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The prevalence of metabolic syndrome and its components in benign and malignant nodular thyroid diseases

Benign nodüler ve malign tiroid hastalıklarında metabolik sendrom ve bileşenlerinin değerlendirilmesi

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Abstract

Purpose: Metabolic syndrome (MetS) is a condition harboring a group of metabolic abnormalities where insulin resistance (IR) plays a major role. The aim of our study is to evaluate MetS and its components in patients with benign and malignant nodular thyroid disease (NTD).

Materials and methods: A total of 800 patients (430 euthyroid benign nodular and 370 euthyroid malignant NTD) were analyzed for MetS and its components. Serum insulin levels and IR estimated by homeostasis model assessment (HOMA-IR), as well as other MetS parameters were evaluated.

Results: Metabolic syndrome was detected in 59.8% of 800 patients. There was no significant difference between benign and malignant NTD groups related to the prevalence of the MetS (61.4% in benign nodular group, 57.8% in malignant nodular group, $p>0.05$). In the whole study group, the most common MetS component was abdominal obesity (65%), followed by low HDL-C level (64.8%), and the least component was high blood glucose level (30.8%). When patients with benign and malignant NTD were evaluated separately, the occurrence of the MetS components were found in similar frequency in the benign group compared to the overall average. In the malignant group, it was determined that low HDL-C level was the most common and high blood pressure was the least common component. There was no significant difference between benign and malignant NTD groups in terms of insulin levels and HOMA-IR.

Conclusions: The results suggest that patients with NTD have significantly increased MetS prevalence compared to patients without NTD. However, there was no significant difference between benign and malignant NTD in this respect.

Key Words: Metabolic syndrome, thyroid, thyroid cancer, insulin resistance.

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Özet

Amaç: Metabolik Sendrom (MetS) insülin direncinin belirgin rol oynadığı ve metabolik anormalliklerin kümelendiği bir tablodur. Bu çalışmanın amacı benign ve malign nodüler tiroid hastalığı olanlarda metabolik sendrom ve bileşenlerini değerlendirmektir.

Gereç ve yöntem: Dörtyüzotuz ötiroid benign nodüler ve 370 ötiroid malign nodüler tiroid hastalığı olan toplam 800 hasta metabolik sendrom ve bileşenleri yönünden incelendi. MetS parametrelerinin yanı sıra insülin düzeyleri ve homeostasis model assessment- IR (HOMA-IR) ile hesaplanan İD seviyeleri değerlendirildi.

Bulgular: Çalışmaya alınan 800 hastanın %59,8'inde metabolik sendrom saptandı. Benign ve malign nodüler tiroid hastalığı olan gruplar arasında metabolik sendrom sıklığı açısından anlamlı fark saptanmadı (benign nodüler grupta %61,4, malign nodüler grupta %57,8, $p>0,05$). Tüm çalışma grubunda en sık karşılaşılan MetS bileşeni abdominal obezite (%65), ardından düşük HDL kolesterol düzeyi (%64,8) ve en az bileşen de yüksek kan glukoz düzeyi (%30,8) idi. Benign ve malign nodüler tiroid hastaları ayrı ayrı incelendiklerinde ise benign grubun MetS bileşen dağılımı genel ortalama ile benzer sıklıkta olup, malign grubun MetS bileşen dağılımında en sık düşük HDL kolesterol düzeyi (%71,9), en az ise kan basıncı yüksekliği (%26,2) olduğu bulundu. Benign ve malign nodüler tiroid hastaları arasında insülin düzeyleri ve insülin direnci açısından anlamlı fark saptanmadı.

Sonuç: Sonuçlar nodüler tiroid patolojisi olan hastaların, nodüler tiroid hastalığı olmayanlara göre anlamlı olarak artmış metabolik sendrom prevalansına sahip olduklarını göstermektedir. Ancak benign ve malign noduler gruplar arasında MetS bileşen dağılımı açısından fark saptanmamıştır.

Anahtar Kelimeler: Metabolik sendrom, tiroid, tiroid kanseri, insülin direnci.

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Introduction

Metabolic syndrome (MetS) is associated with multiple cardiovascular risk factors including abdominal obesity, impaired glucose tolerance or type 2 diabetes mellitus, hypertriglyceridemia, low high-density lipoprotein (HDL) and hypertension, in which insulin resistance (IR) plays an important role as a common denominator [1]. It is well known that insulin acts as a growth factor that stimulates cell proliferation, and chronic hyperinsulinemia has been associated with various types of malignancies such as colorectal, pancreatic, endometrium and breast cancers [2, 3]. Data on the effect of hyperinsulinemia in the development of thyroid nodules or thyroid cancer is limited and recently evolving [4-9]. Previous reports concluded that higher circulating levels of insulin cause increased thyroid proliferation and thyroid nodules, and thyroid volume and nodule prevalence have been shown to be increased in patients with IR [4, 5]. Data is accumulating about the existence of some relations between thyroid functional abnormalities and MetS and its components [10, 11]. Though thyroid morphological pathologies in those with MetS and their associations have also been examined [5, 12-14], an interesting and informative perspective on the subject would be investigating MetS and its components in cases with morphological thyroid abnormalities. There are many previous studies similar to this.

The aim of our study is to evaluate MetS and its components in patients with benign and malignant nodular thyroid disease (NTD), and to compare its prevalence with a reference population.

Materials and methods

Study Subjects

This was a single-center, retrospective study in patients with benign and malignant NTD. The Baskent University Ethics Committee for Human Studies approved the protocol. Consecutive 800 eligible cases, who have visited the outpatient clinic of Department of Endocrinology and Metabolism of Baskent University Hospital between 2009 and 2011 were included. There were 430 patients in benign NTD group and 370 patients in malignant NTD group who had papillary, follicular, and medullary thyroid cancer.

Euthyroidism was defined as thyroid stimulating hormone (TSH; reference range, 0.35-4.0 mIU/L), free tri-iodothyronine (FT3; reference range, 1.71-4.71 pg/ml) and free thyroxine (FT4; reference range, 0.8-1.9 ng/dL) within the normal reference range. Enrollment as a benign NTD case required the display of benign cytology of fine needle aspiration biopsy (FNAB) performed on the solitary nodules of uninodular goiter and on the largest and sonographically suspicious nodules of multinodular goiter cases. Besides, any possible increase in at least two dimensions of the solid component of the biopsied nodule had to be less than 20% during ultrasonographic follow-up performed every 6 to 18 months after FNAB [15]. Malignant NTD diagnosis involved the demonstration of thyroid malignancy on the postoperative histopathological examination report.

The diagnostic criteria proposed by the ATP III of the National Cholesterol Education Program have been used for the definition of MetS. The presence of three or more of the following five criteria indicated MetS: i) abdominal obesity, defined as a waist circumference (WC)>102 cm in men and >88 cm in women; ii) serum triglycerides (TGs) ≥150 mg/dL; iii) serum high density lipoprotein (HDL) <40 mg/dL in men and <50 mg/dL in women; iv) blood pressure ≥130/85 mmHg; and v) fasting plasma glucose ≥110 mg/dL [1]. (Hastaların insülin direnci, tansiyon ve kolesterol ilacı kullanmalarıda pozitif olarak kabul edildi).

Inclusion criteria were being between 18-75 years age and retaining all the parameters mentioned in this section in hospital records. Subjects with any of the following characteristics were excluded from the study: Those with a history of overt or subclinical thyroid dysfunction, high thyroid autoantibody titers. Patients were also excluded if they had hepatic or renal dysfunction, history of diabetes mellitus, heart failure, pregnancy and lactation.

Methods

All of the anthropometric and laboratory data of the study, including cytology and histopathological reports, were obtained from hospital records.

Measurements of subjects' height, weight, and WC were recorded. WC was measured with a folding tape at the natural waistline (the level of the umbilicus) in a horizontal plane. Body mass index (BMI) was obtained by dividing the body weight (kg) by the square of height (m). Blood pressure of each case was measured with a standard sphygmomanometer. The measurements were carried out by three experienced endocrine specialists who worked in the outpatient clinics at the time of patients' visits.

Each venous sample was drawn after a minimum fasting period of 12 hours (h). All samples were collected between 08:00 and 09:00 h. Thyroid function was evaluated by measuring FT4, FT3, and TSH using immunochemoluminescent assays by an automated analyzer (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA, USA). Thyroid antibodies [antithyroid peroxidase (normal range:<50 U/mL) and antithyroglobulin (normal range:<40 U/mL)] were measured by immunochemoluminescent assays employing commercial kits (Diagnostic Products Corp). Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH). Serum insulin level was assayed with a solid-phase competitive chemiluminescent enzyme immunoassay (Diagnostic Product Corp). HDL-C and TG concentrations were measured by enzymatic assay (Boehringer, Mannheim, Germany).

Serum insulin levels, IR, and other MetS parameters were evaluated. Insulin resistance was estimated based on the calculation of the homeostasis model assessment (HOMA) index for each patient. This was done using the formula: (fasting plasma insulin (IU/mL) x fasting plasma glucose (mmol/L)/22.5. HOMA-IR value was accepted as ≥2.5 for insulin resistance [16].

The frequency of metabolic syndrome and its components were derived from these parameters in both groups. The results were also compared with a reference population study on MetS prevalence [17].

Statistical Analysis

Continuous variables were shown as mean ± S.D., and categorical variables as percentage. Student's t-test was used to compare continuous variables and chi square test was used to compare categorical variables. Statistical analyses were performed using SPSS software (version 18.0). $p<0.05$ was considered significant. Bonferroni correction was performed for p value calculation for the comparison with reference population study ($p<0.0167$ was considered significant).

Results

MetS was detected in 59.8 percent (478) of the total 800 patients. Its prevalence was 61.0% among the female population (n=628), and 55.0% in its male counterpart (n=172) ($p>0.05$). The mean age of the patients with MetS was 51.2±12.2; and it was 39.5±13.8 in the non-MetS group ($p<0.001$). The clinical features of the patients are given in Table 1.

There were 430 patients in benign NTD, and 370 in malignant NTD group. There was no significant difference between these groups in terms of prevalence of the MetS (61.4% and 57.8% respectively, $p>0.05$). Also, the frequency of MetS did not differ significantly between the thyroid histopathological subgroups (Table 2).

When MetS components were analyzed, the most common component was abdominal obesity (n=520, 65%), followed by low HDL-C level (n=518, 64.8%), high triglyceride level (n=367, 45.9%), high blood pressure (n=278, 34.8%), and high blood glucose level (n=246, 30.8%). Low HDL-C level (69.9%) was the most common metabolic disorder in female subjects. In male subjects, the most common component was abdominal obesity (57.9%). High blood glucose level was at the bottom in both sexes (30.4% in female and 32.2% in male subjects).

Mean insulin levels, HOMA-IR, and rate of IR were higher in patients with MetS than those without (10.93±5.34 vs 5.86±2.75 IU/mL;3.47±3.06 vs 1.28±0.82; 55.4% vs 9.6%, respectively, $p<0.001$ for all).

Table 1. Demographic characteristics of study groups.

	Gender (Female/Male) (N)	Age (mean±SD)	*p*
Benign NTD	430 (328/102)	48.73±13.84	>0.05
Malignant NTD	370 (301/69)	43.88±14.03	<0.001
MetS	478 (384/94)	51.21±12.24	>0.05
Non-MetS	322 (245/77)	39.48±13.83	<0.001

N: number; SD: standart deviation; NTD, nodular thyroid disease; MetS: metabolic syndrome

Table 2. The prevalence of MetS in the benign and malignant NTD subgroups.

	NG%(N)	MNG%(N)	PTC%(N)	FTC%(N)	MTC%(N)	*p*
MetS (N=478)	54.3% (63)	64% (201)	58.9% (195)	54.8% (17)	25% (2)	>0.05
Non-MetS (N=322)	45.7% (53)	36% (113)	41.1% (136)	45.2% (14)	75% (6)	

MetS, Metabolic syndrome; NTD, Nodular thyroid disease; NG, Benign uninodular goiter; MNG, Benign multinodular goiter; PTC, Papillary thyroid cancer; FTC, Follicular thyroid cancer; MTC, Medullary thyroid cancer

There was no significant difference between benign and malignant NTD groups in terms of insulin levels (9.06±5.3 and 8.68±4.8 IU/mL respectively, $p>0.05$), HOMA-IR (2.74±2.9 and 2.4±2.2 respectively, $p>0.05$), and presence of IR (38.4% and 35.4% respectively, $p>0.05$).

The distribution of MetS components in benign and malignant thyroid groups is depicted in Table 2. The occurrence of the MetS components in the benign nodular group were similar to the overall group in frequency. In malignant group, low HDL-C level was the most common component, and the high blood pressure was the least common one. The intergroup comparison revealed that abdominal obesity and high blood pressure were more prevalent in benign group, whereas low HDL-C level was more frequent in malignant group significantly (Table 3).

The distribution of the number of components of the MetS in benign and malignant groups, and the whole study population was similar across each subgroup, as demonstrated in Figure 1 ($p>0.05$). Among all the subjects with MetS, 58.6% had three components of the syndrome, 32.8% beared four, and the rest 8.6%, five components.

Considering the malignant group, MetS was determined to be significantly more prevalent in stage 3 and stage 4 disease ($p<0.001$) (Table 4).

We compared the major results of the present study with a reference population study on the prevalence of MetS in Turkey performed by Kozan et al. [17]. The prevalence of MetS was found to be significantly higher in each nodular group than that in the population study ($p<0.001$) (Table 5).

Table 3. The distribution of the components of metabolic syndrome in the study groups.

	Benign NTD	Malignant NTD	*p*
Abdominal obesity	68.1%	61.4%	<0.05
High triglyceride	47.4%	44.1%	0.338
Low HDL	58.6%	71.9%	<0.05
High fasting glucose	33.5%	27.6%	0.07
High blood pressure	42.1%	26.2%	<0.05

NTD, nodular thyroid disease; HDL, high density lipoprotein

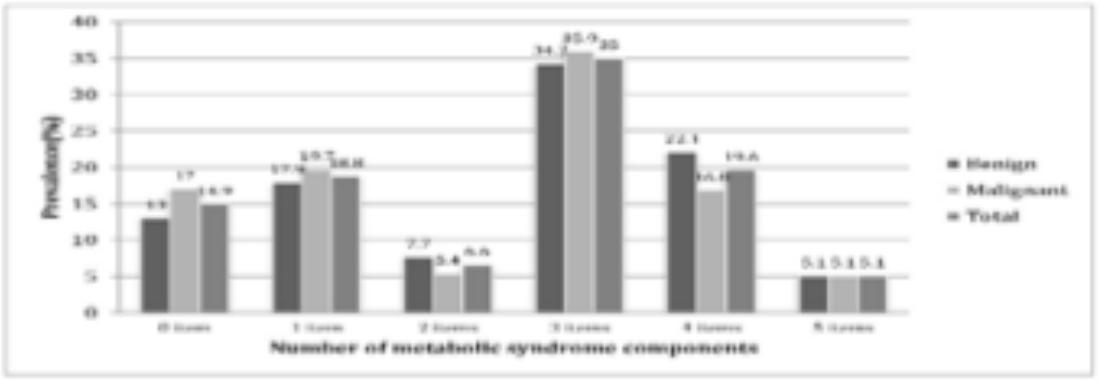

Figure 1. Prevalence of the number of components of the Metabolic Syndrome in benign and malignant nodular groups.

Table 4. Prevalence of metabolic syndrome according to the stage of malignant thyroid disease.

	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)	Stage 4 (%)	*p*
MetS (N=214)	143 (52.4%)	17 (58.6%)	16 (84.2%)	38 (77.6%)	<0.001
Non-MetS (N=156)	130 (47.6%)	12 (41.4%)	3 (15.8%)	11 (22.4%)	

N: number; MetS: metabolic syndrome

Table 5. The comparison of the prevalence of MetS with reference population study (17).

	Population study	Benign NTD	Malignant NTD	*p* *
MetS (N)	33.8% (1442)	57.8% (214)	61.3% (264)	<0.001
Non-MetS (N)	66.2% (2817)	42.2% (156)	38.7% (166)	
Total	4259	370	430	

MetS, metabolic syndrome; NTD, nodular thyroid disease

Discussion

In this study, we reported the prevalence of MetS under the ATP III definition in patients with benign and malignant NTD. The prevalence of MetS was 59.8% (478 out of 800 cases totally). We determined that the frequency of MetS was much higher than that reported by leading prevalence studies in Turkey [17, 18]. Ozsahin et al. and Kozan et al. have determined the prevalence of MetS using the same criteria as 33.4% and 33.9%, respectively [17, 18]. This may potentially be attributable, at least partially, to the selected group. That is, NTD may be a risk factor for MetS.

Thyroid hormones have a potential to act as a general metabolic controller organizing many metabolic processes and, as shown in previous studies, they may be associated with MetS and/or its components [4, 10-11]. Though there is scarce information on the effect of hyperinsulinemia in the development of thyroid nodules or thyroid cancer, recent studies have shown the existence of a relationship between IR and thyroid functional and morphological abnormalities [4, 5]. Rezzonico et al. reported that cases with hyperinsulinemia have larger thyroid glands and a higher prevalence of thyroid nodules [4]. It has also been shown that insulin and insulin-like growth factor-1

(IGF-1) receptors are overexpressed in most thyroid tumors as an early step in thyroid carcinogenesis [2]. Insulin/IGF-1 signaling pathway is known to modulate regulation of thyroid gene expression and might be regarded as other important factors in thyrocyte proliferation, differentiation, and malignant transformation [19]. Sustained exposure to high serum IGF-1 levels is likely to play a role in the development of thyroid proliferation. An additive role for the autocrine/paracrine action of locally produced IGF-1 and IGF-2 is also possible [2, 20]. These genetic events seem to generate an activation of the MAPK pathway, which usually induces cell proliferation and dedifferentiation [21, 22]. Obesity is associated with increased free or bioavailable IGF-1 [23], and several epidemiologic studies have reported a positive association between IGF-1 and cancer risk [24]. This may be one of the causative/contributive factors in nodular thyroid and MetS relationship.

An inpatient population study in Italy demonstrated that MetS is an independent risk factor for the occurrence of multinodular non-toxic goiter in a geographic area with moderate iodine deficiency [25]. We determined no difference in the prevalence of IR between benign and malignant groups (38.4% and 35.4%, respectively, $p>0.05$). Also, we could find no significant difference in the frequency of MetS, neither between benign and malignant thyroid groups, nor between pathological subtypes of malignant thyroid conditions. A national case control study also similarly did not depict, neither MetS nor IR, significant risk factors for differentiated thyroid cancer (DTC) [9]. IR causes thyroid proliferation and progression to nodule formation and thyroid neoplasia. Rezzonico et al. have shown that the rates of IR was higher in DTC than the control groups (50% and 10%, respectively) [6]. They also demonstrated that IR was more frequent in papillary thyroid cancer than follicular subtype [6]. In accord with this and some other previous reports [6, 7, 26], one might expect more IR cases and more prevalent MetS in malignant thyroid group. This discrepancy may be partly explained by insufficient number and inhomogeneous distribution of cases in some subgroups in our study, probably due to issues inherent to study design. Nevertheless, MetS was observed more commonly in stage 3 and stage 4 malignant thyroid diseases in our study. Thus, MetS can be related with advanced stage thyroid cancer. These findings support the suggestion that IR may influence tumor biology negatively [4-7]. Additional prospectively designed studies are needed to further investigate the relationship between metabolic syndrome and the development of malignant thyroid disease.

In our study, the mean age of the group with MetS was significantly higher than the group without MetS, an expected finding supported by other studies [27, 28]. Sanisoglu et al. reported that the prevalence of MetS was the lowest at age group 30-39 (15.34%), while it progressively increased with age until the age group 50-59 (27.98%) [28]. Ford et al. stated that the prevalence of MetS increased with age, and 33-45% of subjects over 50 years met the criteria for MetS [28]. In the present study, there was a clear age-related increase in the prevalence of MetS in a Turkish adult population with NTD.

The prevalence of MetS was found to be similar in both sexes (61% in women, 55% in men). MetS was significantly more prevalent in women in the national prevalence studies by Ozsahin et al. (39.1% vs 23.7%) and Kozan et al. (39.6% vs 28%) [17, 18]. In some countries, MetS has been reported to be more prevalent among women [29-31], whereas in others, the prevalence of the syndrome was similar in two sexes [32-34]. Considering the female dominance of nodular thyroid disorders (i.e. almost 80% of the study group was female), one might expect to see this in MetS prevalence also. Prominently increased frequency of MetS in this special population might have swept away this difference.

The most frequent MetS component in the whole study group was abdominal obesity (65%), followed by low HDL (64.8%). High fasting glucose level was the rarest component (30.8%). In the reference population study by Kozan et al. high blood pressure was the predominant component [17]. In line with our results, abdominal obesity was higher in women than in men. In addition, low HDL level was very common in women. Similarly, high fasting glucose level was the most uncommon component in both sexes [17]. In another population study about MetS among Turkish young adults conducted by Soysal et al, it was shown that the rates of abdominal obesity was higher in women than in men and low HDL level

was higher in men. Again, consistent with our study, high fasting glucose level was the rarest component in both sexes [35].

We also evaluated MetS components in benign and malignant thyroid groups. Significantly lower HDL-cholesterol levels were recorded in malignant group (71.9%). Giusti et al. reported that cholesterol and triglyceride levels were not significantly different between the control and DTC subjects. However, HDL-cholesterol levels were significantly lower in DTC patients than in controls [27]. Our similar finding might make a sense in terms of being a component of MetS. In their study, similar prevalence of hypertension and glucose level was noted in DTC and control subjects [26]. In our study, high blood pressure was more common in benign group, whereas, glucoregulation state was similar in the two groups. In an epidemiologic cohort study, designed to prospectively investigate the impact of metabolic factors on the risk of thyroid cancer, the authors determined an inverse association between glucose, and a positive association between BMI and thyroid cancer risk in women [13].

Kozan et al. found that 3.6% of the population beared 5 MetS components [17]. This rate was 5.1% in our study. This difference might be, at least in part, related to the likely higher prevalence of IR in this cohort.

Retrospective nature, being unable to explain some findings are probable limitations of the present study. Lack of a control group consisting of cases with no morphological thyroid disorder may be another weakness, and the reason for some unexplained issues in the study.

Though retrospective, looking into the MetS-thyroid relationship from a different perspective, and being possibly original in this design in English literature according to our search, may be potential strengths of our study. Comparison of our main findings with a reference population prevalence study on MetS performed in our country, could be another advantage.

In conclusion, when the population data is considered, our results suggest that metabolic syndrome may be a risk factor for nodular thyroid disease. Despite some contrary findings in the literature, we found no significant difference between benign and malignant nodular thyroid disease in terms of prevalence and distribution of components of MetS. Confirmation of the findings in prospectively designed studies may lead us to consider screening cases with nodular thyroid diseases for MetS and its components.

Conflict of Interest: No conflict of interest was declared by the authors.

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