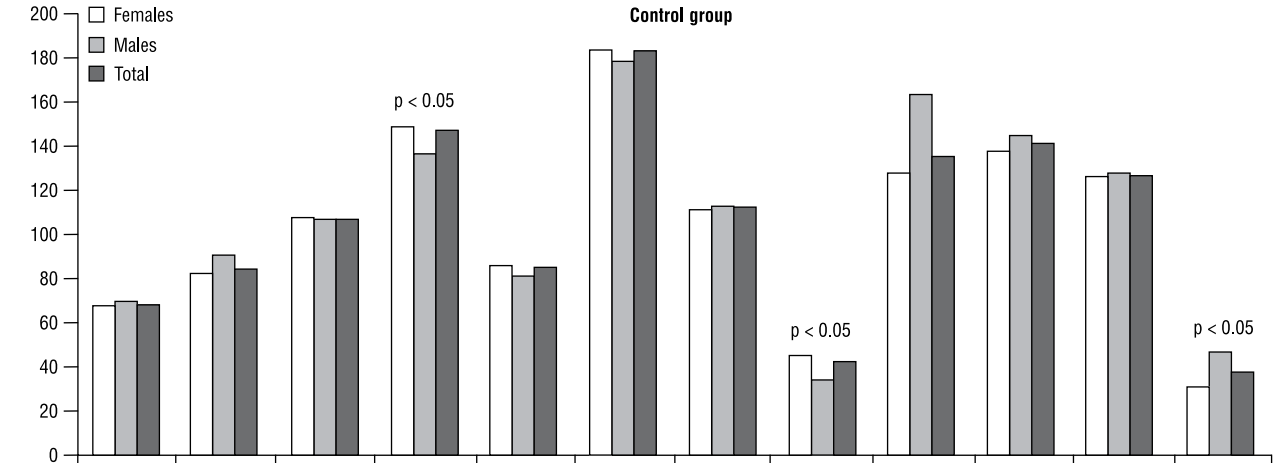
By comparing the study and the control group, statistically significant differences were observed in the mean triglyceride levels (respectively, 161.5 *vs.* 134.8 mg/dL, $p = 0.047$), mean fasting glycaemia (respectively, 111.8 *vs.* 126.1 mg/dL, $p = 0.044$) and TG/HDL ratio (4.74 *vs.* 3.71, $p = 0.043$) (Fig. 4).

The distribution of sex in both groups was similar ($p > 0.05$): women made up 79.1% of the members of the study group ($n = 140$) and 79.55% of the members of the control group ($n = 210$).

By comparing the control and the study groups of women, statistically significant differences were observed only in the mean triglyceride levels (156.1 *vs.* 127.6 mg/dL, $p = 0.023$) (Fig. 5).

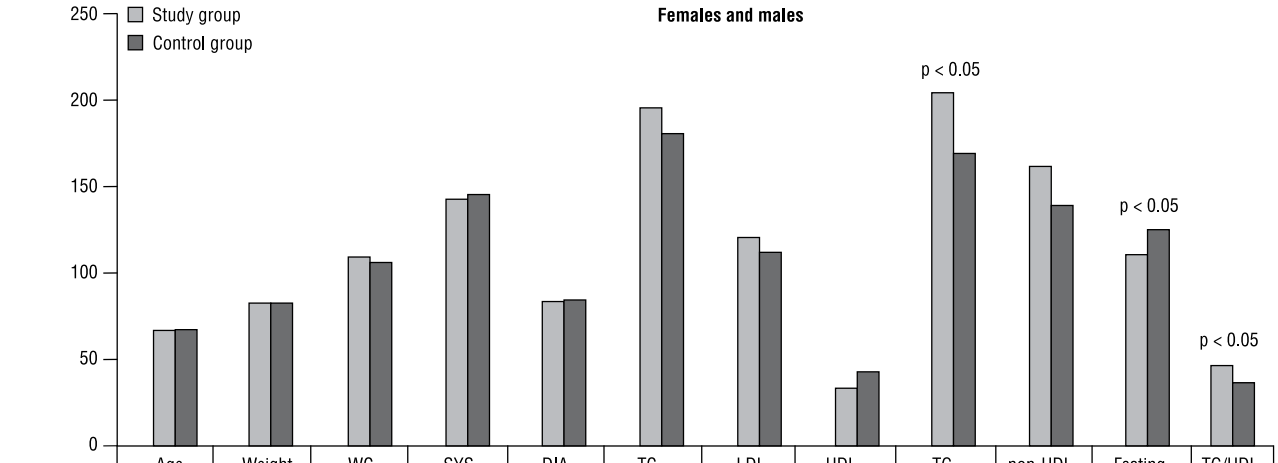
By comparing the control and the study groups of men, no statistically significant differences were observed in the above-listed parameters.

Insulin resistance marked by a hyperinsulinaemic euglycaemic clamp in both groups is presented in Table III.



	Age	Weight [kg]	WC [cm]	SYS [mm Hg]	DIA [mm Hg]	TC [mg/dL]	LDL [mg/dL]	HDL [mg/dL]	TG [mg/dL]	non-HDL [mg/dL]	Fasting glucose [mg/dL]	TG/HDL × 10
Females	67,5	82,4	106,7	148,8	86	183,1	111,9	45,1	127,6	138	125,6	30,8
Males	69,7	89,8	106,2	135,8	80,8	178,3	112,6	34,3	162,6	144	127,7	47,4
Total	68	83,9	106,6	146,2	84,9	182,1	112	42,9	134,8	139,2	126,1	37,1

Figure 2. *Comparison of each parameter according to patient sex in patients in euthyreosis*
Rycina 2. *Porównanie poszczególnych parametrów u pacjentów z prawidłową funkcją tarczycy w zależności od płci*

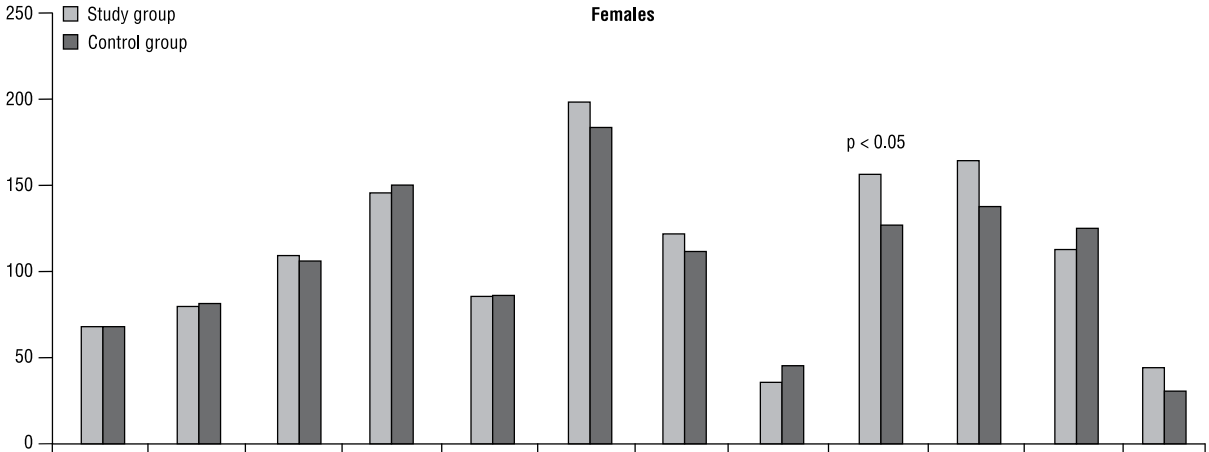


	Age	Weight [kg]	WC [cm]	SYS [mm Hg]	DIA [mm Hg]	TC [mg/dL]	LDL [mg/dL]	HDL [mg/dL]	TG [mg/dL]	non-HDL [mg/dL]	Fasting glucose [mg/dL]	TG/HDL × 10
Study Group	67,5	83,1	109,2	143,2	84,2	196,2	120,2	34,1	161,5	162,1	111,8	47,4
Control Group	68	83,9	106,6	146,2	84,9	182,1	112	42,9	134,8	139,2	126,1	37,1

Figure 3. *Comparison of MetS indicators in the study and control group*
Rycina 3. *Porównanie wskaźników zespołu metabolicznego w grupie badanej i grupie kontrolnej*

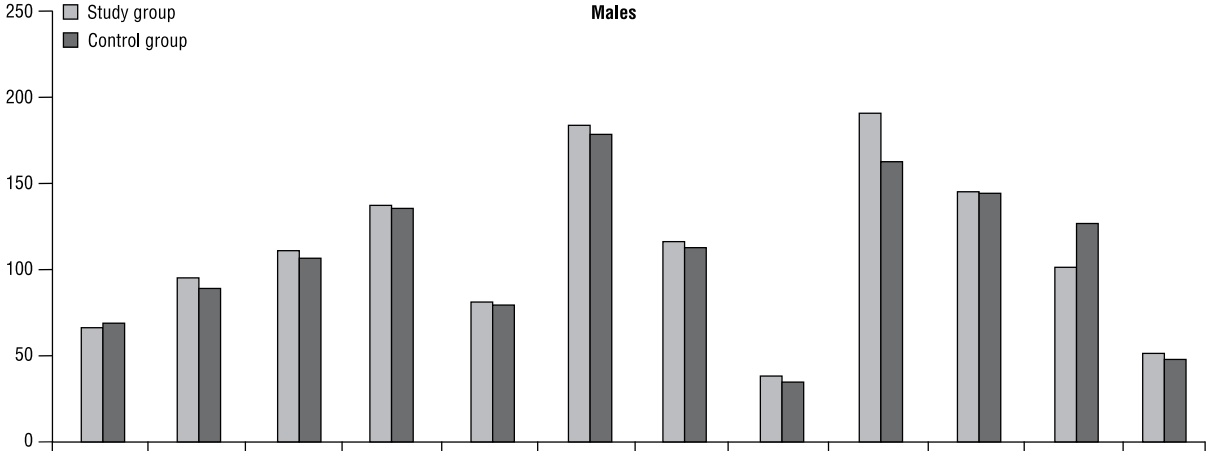
Discussion

The function of the thyroid affects numerous metabolic parameters of the organism, including the metabolism of lipoproteins and cardiovascular risk factors (e.g. blood pressure, abdominal obesity) [9–12]. The study conducted by Roos et al., including 2703 adults, demonstrated that thyroid function is related to the occurrence of metabolic syndrome components. It was observed even in subjects classified as being euthyroid, which suggests that the effect of thyroid function can be visible even when its parameters are within the reference limits [13]. Lee et al. [14], analysing 7270 euthyroid people, described a significant increase in the number of components of metabolic syndrome with increasing TSH level.



	Age	Weight [kg]	WC [cm]	SYS [mm Hg]	DIA [mm Hg]	TC [mg/dL]	LDL [mg/dL]	HDL [mg/dL]	TG [mg/dL]	non-HDL [mg/dL]	Fasting glucose [mg/dL]	TG/HDL × 10
Study Group	67,8	80,2	108,8	145,4	85,5	200,1	122,4	35,3	156,1	164,8	113,2	44,2
Control Group	67,5	82,4	106,7	148,8	86	183,1	111,9	45,1	127,6	138	125,6	30,8

Figure 4. *Comparison of MetS indicators in both groups of women*
Rycina 4. *Porównanie wskaźników zespołu metabolicznego w grupie badanej i grupie kontrolnej u kobiet*



	Age	Weight [kg]	WC [cm]	SYS [mm Hg]	DIA [mm Hg]	TC [mg/dL]	LDL [mg/dL]	HDL [mg/dL]	TG [mg/dL]	non-HDL [mg/dL]	Fasting glucose [mg/dL]	TG/HDL × 10
Study Group	66,9	95,7	111,4	138,8	81,2	183,2	116,2	37,5	191,1	145,7	101,8	50,9
Control Group	69,7	89,8	106,2	135,8	80,8	178,3	112,6	34,3	162,6	144	127,7	47,4

Figure 5. *Comparison of MetS indicators in both groups of men*
Rycina 5. *Porównanie wskaźników zespołu metabolicznego w grupie badanej i grupie kontrolnej u mężczyzn*

Table III. ***Insulin concentration and insulin sensitivity ratio (M) in the study and control group***
Tabela III. ***Stężenie insuliny oraz wskaźnik insulinowrażliwości (M) w grupie badanej i grupie kontrolnej***

	Sex	Study group ± SD	Control group ± SD	Value P
Insulin [U/L]	F	29.88 ± 4.8	25.74 ± 3.4	NS
	M	34.67 ± 5.2	26.24 ± 3.9	< 0.05
	T	33.22 ± 5.1	26.08 ± 3.7	NS
M [μg/kg/min/ins]	F	3.3 ± 0.2	3.5 ± 0.3	NS
	M	2.8 ± 0.4	3.8 ± 0.7	< 0.05
	T	2.9 ± 0.4	3.7 ± 0.6	NS

Hypothyroidism is accompanied by increased insulin resistance, which is considered as the principal disorder and potential basis for the development of metabolic syndrome. Fernandez et al. and Roos et al. [13, 15] indicated that the TSH levels are related to insulin resistance. It was demonstrated that the activity of thyroid hormones affects the expression of factors regulating tissue sensitivity to insulin, including the -2 adrenergic receptors and peroxisome proliferator-activated receptors (PPAR-γ) [16, 17]. This correlation even occurs when thyroid function is within physiological limits and thyroid disorders may decrease tissue sensitivity to insulin [17, 18].

On the other hand, a hypothesis indicating the role of MetS components in the development of thyroid disorders has also been proposed [17]. Chronic inflammation is considered responsible for this phenomenon, since increased levels of inflammatory cytokines, such as Il-6 or TNF-α, were observed in obese people with MetS [19]. Also, a study conducted by Shantha et al. demonstrated that patients with MetS and subclinical hypothyroidism have significantly higher levels of an inflammation marker (hs CRP) [20], which may inhibit thyroid function by acting directly on this gland or via the hypothalamic pituitary axis [18].

The results of our study also confirm the relation between thyroid function and components of MetS. The positive correlation between TSH and serum lipid concentration (TC, TG, LDL-C) was observed in many studies published previously [21]. In the Health ABC study TG levels were positively related to overt and subclinical hypothyroidism. Also in our study the mean TG levels were increased in the study group compared to the control group (161.5 mg/dL *vs.* 134.8 mg/dL, p = 0.047) as well as in females as in males (156.1 *vs.* 127.6 mg/dL and 191.1 *vs.* 162.6 mg/dL, respectively).

The mean TG/HDL-C ratio, which is thought to be a substitute marker of insulin resistance [16], was also increased in the study group compared to the control group (4.74 *vs.* 3.71; p = 0.043). Thus, the group with hypothyroidism, in comparison to the control group, may demonstrate higher insulin resistance and consequently higher risk of development of cardio-vascular diseases.

It is worth noticing that in both the study and the control group, the mean TG/HDL ratio was significantly higher in men than in women (5.09 *vs.* 4.42; p = 0.033 and 4.74 *vs.* 3.08; p = 0.0007, respectively), which can demonstrate higher insulin resistance. Hadaegh et al. [16] found that female gender had lower risk for incident of MetS than male [HR: 0.58 (0.47-0.70)]. Also, Cheserek et al. [22] showed that subclinical hypothyroidism was associated with metabolic syndrome components in males but not in females.

A statistically significant difference was also observed by means of hyperinsulinaemic euglycaemic clamp in men with MetS and hypothyroidism in comparison to those without thyroid disorders. The mean insulin sensitivity ratio (M) was significantly lower in men from the study group compared to the control group. In the group of women similar results were not obtained.

Interestingly, a statistically significant difference was also observed in the mean fasting glycaemia, which was lower in the study group with hypothyreosis. The results are in opposition to those published earlier. The previous studies revealed a positive correlation of hypothyroidism with elevated fasting glucose levels.

Conclusions

Hypothyroidism shows a positive correlation with TG levels and TG/HDL-C ratio and a negative correlation with mean fasting glycaemia in people with MetS. The significantly higher TG/HDL-C ratio and lower mean insulin sensitivity ratio observed in men with hypothyroidism indicated higher insulin resistance in men.

In view of the above, it may be hypothesised that in patients with both MetS and hypothyroidism, especially of male gender, the risk of death from cardiovascular causes is greater due to the severity of MetS components.

Moreover, we suggest that in patients recently diagnosed with MetS, active detection of hypothyroidism should be performed by determining the TSH levels, while patients diagnosed with hypothyroidism (apart from replacement therapy) should be monitored for the possible occurrence of MetS in the future.

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