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Original Article

Metabolic syndrome, including hypertension and impaired fasting glucose, is an independent risk variable for increased thyroid nodule(s) prevalence in euthyroid subjects

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Abstract: Background: The present of thyroid nodule(s) maybe associated with metabolic index. Methods: To investigate the correlation of thyroid nodule(s) with metabolic syndrome or its components in euthyroid subjects, 113 patients with newly diagnosed thyroid nodule(s) and 113 age- and gender-matched healthy subjects were enrolled in this study. Results: Both the level of systolic blood pressure, diastolic blood pressure and fasting glucose were significantly higher in patients with thyroid nodule(s) than that in health control (P=0.002; $P < 0.001$; $P < 0.001$). Percentage of metabolic syndrome (36.28%), hypertension (51.33%) and impaired fasting glucose (27.43%) were also significantly higher in patients with thyroid nodule(s) than those without (12.39%, 30.09% and 11.50%) ($P <$ 0.001, P=0.001, P=0.002). Binary logistic regression analysis showed that higher prevalence of thyroid nodule(s) was associated with increased incidence of hypertension (OR=2.17; 95% CI: 1.24, 3.80) and impaired fasting glucose (OR=2.46; 95% CI: 1.19, 5.10). Meanwhile, the association between the number of nodules and impaired fasting glucose were found (P=0.016). Conclusions: Patients with metabolic syndrome have significantly increased prevalence of thyroid nodule(s). Meanwhile, hypertension and impaired fasting glucose are the most related metabolic parameters as the risk variables for the increased prevalence of thyroid nodule(s). In addition, impaired fasting glucose is associated with the number of nodules.

Keywords: Metabolic syndrome, thyroid nodule(s), impaired fasting glucose

Introduction

Metabolic syndrome (MetS) is a cluster of risk factors which causes a higher risk of cardiovascular diseases and diabetes mellitus [1-3]. Different definitions of MetS have been suggested by different organizations, and the definition by the International Diabetes Federation (IDF) is commonly acceptable which including obesity, dyslipidemia, hypertension, and hyperglycemia. Thyroid hormones take part in many metabolic processes, such as blood pressure, glucose and lipid. Previous studies had reported that thyroid function and thyroid morphology may associate with MetS and its components [4-10]. However, the causality and certain mechanism were still unclear. Obesity, insulin resistance (IR) and diabetes mellitus were the most studied components of MetS. The potential mechanism of the relationships with obesity might be related to the dysfunctional axis of the hypothalamus, pituitary, thyroid, and the adipose tissue [11, 12]. Obese patients often present with IR or impaired glucose regulation, it is hypothesized that IR or impaired glucose regulation may be another potential mechanism of higher prevalence of thyroid nodule(s). Therefore, the prevalence of thyroid nodule(s) may be related to MetS and its components.

The association of MetS and its components with the alteration of thyroid morphology in

Table 1. Metabolic parameters of enrolled subjects

Variable	*Thyroid nodule (s)*	*Normal control*	*P value*
Gender (Male/Female)	113 (86/27)	113 (86/27)	-
Age (years)	47 (32-74)	47 (32-74)	-
BMI (kg/m^2)	25.4 (18.2-37.8)	25.2 (18.2-34.9)	0.400
SBP (mmHg)	127 (101-179)	121 (90-171)	0.002**
DBP (mmHg)	85.76±11.40	80.97±11.49	< 0.001**
FPG (mmol/L)	5.34 (4.17-14.12)	5.06 (3.78-8.54)	< 0.001**
TC (mmol/L)	5.04±0.99	4.91±0.81	0.092
TG (mmol/L)	1.60 (0.38-17.26)	1.31 (0.45-8.16)	0.138
HDL-C (mmol/L)	1.31 (0.00-2.56)	1.35 (0.00-2.15)	0.175
LDL-C (mmol/L)	3.21 (0.00-4.88)	3.00 (0.00-4.77)	0.468
UA (umol/L)	349.80±95.74	354.74±81.33	0.428
FT3 (pmol/L)	4.49 (3.25-6.53)	4.63 (3.36-6.15)	0.268
FT4 (pmol/L)	16.16±1.97	16.08±1.92	0.959
TSH (uIU/mL)	1.84 (0.59-4.19)	1.93 (0.58-4.08)	0.874
TPO-Ab (IU/mL)	0.16 (0.00-2.28)	0.20 (0.00-0.86)	0.638
Tg-Ab (IU/mL)	1.01 (0.30-4.05)	1.16 (0.36-4.10)	0.236

Data are mean ± SD or median (range). $^{**}P < 0.01$.

patient with normal range of thyroid function in China where people have taken iodized salt for 20 years is extremely rare. The objective of this clinical study is to investigate whether MetS is associated with the prevalence of thyroid nodule(s) (including the number and size of nodule(s)) in euthyroid subjects taking iodized salt, and which component is most related.

Materials and methods

Study design and patients

Thyroid nodule(s) (TN) was defined by the ultrasonographic characteristics of thyroid. All subjects recruited in our study were divided into two groups, thyroid nodule(s) and healthy control subjects.

Adults who had complete clinical data (gender, age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), uric acid (UA), free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), anti-thyroid peroxidase antibody (TPO-Ab), antithyroglobulin antibody (Tg-Ab), thyroid ultrasonography, medical history, smoking and drinking history) were included in the case-control study. The population data was from the Health Management Center of Shandong Provincial Qianfoshan Hospital between Jan. 2013 and Dec. 2013. We wished to focus on subject who has thyroid nodule(s) but no other thyroid diseases. So the exclusion criteria were shown below: (1) People who had other thyroid diseases besides thyroid nodule(s). (2) Abnormal thyroid function and antibody (normal range: 3.1 pmol/L ≤ FT3 ≤ 6.8 pmol/L; 12 pmol/L ≤ FT4 ≤ 22 pmol/L; 0.27 uIU/mL ≤ TSH ≤ 4.2 uIU/mL; 0 IU/mL ≤ TPO-Ab ≤ 5.61 IU/mL; 0 IU/mL ≤ Tg-Ab ≤ 4.11 IU/mL). (3) Pregnancy or breast-feeding women. During the selection of the individuals recruited in our study, only 217 TN patients completely met the inclusion criteria. Among them, we picked up 113 newly diagnosed TN patients named as TN group firstly. In addition, 113 healthy control (NC) subjects matched to the TN group for gender and age were enrolled as controls.

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Shandong Provincial Qianfoshan Hospital (Jinan, China). Written informed consent was obtained from all subjects in advance.

Age, medical history, smoking and drinking history were collected by clinicians. Weight and height were measured and BMI was calculated as weight (kg)/height (m^2). All subjects underwent a thyroid examination using a color ultrasonic diagnostic apparatus. The characteristics of thyroid were reported. All the volunteers had the fasting blood test (empty stomach at least 8 hours before blood test) and the serum detections were performed at the same clinical laboratory. Blood pressure higher than 140/90 mmHg or a history of hypertension was defined as hypertension. Fasting plasma glucose higher than 6.11 mmol/L or a history of diabetes mellitus was defined as impaired fasting glucose.

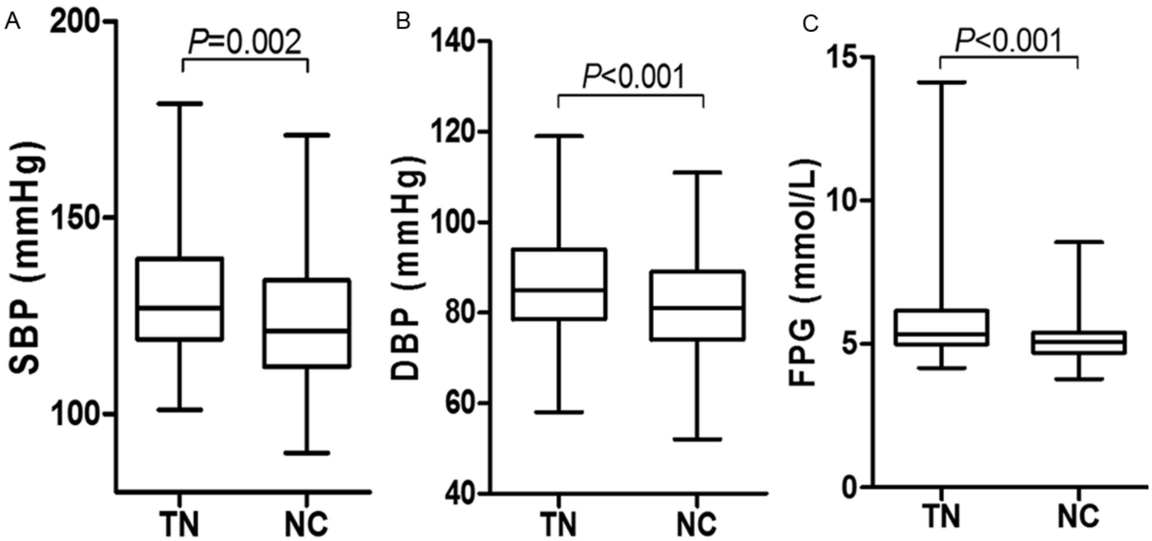

Figure 1. Comparison of metabolic parameters, including SBP (A), DBP (B) and FPG (C), between TN-group and NC-group. TN: thyroid nodule(s); NC: normal control; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose.

Table 2. Prevalence of metabolic syndrome and its components

Components	Thyroid nodule (s) *(n=113)*	*Normal control (n=113)*	*P value*
Metabolic syndrome	36.28	12.39	< 0.001**
BMI ≥ 25.0 kg/m^2	53.98	51.33	0.689
Hypertension	51.33	30.09	0.001**
Impaired fasting glucose	27.43	11.50	0.002**
TG ≥ 1.7 mmol/L	40.71	32.74	0.214
HDL-C < 1.04 mmol/L	0.01	0.00	1.000

Data are percentage (%). $^{**}P < 0.01$. BMI, body mass index; TG, triglycerides; HDL-C, high density lipoprotein cholesterol.

Statistical methods

The data analysis was performed using SPSS version 19.0. Data were expressed as means ± standard deviation (SD) or median (range). The normality of the variables was assessed by the Shapiro-Wilk test. One-way analysis of variance (ANOVA) was used to compare data that was normally distributed. For data that was not normally distributed, the Mann-Whitney U test was applied. Student's *t* test was performed to compare differences between various parameters. Statistical tests were two-sided, and statistical significance was defined as $P < 0.05$.

Results

Table 1 showed the clinical characteristics of the 226 subjects. The median age was 47 year (from 32 to 74), and the median BMI was 25.3 kg/m^2 (from 18.2 to 37.8). All the subjects were divided into two groups: thyroid nodule(s) (TN) and normal control (NC) by their thyroid examination. The mean level of systolic blood pressure in patients with thyroid nodule(s) was 127 mmHg (ranges from 101 to 179 mmHg) and 121 mmHg (ranges from 90 to 171 mmHg) in normal control subjects, which showed significant different (P=0.002). A statistical difference was also found when comparing diastolic blood pressure between these two groups ($P < 0.001$), 85.76 ± 11.40 mmHg in thyroid nodule(s) group and 80.97 ± 11.49 mmHg in normal control group. The mean level and range of fasting plasma glucose in thyroid nodule(s) group was bigger than control, which showed significant difference when compared (**Table 1**; **Figure 1**). And also there were no significant differences in the rest baseline characteristics (such as gender, age and BMI), thyroid functions (including FT3, FT4, TSH, TPO-Ab and Tg-Ab), serum lipid level (including TC, TG, HDL-C and LDL-C) and UA between TN-group and NC-group (**Table 1**).

The overall prevalence of metabolic syndrome was 24.34%. The prevalence of metabolic syn-

Table 3. Association of metabolic parameters as independent variables with the prevalence of thyroid nodule(s) by binary logistic regression analyses

Dependent Variable	*OR (95% CI)*	*P value*
Hypertension		
Crud	2.45 (1.42, 4.23)	0.001**
Adjusted	2.17 (1.24, 3.80)	0.007**
Impaired fasting glucose		
Crud	2.91 (1.43, 5.92)	0.002**
Adjusted	2.46 (1.19, 5.10)	0.015*

OR, odds ratio; CI, confidence interval. $^{*}P < 0.05$, $^{**}P < 0.01$.

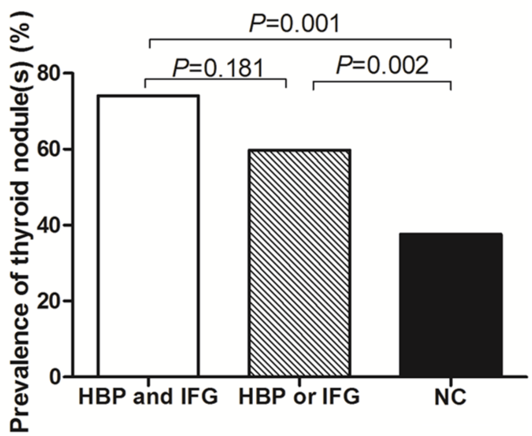

Figure 2. Prevalence of thyroid nodule(s) in different population. HBP: hypertension; IFG: impaired fasting glucose; NC: normal control.

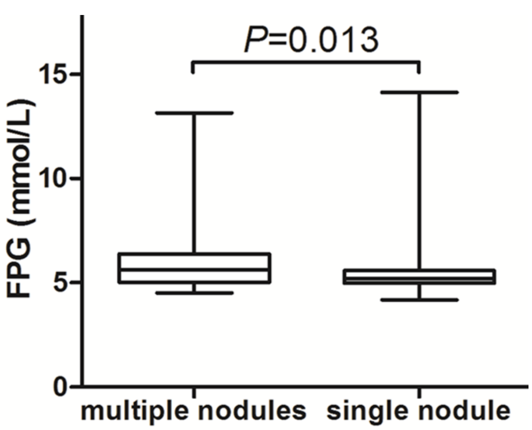

Figure 3. Levels of FPG in patients with thyroid nodule(s). FPG: fasting plasma glucose.

drome was significantly higher in the TN-group than in the NC-group (36.28% vs. 12.39%, $P < 0.001$). The percentage of BMI ≥ 25.0 kg/m², hypertension, impaired fasting glucose and TG ≥ 1.7 mmol/L were all higher and HDL-C < 1.04 mmol/L was lower in patients with thyroid nodule(s) compared with those without. In addition, the difference of hypertension and impaired fasting glucose between TN-group and NC-group was significantly (hypertension: 51.33% vs. 30.09%, *P*=0.001; impaired fasting glucose: 27.43% vs. 11.50%, *P*=0.002) (**Table 2**).

The association of metabolic parameters (including hypertension and impaired fasting glucose) with the prevalence of thyroid nodule(s) was assessed using binary logistic regression analysis (**Table 3**). The prevalence of thyroid nodule(s) in hypertension patients and patients with impaired fasting glucose were 2.17 and 2.46 times relative to none-hypertension and normal glucose metabolism patients, which means higher prevalence of thyroid nodule(s) was associated with increased prevalence of hypertension and impaired fasting glucose.

The subjects were re-divided into three different groups, ① hypertension (HBP) and impaired fasting glucose (IFG), ② HBP or IFG, ③ NC, by the level of blood pressure and fasting plasma glucose as well as the medical history. As a result, 27 patients in HBP and IFG group, 82 patients in HBP or IFG group and 117 subjects in NC group were analyses. Patients had significant higher prevalence of thyroid nodule(s) in HBP and IFG group (74.04%), HBP or IFG group (59.76%) compared with the subjects in NC-group (37.61%). The prevalence of nodule(s) in three groups were significant difference ($P < 0.001$). Although the prevalence was higher in patients who had two disorders than patients who had one, there was no statistical significance. The rest two comparisons were statistic different (**Figure 2**).

Whether the number and size of nodules related to hypertension or impaired fasting glucose were further analyzed. The size of the largest one showed to represent the size in patients with multiple nodules. Patients with multiple nodules have higher level of FPG than patients with single and it had statistical difference (*P*=0.013, **Figure 3**). Meanwhile, higher ratio of multiple nodules was found in impaired fasting glucose patients (77.42%) than normal control (52.44%), and this was significantly different (*P*=0.016). But it was not found in patients with hypertension. The association of the size of nodule with hypertension or impaired fasting glucose was not found in this study.

Patients with MetS had no statistical difference in the level of TSH comparing to subjects without (*P*=0.818), so did hypertension (*P*=0.574) and impaired fasting glucose (*P*=0.281). The level of TSH was not significantly different in subjects of TN-group compared with those of NC-group. The subjects were then re-divided into five groups according to the level of TSH (TSH ≤ 1.0 uIU/mL, 1.0 < TSH ≤ 2.0 uIU/mL, 2.0 < TSH ≤ 3.0 uIU/mL, 3.0 < TSH ≤ 4.0 uIU/mL and TSH > 4.0 uIU/mL). There was still no difference in the prevalence of metabolism syndrome (*P*=0.794) and thyroid nodule(s) (*P*=0.530) among these groups. These data suggested that the TSH level in euthyroid patients with thyroid nodule(s) was not statistically different compared with euthyroid subjects without thyroid nodule(s).

Discussion

Metabolic syndrome (MetS), a series of disorders including abdominal obesity, increased blood pressure, impaired glucose and lipid regulation, has been used to evaluate the risk of cardiovascular disease [1, 13]. The abnormal thyroid hormones and morphology were reported to be associated with MetS and its components [4-10]. It was supposed that the prevalence of thyroid nodule(s) may be related to MetS and its components. But few papers publish this issue. Subjects in previous studies were not euthyroid nor investigated in the iodine sufficient area [9, 10]. The influence of abnormal thyroid function on the metabolic parameters may cause the false positive result, and the iodine deficiency can lead to a higher prevalence of thyroid nodule(s). To exclude both of these factors, subjects with normal range of thyroid function from Jinan (Shandong Province), an iodine-sufficient area of China, were enrolled in this study. The association of the prevalence of thyroid nodule(s) and MetS or its components in euthyroid subjects was discussed. Screen for the risk factors of MetS that affect the prevalence.

Our data suggested that the prevalence of thyroid nodule(s) was significantly higher in euthyroid patients with MetS than euthyroid subjects without MetS in the iodine-sufficient area, which means MetS is a risk factor for thyroid nodule(s). Previous studies agreed with ours either in area of iodine deficiency or in patients both with and without normal thyroid function [9, 10]. Further analysis in our study suggested that both hypertension and impaired fasting glucose are the independent risk variables for thyroid nodule(s). Additionally, patients with hypertension or impaired fasting glucose had higher incidence of thyroid nodule(s) than health subjects. And the association between the number of nodules and impaired fasting glucose were found.

Some researches reported that hypertension is one of the risk factors for thyroid nodule(s) [10, 14, 15]. But how higher blood pressure causes higher incidence of thyroid nodule(s) is not well known. Nowadays, researches about this mechanism mainly concentrate on the relationship between hypertension and thyroid function. The positive correlations between TSH and SBP and DBP were reported which means patients with hypertension have higher level of TSH than those without hypertension [16-18]. Another study showed that both SBP and DBP were positive related to TSH and FT3 in the young people among age 7 to 18 years old, but no relationship was found with FT4 [19]. A research about genetic diversity found that the patients with a family history of hypertension have higher concentration of serum TSH [20]. There was higher incidence of hypothyroidism in hypertension patients and the lower triiodothyronine could return to normal after antihypertensive medical treatment [21, 22]. On other hand, acute hypotension and hypertension have no effect on serum TSH concentrations in male rats [23]. In this case-control study, we did not found any correlation of MetS and its component, including hypertension, with the level of serum TSH in euthyroid subjects. Bakiner et al. [24] also reported the same result in euthyroid obese patients. The different results of different studies including ours may be related to sensitivity of TSH measurement techniques, distributional differences of groups, different reference cut-off points and race differences of normal TSH levels and definition difference of MetS [24-27]. Even though, most epidemiologic study including our study all confirmed that hypertension is the risk factor of thyroid nodule(s), the specific pathogenesis still needs further study. The relationship between hypertension and serum TSH levels needs further verify as well.

Both type 2 diabetes mellitus and thyroid diseases are the most common endocrinology diseases. IR and/(or) hyperinsulinemia are the main pathogenic factors in patients with type 2 diabetes mellitus [28]. It was reported that IR was significantly related to the change of thyroid function and morphology [5, 29]. Increasing evidences showed that the thyroid volume was significant larger in patients with type 1 or type 2 diabetes mellitus than that in control subjects, and the prevalence of thyroid nodule(s) was statistically significant higher in patients with type 2 diabetes mellitus than that in normal control (48% vs. 28%, $P < 0.05$) [30-32]. It was also found in this paper that the number of nodule(s) was statistical related with the level of FPG (P=0.013) and patients with higher ratio of multiple nodules was found in patients with impaired fasting glucose (P=0.016). Rezzonico et al. [4] reported that patients who received metformin have smaller volume of thyroid nodule(s) than patients without received, which also suggested the relationship between glucose metabolism and thyroid nodule(s). Further study showed that patients with type 2 diabetes mellitus have significant high level of serum leptin and TSH [33]. Thyroid hormone and thyrotropin-releasing hormone could be negatively regulated by leptin, [34] and the serum leptin could be further influenced by increased serum insulin [35]. Though our data did not show any relationship between glucose metabolism index and thyroid function in euthyroid subjects, we still found out the correlation of impaired fasting glucose with the incidence of thyroid nodule(s). In addition, it was suggested that impaired fasting glucose could increased the incidence of thyroid nodule(s) by influencing the energy metabolism of thyroid follicular cells. This maybe another mechanism to explain the relationship of higher prevalence of thyroid nodule(s) in euthyroid subjects with abnormal glucose metabolism. Not only the relationship between impaired fasting glucose and the prevalence of thyroid nodule(s) was found in this study, but also the association between the number of nodules and impaired fasting glucose was further suggested. However, the exactly mechanism needs further research.

TSH plays an important role in regulating the growth and development of thyroid cells. The correlation of TSH with the proliferation and differentiation of cells was suggested in vitro studies [36]. And it was found that high TSH level is an independent risk factor for high thyroid volume in MetS patients [10]. But whether higher TSH is shown in thyroid nodule(s) patients is still controversial nowadays. Several researches including ours study showed that TSH level was no significantly different in patients with thyroid nodule(s) and health subjects [37, 38].

Conclusions

In summary, our study was a case-control study performed in euthyroid subjects in the area of iodine sufficient of China. MetS is the risk factor for thyroid nodule(s), and the metabolic parameters, including hypertension and impaired fasting glucose, is the independent risk variable. Patients with the two disorders have higher prevalence of thyroid nodule(s) than who has one and significantly higher than health subjects. Therefore, patients who have hypertension and diabetes mellitus should be suggested to examine their thyroid with ultrasonography. Patients who have thyroid nodule(s) should be suggested to check their blood pressure and glucose. But the sample should be enlarged to confirm these conclusions further. Meanwhile, both the underlying mechanisms for the association of MetS (especially, hypertension and impaired fasting glucose) with thyroid nodule(s) and the number of nodules with impaired fasting glucose still unclear and should be further studied. Also, the relationship of these metabolism indexes with the type of nodules (which may evaluate by FNA and surgery) and the risk of malignancy should be further studied.

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Disclosure of conflict of interest

None.

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