original article

Secondary metabolic syndrome: the frequency of factors which may underlie the parameters of metabolic syndrome

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BACKGROUND AND OBJECTIVES: Each of the metabolic syndrome (MetS) components (central obesity, hypertriglyceridemia, hypertension, low high-density lipoprotein cholesterol, and insulin resistance) may arise from an underlying disease or factors such as hormonal or pharmacological factors. These components arising secondary to a reason other than life style disturbances cause secondary MetS. The present study aimed to present, for the first time, the factors affecting secondary MetS.

DESIGN AND SETTINGS: An observational study at Medeniyet University Goztepe Training and Research Hospital, Istanbul, from June 2010 to February 2011.

PATIENTS AND METHODS: The underlying causes in 902 MetS patients with a mean age of 53.5 (12.9) years, of whom 79% were female, were investigated. A detailed evaluation was made, which comprised a history for drugs, diseases and habits that may manifest MetS parameters, physical examination, and laboratory analysis.

RESULTS: In 10.6% of the patients, hypothyroidism was determined as the main factor affecting secondary MetS, and in 4.1% the use of corticosteroid was determined as the main factor. Other factors underlie affecting secondary MetS are as follows: the use of thiazide diuretics (22.8%), beta-blockers (12.5%), antiphysichotics (2.1%), insulins (12.8%), insulin secretagog oral hypoglycemics (13.8%), thiazolidinediones (4.9%), oral contraceptives (0.8%), and alcohol intake (2.2%).

CONCLUSION: Hypothyroidism and corticosteroid treatment are the leading causes of secondary MetS. While evaluating the patients, it is a prerequisite to determine the high frequency of other factors that may affect the presence and the degree of MetS parameters.

Metabolic syndrome (MetS) is a complex multifactorial endocrine disease arising due to numerous underlying mechanisms and is a significant public health problem worldwide. From the beginning of the 20th century to date, various definitions and names such as "syndrome X," "the deadly quartet," and "the insulin resistance syndrome" have been established for MetS.[1]

Various diseases among MetS components or those sharing common risk factors of MetS include coronary artery disease, type 2 diabetes mellitus (DM), dyslipidemia, hypertension, polycystic ovary syndrome, and non-alcoholic fatty liver disease.[2-4] Early diagnosis and treatment of MetS may enable the prevention of a group of diseases causing significant morbidity and mortality. In addition to pharmacological treatment, lifestyle modifications have also been emphasized in the treatment of MetS.[5,6]

Each of the MetS components (central obesity, hypertriglyceridemia, hypertension, low high-density lipoprotein [HDL] cholesterol, and insulin resistance) arise due to an underlying disease or factors such as hormonal or pharmacological factors. These components arising secondary to a reason other than life style disturbances cause secondary MetS. Awareness on the factors and diseases leading to secondary MetS, and planning the treatment approaches toward these are of importance in the prevention of MetS.

Despite the high prevalence of MetS, the frequency of secondary MetS is not known. In patients diagnosed

with MetS, the reasons and risk factors leading to this condition should be well defined. As patients with dyslipidemia, hyperglycemia, hypertension, or obesity are initially evaluated for secondary factors leading to these disorders, we believe that secondary causes should also be initially evaluated in patients with MetS. Thus, we consider that incorporation of the notion of "secondary metabolic syndrome" into the medical published reports will be worthwhile. The present study aimed to present, for the first time, the factors that affect MetS. In this study, patients with MetS were evaluated from multiple aspects, the underlying pathological conditions were assessed, and the causes that could lead to secondary MetS were evaluated.

PATIENTS AND METHODS

A total of 902 consecutive patients who were admitted to the Internal Medicine, Diabetes, Cholesterol, Obesity, and Endocrinology Outpatients Clinics of Goztepe Training and Research Hospital between June 2010 and February 2011 and diagnosed with MetS were included in the present study. The study was approved by the ethical committee, and informed consents were obtained from the patients. The diagnosis of MetS was established based on the criteria presented in **Table 1**; patients with 3 of the 5 criteria were considered to have MetS.[7]

Demographic and clinical data of the patients were recorded. The patients were questioned regarding their diseases, the medications used, and alcohol use. Physical examinations were performed, blood pressures and waist circumferences (WCs) were measured, and the analyses were repeated (fasting blood glucose [FBG], urea, creatinine, uric acid, total cholesterol [total-C], HDL, low-density-lipoprotein [LDL], triglyceride [TG], aspartate aminotransferase [AST], alanine aminotransferase [ALT], thyroid stimulating hormone [TSH], glycosylated hemoglobin [HbA1c], insulin, and cortisol levels with 12 hours fasting at 8 am). According to thyroid function tests, patients with a TSH level of ≤4.5 mIU/L were considered to have regulated hypothyroidism if they had a history of hypothyroidism; those with a TSH level of ≤4.5 mIU/L without a history of hypothyroidism were considered euthyroid.[8] Factors that may lead to MetS were determined.

RESULTS

The mean age of the 902 patients included in the study was 53.5(12.9) years, and 79% of the patients were female. Of the patients, 48.8% had dyslipidemia (those who were aware of their dyslipidemia); whereas, the rate of those who were unaware of their dyslipidemia but had a TG level of ≥150 mg/dL was 24.4%. The rate of patients with a TG level of ≥150 mg/dL among the whole study group was 54.2%. The rate of patients with an FBG level of ≥100 mg/dL was 64.3%, and blood pressure (BP) was ≥130/85 mm Hg in 72.7% of the patients. The rate of female patients with a WC of ≥80 cm was 99.7%, and the rate of female patients with a WC of ≥88 was 95.3%. The rate of male patients with a WC of ≥94 cm was 93.7%; the rate of male patients with a WC of ≥102 cm was 55.6%. The rate of female patients with an HDL level of <50 mg/dL was determined to be 46.3%, and the rate of male patients with an HDL level of <40 mg/dL was determined to be 24.9%.The general characteristics of the patients are summarized in **Table 2**.

In 10.6% of the patients, hypothyroidism was determined as the main factor affecting secondary MetS, and in 4.1% the use of corticosteroid was determined as the main factor. Other factors that may underlie the parameters of MetS and their frequencies are as follows: use of thiazide diuretics (22.8%), beta-blockers (12.5%), antiphysichotics (2.1%), insulins (12.8%), insulin secretagog oral hypoglycemics (13.8%), thiazolidinediones

Table 1. Criteria for clinical diagnosis of the metabolic syndrome.

Measure	Categorical cut points
Elevated waist circumference	>80 for female, >94 for male
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL (5.5 mmol/L)

HDL-C: high-density lipoprotein cholesterol.

Table 2. General characteristics of the patients with metabolic syndrome.

Characteristics	All subjects	Subjects with type 2 diabetes (n=489)	Subjects without type 2 diabetes (n=412)	*P* value[a]
Age (y)	53.5 (12.9)	57.2 (10.9)	49.2 (13.9)	<.001
Gender				
Female	713 (79.0%)	368 (75.3%)	344 (83.5%)	.003
Male	189 (21.0%)	121 (24.7%)	68 (16.5%)	
Waist circumference (cm)				
Female	107.9 (34.9)	108.8 (47.2)	106.9 (12.5)	.53
Male	105.3 (10.8)	104.6 (10.6)	106.5 (11.2)	.21
Height (cm)	161.3(9.0)	161.1 (8.9)	161.4 (9.2)	.46
Weight (kg)	84.5 (16.3)	83.7 (16.5)	85.5 (16.1)	.04
BMI (kg/m^2)	32.6 (6.9)	32.4 (7.4)	32.9 (6.2)	.03
Triglyceride (mmol/L)	2.0 (1.4)	2.0 (1.1)	1.9 (1.7)	.003
HDL cholesterol (mmol/L)				
Female	1.3 (0.2)	1.3 (0.2)	1.3 (0.3)	.64
Male	1.2 (0.2)	1.2 (0.3)	1.1 (0.2)	.035
FBG (mmol/L)	7.1 (3.0)	8.4 (3.5)	5.5 (1.0)	<.001
BP systolic (mmHg)	136.3 (23.7)	137.5 (24.3)	134.7 (22.9)	.12
BP diastolic(mmHg)	83.7 (12.6)	82.9 (12.2)	84.6 (12.8)	.02
TSH (mIU/L)	2.7 (5.5)	2.4 (4.2)	3.0 (6.7)	.007
HbA1c (mmol/mol)	49.7 (4.9)	57.3 (2.7)	39.8 (18.8)	<.001
Insulin	12.05 (9.5)	12.8 (11.6)	11.3 (6.5)	.7
Cortisol (µg/dL)	15.1 (38.7)	16.7 (50.9)	13.2 (15.1)	.03

[a]The values are presented as mean (standard deviation) or n (%), where appropriate.

BMI: Body mass index; HDL: high-density lipoprotein, FBG: fasting blood glucose, BP: blood pressure; TSH: thyroid stimulating hormone; HbA1c: glycosylated hemoglobin.

(4.9%), oral contraceptives (0.8%), and alcohol intake (2.2%) (**Table 3**).

DISCUSSION

Proper definition of the causes and risk factors of MetS is mandatory for prevention and/or treatment of MetS. In addition to the well-defined risk factors for MetS, there are diseases and conditions that lead to MetS secondarily. Knowing these conditions and defining them as risk factors is of importance in the approach toward patients with MetS. In the present study, in which we aimed to determine the factors that would lead to secondary MetS, the characteristics of 902 patients with MetS were evaluated.

Among the conditions that could lead to secondary MetS, accompanying diseases, hormonal changes, and drug treatments have been investigated, and various reports have been published. Hjelmesaeth et al[9] reported the parathyroid hormone level to be an independent predictor of MetS in morbidly obese individuals. It has been demonstrated that when the testosterone dominates the hormonal milieu during the menopausal transition, the prevalence of MetS increases independent of aging and other known risk factors.[10] Rendina et al,[11] in their study, reported that MetS was associated with a twofold higher occurrence of objectively demonstrated nephrolithiasis and that insulin resistance was the common factor of these 2 conditions. The prevalence of MetS in patients with cryptogenic cirrhosis has been found to be higher than in patients with cirrhosis due to

other causes.[12] The MetS prevalence has been reported to be high in MetS patients followed-up due to dyslipidemia.[13] In a study investigating the relationship between primary aldosteronism and MetS prevalence, the prevalence of MetS was reported to be 62% in patients with idiopathic hyperaldosteronism, 34% in patients with unilateral aldosterone-producing adenoma, and 56% in patients with essential hypertension.[14] The prevalence of MetS in psychiatric patients has been shown to be higher than that in the general population.[15] Mclntyre et al[16] reported that patients with bipolar disorder exhibited a high rate of concurrent MetS and stated that this rate was higher in the normal population.

In a study performed based on the notion that social isolation has been associated with various chronic health conditions, loneliness was found to be associated with MetS.[17]

There are conflicting data regarding the prevalence of MetS in patients with subclinical hypothyroidism. Liu et al,[18] in their study, used the IDF criteria to establish MetS diagnosis, and subclinical hypothyroidism was defined as a TSH level of >4.5 mIU/L and normal levels of free triiodothyronine (FT3) and free thyroxine (FT4). Accordingly, 21.5% of the 6560 participants were diagnosed with MetS, and 8.2% was diagnosed with subclinical hypothyroidism. In addition, MetS was determined in 21.3% of the euthyroid cases and in 25.7% of those with subclinical hypothyroidism; after adjusted for age, no significant difference was found. As a result, Liu et al[18] did not found subclinical hypothyroidism to be an independent risk factor for MetS in their study. Nevertheless, there are also studies reporting an association between subclinical or overt hypothyroidism and MetS.[19,20] In the study by Lai et al[21] performed on 1534 adults, the serum TSH levels in patients with MetS were found to be higher in the control group (2.54 mIU/L vs 2.22 mIU/L, $P<.05$), and a slight increase in the level of serum TSH was shown to be a possible risk factor for MetS. Even within the normal range, FT4 levels have been reported to negatively correlate with the lipid levels and the insulin resistance.[22] In our study, hypothyroidism (TSH >4.5 mIU/L) was determined in 10.6% of patients with MetS.

Glucocorticoids are well known for their diabetogenic potential, effects on the risk of increasing blood pressure, and effects on lipid changes.[23] Elevated cortisol levels resulted from hyperactivity of the hypothalamic–pituitary–adrenal axis has been considered to have a potential role in the pathogenesis of MetS. Increased exposure to cortisol leads to an increase in the fat accumulation in visceral depots.[24] It has been suggested that the cortisol levels are higher in individuals with hypertension and glucose intolerance and that the increased glucocorticoid levels are independent risk factors for cardiovascular diseases.[25] In our study, 4.1% of the patients were on corticosteroid therapy.

Cushing syndrome and MetS share common components. Almost all patients with Cushing syndrome are obese or overweight, and the majority has abdominal obesity, an abnormality of the glucose metabolism, hypertension, and hypertriglyceridemia.[26,27] Approximately two-thirds of those with Cushing syndrome have at least 3 of the MetS criteria.[26] In the present study, the rate of patients with Cushing syndrome was determined to be 0.1%.

Protective, detrimental, or J-shaped associations have been reported in the studies evaluating the rela-

Table 3. Factors may lead to secondary metabolic syndrome or its components.

Factors	Frequency (%)
Factors may lead to secondary MetS	
Hypothyroidism (those with a TSH level of >4.5)	10.6
Unregulated hypothyroidism	6.0
Hypothyroidism, initial diagnosis	4.6
Cushing	0.1
Corticosteroid	4.1
Antipsychotic	2.1
Alcohol use	2.2
Factors may lead to dyslipidemia	
Hypothyroidism	10.6
Thiazides (HCTZ+indapamide)	22.2
Beta-blockers	12.5
Oral contraceptives	0.8
Factors may increase the WC (drugs contributing to the frequency of MetS by increasing the WC in those with type 2 DM)	
Insulin	12.8
Glinide	2.2
Sulfonylurea	11.6
Glitazone	4.9
Factors may increase the hyperglycemia	
Corticosteroid	4.1
Thiazides (HCTZ+indapamide)	22.2
Beta-blockers	12.5

MetS: Metabolic syndrome; TSH: thyroid stimulating hormone; WC: waist circumference; DM: diabetes mellitus, HCTZ: hydrochlorothiazide, MetS: metabolic syndrome

tionship between alcohol consumption and MetS.[28] This controversy results from the complex mechanisms between alcohol and the components of MetS or the study designs. Furthermore, it is known that the consumption of a large amount of alcohol has toxic effects on every tissue of the body. Excessive alcohol has detrimental effects on blood glucose and blood pressure.[28] In a population-based study performed on 19 215 participants in China, Jin et al[28] investigated the relationship between alcohol consumption and MetS and demonstrated that excessive consumption of wine (alcohol ≥50 g/d) was associated with an increased prevalence of MetS in men.

Some drugs may lead to an increased risk of MetS by causing weight increase or by altering glucose metabolism. Health care professionals should be aware of these types of risks associated with drug treatments, and patients should be monitored in terms of metabolic changes. Beta-blockers, diuretics, corticosteroids, danazol, growth hormone, oral contraceptives, thiazolidinediones, antipsychotics, antidepressants, antiepileptics, immunosuppressants, niacin, protease inhibitors, and retinoids are among the drugs that increase the risk of MetS.[23]

Usually, type 2 DM is itself a MetS. The patients use sulfonylurea and insulin for the treatment of MetS. Hypertension, abdominal obesity, and high TG levels are frequently observed in patients with type 2 DM. Due to the fact that drugs for type 2 DM contribute to abdominal obesity, even if the MetS criteria are not fulfilled by type 2 diabetic patients, these drugs may cause MetS.

An increase in weight is observed in diabetic patients after commencement of insulin. It is known that patients with poor metabolic control and greater weight loss prior to treatment gain more weight.[29] In our study, 12.8% of the patients were on insulin treatment. Although it has been suggested that pioglitazones are associated with increased subcutaneous fat rather than increased intra-abdominal fat, this finding has not been widely supported. However, insulin and secretagogues have an association. In individuals in whom the MetS criteria are not fulfilled, the use of these drugs leads to the development of obesity and the fulfillment of MetS criteria. If it is possible not to use these drugs in the treatment, or if another antidiabetic drug is used, it may be possible to correct the abdominal obesity and consequently avoid MetS in an individual with type 2 DM by lifestyle modifications. It may be beneficial to evaluate the early-stage type 2 DM as a reversible condition, like MetS, that can be corrected by lifestyle modifications. Unfortunately, antidiabetic treatment aimed at only controlling the hyperglycemia instead of an effective fight against obesity markedly increases the rate of obese type 2 diabetic patients, and consequently, contributes to a higher prevalence of secondary MetS.

Antipsychotic drugs may cause an increase in weight, changes in the glucose metabolism and hyperlipidemia.[23] In the study by Sicras et al,[30] the prevalence of MetS was reported to be higher in schizophrenic patients and patients with bipolar disorder who were on antipsychotic treatment (27%) than those in the control group (14.4%). In our patient population, 2.1% of the patients were on antipsychotics.

In the treatment of hypertension, which is a component of MetS, it is recommended to avoid the use of high doses of thiazide-like diuretics, the use of beta-blockers unless absolutely indicated, and the use of the thiazide+beta-blocker combination.[31] During antihypertensive treatment with diuretics and beta-blockers, changes occur in the metabolic components, primarily in the lipid profile and insulin resistance, and this condition is considered to cause a lower decrease in cardiovascular morbidity and mortality than expected.[31] Use of thiazides, particularly at high doses, causes an increase in total-C, LDL, and TG levels. Furthermore, thiazides deteriorate the control of glycemia in diabetic patients and contribute to insulin resistance.[23] Hyperuricemia and hypokalemia have also been suggested to play a role in exacerbation of MetS during treatment with thiazides.[32] The use of beta-blockers may also increase the insulin resistance and the risk of type 2 DM. Furthermore, the increase in weight caused by beta-blockers lead to unwanted metabolic effects.[23] In our study, 22.2% of the patients were on thiazides and 12.5% of the patients were on beta-blockers. Longitudinal data would be interesting in this regard.

High-dose oral contraceptives frequently lead to an abnormal glucose tolerance test. Lowdose combinations also cause minimal changes in glucose tolerance or insulin resistance. The hormonal components of oral contraceptives also exert negative effects on lipoprotein metabolism.[23] In the present study, 0.8% of our patients were on oral contraceptives.

Those who use these drugs do not necessarily have secondary MetS; however, it is prudent to keep in mind that MetS parameters may be effected from these drugs.

In conclusion, in addition to the known components of MetS, which is an important cause of morbidity and mortality worldwide, the factors that may lead to secondary MetS should also be defined. The thyroid function tests should be performed in patients with MetS, and the reasons leading to MetS, such as antipsychotic

and corticosteroid use, should be investigated and eliminated. Each of the MetS components should be investigated individually, and the factors that may lead to this condition should be evaluated secondarily. To implement an optimal treatment and eliminate the preventable factors, the causes of secondary MetS should be well defined, and it is a prerequisite to determine these factors by a detailed assessment in patients with MetS.

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