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The Prevalence of Thyroid Nodules and Their Association with Metabolic Syndrome Risk Factors in a Moderate Iodine Intake Area

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Abstract

Background: To investigate the prevalence of thyroid nodules (TNs) and to evaluate the association between TNs and metabolic syndrome (MetS) in the moderate iodine intake area of Jiangsu, China.
Subjects and Methods: A cross-sectional study was carried out in a Chinese community-based epidemiological investigation from January to December 2014. A questionnaire was completed by 6494 subjects (2427 men and 4067 women). Thyroid ultrasound was performed by using a 7.5-MHz linear probe. MetS was defined according to the 2006 International Diabetes Federation criteria.
Results: The prevalence of TNs in the study population was 17.7% (12.9% for men and 20.6% for women) and significantly higher in subjects with MetS [MetS(+)] than in those without MetS [MetS(−)] (25.8% vs. 15.5%, $\chi^2 = 78.471$, $P < 0.001$). Binary logistic regression indicated that (in addition to female sex and increased age) increased fasting plasma glucose (FPG), waist circumference (WC), hypertension, and smoking were positively associated with the prevalence of TNs.
Conclusions: Our findings indicated a positive association between MetS and formation of TNs. Increased WC and FPG, as well as hypertension, might increase the prevalence of TNs.

Keywords: fasting plasma glucose, hypertension, metabolic syndrome, thyroid nodules, waist circumference

Introduction

Thyroid nodules (TNs), discrete lesions within the thyroid gland, are found in 3%–7% of adults when assessed by physical examination. However, using more sensitive techniques such as sonography, TNs are present in 13%–67% of adults and may be incidentally discovered on ultrasound examinations used to investigate the neck for other possible diseases.[1] The prevalence of TNs increases with age. TNs may be solitary or multiple and functional or nonfunctional.

The recent rapid increase in TN prevalence may be attributable to multiple factors such as genetic predisposition, autoimmune disorders, environmental endocrine disruptors, iodine intake level, and other factors.[2,3] Previous studies have found a close association between TNs and iodine intake.[4]

At the same time, metabolic syndrome (MetS) has been increasing in prevalence in the past few years and its major pathophysiological mechanism is insulin resistance (IR). It combines a group of disorders, such as glucose intolerance, central obesity, dyslipidemia, and hypertension, and has been used to identify individuals at risk of cardiovascular disease. Recently, an intriguing area of research in thyroidology is the association of MetS (or its related components) with thyroid functional/morphological abnormalities.[5] Therefore, the aim of our study was to investigate the prevalence of TNs and to unravel the association between TNs and MetS and its diagnostic parameters in the general population of China.

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Subjects and Methods

Subjects

According to a stratified cluster sampling method, a cross-sectional study was carried out from January to December 2014. The subjects originated from the urban, rural, and suburban regions of Jiangsu, which was designated as a moderate iodine intake area after the introduction of universal salt iodization in China. Local residents, aged ≥20 years, who had lived in the vicinity for at least 5 years were eligible for inclusion. All study subjects were personally interviewed by trained interviewers and details of their demographics, clinical and family history, smoking and dietary habits, ethnicity, and profession were recorded. Informed consent was obtained from all enrolled subjects. Subjects accepting hypoglycemic, antihypertensive, and/or lipid-lowering treatment were also registered, but these treatments were noted. The study protocol was approved by the institutional ethics committee of Nanjing University of Chinese Medicine.

Methods

Anthropometric measurements. The subjects' height, weight, and waist circumference (WC) were measured and recorded by clinical professionals. Measurement of height and weight was done with the subjects wearing light clothes and no shoes. WC was measured with a folding tape at the midpoint connection of the anterior superior iliac crest spine and the edge of the 12th rib in a horizontal plane. The measured values were to the nearest 0.1 cm. Blood pressure (BP) was measured with a standard mercury sphygmomanometer on the right upper arm after the participants had been seated quietly for at least 5 min. Smoking was defined as one or more cigarettes per day for ≥6 months. Drinkers were defined as people who drank alcohol at least twice per month in the past year.

Thyroid ultrasound scan. Ultrasonography of the thyroid was performed using a GE Logiq7 linear array probe (7.5 MHz) by a single technician. All participants were examined in the supine position with the head tilted backward. The length, width, and thickness of the bilateral thyroid gland were recorded to calculate the volume. At the same time, the location, size, number, boundaries, and calcification of TNs were noted. The volume of the thyroid gland and any nodules were calculated according to the ellipsoid formula: volume (mL) = depth (cm) × width (cm) × length (cm) × $\pi/6$.[6]

Laboratory evaluations. A blood sample was drawn and processed at the examination center after a minimum fasting period of 12 hrs and transported to a central clinical laboratory in Nanjing where fasting plasma glucose (FPG), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were measured using an Olympus AU2700 automatic chemistry analyzer (Olympus Corporation, Tokyo, Japan). FPG was measured using a modified hexokinase enzymatic method. TGs and HDL-C were directly analyzed enzymatically with commercial reagents.

Definition of MetS. According to the 2006 criteria of the International Diabetes Federation (IDF), MetS in the study was defined as central obesity (defined as a WC ≥90 and ≥80 cm for Chinese men and women, respectively) plus any two of the following four factors: (1) elevated TG: serum TG level ≥1.70 mM (150 mg/dL) or specific treatment for this lipid abnormality; (2) reduced HDL-C: HDL-C level <1.03 mM (40 mg/dL) in men or <1.29 mM (50 mg/dL) in women or specific treatment for this lipid abnormality; (3) elevated BP: BP ≥130/85 mmHg and/or use of antihypertensive medications; and (4) elevated FPG: serum glucose level ≥5.6 mM (100 mg/dL) and/or previously diagnosed type 2 diabetes.[7]

Statistical analyses

The data were entered in the double-track system by EpiData 3.0 software (EpiData Association, Odense, Denmark). Statistical analyses were performed by PASW, version 17.0 for Windows (PASW, Chicago, IL). Data for categorical variables were expressed either in number or percentage (*N*, %). Numerical data for continuous variables are expressed in the form of mean ± standard error of the mean. Student's *t*-test as appropriate was conducted for comparisons of continuous variables; chi-square test for comparisons of proportions; and multivariable analyses using binary logistic regression to identify determinants for TNs. All statistical tests were two-tailed, and *P* values <0.05 were considered significant.

Results

The characteristics of the study population are presented in Table 1. The cross-sectional study included a total of 6494 (2427 men and 4067 women) participants who finished the questionnaire, physical examination, thyroid ultrasound, and laboratory measurements. The prevalence of TNs in the total population was 17.7% (12.9% for men and 20.6% for women). Prevalence of MetS was significantly higher in subjects with TNs than in controls (male: 37.8% vs. 21.6%, respectively, $\chi^2 = 39.532$, $P < 0.001$; female: 28.8% vs. 17.9%, respectively, $\chi^2 = 48.78$, $P < 0.001$).

As expected, subjects with TNs were older than controls and had higher levels of cardiovascular risk factors, including body mass index, WC, FPG, TGs, and BP, but the level of HDL-C was not significantly different between groups. The percentage of smokers was significantly higher in subjects with TNs compared with controls (male: 62.3% vs. 53.9%, respectively, $\chi^2 = 7.427$, $P = 0.005$; female: 16.6% vs. 8.5%, respectively, $\chi^2 = 47.302$, $P < 0.001$), while the percentage of drinkers showed no difference between the TN group and the control group (male: 48.4% vs. 44.7%, respectively, $\chi^2 = 1.478$, $P = 0.224$; female: 11.8% vs. 10.9%, respectively, $\chi^2 = 0.562$, $P = 0.453$). The thyroid volume was greater in the TN group than the control group (male: 12.9 vs. 11.4, respectively, $t = 4.872$, $P < 0.001$; female: 11.7 vs. 9.9, respectively, $t = 7.047$, $P < 0.001$).

As shown in Fig. 1, subjects were stratified according to age into five subgroups: 20–29, 30–39, 40–49, 50–59, and ≥60 years old. The prevalence of TNs was significantly lower in males than in females except in the 20–29 and 30–39 subgroups. A trend chi-square test showed that the prevalence of TNs increased with increasing age in both sexes.

Table 2 shows that the prevalence of TNs was significantly higher in MetS(+) subjects than MetS(−) subjects (25.8% vs. 15.5%, $\chi^2 = 78.471$, $P < 0.001$). The odds ratio (OR) for the formation of TNs in subjects with MetS was 1.89 [95% (confidence interval) CI 1.64–2.17] and, after adjustment for age and sex, it was 1.21 (95% CI 1.08–1.49). In univariate analyses, each component of MetS was associated with TNs, except reduced HDL-C.

In a binary logistic regression analysis summarized in Table 3, the determinants for TNs are shown. In addition to female sex and increased age, elevated FPG [OR = 1.357 (95%

TABLE 1. BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS BY PRESENCE OF THYROID NODULES

	Male			*Female*		
Variables	*TN*	*Control*	P	*TN*	*Control*	P
N	312	2115	—	838	3229	—
Age (years)	56.9 ± 0.70	48.8 ± 0.31	<0.001	56.0 ± 0.42	47.9 ± 0.23	<0.001
BMI (kg/m^2)	25.0 ± 0.20	24.4 ± 0.08	0.008	24.9 ± 0.13	24.0 ± 0.07	<0.001
WC (cm)	87.6 ± 0.57	81.2 ± 0.21	<0.001	84.2 ± 0.33	75.9 ± 0.17	<0.001
FPG (mM)	5.5 ± 0.11	4.9 ± 0.04	<0.001	5.5 ± 0.06	4.7 ± 0.03	<0.001
Systolic BP (mmHg)	133.3 ± 1.12	127.6 ± 0.40	<0.001	131.6 ± 0.69	123.3 ± 0.34	<0.001
Diastolic BP (mmHg)	85.1 ± 0.67	83.1 ± 0.24	0.005	83.0 ± 0.34	79.7 ± 0.19	<0.001
HDL-C (mM)	1.24 ± 0.02	1.25 ± 0.01	0.269	1.33 ± 0.01	1.35 ± 0.01	0.124
TGs (mM)	1.82 ± 0.09	1.41 ± 0.03	<0.001	1.84 ± 0.05	1.29 ± 0.02	<0.001
MetS (%)	37.8	21.6	<0.001	28.8	17.9	<0.001
Thyroid volume (mL)	12.9 ± 0.29	11.4 ± 0.09	<0.001	11.7 ± 0.24	9.9 ± 0.08	<0.001
Smoking (%)	62.3	53.9	0.005	16.6	8.5	<0.001
Drinking (%)	48.4	44.7	0.224	11.8	10.9	0.453

Data are presented as mean ± SEM or percentage as appropriate.
BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; SEM, standard error of the mean; TGs, triglycerides; TNs, thyroid nodules; WC, waist circumference.

CI 1.152–1.600), $P < 0.001$], elevated WC [OR = 1.264 (95% CI 1.091–1.466), $P = 0.002$], hypertension [OR = 1.328 (95% CI 1.141–1.546), $P < 0.001$], and smoking [OR = 1.309 (95% CI 1.099–1.558), $P = 0.003$] were significantly correlated with TNs, whereas elevated TGs [OR = 1.143 (95% CI 0.982–1.331), $P = 0.083$] were not significantly associated with TNs.

Discussion

In this study, we demonstrated a high prevalence of TNs in a community-based population in Jiangsu, China, which is a moderate iodine intake area. Female sex, age, and smoking might increase the risk of occurrence of TNs. Furthermore, participants with MetS were more prone to TN occurrence. In general, most studies have found that the prevalence of TNs is higher among women than among men.[8,9] Xu et al. found that estrogen is a potent stimulator of the growth of thyroid stem/progenitor cells.[10] The size of pre-existing TNs was increased and new TNs were formed during pregnancy.[11] The volume of benign TNs shows no significant changes in the majority of women after menopause.[12] Thus, estrogen may at least partly account for the higher incidence in females. The increased prevalence of TNs that we observed with increasing age is in agreement with previous studies.[13,14]

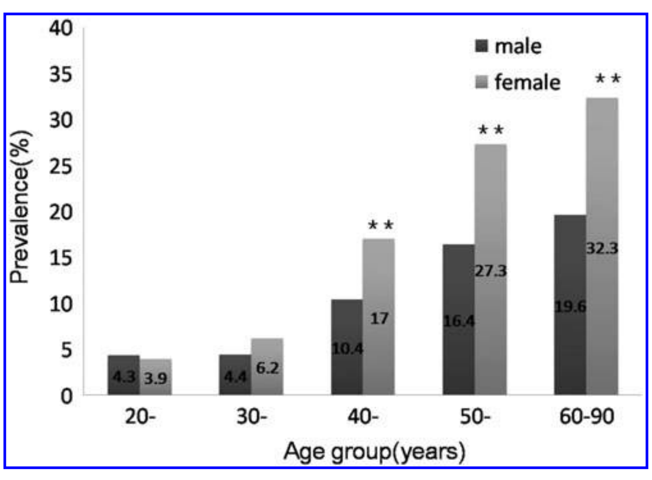

FIG. 1. Prevalence of TNs in different age groups in males and females. *$P < 0.05$, **$P < 0.01$. TNs, thyroid nodules.

We observed a higher risk of occurrence of TNs in people with MetS regardless of other risk factors, which is consistent with reports of increased prevalence of TNs in IR.[5] TNs are the most prevalent thyroid diseases whose established risk factors (age, female sex, and family history) cannot be modifiable. In recent years, epidemiological studies have shown that the prevalence of TNs is rapidly increasing, which is probably due to more frequent diagnoses as a result of the extensive use of neck ultrasonography in the general population.

However, it is also possible that this increasing incidence rate of TNs is related to the increasing prevalence of obesity and IR. MetS is a cluster of metabolic disorders associated with IR and visceral adiposity. IR is one of the fundamental conditions associated with MetS and is characterized by an inadequate physiological response of peripheral tissues to circulating insulin. IR plays a core role in the pathogenesis of MetS and it is also an important regulator of thyroid cell function and growth.

In the present study, we found that subjects whose WC was greater than normal were prone to TNs. Previous studies assessing thyroid functional changes in obesity found that the serum level of thyroid-stimulating hormone (TSH) was higher in patients with MetS than in controls.[15,16] WC was significantly positively associated with the TSH level, which may be explained by some humoral or hormonal mediators from adipose tissue stimulating the hypothalamus–pituitary–thyroid axis to increase TSH secretion.[17,18] In most of these studies, increasing WC is used as an indicator of increased visceral adipose tissue.

Visceral adipose tissue is considered not only as an energy store but it can also secrete adipokines that regulate energy metabolism. Leptin is a major secretory product of white adipose tissue and this hormone is produced in proportion to the amount of stored body fat and has multiple endocrine functions, as well as being linked with the pathogenesis of obesity. A dysregulated axis between the hypothalamus, pituitary, thyroid, and the adipose tissue has been hypothesized

Table 2. Prevalence and Odds Ratio of Thyroid Nodules Among Participants With and Without Components of the Metabolic Syndrome

			OR (95% CI)	
Variables	N	*Prevalence (%)*	*Unadjusted*	*Age and sex adjusted*
Metabolic syndrome				
No	5100	15.5	1.00	1.00
Yes	1394	25.8	1.89 (1.64–2.17)	1.21 (1.08–1.49)
Elevated WC				
No	3918	14.3	1.00	1.00
Yes	2576	22.9	1.79 (1.57–2.03)	1.18 (1.06–1.37)
Elevated BP				
No	4097	14.2	1.00	1.00
Yes	2397	23.8	1.89 (1.66–2.15)	1.24 (1.12–1.41)
Elevated FPG				
No	5238	16.4	1.00	1.00
Yes	1256	23.2	1.54 (1.32–1.78)	1.09 (1.02–1.36)
Elevated TGs				
No	4847	17.0	1.00	1.00
Yes	1647	19.9	1.22 (1.06–1.40)	1.05 (1.01–1.26)
Reduced HDL-C				
No	5263	17.4	1.00	1.00
Yes	1231	18.9	1.10 (0.94–1.23)	1.01 (0.78–1.16)
No. of components				
0	1375	9.5	1.00	1.00
1	1763	13.3	1.46 (1.17–1.83)	1.07 (0.77–1.53)
2	1474	19.7	2.33 (1.86–2.90)	1.27 (1.04–2.11)
3	1073	22.6	2.77 (2.20–3.48)	1.53 (1.24–2.86)
4	566	29.0	3.87 (3.00–5.00)	1.93 (1.41–2.91)
5	243	36.6	5.49 (4.00–7.54)	2.81 (2.08–4.07)

95% CI, 95% confidence interval; OR, odds ratio.

as an underlying pathophysiologic mechanism for obesity.[19] Experimental data in animals have indicated a possible association between leptin and thyroid function, mediated through an effect of leptin on the negative feedback adjustment of thyroid hormones and thyrotropin-releasing hormone (TRH) expression. Leptin may act directly on TRH neurons through leptin receptors on these cells.[20]

Epidemiologic surveys have recently suggested that the incidence of prediabetes and diabetes is dramatically increasing in the adult population due to the growing prevalence of obesity and immobility in China.[21] Our finding of increased morbidity of TNs in both sexes with aberrant blood glucose suggests that impaired glucose metabolism may be a risk factor for increased TN prevalence in adults.

It is well known that IR and compensatory hyperinsulinemia are the pivotal factors in the pathogenesis of diabetes. The risk of increasing thyroid volume and nodule prevalence was found to be positively associated with abnormal glucose metabolism.[22] A study from Poland found that TNs and parenchymatous goiter occurred more frequently in type 2 diabetic patients.[23] TSH is an important regulator of growth and differentiation of thyroid cells.[24]

The present study has shown that the occurrence and average volume of TNs were significantly higher in patients with MetS ($P<0.001$). Thus, the results of this study demonstrate a positive correlation between TNs and MetS. Ayturk et al. found that IR appeared to play an important role in thyroid volume and the development of TNs.[9]

It is well known that insulin acts as a growth factor that stimulates cell proliferation. It has been observed that insulin receptors were overexpressed in most benign thyroid adenomas as an early step in thyroid carcinogenesis.[25]

Insulin-like growth factor-1 (IGF-1) is an important hypertrophic and cell cycle progression factor for a number of cell

Table 3. Multivariate Binary Logistic Regression Analyses for Risk of Thyroid Nodules

				95% CI for OR	
Risk factor	χ^2	P	*OR*	*Lower*	*Upper*
Female sex	63.957	<0.001	2.012	1.695	2.389
Age	189.529	<0.001	1.040	1.034	1.045
Elevated WC	9.673	0.002	1.264	1.091	1.466
Elevated FPG	13.293	<0.001	1.357	1.152	1.600
Elevated TGs	2.977	0.083	1.143	0.982	1.331
Hypertension	13.389	<0.001	1.328	1.141	1.546
Smoking	9.139	0.003	1.309	1.099	1.558

types. TSH in cooperation with insulin or IGF-1 stimulates cell cycle progression and proliferation in various thyrocyte culture systems.[26] The insulin/IGF-1 signaling pathway has long been known to modulate regulation of thyroid gene expression and might be considered as an additional important factor in thyrocyte proliferation and differentiation.[26,27]

In conclusion, we found that the prevalence of TNs is very high, and significantly higher in subjects with MetS, in this community-based population in a moderate iodine intake area of China. Moreover, we concluded that critical components of MetS are positively correlated with TN formation, including elevated WC, FPG, and hypertension.

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Author Disclosure Statement

No conflicting financial interests exist.

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