Association Between Metabolic Syndrome and Clinicopathological Features of Differentiated Thyroid Cancer

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Abstract

Purpose: Metabolic syndrome (MetS) is a risk factor for differentiated thyroid cancer (DTC). Whether MetS impacts the aggressiveness of DTC is still unclear. We carried out this study to clarify this issue.

Methods: We evaluated 455 consecutive DTC patients treated with surgery. The patients were divided into three groups based on their number of MetS components: patients without any MetS components, patients with one to two MetS components, and patients with three to five MetS components. The clinical features and histological aggressiveness of DTC at the time of diagnosis were evaluated.

Results: A total of 455 patients were included in this study. Eighty-five patients had three or more metabolic components and were diagnosed as having MetS. Those patients with one or two metabolic components had higher risks for bilaterality (OR = 1.90, 95% CI: 1.04–3.46) and capsule invasion (OR = 1.68, 95% CI: 1.05–2.70). MetS was a risk factor for larger tumors (OR = 2.25, 95% CI: 1.25–4.06), more lymph node metastasis (OR=3.14, 95% CI: 1.68–5.87), multifocal tumor (OR = 2.38, 95% CI: 1.30–4.35), bilateral disease (OR = 3.39, 95% CI: 1.67–6.90), capsule invasion (OR = 2.26, 95% CI: 1.15–4.45), and extrathyroid invasion (OR = 4.44, 95% CI: 1.67–11.81) after correction for age, sex, and the thyroid-stimulating hormone level (TSH).

Conclusions: In our hospital-based cohort study, MetS was associated with the aggressiveness of DTC. This association was still significant after being adjusted for age, sex, and TSH.

Instruction

The incidence of thyroid cancer in China has significantly increased over the past 2 decades [1]. It is more common in women, with a 3:1 female-to-male ratio. Differentiated thyroid cancer (DTC) is the most common histologic subtype of thyroid cancer, accounting for 90% of new cases, and has the best prognosis. Increased detection of subclinical thyroid cancers by the increased utilization of ultrasonography, and fine-needle biopsies may partly account for the rise in the incidence of thyroid cancer [2]. However, this does not sufficiently explain the increase in the incidence of large tumors in all size categories. Therefore, the effect of other modifiable factors including changes in lifestyle and environmental factors cannot be ignored.

Metabolic syndrome (MetS), which indicates a cluster of metabolic abnormalities, including central obesity, hyperglycemia, hypertension, and dyslipidemia, has been considered to be a risk factor for a variety of cancers, including thyroid cancer [3]. The major mechanism of MetS is insulin resistance. Several studies have investigated the association between MetS and thyroid cancer [4–6]. Park et al. followed 9,890,917 adults for 7 years and found that the thyroid cancer risk was higher in a MetS group than in a non-MetS group (HR = 1.15; 95% CI 1.13–1.17) [5]. A meta-analysis by Yin et al. also showed metabolic components, including hyperglycemia, high BMI, and hypertension significantly increased the thyroid cancer risk [4].

The prevalence of obesity and unhealthy metabolic status, such as MetS, has markedly increased in recent years. A substantial portion of DTC patients suffer from MetS. It is a reversible condition associated with the modern Western lifestyle. It is important to clarify whether MetS affects the clinical features and prognosis of DTC. However, to the best of our knowledge, few studies have focused on this issue. Therefore, we carried out this study to investigate the association between MetS and the clinicopathologic features of DTC.

Materials And Methods

Population

A hospital-based cohort of patients that were diagnosed with DTC at the Renmin Hospital of Wuhan University from April 2020 to November 2020 was included in this study. All of the included patients received surgery treatment. Patients were excluded if there was no documentation of their past history of disease and/or if they were diagnosed with medullary or anaplastic thyroid cancer. This study was performed with the approval of the Ethics Committee of the Renmin Hospital of Wuhan University (NO. WDRY2020-K231), and all of the participating patients were provided written, informed consent for their clinical data to be reviewed and applied in this study.

Data collection

A comprehensive questionnaire was used to obtain the basic information, including medical history, the family history of chronic diseases, current medication use, and smoking and drinking status. Height, weight, waist circumference, and blood pressure were measured based on standardized protocols. Height and body weight were measured without shoes and heavy clothes. The waist circumference, midway between the base of the costal arch and the top of the iliac crest, was measured in upright standing subjects. Blood pressure was taken using the same electronic monitor in the center in a seated position after at least 5 minutes of rest. Blood sampling was conducted after overnight fasting. Biochemical measurements were taken for thyroid stimulating hormone (TSH), fasting blood glucose (FBG), triglycerides (TG), total cholesterol, and high-density lipoprotein cholesterol (HDL-C), utilizing the same laboratory techniques as those used at the center.

Diagnosis and definition

All the patients received surgical treatment for primary tumors. Thyroid surgery was performed by experienced surgeons who had 5–20 years of experience. Central lymph node dissection was routinely performed on these patients. An intraoperative frozen section was performed on all the patients to determine nodule malignancy. The inclusion of lateral lymph node dissection was performed based on preoperative imaging results, fine needle aspiration, and intraoperative exploration. The central neck refers to level VI and VII, whereas the lateral neck includes levels II, III, IV, and V in the present study.

A routine pathologic diagnosis was performed on the specimens of the thyroid and fatlike tissues with 2–3µm sections. Hematoxylin and eosin (HE) staining combined with or without immunohistochemistry was performed to determine the pathologic types. A solitary focus means only one tumor in the thyroid, and multiple focus mean two or more foci limited to the thyroid. Bilaterality is defined as the presence of DTC foci in the right and left lobes of the thyroid. Capsular invasion means that the tumor invades up to and possibly into the thyroid capsule, but does not penetrate it. In contrast, extrathyroid invasion is defined as when the tumor penetrates through the capsule and into the strap muscle or perithyroidal fibrofatty tissues.

The criteria for the diagnosis of MetS in our study were provided by the Chinese Diabetes Society. MetS was defined by the presence of three to five of the following variables: (1) abdominal adiposity (defined as waist circumference ≥ 90 cm in Chinese men and waist circumference ≥ 85 cm in Chinese women), (2) TG concentration ≥ 1.70 mmol/L, (3) HDL concentrations < 1.00 mmol/L, and (4) blood pressure $\geq 130/85$ mmHg or previous hypertension diagnoses, which were described as raised blood pressure, (5) fasting glycemia > 5.6 mmol/L, or a previous type 2 diabetes diagnosis.

Statistical analysis

All of the statistical analyses were performed using Stata version 15.1 (Stata Corp, College Station, Texas). Continuous variables were described as the mean ($x \pm SD$). Categorical variables were described by using percentages. The distribution of clinical and pathologic features of the patients with or without MetS were evaluated and compared using chi-square tests for categorical variables and the student's t test (age) or rank sum test for continuous variables (tumor size and TSH). A test for interaction was used to analyze the interaction effect of gender and age and MetS on the clinicopathological characteristics of DTC. Univariate and multivariate binary logistic analyses were used to explore the associations between MetS and the clinicopathological characteristics of DTC. In the multivariate logistic regress model, age, sex, and TSH were adjusted. Furthermore, we analyzed the association between different numbers of MetS components and the clinicopathological characteristics of DTC. All statistical tests were two-tailed, and a p value < 0.05 was considered statistically significant.

Results

Characteristics of participants

A total of 455 patients, including 126 male and 329 females with DTC, participated in this study. Table 1 describes the pathological characteristics of DTC and the metabolic characteristics of the participants at recruitment. The mean age of the participants was 44.19. The mean dimension of the primary tumor was 1.22 cm, and in most cases, was less than 4 cm. About 44.40% of the participants had a tumor size less than 1cm. All the included participants received central lymph node dissection according to our surgical protocol. And lateral lymph node dissection was performed in 44 participants (9.67%). A total of 202 (44.4%) participants had metastatic lymph nodes. About 40% of the tumors were multifocal, and approximately 20% of the tumors were bilateral. Capsule invasion was found in 71.87% (327/455) of the

cases. Extrathyroid invasion was found in 8.57% (39/455) of the patients. Almost 38% of the patients had blood pressure $\geq 130/85$ mmHg, and 6.81% of the patients had diabetes. High TG was detected in 24.62% (112/455) of the participants. While low HDL was detected in 23.52% (107/455) of the participants, 82 of the participants had abdominal adiposity. A total of 221 (48.57%) patients had one or two metabolic components, and 85 (18.68%) patients had three or more than three metabolic components and were diagnosed as MetS.

Table 1
Clinicopathological characteristics of included patients.

Characteristics	Patients (n = 455)	%
Sex		
Male	126	27.69
Female	329	72.31
Age	44.19 ± 11.68	/
TSH	2.03 ± 1.47 IU/ml	/
Tumor size		
Mean	1.22 ± 0.94 cm	/
≤ 1cm	243	53.41
> 1cm	212	46.59
Lymph node metastasis		
Negative	253	55.60
Positive	202	44.40
Multifocal tumor		
No	314	69.01
Yes	141	30.99
Bilaterality		
No	355	78.02
Yes	100	21.98
Capsule invasion		
No	128	28.13
Yes	327	71.87
Extrathyroid invasion		
No	416	91.43
Yes	39	8.57

Values are expressed as mean ± standard deviation or number (%).

TSH, thyroid stimulating hormone. TG, triglycerides. HDL-C, high-density lipoprotein cholesterol. MetS, metabolic syndrome.

Characteristics	Patients (n = 455)	%
Blood pressure $\geq$ 130/85mmHg		
No	284	62.42
Yes	171	37.58
Diabetes		
No	424	93.19
Yes	31	6.81
High TG ($\geq$ 2.3 mmol/L)		
No	343	75.38
Yes	112	24.62
Low HDL-C ($<$ 1.0 mmol/L)		
No	348	76.48
Yes	107	23.52
Abdominal adiposity		
No	373	81.98
Yes	82	18.02
Number of MetS components		
0	149	32.82
1–2	221	48.57
3–5	85	18.68
Values are expressed as mean $\pm$ standard deviation or number (%).		
TSH, thyroid stimulating hormone. TG, triglycerides. HDL-C, high-density lipoprotein cholesterol. MetS, metabolic syndrome.		

Relationship between MetS and clinicopathological features of DTC

The clinical data and the tumor characteristics, according to the presence or absence of MetS, are reported in Table 2. More men suffered from metabolic syndrome than women. No significant difference in TSH levels was observed between those patients with and without MetS. The patients with MetS were older ($p = 0.035$) and had larger tumors ($p = 0.019$) and more lymph node metastasis ($p = 0.007$) than the patients without any components of MetS. The cases with one or two metabolic components showed

intermediate figures. In the MetS group, the patients more frequently had a multifocal ($p = 0.001$) and bilateral ($p = 0.016$) disease compared to patients without MetS. Patients with MetS also had a higher risk of developing capsule invasion ($p = 0.016$) and extrathyroid invasion ($p = 0.014$).

Table 2
Clinicopathologic characteristics for patients with and without metabolic syndrome

Characteristics	Non-MetS		MetS	p
	0 components	1–2 components	3–5 components	
Sex				
Male	17 (11.41)	65 (29.41)	44 (51.76)	0.001
Female	132 (88.59)	156 (70.59)	41 (48.24)	
Age (mean ± SD)	42.30 ± 12.72	45.02 ± 11.10	45.36 ± 10.95	0.035
TSH (mean ± SD)	2.00 ± 1.29 IU/ml	2.00 ± 1.57 IU/ml	2.15 ± 1.55 IU/ml	0.318
Tumor size				
Mean ± SD	1.14 ± 0.86 cm	1.21 ± 1.03 cm	1.40 ± 0.84 cm	0.019
≤ 1	90 (60.40)	122 (55.20)	31 (36.47)	0.001
> 1	59 (39.60)	99 (44.80)	54 (63.53)	
Lymph node metastasis				
No	93 (62.42)	125 (56.56)	35 (41.18)	0.007
Yes	56 (37.58)	96 (43.44)	50 (58.82)	
Multifocal tumor				
No	108 (72.48)	159 (71.95)	47 (55.29)	0.010
Yes	41 (27.52)	62 (28.05)	38 (44.71)	
Bilaterality				
No	127 (87.59)	171 (78.44)	57 (67.06)	0.001
Yes	18 (12.41)	47 (21.56)	28 (32.94)	
Capsule invasion				
No	54 (36.24)	57 (25.79)	17 (20.00)	0.016
Yes	95 (63.76)	164 (74.21)	68 (80.00)	
Extrathyroid invasion				
No	140 (93.96)	205 (92.76)	71 (83.53)	0.014
Values are expressed as mean ± standard deviation or number (%). A two-tailed P value of less than 0.05 was considered statistically significant.				
TSH, thyroid stimulating hormone. MetS, metabolic syndrome.				

Characteristics	Non-MetS		MetS	p
	0 components	1–2 components	3–5 components	
Yes	9 (6.04)	16 (7.24)	14 (16.47)	
Values are expressed as mean $\pm$ standard deviation or number (%). A two-tailed P value of less than 0.05 was considered statistically significant.				
TSH, thyroid stimulating hormone. MetS, metabolic syndrome.				

A multivariate analysis was performed to detect the correlation between MetS and the clinicopathological features. As shown in Table 3, after correction for age, sex, and TSH, MetS was still a risk factor for larger tumors (OR = 2.25, 95% CI: 1.25–4.06), lymph node metastasis (OR = 3.14, 95% CI: 1.68–5.87), multifocal tumor (OR = 2.38, 95% CI: 1.30–4.35), bilateral disease (OR = 3.39, 95% CI: 1.67–6.90), capsule invasion (OR = 2.26, 95% CI: 1.15–4.45), and extrathyroid invasion (OR = 4.44, 95% CI: 1.67–11.81). Those patients with one or two metabolic components had higher risks for bilaterality (OR = 1.90, 95% CI: 1.04–3.46) and capsule invasion (OR = 1.68, 95% CI: 1.05–2.70). However, no differences were found in tumor size, lymph node metastasis, multifocal tumors, and extrathyroid invasion between patients with one or two metabolic components and patients without any metabolic components.

Table 3

Multivariate ORs of metabolic syndrome for prognostic factors of differentiated thyroid cancer

Clinicopathological features	Non-MetS (0 components)	Non-MetS (1–2 components)	P	MetS (≥ 3 components)	P
Tumor size	1	1.17 (0.75–1.82)	0.481	2.25 (1.25–4.06)	0.007
Lymph node metastasis	1	1.53 (0.96–2.45)	0.075	3.14 (1.68–5.87)	0.001
Multifocal tumor	1	1.07 (0.67–1.73)	0.773	2.38 (1.30–4.35)	0.005
Bilaterality	1	1.90 (1.04–3.46)	0.037	3.39 (1.67–6.90)	0.001
Capsule invasion	1	1.68 (1.05–2.70)	0.031	2.26 (1.15–4.45)	0.018
Extrathyroid invasion	1	1.44 (0.60–3.43)	0.413	4.44 (1.67–11.81)	0.003
Adjusted for age, sex and thyroid stimulating hormone.					
MetS, metabolic syndrome.					

Relationship between metabolic components and clinicopathological features of DTC

We further analyzed the relationship between each of the five metabolic components and the clinicopathological features of DTC. As shown in Fig. 1, after adjusting for age, sex, and TSH, a blood pressure $\geq 130/85$ mmHg was associated with lymph node metastasis (OR = 1.58, 95% CI: 1.03–2.40), bilateral disease (OR = 2.63, 95% CI: 1.62–4.25), and extrathyroid invasion (OR = 3.50, 95% CI: 1.71–7.16). Diabetes had no significant association with any of the clinicopathological features. Abdominal adiposity was associated with lymph node metastasis (OR = 2.06, 95% CI: 1.23–3.46). High TG was a risk factor for multifocal tumors (OR = 1.72, 95% CI: 1.08–2.74) and capsule invasion (OR = 1.90, 95% CI: 1.09–3.32). Low HDL was associated with lymph node metastasis (OR = 3.02, 95% CI: 1.83–4.99), multifocal tumors (OR = 1.94, 95% CI: 1.19 – 3.17), bilateral tumors (OR = 1.91, 95% CI: 1.12 – 3.26), and extrathyroid invasion (OR = 2.29, 95% CI: 1.06 – 4.94).

Discussion

To our knowledge, this is the first study to determine the association between MetS and the clinicopathological features of DTC. This hospital-based cohort study revealed that patients with MetS tended to have larger tumors. Such a risk is likely to be rather the expression of a general dysmetabolic condition than of a specific dysmetabolic trait. More invasive characteristics, including multifocal disease, capsule invasion, and extrathyroid invasion, were also observed in patients with MetS. Furthermore, the risk of lymph node metastasis was more than triple in patients with MetS. Blood pressure $\geq 130/85$ mmHg, abdominal adiposity, and low HDL were risk factors for lymph node metastasis.

Previous studies had well defined the relationship of MetS and thyroid cancer. MetS and each component of the MetS are associated with an increased risk of thyroid cancer. Few studies have focused on the effects of MetS on the aggressiveness and prognosis of thyroid cancer. A study by Chen et al. demonstrated that multifocal tumor was more common in patients with diabetes. But no significant differences in tumor size, lymph node metastasis, and soft tissue invasion were noted between the patients with diabetes and the control group, which was similar with the results in our study [7]. Qin et al. carried out a comparative analysis of the serum proteome profiles of thyroid cancer. In their study, TG and HDL levels were significantly different between patients with thyroid cancer and control groups. And among patients with DTC, a low HDL level was associated with lymph node metastasis. No significant association was observed between the TG level and lymph node metastasis [8]. Epidemiology studies have reported a positive association between obesity and thyroid cancer risk. The correlation between BMI and aggressiveness of DTC has been reported in several studies, but the results have been inconsistent [9, 10]. In the study by Kim et al., a higher BMI was associated with more aggressive tumor features, such as lymph node metastasis, lymphatic invasion, and tumor multiplicity in patients ≥ 45 years of age. However, Matrone et al. did not demonstrate any association between BMI and the aggressiveness of DTC in 1058 patients [6]. In another study by Grani et al., they detected no association between obesity and the aggressive features of thyroid cancer [5]. Body mass index (BMI) was used as a

major measurement in most of the studies. But body fat distribution and impaired adipose tissue function, rather than total fat mass, could better predict insulin resistance and related complications at the individual level [7]. Abdominal adiposity might play a more significant role in thyroid carcinogenesis and the progression of thyroid cancer. Few studies have focused on the impact of abdominal adiposity on the aggressiveness of DTC. In our study, we demonstrated that abdominal adiposity was significantly associated with lymph node metastasis. However, we are not aware of any previous studies of hypertension and the aggressiveness of DTC. We found that blood pressure $\geq 130/85$ mmHg was associated with lymph node metastasis, bilateral disease, and extrathyroid invasion.

Several biologic mechanisms may explain the link between MetS and the aggressiveness of DTC. First, insulin resistance is a key factor in the pathophysiology of MetS. It was reported that insulin assist many tumors' generation and progression. An increased level of insulin may stimulate vascular endothelial growth factor expression and promote the proliferation of vascular endothelial cells in cancer [11]. Insulin resistance can increase proliferation, angiogenesis, cellular mobility, apoptosis, and damage to the DNA molecules of cancer cells by active oxygen forms due to excess glucose. Furthermore, thyroid cancer cells overexpress both insulin-like growth factor (IGF) ligands and their receptors. The IGF axis, which is activated by insulin resistance in MetS, can promote cell proliferation and inhibit programmed cell death [12]. Second, TSH is involved in mitogenic pathways of the thyroid gland. Cross-sectional studies have found correlations between TSH and the components of MetS [13, 14]. Previous studies have indicated that the prevalence of dyslipidemia increases along with higher TSH concentrations [15, 16]. In our study, then TSH level was higher but not statistically significant in patients with MetS. Increased serum TSH levels may stimulate thyroid cell proliferation and growth and promote the progression of thyroid cancer. Third, the low-grade chronic and systemic inflammation in MetS may also affect the aggressiveness of thyroid cancer. MetS could result in NF- κ B activation and increase the synthesis and secretion of chemokines, which play a central role in the progression of thyroid cancer [17, 18]. Other factors, such as increased levels of estradiol, may also play important role in thyroid cancer progression [19].

In the present study, we investigated the association between MetS and the aggressiveness of DTC and did find such an association. Our study has several limitations. We included a relatively small number of patients in this study. Due to the limited duration of follow-up, our study has no information about follow-up evaluations of the patients for potential development of future metastases. In addition, some potential confounding factors (i.e., the duration of metabolic syndrome duration and treatment and smoking) were not taken into account in our analysis.

In conclusion, in our hospital-based cohort study, MetS was associated with the aggressiveness of DTC. This association was still significant after being adjusted for age, sex, and TSH. MetS is a reversible condition associated with modern lifestyle. Dietary adjustment may help to regress MetS and the aggressiveness of DTC.

Declarations

Author contributions:

Song, Jun-Long. Study design, analysis of data; drafting the work. Ling-Rui Li, Xi-Zi Yu and Ling Zhan: Acquisition and analysis of data; Zhi-Liang Xu and Juan-Juan Li and Sheng-Rong Sun: interpretation of data. Chuang Chen supervised the study and approved the final manuscript.

Compliance with ethical standards**Conflicts of interest:**

None.

Ethical approval:

This study was performed with the approval of the Ethics Committee of the Renmin Hospital of Wuhan University.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Data Availability:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Multivariate analysis for relationship between five metabolic components and clinicopathological features.