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Association between thyroid function and metabolic syndrome in male and female schizophrenia patients

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ABSTRACT

Background: The aim of this study was to analyse the relationship between thyroid function and the diagnosis of metabolic syndrome (MS) and its components in schizophrenia patients to improve the overall clinical care.
Methods: We examined 106 schizophrenia patients (64 females and 42 males, aged 18–69 years). Sociodemographic, psychometric, anthropometric, and biochemical measures; eating habits, and the use of selected drugs were assessed during the enrolment and after 8 to 10 weeks of observation.
Results: An association between hyperglycaemia and hypothyroidism was observed. Compared to females, adverse metabolic profiles in male subjects were more common after follow-up, particularly in the presence of hypothyroidism. There was a significant reduction in hip circumference, blood glucose, and systolic blood pressure values after the follow-up period.
Conclusions: Based on hypothyroidism incidence in the studied sample and the association between thyroid-stimulating hormone (TSH) values and MS criteria, we suggest regular assessment of TSH levels in schizophrenia patients with a diagnosis of MS. Programs of MS and thyroid dysfunction prevention and treatment in schizophrenia patients should be differentiated according to gender. An indirect conclusion is that even a minute element such as conducting the interview about lifestyle may trigger patients to change their habits.

1. Introduction

Schizophrenia is a multifactorial disease with a variable phenotypic expression and complex cause that involves environmental factors as well as genetic susceptibility (Jablensky, 1995). Not less important are organic, biochemical, neurodevelopmental, and sociopsychological determinants (Tamminga and Medoff, 2000). Life expectancy of patients with schizophrenia is 15 to 25 years shorter compared with the general population (Meyer and Nasrallah, 2009; Tilhonen et al., 2009). The mortality rate among these individuals is at least twice to three times higher than among persons not suffering from schizophrenia (Saha et al., 2007). Although, suicidality in schizophrenia reaches extremely high rates, the excess mortality is mostly related to natural causes (Crump et al., 2013; Laursen 2011; Laursen et al., 2012; Suvisaari et al., 2007). Serious health problems in schizophrenics result from cardiovascular disease, body mass changes, altered glucose and lipid metabolism, and high blood pressure. Some of these disorders constitute criteria of metabolic syndrome (MS), which are abdominal obesity, hyperglycaemia, hypertriglyceridemia, low level of high-density lipoprotein (HDL), and elevated blood pressure (Shakeri et al., 2016). According to European reports, the incidence of MS in schizophrenia individuals is estimated at 19 to 35% (Saari et al., 2005; Hagg et al., 2006; de Hert et al., 2006; Mackin et al., 2007; Suvisaari et al., 2007; Boke et al., 2008; Sicras-Mainar et al., 2015; Medved et al., 2009), and it is estimated at 35 to 52% in the United States (Hagg et al., 2006). Moreover its prevalence differs between genders (McEvoy et al., 2005).

Thyroid hormones are essential for the maintenance of cellular

Abbreviations: BMI, body mass index; CHOL-T, total cholesterol; FT3, triiodothyronine; FT4, thyroxine; HDL, high density lipoprotein; IDF, International Diabetes Federation; LDL, low density lipoprotein; MAP, mean arterial pressure; PANSS, The Positive and Negative Syndrome Scale; TGs, triglycerides; TSH, thyroid stimulating hormone; WHR, waist-hip ratio

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energy homeostasis. They affect lipid metabolism, blood pressure, and plasma glucose, which, in case of abnormal values, serve as MS components (Friis and Pedersen, 2011; Fommei and Iervasi, 2002; Knudsen et al., 2005; Roos et al., 2007). Case reports indicate that patients with hyperthyroidism may develop psychosis with positive symptoms, similar to that observed in patients with schizophrenia (Marian et al., 2009; Snabboon et al., 2009; MacDonald and Schulz, 2009). In turn, hypothyroidism individuals may show symptoms of mood disorders: decreased motivation and depressiveness similar to negative symptoms in schizophrenia (MacDonald and Schulz, 2009). Subclinical hypothyroidism may occur in patients not treated for schizophrenia previously, and administration of antipsychotic drugs could increase their basal thyroid-stimulating hormone (TSH) concentration (Martinos et al., 1986). Navarro et al. (2017) suggested that the prevalence of hypothyroidism is lower among individuals with serious mental disorders than in the general population. On the other hand, a population-based study reported that schizophrenia was more frequent in patients with hypothyroidism (Sharif et al., 2018). Radhakrishnan et al. (2013) found that thyroid dysfunction was more commonly seen in patients with schizophrenia-spectrum disorders as compared with mood disorders. However, no significant gender differences in thyroid dysfunction were observed.

It is believed that MS may be the result of abnormal thyroid function. There have been several studies on the prevalence of MS and its relationship with thyroid dysfunction, but their results are contradictory (Agarwal et al., 2011; Park et al., 2011). Most studies focus on subclinical hypothyroidism, as even latent hypothyroidism contributes to an increase in cholesterol and blood pressure levels (Gyawali et al., 2015). Only few studies focus on the metabolic differences between males and females (Mierzecki et al., 2013). Moreover, to date, research on the relationship between MS and thyroid function in patients with schizophrenia has been scarce. It is very important, as abnormalities in thyroid function are common in patients suffering from schizophrenia, even if clinical markers of thyroid dysfunction are not observed (Sim et al., 2002).

Therefore the aim of this study was to analyse the relationship between thyroid function and MS, as well as its components and anthropometric and metabolic measures in male and female schizophrenia patients to improve overall clinical care.

2. Methods

This study was approved by the local Bioethics Committee (KB-0012/72/11). The participants, having been informed of its terms, gave their written informed consent to participate in the study.

2.1. Study sample

The study included 106 adult schizophrenia patients (64 females and 42 males) aged 18 to 69 years (mean age 41.89 ± 9.7 years). Mean illness duration was 14.61 ± 9.7 years. Recruitment of participants was held in the Department of Psychiatry of the Pomeranian Medical University in Szczecin (Poland), at inpatient psychiatric units, at day care psychiatric wards, and at the outpatient clinic in from 2011 to 2016. No patients was hospitalized during the study. Schizophrenia had been diagnosed using the ICD-10 criteria after assessment of clinical history and psychiatry records. Clinical characteristics of patients and baseline values of all measured parameters are presented in Table 1.

Inclusion criteria were patients with schizophrenia during the remitted state of the disease in regard to acute psychotic symptoms, aged 18 to 70 years, and treated with antipsychotic drugs in a fixed dosage over a period of at least 3 months. Doses of antipsychotic drugs (typical and atypical) were converted into chlorpromazine equivalents (Szafrański, 2014; Danivas and Venkatasubramanian, 2013). Among all atypical drugs, the following were distinct: clozapine and olanzapine with the highest potential of MS risk induction, aripiprazole with a protective effect on the MS, and quetiapine because of the effect it has on thyroid function. Both patients' groups were treated mainly with atypical neuroleptics in polytherapy, and only two patients were treated in monotherapy with typical neuroleptics (flupenthixol and zuklopenthixol). The starting point for further analysis was the observation that there were no statistically significant differences between the doses of antipsychotics and other psychotropic medications at baseline and after 8 to 10 weeks.

Exclusion criteria were a history of substance use disorders, dementia syndromes, liver and/or kidney dysfunction, severe cardiac disorders, electrolyte imbalance, anaemia, prostate disease, pregnancy, inflammatory diseases, Cushing syndrome, and thyroid disease treatment.

After qualification, all patients were subjected to a psychometric test; they were asked for information concerning their age, gender, and duration of the disease and then interviewed about selected eating habits, including consumed beverages, addictions, and physical activity. They underwent anthropometric measurements, had their blood pressure and heart rate measured, and had blood samples collected to interpret laboratory tests, including thyroid function examination. In the next stage of the study, after approximately 8 to 10 weeks, follow-up appointments were scheduled and attended by 102 patients from the sample (63 females and 39 males). Characteristics of patients after the observation period are presented in Table 1.

Table 1
Clinical characteristics of the study sample at baseline (n = 106) and after an 8–10 weeks of observation (n = 102).

Measured parameters	T1 (n = 106) Mean ± SD or n/%	T2 (n = 102) Mean ± SD or n/%
Patients with MS	64 (60.38%)	63 (61.77%)
Height [cm]	169.9 ± 9.78	–
Body mass [kg]	84.3 ± 20.9	83.22 ± 19.78
BMI [kg/m2]	29.16 ± 8.86	29.16 ± 8.86
Waist [cm]	97.3 ± 16.1	97.3 ± 16.1
Hips [cm]	105.34 ± 13.18	105.34 ± 13.18
WHR [cm]	0.92 ± 0.09	0.92 ± 0.09
CHOL-T [mg/dl]	193.54 ± 44.43	190.7 ± 40.35
TGs [mg/dl]	159.27 ± 89	158.95 ± 90.39
LDL [mg/dl]	121.9 ± 37.18	120.17 ± 34.90
HDL [mg/dl]	48.15 ± 13.58	48.63 ± 13.34
Blood glucose [mg/dl]	99.16 ± 35.55	94.23 ± 20.85
SBP [mmHg}	121.46 ± 10.55	119.06 ± 9.27
DBP [mmHg]	74.67 ± 8.87	74.8 ± 7.92
MAP [mmHg]	90.26 ± 8.84	89.55 ± 7.18
HR [heartbeats/min]	79.67 ± 9.03	76.98 ± 7.31
CIGARETTES [number/d]	8.01 ± 10.01	7.14 ± 9.20
COFFEE [ml/d]	1.11 ± 1.22	0.95 ± 1.00
TEA [ml/d]	1.04 ± 1.28	0.96 ± 1.23
SWEETS [g/d]	31.88 ± 56.20	15.2 ± 35.67
SODAS [ml/d]	69.33 ± 319.86	63.72 ± 324.20
SUGAR [tblsp/d]	1.57 ± 2.55	0.93 ± 1.49
Low physical activity	15/14.15	16/15.68
Moderate physical activity	71/66.98	64/62.74
High physical activity	20/18.86	22/21.56
TSH [uIu/mL]	2.28 ± 1.46	2.44 ± 1.33
FT3 [pg/ml]	3.13 ± 0.64	2.99 ± 0.51
FT4 [ng/dl]	1.22 ± 0.20	1.22 ± 0.27
MS	54 (50.94%)	44 (43.13%)
Females with MS	32 (30.19%)	22 (21.5%)
Males with MS	22 (20.75%)	22 (22.5%)

T1 - evaluation at baseline; T2 - evaluation after 8–10 weeks; TSH - thyroid stimulating hormone; BMI - body mass index; WHR - waist-to-hip ratio; CHOL-T - total cholesterol; TGs - triglycerides; LDL - low density lipoprotein; HDL - high density lipoprotein; SBP - systolic blood pressure; DBP - diastolic blood pressure; MAP - mean arterial blood pressure; Cigarettes - the number of cigarettes smoked in units / d; COFFEE - amount of strong coffee / d; TEA - amount of strong tea / d; SWEETS- amount of sweets / d; SODAS - amount of consumed sweetened carbonated beverages / d; SUGAR - sugar intake / d; MS- metabolic syndrome; F- female; M-male.

During either baseline or follow-up assessment, patients were not educated on healthy lifestyle by the investigators, nor were there any significant changes in their treatment. Despite the absence of any intervention aimed at changing their current lifestyle, patients were able to have access to their test results and consult their general practitioner or psychiatrist if they felt the need to do so.

2.2. Clinical and biochemical assessment

All patients underwent the following anthropometric measurements: height, weight, and waist and hip circumferences. Their body mass index (BMI), waist-hip ratio (WHR), blood pressure (average of two measurements), and heart rate were calculated. Their mean arterial pressure (MAP) was determined following the formula MAP = 1/3 × systolic blood pressure (SBP) + 2/3 × diastolic blood pressure (DBP). Electrocardiography was performed as a control measure to exclude any significant deviations that might disqualify a patient from the study.

Laboratory tests included blood morphology, glutamic oxoloacetic transaminase, glutamic pyruvic transferase, total bilirubin, total cholesterol (CHOL-T), triglycerides (TGs), HDL, low-density lipoprotein (LDL) cholesterol, glucose (in patients whose blood glucose level was ≥100 mg/dL, an oral glucose tolerance test was conducted to exclude diabetes), creatinine, sodium, potassium, TSH, triiodothyronine (FT3), and thyroxine (FT4). Based on reference standards and available literature, in this study we assumed TSH values ≥ 4.50 uIU/mL as indicative of hypothyroidism and TSH levels ≥ 2.50 uIU/mL as an increased risk of hypothyroidism. Such values may be related to the development of obesity and MS, which increase cardiovascular risk (Deary et al., 2012; de Souza et al., 2016; Surks and Hollowel, 2007; Surks and Boucai, 2010).

Patients were interviewed about selected eating habits and addictions (consumed sweets, soft drinks, sugar, coffee and strong black tea, and smoking cigarettes). Also their physical activity was assessed on a three-tier scale: 1, low physical activity (sedentary lifestyle); 2, average physical activity (sedentary life with occasional physical activity); or 3, high physical activity (frequent exercise). The severity of schizophrenia symptoms was assessed with the use of The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Each symptom was assessed on a 7-point ordinal scale. MS was diagnosed according to the International Diabetes Federation (IDF) 2005 criteria, which involve the following:

1. Abdominal obesity: waist circumference of ≥80 cm in females and ≥94 cm in males and 2 out of 4 of the following:

1 TGs ≥ 150 mg/dL (≥1.7 mmol/L) or treatment of hypertriglyceridemia
2 HDL < 40 mg/dL (<1.03 mmol/L) in males <50 mg/dL (<1.29 mmol/L) in females or treatment of that lipid disorder
3 Arterial blood pressure: systolic ≥130 mm Hg or diastolic ≥85 mm Hg blood pressure or treatment of hypertension
4 Increase in fasting blood glucose ≥100 mg/dL or treatment of type 2 diabetes

2.3. Statistical analysis

All calculations were performed with the use of Statistica 12 software. The majority of the analysed variables had distribution significantly different from normal ($p < 0.05$, Shapiro-Wilk test), therefore we used nonparametric tests. For comparison of parameters at two time points, the Wilcoxon matched pairs test was used, whereas for comparisons of independent groups, the Mann-Whitney U test was used. The strength of the correlation between variables was assessed using Spearman's rank correlation coefficient. Relationships between dichotomous variables were analysed with two-sided Fisher's exact test. Statistical significance was set at $p < 0.05$. The statistical power of the study with 100 participants was sufficient to detect with 80% probability significant correlation if the true effect size for association in the studied population corresponded to a correlation coefficient equal to ± 0.28.

3. Results

Baseline measurements were indicated as T1, whereas follow-up observations after an 8- to 10-week period were labelled T2. In the study sample ($n = 106$) we distinguished a subgroup with the baseline (T1) diagnosis of MS ($n = 54$), and likewise, from the group who reported to the follow-up appointment (T2, $n = 102$), we also selected a subgroup with the diagnosed MS ($n = 44$). At baseline, MS was more prevalent in women, but after reassessment, its rate decreased significantly. In the study group, TSH values ≥4.50 uIU/mL, indicating the presence of hypothyroidism, were reported in 10 patients (9.43%), whereas TSH values ≥2.50 uIU/mL were observed in 33 patients (31.13%).

The initial (T1) mean PANSS score was 55.75 ± 21.19, with the positive symptom score (P) of 12.57 ± 6.78 points, the negative symptom score (N) of 15.58 ± 6.36 points, and the general symptoms score (G) of 27.68 ± 10.64 points. The follow-up (T2) mean PANSS score was 44.45 ± 11.21, with the positive symptom score (P) of 9.23 ± 3.00 points, the negative symptom score (N) of 12.71 ± 4.08 points, and the general symptoms score (G) of 22.60 ± 6.39 points.

3.1. Correlations between TSH, FT3, FT4, and anthropometric and metabolic parameters

The analyses commenced with verification of correlations between anthropometric and metabolic parameters and concentrations of thyroid hormones (Table 2). Because of the large amount of data in Table 2, we present only the statistically significant results. At baseline, we observed a significant positive correlation between TSH level and TG concentration and a negative correlation between TSH and HDL levels. In turn, FT4 concentration correlated negatively with the concentration of CHOL-T and LDL. At 8- to 10-week follow-up, a significant positive correlation between TSH and TG levels again were recorded. There were also positive correlations between TSH and body weight, waist circumference, WHR, and blood pressure. Furthermore, we observed positive significant correlation between FT3 and SBP. There was also a significant negative correlation between the level of FT4 and

Table 2
Correlations of TSH, FT3 and FT4 levels with anthropometric and metabolic parameters at T1 and T2.

CORRELATION	T1 ($n = 106$)		T2 ($n = 102$)	
	R	p value	R	p value
TSH & WEIGHT	0.14	0.15	0.22	**0.024**
TSH & WAIST	0.14	0.15	0.21	**0.03**
TSH & WHR	0.13	0.19	0.25	**0.012**
TSH & TGs	0.26	**0.008**	0.27	**0.005**
TSH & HDL	−0.24	**0.012**	−0.15	0.13
TSH & SBP	0.057	0.56	0.22	**0.02**
TSH & DSP	0.097	0.32	0.19	**0.046**
FT3 & SBP	−0.029	0.77	0.25	**0.01**
FT4 & CHOL-T	−0.30	**0.002**	−0.23	**0 02**
FT4 & LDL	−0.28	**0.003**	−0.16	**0.09**

T1 - evaluation at baseline; T2 - evaluation after 8–10 weeks; TSH - thyroid stimulating hormone; FT3 - triiodothyronine; FT4 - thyroxine; WEIGHT - body weight; WAIST- waist circumference; WHR - waist-to-hip ratio; CHOL-T - total cholesterol; TGs - triglycerides; LDL - low density lipoprotein; HDL - high density lipoprotein; SBP - systolic blood pressure; DSP - diastolic blood pressure.
p - calculated with Spearman's rank correlation test; significant correlations were marked in bold characters.

Table 3
Changes in anthropometric, metabolic and thyroid parameters between baseline (T1) and follow-up after 8–10 weeks (T2).

	PARAMETERS	T1 (n = 106) Mean ± SD	T2 (n = 102) Mean ± SD	ΔT Mean ± SD	p value
Anthropometric parameters	Body mass [kg]	84.3 ± 20.9	83.22 ± 19.78	−0.40 ± 3.27	0.18
	BMI [kg/m2]	29.16 ± 6.86	28.92 ± 6.33	−0.15 ± 1.10	0.11
	waist [cm]	97.3 ± 16.1	96.6 ± 15.75	−0.36 ± 4.13	0.26
	hips [cm]	105.34 ± 13.18	104.6 ± 12.58	−0.47 ± 3.93	**0.04**
	WHR [cm]	0.92 ± 0.09	0.92 ± 0.09	0.00 ± 0.02	0.87
Metabolic parameters	CHOL-T [mg/dl]	193.54 ± 44.43	190.7 ± 40.35	−3.41 ± 30.30	0.52
	TGs [mg/dl]	159.27 ± 89	158.95 ± 90.39	−2.11 ± 59.07	0.27
	LDL [mg/dl]	121.9 ± 37.18	120.17 ± 34.90	−1.56 ± 24.00	0.51
	HDL [mg/dl]	48.15 ± 13.58	48.63 ± 13.34	0.16 ± 8.23	0.93
	BG [mg/dl]	99.16 ± 35.55	94.23 ± 20.85	−4.8 ± 33.43	**0.008**
	SBP [mmHg]	121.46 ± 10.55	119.06 ± 9.27	−2.45 ± 10.28	**0.017**
	DBP [mmHg]	74.67 ± 8.87	89.55 ± 7.18	0.14 ± 8.57	0.83
Thyroid parameters	TSH [uIU/ml]	2.28 ± 1.46	2.44 ± 1.33	0.13 ± 1.23	**0.047**
	FT3 [pg/ml]	3.13 ± 0.64	2.99 ± 0.51	−0.13 ± 0.55	**0.02**
	FT 4 [ng/dL]	1.22 ± 0.20	1.22 ± 0.27	0.003 ± 0.29	0.40

T1 - evaluation at baseline; T2 - evaluation after 8–10 weeks; ΔT - observed changes; WHR - waist hip ratio; BMI - body mass index CHOL -T- total cholesterol; TGs - triglycerides; LDL - low density lipoprotein; HDL - high density lipoprotein; BG – blood glucose, SBP - systolic blood pressure; DBP - diastolic blood pressure; TSH - thyroid stimulating hormone; FT3 - triiodothyronine; FT4 - thyroxine; SD - standard deviation;.
p - Wilcoxon matched pairs test; significant correlations were marked in bold characters.

CHOL-T concentration (see Table 2).

3.2. Differences between baseline and 8- to 10-week follow-up values of selected anthropometric, metabolic, and thyroid parameters in males and females

Although there were no interventions involving any forms of health education for patients, we observed a clear downward trend in anthropometric parameters after the observation period. They did not, however, differ significantly from baseline except for the reduction in hip circumference. However, significant reductions after the observation period were found in metabolic parameters (glucose and SBP levels). We also observed a statistically significant increase in TSH and a decrease in FT3 values (Table 3).

Because of significant differences in the evaluated parameters between males and females, we have also performed comparisons of changes between two time points according to gender (baseline vs. follow-up; Table 4). Male patients had significantly higher body weight, waist circumference, and WHR compared with women, who were characterized by significantly higher hip circumference. Interestingly, both at baseline and follow-up, men had significantly higher levels of TGs and SBP and significantly lower concentrations of HDL. After the observation period, we also recorded significantly higher values of DBP, TSH, FT3, and FT4 in male patients. The most significant difference regarded BMI (p = 0.036), which decreased among women.

Correlations of metabolic parameters with age and the duration of the disease, as well as correlations between metabolic parameters and thyroid function, were performed additionally in the subgroups of male and female patients at T1 and T2. Regarding T1, the following positive significant correlations were observed: age and glucose concentration (p = 0.02) among females and age and DBP (p = 0.02), TSH and TGs (p = 0.01), and FT3 and glucose concentration (p = 0.03) among males. Negative significant correlations were present only among males: TSH and HDL (p = 0.004), FT4 and CHOL-T (p = 0.001), and FT4 and LDL (p = 0.01). Regarding T2, the following positive correlations were found: age and TGs (p = 0.01) and FT3 and SBP (p = 0.01) among females and duration of illness and CHOL-T (p = 0.02), TSH and TGs (p = 0.002), and FT4 and glucose concentration (p = 0.04) among males. Negative significant correlations were present only among males: age and weight (p = 0.03) and FT4 and CHOL-T (p = 0.03).

Table 4
Comparison of anthropometric, metabolic and thyroid parameters between male and female patients at T1 and T2.

	Parameter	T1 (n = 106) F (n = 64) Mean ± SD	M (n = 42) Mean ± SD	p value	T2 (n = 102) F (n = 63) Mean ± SD	M (n = 39) Mean ± SD	p value
Anthropo-metric parameters	body mass [kg]	80.67 ± 20.36	89.80 ± 20.74	**0.02**	78.62 ± 17.84	90.66 ± 20.69	**0.003**
	BMI [kg/m2]	29.77 ± 7.07	28.23 ± 6.02	0.21	29.14 ± 6.52	28.55 ± 6.08	0.62
	Waist [cm]	95.89 ± 16.30	99.45 ± 15.71	0.25	94.32 ± 14.64	100.28 ± 16.93	0.11
	hips [cm]	107.67 ± 13.95	101.80 ± 11.15	**0.01**	106.15 ± 12.37	102.10 ± 12.66	**0.03**
	WHR [cm]	0.89 ± 0.07	0.97 ± 0.08	**<0.00001**	0.88 ± 0.07	0.97 ± 0.08	**<0.00001**
Metabolic parameters	CHOL-T [mg/dl]	197.60 ± 47.36	187.35 ± 39.30	0.27	190.79 ± 44.03	190.62 ± 34.13	0.93
	TGs [mg/dl]	145.5 ± 76.22	180.17 ± 34.13	**0.04**	141.06 ± 75.83	187.86 ± 104.62	**0.01**
	LDL [mg/dl]	122.56 ± 39.92	120.88 ± 33	0.77	118.60 ± 38.92	122.71 ± 27.49	0.54
	HDL [mg/dl]	52.89 ± 13.77	40.93 ± 9.61	**<0.00001**	52.64 ± 13.64	42.16 ± 9.99	**0.00003**
	Blood glucose [mg/dl]	102.42 ± 44.25	94.18 ± 13.56	0.69	96.96 ± 24.69	89.84 ± 11.35	0.39
	SBP [mmHg]	119.76 ± 10.74	124.04 ± 9.83	**0.02**	117.46 ± 9.62	121.67 ± 8.13	**0.02**
	DBP [mmHg]	73.35 ± 9.08	76.67 ± 8.23	0.11	72.61 ± 7.39	78.33 ± 7.55	**0.00002**
Thyroid parameters	TSH [uIU/ml]	2.12 ± 1.35	2.52 ± 1.60	0.18	2.12 ± 1.23	2.95 ± 1.33	**0.0009**
	FT3 [pg/ml]	3.09 ± 0.67	3.20 ± 0.50	0.28	2.88 ± 0.51	3.16 ± 0.46	**0.01**
	FT4 [ng/dL]	1.20 ± 0.18	1.23 ± 0.21	0.47	1.21 ± 0.31	1.23 ± 0.19	**0.04**

T1 - evaluation at baseline; T2 - evaluation after 8–10 weeks; WHR - waist hip ratio; BMI - body mass index CHOL -T- total cholesterol; TGs - triglycerides; LDL - low density lipoprotein; HDL - high density lipoprotein; SBP - systolic blood pressure; DBP - diastolic blood pressure; TSH - thyroid stimulating hormone; FT3 - triiodothyronine; FT4 - thyroxine; SD - standard deviation;.
p - value of the Mann-Whitney U test; significant correlations were marked in bold characters.

Table 5
MS criteria and diagnosis in patients with TSH < 2.50 and ≥ 2.50 uIU/ML, and < 4.50 and ≥ 4.50 uIU/ML at T1 and T2.

	T1 (*n* = 106) TSH < 2.50uIU/ml *n* (%)	TSH ≥ 2.50uIU/ml *n* (%)	p value	T2 (*n* = 102) TSH < 2.50uIU/ml *n* (%)	TSH ≥ 2.50uIU/ml *n* (%)	*p* value
WAIST (+)	53 (72.60)	29 (87.88)	0.13	52 (75.36)	26 (78.79)	0.80
TG (+)	31 (42.47)	20 (60.61)	0.09	28 (40.58)	18 (54.55)	0.20
HDL (+)	43 (41.10)	21 (63.64)	0.67	32 (46.38)	18 (54.55)	0.52
BP (+)	24 (32.8)	16 (48.48)	0.13	20 (28.99)	13 (39.39)	0.36
HA (+)	28 (38.36)	18 (54.55)	0.14	25 (36.23)	14 (42.42)	0.66
Blood glucose (+)	19 (26.03)	10 (30.30)	0.47	12 (17.39)	5 (15.15)	0.1
DM (+)	19 (26.03)	10 (30.30)	0.64	14 (20.29)	5 (15.15)	0.59
MS (+)	34 (46.58)	20 (60.61)	0.21	28 (40.58)	16 (48.48)	0.52
	TSH < 4.50uIU/ml *n*(%)	TSH ≥ 4.50uIU/ml *n*(%)	*p* value	TSH < 4.50uIU/ml *n*(%)	TSH ≥ 4.50uIU/ml *n*(%)	*p* value
WAIST (+)	72 (75.00)	10 (100)	0.11	69 (75.00)	9 (90.00)	0.44
TG (+)	44 (45.83)	7 (70.00)	0.19	41 (44.57)	5 (50.00)	0.75
HDL (+)	58 (60.42)	6 (60.00)	0.10	45 (48.91)	5 (50.00)	0.1
BP (+)	34 (35.42)	6 (60.00)	0.17	29 (31.52)	4 (40.00)	0.72
HA (+)	40 (41.67)	6 (60.00)	0.32	35 (61.96)	4 (40.00)	0.1
Blood glucose (+)	20 (20.83)	7 (70.00)	**0.002**	14 (38.04)	3 (30.00)	0.36
DM (+)	22 (22.92)	7 (70.00)	**0.004**	16 (17.39)	3 (30.00)	0.39
MS (+)	46 (47.92)	8 (80.00)	0.09	40 (43.48)	4 (40.00)	0.1

T1 - evaluation at baseline; T2 - evaluation after 8–10 weeks; MS - metabolic syndrome; (+) - met the criteria, diagnosis of MS; WAIST- waist circumference ≥ 80 cm in women and ≥ 94 cm in men (for Europeans); TG - triglyceride high TG levels ≥ 150 mg / dl; HDL - HDL criterion for MS; BP - increase in blood pressure: systolic > = 130 mmHg, or diastolic blood pressure > = 85 mmHg; HA - MS Hypertension criterion; DM - MS criterion for diabetes.
p - 2-sided Fisher's exact test; significant correlations were marked in bold characters.

3.3. Relationship between hypothyroidism diagnosis, thyroid hormone levels, MS, and its components in males and females

There was no significant association between the diagnosis of MS and the risk of developing hypothyroidism in either the initial or the follow-up measurement. At baseline we found a relationship between hypothyroidism (TSH ≥ 4.50 uIU/mL) and blood glucose levels (≥100 mg/dL), as well as meeting criteria of diabetes (Table 5).

The association of possible hypothyroidism with MS components was additionally analysed in the subgroups of male and female patients at T1 and T2. In the initial measurement, females with a concentration of TSH ≥ 4.5 uIU/mL were characterized with significantly higher values of DBP. Among males with a concentration of TSH ≥ 4.5 uIU/mL higher BMI and LDL, lower HDL and significantly higher concentrations of glucose were noted (Table 6).

Among males with TSH ≥ 4.5 uIU/mL, significantly lower concentrations of HDL were observed in the follow up (Table 7). Patients who met hypertriglyceridemia criterion for MS were characterized with significantly higher levels of TSH in both measurements (Table 8).

4. Discussion

This study was based on the hypothesis of a link between thyroid function and MS in schizophrenia patients. We observed associations between hyperglycemia and hypothyroidism. Importantly, we observed more adverse metabolic profiles in male subjects compared with female subjects, particularly in the presence of hypothyroidism.

Many authors confirm the association between thyroid function and MS prevalence in populations not affected by schizophrenia. An analysis carried out on a sample of 5422 patients showed that individuals with hypothyroidism were at a higher risk of developing MS, abdominal obesity, and hypertriglyceridemia compared with the subjects diagnosed with subclinical hypothyroidism and/or hyperthyroidism (Mehran et al., 2017). A study conducted on another large group found that thyroid function is associated with the occurrence of MS. These observations were confirmed in euthyroid patients, suggesting that the effects of thyroid hormones on metabolic components may be visible even if thyroid hormones levels are within reference values (Roos et al., 2007). Hence, Lee et al., analysing data collected from a group of 7270 subjects, described a significant increase in the number of MS components with increasing levels of TSH (Lee et al., 2011). The very same findings were reported by Meng et al. (2015), who, in their study, analysed almost twice as many patients.

Some studies indicate a relationship between thyroid dysfunction and individual components of MS, including glucose concentration. Swamy et al. (2012) analysed 116 subjects and demonstrated that patients with diabetes had significantly higher levels of TSH ($p < 0.001$). Similar findings were reported by Pranav et al. (2015) and Vij et al. (2012) (Pranav et al., 2015; Vij et al., 2012). In analysis carried out on a group of 441 patients with MS, Gierach and Junik (2015) demonstrated that these individuals had a significantly higher mean level of TGs compared with the control group (161.5 mg/dL vs. 134.8 mg/dL; $p = 0.047$), and their hypothyroidism positively correlated with TG level but negatively with the mean fasting glucose level (Gierach and Junik, 2015). It was also found that with increasing concentration of TSH in euthyroid patients, subjects with a TSH level within upper limits of normal (2.5 - 4.5 mU/L) were more obese, had higher TG levels, and higher risk of MS (Ruhla et al., 2010). Recent studies suggest that free thyroxine concentration within the lower limit of normal is associated with hyperlipidaemia (Johnson, 2006). Thyroid dysfunction may constitute complications of MS or type 2 diabetes, and epidemiological studies indicate that they have proved to be more prevalent among diabetic patients, compared with the general population (Feely and Isles, 1979). The incidence of thyroid dysfunction in the population of patients with type 2 diabetes is 13.4%, with a higher incidence (31.4%) in women compared with men (6.9%) (Perros et al., 1995). It is known that an excess of thyroid hormones causes increased glucose production in the liver, rapid absorption of glucose through the intestine, and increased insulin resistance (Johnson, 2006). Moreover, it has been proved that both subclinical hypothyroidism and subclinical hyperthyroidism are associated with an increased risk of developing cardiovascular diseases and increased mortality (Biondi, 2012; Cappola et al., 2006; Gencer et al., 2012; Hak et al., 2000; Westerink et al., 2011). Some studies suggest a link between TSH and free thyroid hormones, even in the euthyroid state, and the risk of developing cardiovascular diseases (Dullaart et al., 2007; Takamura et al., 2009). One

Table 6
Comparison of anthropometric and metabolic parameters between patients with and without hypothyroidism in female and male subgroups at T1 (n = 106).

T1	FEMALE n(%) = 64 [60.4%] TSH <4.50uIU / ml n(%) = 57 [89.06]		TSH ≥4.50uIU/ ml n(%) = 7 [10.93]			MALE n(%) = 42 [39.6%] TSH <4.50uIU / ml n(%) = 39 [92.85]		TSH ≥4.50uIU/ ml n (%) = 3 [7.14]		
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	p	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	p
WAIST [cm]	95.35 ± 16.7	94.5 (81.25–107.75)	100.28 ± 12.65	94 (91–109)	0.39	98.66 ± 15.64	96.5 (85.75–109.5)	109.66 ± 15.5	102 (94–113.75)	0.27
HIPS [cm]	107.33 ± 14.12	108 (98–113.75	110.42 ± 13.16	103 (99.75–117.5)	0.67	100.92 ± 10.68	99 (92–108.25)	113.33 ± 12.85	106 (104–113)	0.09
WEIGHT [kg]	80.41 ± 20.91	79.5 (65–89.25)	82.85 ± 16.3	76 (70.25–90.25)	0.73	88.58 ± 20.61	85.5 (72–97.25	105.66 ± 18.5	96.5 (87–110.5	0.14
BMI [kg/m2]	29.5 ± 7.19	28.78 (23.35–33.49)	31.97 ± 5.91	30.24 (26.64–33.03)	0.24	27.82 ± 5.82	27.14 (22.83–30.45)	33.53 ± 7.27	29.36 (28.73–32.97)	0.09
CHOL-T [mg/dl]	916.32 ± 48.4	193.5 (160.85–227.75)	208 ± 39.38	192 (117–219.25)	0.54	185.32 ± 38.48	180 (157.77–210)	213.66 ± 49.09	185.5 (180–210.75)	0.32
TGs [mg/dl]	143.57 ± 7.89	129 (76.75–185)	161.71 ± 63.44	148.5 (109.5–186.75)	0.38	175.8 ± 103.86	159 (99.75–203.5)	237 ± 86.08	190 (162–246.25)	0.19
HDL [mg/dl]	52.97 ± 13.81	48 (43–61)	52.28 ± 14.41	49 (38.75–57.5)	0.74	41.57 ± 9.63	39 (35.8–45.5)	32.66 ± 4.72	30 (29–32.75)	0.06
LDL [mg/dl]	121.4 ± 39.0	121.5 (89.95–154.5)	132 ± 49.16	122 (77–157.25)	0.63	118.43 ± 32.13	113 (94.5–136)	152.36 ± 32.86	134.5 (125–155.25)	0.07
SBP [mmHg]	119.21 ± 10.8	120 (110–130)	124.28 ± 9.75	120 (117.5–130)	0.18	123.84 ± 10.09	120 (120–130)	126.66 ± 5.77	125 (120–130)	0.55
DBP [mmHg]	72.54 ± 9.11	70 (66.25–80)	80 ± 5.77	80 (73.75–85)	**0.02**	76.66 ± 8.45	70 (70–80)	76.66 ± 5.77	75 (70–80)	0.8
BG [mg/dl]	98 ± 23.95	93 (85.5–98.97)	138.42 ± 116.24	92.5 (78–114.75)	0.64	93.22 ± 13.58	92 (84.75–98)	106.66 ± 3.51	105 (103–107.75)	**0.01**

IQR – interquartile range.
*p calculated with Mann-Whitney U test for difference between patients with TSH <4.50 μIU/ml and ≥4.50 μIU/ml.
WEIGHT - body weight; HIPS - hips circumference; WAIST – waist circumference; BMI – Body Mass Index; CHOL-T - total cholesterol; TGs - triglycerides; LDL - low density lipoprotein; HDL - high density lipoprotein; SBP - systolic blood pressure; DBP - diastolic blood pressure; BG – blood level of glucose.

Table 7
Comparison of anthropometric and metabolic parameters between patients with and without hypothyroidism in female and male subgroups at T2 (n = 102).

T2	FEMALE n(%) = 63 [61.8%] TSH <4.50uIU/ml n(%) = 56 [88.8%]		TSH ≥4.50uIU/ml n(%) = 7 [11.1]			MALE n(%) = 39 [38.2%] TSH <4.50uIU/ml n(%) = 36 [92.3]		TSH ≥4.50uIU/ ml n(%) = 3 [7.69]		
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	p	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	p
WAIST [cm]	93.72 ± 14.96	94 (81–104)	99.14 ± 11.62	92.5 (89–108)	0.38	99.5 ± 16.67	96 (88–111)	109.66 ± 21.03	99.5 (88–115.75)	0.31
HIPS [cm]	105.6 ± 12.85	106 (98–111)	110.57 ± 13.17	103 (100.5–117.25)	0.51	101.22 ± 12.13	98 (93–106)	112.66 ± 17	103 (100–112.5)	0.13
WEIGHT [kg]	78.26 ± 18.12	77 (64–86)	81.5 ± 16.36	74.5 (66.87–89.25)	0.7	89.33 ± 20.3	86 (74–98.5)	106.66 ± 22.5	95.5 (84–112.5)	0.2
BMI [kg/m2]	28.86 ± 6.58	27.9 (23.7–32.8)	31.46 ± 6.02	29.29 (25.64–33.25)	0.24	28.1 ± 5.77	27.47 (22.79–30.02)	33.87 ± 8.52	29 (27.74–33.6)	0.12
CHOL-T [mg/dl]	189.55 ± 44.47	188 (147–225)	200.71 ± 42.12	186.5 (163.5–206.75)	0.51	189.36 ± 33.81	188 (168–212)	205.66 ± 41.93	181.5 (179–201.5)	0.57
TGs [mg/dl]	143.6 ± 78.87	125 (92–182)	120.71 ± 42.94	119.5 (77.75–143.75)	0.7	175.55 ± 93.73	156 (105–215)	335.66 ± 136.84	283 (181–399)	0.05
HDL [mg/dl]	52.08 ± 13.17	49 (43–59)	57.14 ± 17.5	58 (36.25–67.5)	0.37	43.51 ± 9.64	41 (37.6–47.4)	30.33 ± 6.5	27 (24–31.75)	**0.01**
LDL [mg/dl]	117.5 ± 38.63	114 (86–144)	127.44 ± 43.29	106.5 (88.5–147)	0.69	121.38 ± 27.71	120 (101–135)	138.66 ± 22.54	127 (117–143.25)	0.2
SBP [mmHg]	117.23 ± 9.71	120 (110–120)	119.28 ± 9.32	115 (110–126.25)	0.54	120.83 ± 7.51	120 (115–130)	131.66 ± 10.4	127.5 (120–136.25)	0.05
DBP [mmHg]	72.23 ± 7.56	70 (70–80)	75.71 ± 5.34	75 (70–80)	0.15	78.33 ± 7.65	80 (70–80)	78.33 ± 7.63	75 (70–81.25)	0.84
BG [mg/dl]	96.9 ± 25.62	90 (83–96)	97.34 ± 16.86	88 (81–109)	0.86	89.58 ± 11.76	88 (82–93)	93 ± 3.6	91 (90–93.25)	0.23

IQR – interquartile range.
*p calculated with Mann-Whitney U test for difference between patients with TSH <4.50 μIU/ml and ≥4.50 μIU/ml.
WEIGHT - body weight; HIPS - hips circumference; WAIST – waist circumference; BMI – Body Mass Index; CHOL-T - total cholesterol; TGs - triglycerides; LDL - low density lipoprotein; HDL - high density lipoprotein; SBP - systolic blood pressure; DBP - diastolic blood pressure; BG – blood level of glucose.

Table 8
Thyroid hormone levels in patients according to the diagnosis (+) or (-) of MS and its components atT1 and T2.

	T1 (n = 106)			T2 (n = 102)			
MS CRITERION	n	TSH (uIU/mL) Mean ± SD	FT3 (pg/ml) Mean ± SD	FT4 (ng/dl) Mean ± SD	n	TSH (uIU/mL) Mean ± SD	FT3 (pg/ml) Mean ± SD	FT4 (ng/dl) Mean ± SD
WAIST (+)	82	2.41 ± 1.57	3.14 ± 0.64	1.19 ± 0.18	78	2.52 ± 1.32	3.00 ± 0.49	1.22 ± 0.29
WAIST (-)	24	1.88 ± 0.88	3.10 ± 0.61	1.28 ± 0.22	24	2.16 ± 1.33	2.96 ± 0.57	1.22 ± 0.22
***p* value**		0.22	0.78	0.06		0.2	0.58	0.48
HYPTG (+)	51	2.59 ± 1.64	3.20 ± 0.75	1.20 ± 0.19	46	2.79 ± 1.37	3.02 ± 0.49	1.19 ± 0.30
HYPTG (-)	55	1.99 ± 1.22	3.07 ± 0.5	1.22 ± 0.2	56	2.15 ± 1.22	2.97 ± 0.53	1.23 ± 0.25
***p* value**		**0.02**	0.52	0.5		**0.02**	0.34	0.18
HDL (+)	64	2.4 ± 1.52	3.11 ± 0.56	1.2 ± 0.18	50	2.61 ± 1.45	2.92 ± 0.48	1.2 ± 0.24
HDL (-)	42	2.11 ± 1.37	3.17 ± 0.73	1.23 ± 0.21	52	2.28 ± 1.19	3.05 ± 0.54	1.23 ± 0.3
***p* value**		0.21	0.92	0.37		0.35	0.15	0.74
HA (+)	46	2.52 ± 1.72	3.16 ± 0.57	1.23 ± 0.18	39	2.65 ± 1.37	3.09 ± 0.41	1.17 ± 0.17
HA (-)	60	2.10 ± 1.21	3.12 ± 0.69	1.20 ± 0.2	63	2.31 ± 1.29	2.93 ± 0.56	1.25 ± 0.32
***p* value**		0.38	0.72	0.49		0.17	0.13	0.24
DM (+)	29	2.53 ± 2.06	3.08 ± 0.62	1.22 ± 0.18	19	2.29 ± 1.30	2.9 ± 0.44	1.19 ± 0.18
DM (-)	77	2.19 ± 1.17	3.16 ± 0.64	1.21 ± 0.2	83	2.47 ± 1.34	3.01 ± 0.53	1.22 ± 0.29
***p* value**		0.87	0.48	0.82		0.57	0.44	0.74
MS (+)	54	2.54 ± 1.66	3.12 ± 0.56	1.19 ± 0.17	44	2.72 ± 1.4	3.00 ± 0.47	1.17 ± 0.17
MS (-)	52	2.01 ± 1.17	3.15 ± 0.7	1.24 ± 0.22	58	2.22 ± 1.24	2.98 ± 0.54	1.25 ± 0.33
***p* value**		0.09	0.88	0.21		0.09	0.75	0.24

T1 - evaluation at baseline; T2 - evaluation after 8–10 weeks; TSH - thyroid stimulating hormone; FT3 - triiodothyronine; FT4 - thyroxine; MS - metabolic syndrome; (+) - criterion met; (-) criterion not met; WAIST- waist circumference ≥ 80 cm in women and ≥ 94 cm in men (for Europeans); HYPTG - MS hypertriglyceridemia criterion; HDL - HDL criterion for MS; HA - MS Hypertension criterion; DM - MS diabetes criterion; SD - standard deviation;.
p - value of the Mann-Whitney U test; significant correlations were marked in bold characters.

study showed a relationship between elevated FT3 levels and increased incidence of coronary events (Peters et al., 2000), and another one reported an inverse correlation between the level of FT4 and calcification of the coronary arteries in the euthyroid state in healthy subjects (Kim et al., 2012).

Our findings confirm reports by Swamy et al. (2012) concerning patients with schizophrenia. A significant association between hyperglycemia and hypothyroidism was demonstrated. Curiously, such dependence was not demonstrated in the study sample at follow-up (after the observation period). Observed improvement within the investigated metabolic parameters may have been affected by psychoeducational factors associated with the interview about lifestyle and dietary habits at the beginning of the study and possible modification of the pharmacological treatment of comorbid (somatic) conditions. Although patient education was not planned and, as such, did not take place, it is likely that access to their test results and the opportunity to inquire about certain health issues made our subjects interested in changing their current lifestyle.

Because of observed, significant differences in clinical parameters between men and women analysed in this study, we decided to conduct a comparative analysis of these two subgroups. Differences in metabolic status between males and females were described by many researchers who indicated that usually men are characterized by a more unfavourable profile, mainly because of sex-hormone functions and lifestyle (Huang et al., 2009; Mierzecki et al., 2013; Bener et al., 2014). In a study conducted in 2016 on 60 patients with first-episode psychosis, Chen et al. (2016) observed higher levels of TGs and LDL and lower levels of HDL in male patients. In another study published in 2016 focusing on the population of schizophrenia patients, Kim et al. (2016) reported similar findings - BMI and all components of MS were significantly more adverse in men than in women. However, Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) in schizophrenia patients found that MS is more frequent among females compared with males (51.6% vs. 36.0%). This relationship resulted mainly from the higher prevalence of obesity in an examined population of females originating from the U.S. (McEvoy et al., 2005). In our study at baseline, MS was also more prevalent in women than in men (30.19% vs. 20.75%), but after reassessment, its rate decreased significantly (21.5% vs. 22.5%). Interestingly, this beneficial change was observed because of a significant change in BMI values. Thus similarly to U.S. population, Polish women with schizophrenia analysed in our study were characterized with a higher frequency of obesity. It was surprising that females changed their lifestyles and were able to significantly improve their anthropometric measures. Their modifications were introduced so restrictively that, after follow-up, males represented more adverse metabolic profiles, which could also be related to higher TSH levels.

Studies on the relationship between thyroid hormone function and MS in schizophrenia patients are scarce. In this study we managed to demonstrate a link between MS and hypothyroidism in schizophrenia patients for the first time. However, our research has some limitations such as a small study sample and requires further analyses on larger groups of patients with a longer follow-up period.

5. Conclusions

Based on hypothyroidism incidence in the studied sample and the association between TSH values and MS criteria, we suggest regular assessment of TSH levels in schizophrenia patients with a diagnosis of MS. Programs of MS and thyroid dysfunction prevention and treatment in schizophrenia patients should be differentiated according to gender. An indirect conclusion is that even such a minute element as collecting the interview about lifestyle may trigger patients to change their habits.

Contributors

Sylwia Kalinowska contributed with definitions of the study design and protocol procedures; she also contributed collecting data and analyzing the results; she contributed in the first draft of the manuscript and in the final version.

Beata Trześniowska-Drukała contributed with definitions of the study design and protocol procedures; she also contributed collecting data and analyzing the results; she contributed in the first draft of the manuscript and in the final version.

Krzysztof Safranow contributed with the statistical analysis and description of the results. He also reviewed and contributed in the final version of the manuscript.

Justyna Pełka-Wysiecka contributed with definitions of the protocol procedures; She reviewed and contributed in the final version of the manuscript.

Karolina Kłoda contributed with the interpretation of results, writing the first draft and in the final version of the manuscript.

Błażej Misiak contributed in the final version of the manuscript.

Jerzy Samochowiec contributed with definitions of the study design. He contributed in interpretation of results and in the final version of the manuscript.

Author disclosure

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Supplementary materials

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