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ORIGINAL ARTICLE

PREVALENCE OF METABOLIC SYNDROME AND ITS COMPONENTS IN PATIENTS WITH CONTROLLED GRAVES' DISEASE

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Abstract. Aim: *Our aim was to assess the prevalence of the metabolic syndrome (MetS) and its components in patients with controlled Graves' disease (GD).* ***Methods:*** *This was a cross-sectional study involving 95 consecutive patients with GD referred to our tertiary care inpatient clinical center meeting the following inclusion criteria: controlled hyperthyroidism, treatment with antithyroid drugs, untreated Graves' orbitopathy (GO), if present. Patients' anthropometric parameters were evaluated and laboratory tests were performed with measurement of fasting blood glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, thyroid hormone and antibody levels. The presence of the MetS and its components as defined by the International Diabetes Federation from 2009 were evaluated.* ***Results:*** *In our patient cohort 82.1% were females, 17.9% were males, mean age 50.2 ± 13 years, with median duration of GD 16.5 months. The MetS was observed in 32.6% of our patients, obesity – in 34.7%, hyperglycemia in 38.9%, arterial hypertension – in 36.8%, low HDL-cholesterol – in 23.2% and hypertriglyceridemia – in 13.7%. There was not statistical difference neither between the prevalence of the MetS, nor between the prevalence of its individual components in female and male GD patients. The MetS was significantly more frequent in older patients, as well as abdominal obesity, hyperglycemia and arterial hypertension. There was not statistical difference in the frequency of the MetS and its components between GD patients with and without GO, except for waist circumference, which was significantly higher in patients with GO.* ***Conclusions:*** *The presence of the MetS and its components among GD patients are to great extent similar to those reported in the general population, which underlines the need for their screening and proper treatment in this subpopulation.*

Key words: *Graves' disease, metabolic syndrome, obesity, arterial hypertension, hyperglycemia, dyslipidemia*

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INTRODUCTION

Graves' disease (GD) is a chronic organ-specific autoimmune disorder and is the commonest cause of hyperthyroidism accounting for 70-80% of all cases [1]. It affects 0.5-2% of women in developed countries without iodine deficiency, while men show 5-10-fold lower prevalence. Patients suffering from GD are usually between 30 and 60 years of age. Its etiology is not fully elucidated, but

the combination between genetic susceptibility and environmental factors is considered to play a crucial role in GD development [2]. The major factor in GD pathogenesis are TSH-receptor antibodies (TRAb) [3]. They possess different biological activities and some of them are capable of stimulating and activating thyroid hormone production, as well as thyroid cell division resulting in thyrotoxicosis and goiter. Usual complaints of patients with active GD are related to increased catabolic rate (weight loss, sweating, heat intolerance), overstimulated central nervous system (nervousness, anxiety, irritability, sleep deprivation, tremor, enhanced reflexes), increased sympathetic tone (increased and/or irregular heartbeat, hypertension) and enhanced protein catabolism (muscle weakness, osteoporosis) [4]. There are three therapeutic options for GD – antithyroid drugs (ATDs), radioiodine therapy and surgery [5].

Weight loss is one of the most frequent symptoms of active GD. Several studies reported weight regain during and after treatment for GD, which sometimes exceeded the weight loss at GD presentation [6-10]. Persistently increased appetite, changes in neurotransmitter levels and/or adipocytokine levels, diminished lean body mass with concomitantly increased fat mass and decrease in resting energy expenditure are some of the proposed mechanisms [8, 10]. Pre-existing obesity, prior weight loss due to thyrotoxicosis, iatrogenic hypothyroidism (even transient) and long follow-up period independently predicted weight gain in patients with GD treated with one of the three therapeutic options [7]. Some, but not all, studies showed that patients who underwent thyroidectomy or radioiodine therapy tended to gain more weight compared to patients treated with ATDs [8]. Thyroid hormones are also involved in the regulation of blood pressure [11]. The effects of hyperthyroidism include increased cardiac output and contractility, tachycardia, widened pulse pressure, decreased systemic vascular resistance, which leads to increased systolic and decreased diastolic blood pressure. Thyroid hormones also affect glucose homeostasis by increasing hepatic glucose output, decreasing glycogen stores in the liver and skeletal muscle, altering glucose intestinal absorption and metabolism, decreasing active insulin output from the pancreas, and increasing renal insulin clearance [12]. In thyrotoxicosis all these actions are exaggerated leading to hyperglycemia and predisposing diabetic patients to develop diabetic ketoacidosis. The thyrotoxic state affects the lipid profile as well, causing acquired hypocholesterolemia and probably hypotriglyceridemia [13]. Indeed, even within the normal range of TSH values, a linear decrease in total cholesterol, LDL-cholesterol and triglycerides, and a linear increase in HDL-cholesterol has been observed with decreasing TSH.

Metabolic syndrome (MetS) is a combination of interrelated metabolic disturbances that increases the risk of type 2 diabetes mellitus and cardiovascular morbidity and constitutes a significant health and socioeconomic problem worldwide [14]. According to the definition of the International Diabetes Federation, the MetS is diagnosed in case of presence of three or more of the following criteria: increased body weight, more specifically central obesity, elevated fasting plasma glucose or previously diagnosed diabetes mellitus, lowered HDL-levels, increased triglycerides and raised blood pressure [15]. The prevalence of the MetS is between 25%-50% and varies widely depending on sex, age, ethnicity, socioeconomic and cultural factors [16-18]. As a result of its progressively increasing incidence, it comes as no surprise that it is more and more often seen in patients with other endocrinopathies, such as thyroid diseases, including GD. The combination of the two disorders additionally affects patients' quality of life and well-being and leads to increased burden for the Health Care System.

Our aim was to assess the prevalence of the MetS and its components in patients with controlled GD.

MATERIALS AND METHODS

This was a cross-sectional study involving 95 consecutive patients with GD referred to our tertiary care inpatient clinical center (University Hospital of Endocrinology, Sofia). The patients met the following selection criteria: inclusion criteria – controlled hyperthyroidism, treatment with ATDs, untreated GO, if present; exclusion criteria – uncontrolled hyperthyroidism or iatrogenic hypothyroidism, previous radioiodine therapy or thyroid surgery, Graves' orbitopathy (GO) treated with glucocorticoids. The confidence level and margin of error for the sample size of 95 patients with GD were 99% and 4%, respectively.

The diagnosis of GD was previously established based on the typical clinical manifestations and confirmed hormonally and immunologically, as well as by thyroid ultrasound. Data on GD duration, previous and current treatment, concomitant diseases, including GO, arterial hypertension, diabetes mellitus, prediabetes, dyslipidemia and their therapy, and smoking habits was acquired by patients' medical history. Then, patients' anthropometric parameters were evaluated – height in meters and weight in kilograms, on the basis of which the body mass index (BMI) was calculated according to the formula: BMI [kg/m^2] = body weight [kg]/height [m^2]. Waist cir-

cumference was measured in centimeters with non-stretchable tape at the level of the midpoint between the bottom of the ribcage and the highest points of the iliac crest. Blood pressure was measured twice in a sitting position, at rest, with a manual sphygmomanometer with a 5-minute interval between individual measurements.

Subsequently, laboratory tests were performed after overnight fasting with measurement of fasting blood glucose by hexokinase enzyme method, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides by enzymatic colorimetric method, thyroid hormone levels (TSH by immunoradiometric method and fT4 by electrochemiluminescence immunoassay) and antibody levels (TRAb by radioreceptor method, thyroid-peroxidase antibodies and antithyroglobulin antibodies by electrochemiluminescence immunoassay).

After all tests were performed, the presence of the MetS and its components as defined by the International Diabetes Federation from 2009 were evaluated [15] (Table 1).

Table 1. Diagnostic criteria of metabolic syndrome

Diagnostic criteria (3 or more)		
Obesity	Waist circumference	♂ ≥ 94 см ♀ ≥ 80 см
Hyperglycemia	Fasting blood glucose	≥ 5.6 mmol/l or known diabetes mellitus
Dyslipidemia	HDL-cholesterol	♂ < 1.0 mmol/l ♀ < 1.3 mmol/l or antilipidemic therapy
	Triglycerides	≥ 1.7 mmol/l or antilipidemic therapy
Arterial hypertension	Blood pressure	Systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or antihypertensive therapy

Ethical approval

The study protocol was approved by the Institutional Ethical Committee and was in accordance with the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

The results were analyzed using SPSS version 19 (IBM SPSS, v.19.0. Armonk, NY: IBM Corp.). First, descriptive analysis and the Shapiro-Wilk test for normality were performed. Continuous variables were presented as means and standard deviations or as medians with minimum and maximum values according to the data distribution. Categorical variables were presented as count and/or proportion. When comparing two continuous variables, the Student's t-test or the non-parametric Mann-Whitney test were used depending on the distribution of the data. Categorical variables were tested by χ^2 test. Bivariate correlation test with Spearman's coefficient was used to assess the correlations between some continuous variables. A p-value of less than 0.05 was considered an indicator of statistical significance.

RESULTS

Baseline parameters

In our patient cohort 82.1% were females, 17.9% were males, mean age 50.2 ± 13 years, with median duration of GD 16.5 months (Table 2). In Table 2 are also presented the baseline metabolic parameters.

Table 2. Baseline characteristics

Demographics	**N = 95**
Sex, n (%) Females Males	 78 (82.1) 17 (17.9)
Age, yearsa	50.2 (± 13)
Smoking habits, n (%) ● Current ● Ex-smokers ● Non-smokers	 42 (44.2) 12 (12.6) 41 (43.2)
Clinical characteristics of GD	
Duration of GD, months[b]	16.5 (2-134)
GO, n (%)	48 (50.5)
TSH, mIU/l[b]	0.89 (0.5-4.2)
fT4, pmol/l[b]	14.6 (9-21)
TSH-receptor antibodies, IU/l[b]	2.9 (1-40)
Anti-TPO antibodies positivity, %	56.6
Anti-Tg antibodies positivity, %	38.3
Metabolic parameters	
BMI, kg/m^{2}[a]	25.3 (± 5)
Waist circumference, cma	87.9 (± 14.6)
Total cholesterol, mmol/L[b]	5.3 (3.6-10.8)
LDL-cholesterol, mmol/L[b]	3.3 (2-8.5)
HDL-cholesterol, mmol/L[b]	1.5 (0.9-2.9)
Triglycerides, mmol/L[b]	0.9 (0.4-3.1)
Blood glucose, mmol/L[a]	5.5 (± 0.52)
Patients on antihypertensive therapy, n (%)	32 (33.7)
Patients on antidiabetic therapy, n (%)	10 (10.5)
Patients on antilipidemic therapy, n (%)	6 (6.3)

[a]Data are presented as means, data in the parenthesis are standard deviations. [b]Data are presented as medians, data in parenthesis are minimum and maximum value.

GD Graves' disease, GO Graves' orbitopathy, BMI Body mass index

Prevalence of the MetS and its components

The frequency of the MetS and its components is presented in Fig. 1. The MetS was observed in 32.6% of our patients, obesity – in 34.7%, hyperglycemia in 38.9%, arterial hypertension – in 36.8%, low HDL-cholesterol – in 23.2% and hypertriglyceridemia – in 13.7%.

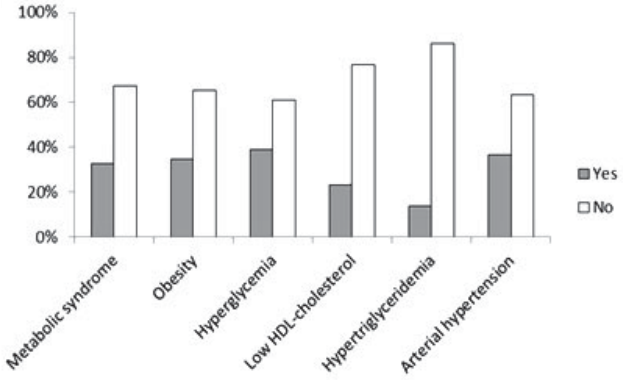

Fig. 1. Prevalence of metabolic syndrome and its components among patients with Graves' disease

Prevalence of the MetS and its components depending on sex and age

There was no statistical difference neither between the prevalence of the MetS, nor between the prevalence of its individual components in female and male GD patients (Fig. 2).

When comparing the prevalence of the MetS in patients < 50 years and > 50 years, we found that it was significantly more frequent in older patients (49% vs 11.9%, $p < 0.01$) (Fig. 3). Abdominal obesity, hyperglycemia and arterial hypertension were also significantly more often observed in older patients (73.6% vs 54.8%, $p = 0.04$; 54.7% vs 19%, $p < 0.01$ and 58.5% vs 9.5%, $p < 0.01$, respectively), whereas the rates of dyslipidemia were similar in the two age groups.

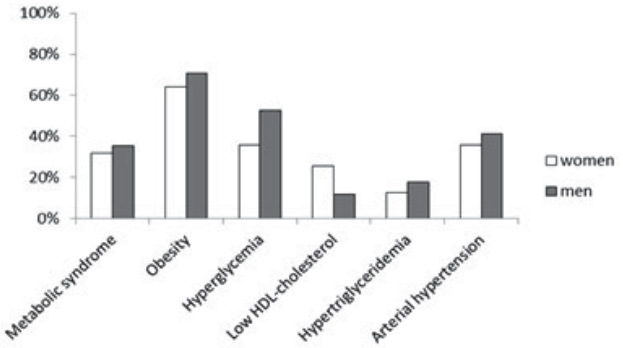

Fig. 2. Prevalence of metabolic syndrome and its components among patients with Graves' disease depending on sex

Metabolic disturbances in patients with GD and GO

Baseline characteristics of patients with GD with and without GO did not differ significantly, except for TAT positivity, which was higher in patients with GO (55% vs 22%, $p < 0.01$) (Table 3). In terms of the metabolic parameters, waist circumference was significantly higher in patients with GO (91.4 ± 14.9 vs 84.3 ± 13.5, $p = 0.04$), as well as BMI (27 ± 5.6 vs 24.7 ± 5, $p = 0.04$). However, when comparing the frequency of the MetS and its components, we did not find a significant difference between GD patients with and without GO (Fig. 4).

Associations between some clinical and metabolic parameters

Weight, BMI and waist circumference correlated positively with age and duration of GD (Table 4). Blood glucose correlated positively with age. Total cholesterol correlated positively with age and TSH and negatively with fT4. Triglycerides correlated positively with age. Total cholesterol, LDL-cholesterol and triglycerides correlated positively with waist circumference, while HDL-cholesterol – negatively.

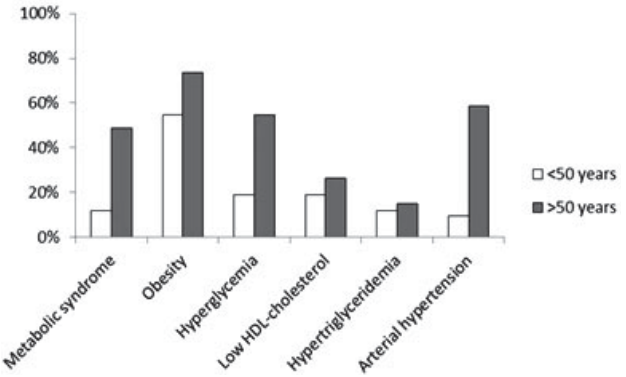

Fig. 3. Prevalence of metabolic syndrome and its components among patients with Graves' disease depending on age

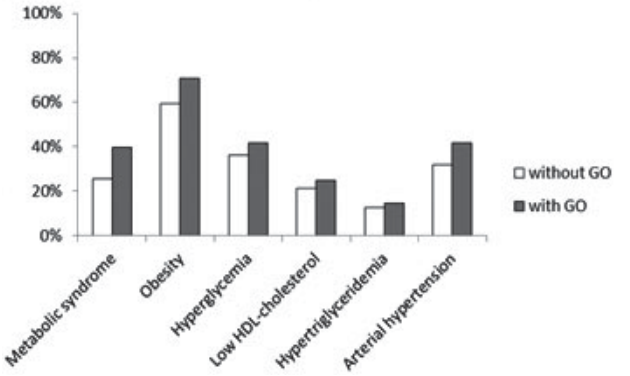

Fig. 4. Prevalence of metabolic syndrome and its components among patients with Graves' disease with and without Graves' orbitopathy

Table 3. Comparison between the baseline characteristics of patients with Graves' disease with and without Graves' orbitopathy

Demographics	GD without GO, n = 47	GD with GO, n = 48	p
Sex, n (%)[c] Females Males	 40 (85.1) 7 (14.9)	 38 (79.2) 10 (20.8)	0.45
Age, yearsa	49 (± 14.4)	53 (± 12.7)	0.16
Smoking habits, n (%)[c] ● Current ● Ex-smokers ● Non-smokers	 19 (44.2) 6 (12.6) 22 (43.2)	 23 (44.2) 6 (12.6) 19 (43.2)	0.75
Clinical characteristics of GD			
Duration of GD, months[b]	13.5 (2-108)	21 (3-134)	0.17
Duration of GO, months[b]	48 (50.5)		
TSH, mIU/l[b]	1.2 (0.7-4.2)	0.7 (0.5-4)	0.43
fT4, pmol/l[b]	14.3 (12-21)	14.8 (9-21)	0.73
TSH-receptor antibodies, IU/l[b]	2.1 (1-40)	3.3 (1-40)	0.33
Anti-TPO antibodies positivity, % [c]	58.5	45.2	0.73
Anti-Tg antibodies positivity, % [c]	55	22	< 0.01
Metabolic parameters			
BMI, kg/m^2[a]	24.7 (± 5)	27 (± 5.6)	0.04
Waist circumference, cm[a]	84.3 (± 13.5)	91.4 (± 14.9)	0.02
Total cholesterol, mmol/L[b]	5.1 (3.6-8.8)	5.4 (3.6-10.8)	0.45
LDL-cholesterol, mmol/L[b]	3.3 (2-6.1)	3.5 (2-8.5)	0.30
HDL-cholesterol, mmol/L[b]	1.5 (0.9-2.3)	1.4 (0.9-2.9)	0.69
Triglycerides, mmol/L[b]	0.9 (0.4-2.5)	1.0 (0.4-3.1)	0.25
Blood glucose, mmol/L[a]	5.5 (± 0.5)	5.5 (± 0.6)	0.72

[a]Data are presented as means, data in the parenthesis are standard deviations, p-value is calculated using Student T-test. [b]Data are presented as medians, data in parenthesis are minimum and maximum value, p-value is calculated using Mann-Whitney U test. [c]P-value is calculated using the Chi-Square test.

GD Graves' disease, GO Graves' orbitopathy, BMI Body mass index

Table 4. Relationship between some clinical, biochemical and metabolic parameters

	Weight	BMI	Waist	Age	GD duration	Glucose	TC	LDL-C	HDL-C	TG	TSH	fT4
Weight		ρ = 0.89 p < 0.01	ρ = 0.84 p < 0.01	ρ = 0.21 p = 0.04	ρ = 0.29 p = 0.01	ρ = 0.22 p = 0.03	ρ = 0.09 p = 0.41	ρ = 0.15 p = 0.16	ρ = -0.25 p = 0.02	ρ = 0.19 p = 0.07	ρ = 0.07 p = 0.49	ρ = 0.15 p < 0.16
BMI	ρ = 0.89 p < 0.01		ρ = 0.86 p < 0.01	ρ = 0.24 p = 0.02	ρ = 0.28 p = 0.01	ρ = 0.24 p = 0.02	ρ = 0.16 p = 0.13	ρ = 0.18 p = 0.08	ρ = 0.18 p = 0.07	ρ = 0.26 p = 0.01	ρ = 0.07 p = 0.48	ρ = 0.03 p = 0.77
Waist	ρ = 0.84 p < 0.01	ρ = 0.86 p < 0.01		ρ = 0.21 p = 0.04	ρ = 0.34 p < 0.01	ρ = 0.30 p < 0.01	ρ = 0.25 p = 0.02	ρ = 0.29 p = 0.01	ρ = -0.25 p = 0.02	ρ = 0.28 p = 0.01	ρ = 0.08 p = 0.45	ρ = 0.01 p = 0.91
Age	ρ = 0.21 p = 0.04	ρ = 0.24 p = 0.02	ρ = 0.21 p = 0.04		ρ = 0.05 p = 0.61	ρ = 0.39 p < 0.01	ρ = 0.32 p < 0.01	ρ = 0.33 p < 0.01	ρ = -0.01 p = 0.92	ρ = 0.31 p < 0.01	ρ = 0.02 p = 0.83	ρ = 0.08 p = 0.45
GD duration	ρ = 0.29 p = 0.01	ρ = 0.28 p = 0.01	ρ = 0.34 p < 0.01	ρ = 0.05 p = 0.61		ρ = 0.05 p = 0.64	ρ = 0.04 p = 0.73	ρ = 0.04 p = 0.74	ρ = -0.14 p = 0.20	ρ = 0.04 p = 0.73	ρ = 0.31 p < 0.01	ρ = 0.03 p = 0.81
Glucose	ρ = 0.22 p = 0.03	ρ = 0.24 p = 0.02	ρ = 0.30 p < 0.01	ρ = 0.39 p < 0.01	ρ = 0.05 p = 0.64		ρ = 0.15 p = 0.15	ρ = 0.14 p = 0.17	ρ = -0.01 p = 0.89	ρ = 0.30 p < 0.01	ρ = 0.06 p = 0.57	ρ = -0.11 p = 0.27
TC	ρ = 0.09 p = 0.41	ρ = 0.16 p = 0.13	ρ = 0.25 p = 0.02	ρ = 0.32 p < 0.01	ρ = 0.04 p = 0.73	ρ = 0.15 p = 0.15		ρ = 0.93 p < 0.01	ρ = 0.24 p = 0.01	ρ = 0.40 p < 0.01	ρ = 0.23 p = 0.03	ρ = -0.23 p = 0.03
LDL-C	ρ = 0.15 p = 0.16	ρ = 0.18 p = 0.08	ρ = 0.29 p = 0.01	ρ = 0.33 p < 0.01	ρ = 0.04 p = 0.74	ρ = 0.14 p = 0.17	ρ = 0.93 p < 0.01		ρ = 0.01 p = 0.95	ρ = 0.42 p < 0.01	ρ = 0.14 p = 0.17	ρ = -0.21 p = 0.04
HDL-C	ρ = -0.25 p = 0.02	ρ = -0.18 p = 0.07	ρ = -0.25 p = 0.02	ρ = -0.01 p = 0.92	ρ = -0.14 p = 0.20	ρ = -0.01 p = 0.89	ρ = 0.24 p = 0.01	ρ = 0.01 p = 0.95		ρ = -0.33 p < 0.01	ρ = 0.15 p = 0.16	ρ = -0.05 p = 0.60
TG	ρ = 0.19 p = 0.07	ρ = 0.26 p = 0.01	ρ = 0.28 p = 0.01	ρ = 0.31 p < 0.01	ρ = 0.04 p = 0.73	ρ = 0.30 p < 0.01	ρ = 0.40 p < 0.01	ρ = 0.42 p < 0.01	ρ = -0.33 p < 0.01		ρ = -0.11 p = 0.30	ρ = 0.08 p = 0.45
TSH	ρ = 0.07 p = 0.49	ρ = 0.07 p = 0.48	ρ = 0.08 p = 0.45	ρ = 0.02 p = 0.83	ρ = 0.31 p < 0.01	ρ = 0.06 p = 0.57	ρ = 0.23 p = 0.03	ρ = 0.14 p = 0.17	ρ = 0.15 p = 0.16	ρ = -0.11 p = 0.30		ρ = -0.25 p = 0.02
fT4	ρ = 0.15 p < 0.16	ρ = 0.03 p = 0.77	ρ = 0.01 p = 0.91	ρ = 0.08 p = 0.45	ρ = 0.03 p = 0.81	ρ = -0.11 p = 0.27	ρ = -0.23 p = 0.03	ρ = -0.21 p = 0.04	ρ = -0.05 p = 0.60	ρ = 0.08 p = 0.45	ρ = -0.25 p = 0.02	

DISCUSSION

In the present study we found that approximately one third of our patients with controlled GD had the MetS. Sengupta et al. conducted a study in India having similar to our design including GD patients with minimum duration of GD of 12 months [19]. The authors found that the prevalence of the MetS was 36%, which is comparable with our results, as well as with the reported prevalence of the MetS in the Indian population (30%) [20]. The frequency of the MetS in the general population actually varies a lot and is influenced by several factors, such as: age, sex, ethnical, cultural and socio-economic background [16-18]. The latest data on the prevalence of the MetS in the Bulgarian population are from 2012, when the prevalence of the MetS was 35.7% – similar to that of our GD patients. However, there is a well-known trend for a gradual increase in the frequency of the MetS over the years [16]. For example, over a five-year period, from 2007 to 2012, the prevalence of the MetS in Bulgaria increased by approximately 5% according to the results reported by Borissova et al. [21, 22]. We could assume that the prevalence of the MetS in Bulgaria increased further during the last decade. Unfortunately, due to the lack of current data on this topic, we are not able to directly compare our results on GD patients with the general population.

The prevalence of visceral obesity assessed by measurement of waist circumference in our GD patient cohort was approximately 35%, which is lower than the reported by Borissova et al. in their study on the features of the MetS in the unselected Bulgarian population (62.5%) [23]. Although the median duration of GD in our patients cohort was 16.5 months, in some of them the disease was actually recently diagnosed. The latter may be the cause for undercompensated weight after the initial catabolic weight loss due to hyperthyroidism. The frequency of hyperglycemia in Bulgarian population in 2012 reported by Borissova et al. is lower than what we observed in our study (25.2% vs 38.9%) [23]. However, our results are comparable with the findings of more recent studies evaluating the prevalence of diabetes and prediabetes in the general population [24, 25]. So, the discrepancies between the results of Borissova et al. and ours might be due the fact that the prevalence of hyperglycemia had changed over the last decade being much more common now. In our study the proportion of patients taking antidiabetic therapy was relatively low compared to the prevalence of hyperglycemia, which might be due to the lack of active search for diabetes and prediabetes among the GD population by endocrinologists. The prevalence of arterial hypertension in our study was 36.8% which is similar to that in the general population in Bulgaria (38.9%) [26]. Almost all patients having arterial hypertension were already on antihypertensive therapy at the time of the inclusion in the study. The reported prevalence of dyslipidemia in Bulgarian population is 33.7% for hypertriglyceridemia and 32.9% for low HDL-cholesterol, and these percentages are much higher than what we observed in our study (13.7% and 23.2%, respectively) [27]. Interestingly, only 6.3% of our patients were on antilipidemic therapy. Unlike arterial hypertension, dyslipidemia is asymptomatic and it appears to be underdiagnosed or undertreated in GD patients. This finding underlines the importance of the active screening for dyslipidemia in this group of patients. We found that the level of triglycerides and that of HDL-cholesterol correlated positively and negatively, respectively, with waist circumference – findings confirmed in previous studies [28, 29]. Therefore, it is not surprising that our patient cohort, characterized by lower presence of visceral obesity compared to the general population, had a lower frequency of dyslipidemia, as well.

When evaluating the presence of the MetS and its components in different age and sex groups, we found that the MetS was much more common in older individuals, which is in accord with previous studies [16, 18, 23]. Borissova et al. reported higher prevalence of the MetS in men than in women (40.9% vs 31.1%), whereas in our study the rates of the MetS were similar in both sexes. It could be that the relatively small number of males included in our study lead to inability to establish existing patterns. Our results showed that the prevalence of abdominal obesity between the two genders was the same, but it was more frequently seen in older individuals, which is consistent with the observed positive correlation between weight, BMI and waist circumference, and age. Some population-based studies report similar results, including one Bulgarian study [23, 30-32]. We found that blood glucose level correlated positively with age and hyperglycemia was more commonly seen in older individuals. These results are comparable with those of Borissova et al., who studied the prevalence of diabetes and prediabetes in the Bulgarian population [33]. The prevalence of arterial hypertension increases with age as seen in our study and that of Borissova et al., which focused on the general population in Bulgaria (26). Additionally, in their study arterial hypertension was more frequent in men. According to our results, there was a positive correlation between triglyceride levels and age. However, we were not able to demonstrate a significant age- and sex-related difference between the preva-

lence neither of hypertriglyceridemia, nor of low HDL-cholesterol level. On the opposite, Borrisova et al. observed higher prevalence of hypertriglyceridemia in men (46.9 vs 22.2, $p < 0.01$), whereas the prevalence of low HDL-cholesterol was more common in women (35.8 vs 29.7, $p < 0.01$) [27]. Additionally, higher rates of hypertriglyceridemia were found in older individuals, while regarding HDL-cholesterol there was no difference between the different age groups.

Our results demonstrated positive correlation between total cholesterol level and TSH, even the latter being within the normal range. This finding is in accord with the results of previous studies, which also reported a linear increase of LDL-cholesterol and triglycerides and a linear decrease in HDL-cholesterol with increasing TSH within the normal range [34]. In addition, in our study a negative correlation between total cholesterol and fT4, again within the normal limits, was observed. These findings accentuate the great influence of thyroid function on lipid profile and the importance of adequate treatment doses.

When analyzing the metabolic parameters in patients with and without GO, we found that patients with GO had significantly higher BMI and waist circumference. It might be that the propensity for accumulation of adipose tissue in the visceral area is somehow related to the fat deposition in retroorbital spaces seen in GO. Zhang et al. found some common features between orbital fat tissue and white and brown adipose tissue [35]. Whether the obesity-related chronic low-grade inflammation could increase the risk for development of allergies and autoimmune disorders, is still debatable [36]. However, this is a relevant speculation, taking into account the changed levels of some visceral fat-derived adipocytokines and cytokines in obese individuals, which could alter the immune response [37]. It is possible that obesity promotes more severe immune disturbances in patients with GD, whose phenotypic manifestation could be GO.

LIMITATIONS

Our study has several limitations. First, the relatively low number of GD patients in the different age and sex groups decreases the statistical power of the conclusions. Further larger studies are needed to confirm our results. Second, in the present study we did not evaluate some additional MetS-related parameters, such as: fasting insulin level and insulin resistance, uric acid level and levels of adipocytokines. A major limitation of our study is the lack of sex-, age- and BMI-matched control groups, which does not allow a correct assessment of the influence of hyperthyroidism on the frequency and characteristics of the metabolic syndrome and reduces the informativeness and interpretability of the obtained results. Due to lack of current data on the MetS and its components in the general population in Bulgaria, we were opted to compare our results with those of earlier studies in Bulgaria or recent studies from other countries. Last, our study was a tertiary hospital-based study, which might have led to Berkson's bias, as patients referred to our center usually have more severe GD and/or GO.

CONCLUSIONS

The results of the present study indicate that the presence of the MetS and its components among GD patients are to a great extent similar to those reported in the general population, except for dyslipidemia, which appears to be the most sensitive component of the MetS to the action of thyroid hormones. There were age-related differences regarding the proportion of GD patients with the MetS, obesity, hyperglycemia and arterial hypertension. Both hyperglycemia and dyslipidemia are often underdiagnosed and undertreated in GD patients. The presence of GO is associated with significantly increased anthropometric indicators of obesity, but does not affect the frequency of the MetS and its individual components in the population of patients with GD. These findings underline the need for screening for the MetS and its components and their proper treatment in GD patients, especially the older ones.

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