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Original Article

An epidemiological study of risk factors of thyroid nodule and goiter in Chinese women

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Abstract: Thyroid nodule (TN) and goiter are two common disorders of the thyroid. Despite their benign nature, both conditions are associated with multiple pathologic conditions including thyroiditis, endocrine dysregulation, and autoimmune disease. In this study we conducted a large-scale epidemiological study in Chinese women to identify risk factors implicated in the pathogenesis of TN and goiter. We analyzed demographic data, medical history, menstrual status, smoking, alcohol consumption, body height, weight, waist circumference, and body mass index (BMI). Thyroid ultrasonography was performed for all subjects. Our results showed that age, menstrual status, BMI, waist circumference, hypertension, dyslipidemia and hyperglycemia had a significant relationship with the prevalence of TN and goiter. There was also a significant association between parity, educational level, smoking, seafood consumption, salt consumption and TN. Waist-hip ratio, BMI, and triglyceride had a significant association with both TN and goiter, and total cholesterol only correlated with TN. Medical management of hypertension significantly affected TN prevalence. Our study also demonstrated age to be a strong predictor of TN and goiter, and obesity a predictor of the likelihood of developing goiter. Thus, our study suggests that the female Chinese population with advance age, menopause, obesity and metabolic syndrome be examined for TN and goiter, and those patients with confirmed TN and goiter be screened for age and obesity related disorders such as metabolic syndrome.

Keywords: Thyroid nodule, goiter, risk factor, Chinese women

Introduction

Thyroid nodule (TN) and goiter are two common benign thyroid disorders that have global influence [1-5]. The presentation of these two conditions range from mild changes in thyroid structure without clinical manifestations to severe symptoms such as breathing and/or swallowing difficulties that affect life quality and expectancy. In one study, Allan Carlé et al. reported approximately 10% of the world population was affected by goiter [4]. Research on the prevalence of TN otherwise reported that it approached 50% when the nodules were detected by ultrasound and/or other radiologic methods [6]. In addition, both conditions have been associated with multiple pathologic conditions of the thyroid including thyroiditis, endocrine dysregulation, and autoimmune disease [1-5].

TN and goiter have multiple known risk factors, which include demographic parameters and clinical history. Age and sex respectively correlates with the pathogenesis, increasing the prevalence of TN and goiter in residents of the United States [7, 8]. Similar observation was made by the studies conducted in the Chinese population [9, 10]. Interestingly, both diseases have a pattern of female predominance [11-13]. The Framingham study conducted on 5234 participants over 60 years of age showed that 6.4% of women and 1.5% of men were affected by TN [14]. Another independent research also reported that highest prevalence of goiter occurred in pre-menopausal females and that ratio of female/male was greater than 4:1 [15]. In life style, smoking was identified by multiple studies that predisposed the study population to TN and goiter [16, 17]. Further, thyroid volume, a mathematical quantitation of the goiter, posi-

tively correlated with increased body mass index (BMI) [18], and hyperglycemia in patients with impaired glucose metabolism [19]. Last, incidence of goiter was increased in individuals with clinically diagnosed hypertension [20] and diabetes [13].

In this manuscript, we conducted a large-scale epidemiological study to explore the risk factors in the pathogenesis of TN and goiter in Chinese women. We included test parameters such as life style, obstetrical history and common medical comorbidities. We identified age, menopause, BMI, and waist circumference as individual risk factors. Our study proposes that female patients in the Chinese population with advance age, menopause, obesity and metabolic syndrome should be examined by physicians and imaging tests for TN and goiter, and patients with these two confirmed conditions should be screened for age and obesity related disorders such as cardiovascular disease and diabetes mellitus.

Materials and methods

Subjects

The study was conducted in Daxing district of Beijing, China from August to December in 2013. A total of 6323 volunteers received the questionnaire and were examined by thyroid ultrasonography (US). All participants were 18 years or older. Pregnant women and those with severe cardiac, hepatic or renal disease were excluded. Participants with one or more of the following characteristics were also excluded from the study: (1) history of thyroid procedures such as thyroid surgery or radiotherapy in thyroid, head and neck; (2) ongoing medical treatments including thyroxine, iodine or antithyroid medications such as amiodarone; (3) incomplete history or data acquisition errors; (4) participants who did not comply with physical examination and/or laboratory tests. A final 3084 females were analyzed by the study. All participants provided informed consent.

Anthropometric measurements

Each participant completed a detailed questionnaire for demographic data, life style and medical history. Demographic data included gender and age. Life style included salt intake, smoking and alcohol consumption. Medical history included hypertension, dyslipidemia, diabetes mellitus, menstrual status and thyroid disease. Participants were measured for body height, weight, waist circumference and BMI. Blood pressure was measured three times with an automated blood pressure monitor (HEM-7117 OMRON Co. Inc, Dalian, China) on the right upper arm after participants rested for a minimal of 5 minutes. Average value of the triple readings was used for the study.

Laboratory medicine measurement

All participants were fasted overnight. Venous blood was collected and stored in refrigerator until tested. Oral glucose tolerance test (OGTT) with 75 grams of glucose was performed for participants without diagnosed diabetes or receiving hypoglycemic medications. Fasting plasma glucose (FPG), 2 hours postprandial glucose (PPG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were analyzed by an HITACHI automated biochemical analyzer (7600 HITACHI Ltd. Tokyo, Japan).

Thyroid ultrasound

Thyroid ultrasound examination was performed by certificated ultrasound technologists using a portable SonoScape ultrasound device with 5-10 MHz linear probe, and a GE LOGIQ e device with 7-10 MHz linear probe. Volume of each thyroid lobe was determined by the Ellipsoid formula: Volume (mL) = Length (cm) × Width (cm) × Thickness (cm) × 1/6 π. Goiter is defined as the total volume larger than 18 mL in women and 25 mL in men [21].

Definitions and normal values

Hypertension was defined according to the European Society of Hypertension (ESH) 2013 guidelines as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. Hypertensive patients were defined as participants meeting the above criteria or taking oral anti-hypertensive medications. Hyperglycemia was classified into pre-diabetes and diabetes according to the American Diabetes Association 2013 guidelines. Pre-diabetes has high risk in developing diabetes and complications. It was diagnosed by any of the following criteria: impaired fasting

Table 1. Characteristics of the Study Population and Thyroid Nodule

Variables	Positive rate of thyroid nodule		Variables	Positive rate of thyroid nodule	
	M/N (%)	*P value*		M/N (%)	*P value*
Education		<0.001	Age (%)		<0.001
uneducated	145/219 (66.2)		<30	23/81 (28.4)	
elementary	407/682 (59.7)		~40	117/338 (35.1)	
middle school	660/1317 (50.1)		~50	337/758 (44.5)	
high school	321/642 (50.0)		~60	571/1026 (55.7)	
junior collage	67/160 (41.9)		~70	467/739 (63.2)	
undergraduate and above	18/64 (28.1)		≥70	103/147 (70.1)	
marital status (%)		0.336	BMI		<0.001
married	1609/3069 (52.4)		<25	465/975 (47.7)	
divorced or widowed	9/15 (60)		≥25	1153/2109 (54.7)	
Parity		<0.001	Seafood consumption		0.002
1	644/1420 (45.4)		never	264/448 (58.9)	
2 or 3	897/1550 (57.8)		occasional	1259/2420 (52.0)	
≥4	75/112 (67.0)		frequent	88/198 (44.4)	
Menopause (%)		<0.001	Hypertension (%)		<0.001
no	514/1236 (41.6)		no	765/1671 (45.8)	
yes	1104/1848 (59.7)		yes	853/1413 (60.4)	
Alcohol consumption		0.396	Smoking history		0.002
never	1557/2969 (52.4)		never	1496/2897 (51.6)	
prior	11/16 (68.8)		prior	28/43 (65.12)	
active	50/99 (50.5)		active	94/144 (65.28)	
Waist circumference		<0.001	Dyslipidemia (%)		0.009
<80	253/637 (39.7)		no	772/1541 (50.1)	
≥80	1365/2447 (55.8)		yes	846/1543 (54.8)	
Hyperglycemia level		<0.001	Salt intake		0.027
normal	649/1351 (48.0)		mild	355/707 (50.2)	
prediabetes	520/1024 (50.8)		medium	738/1438 (51.3)	
diabetes	449/709 (63.3)		high	521/928 (56.1)	
Exercise intensity		0.361	Hyperuricemia (%)		0.102
high	7/19 (36.8)		no	1534/2942 (52.1)	
medium	118/225 (52.4)		yes	84/142 (59.2)	
mild	1424/2680 (53.1)				

M refers to the number of thyroid nodule in each subgroup, N refers to the total number of each subgroup.

glucose (IFG): FPG 5.6-6.9 mmol/L; impaired glucose tolerance (IGT): 2 hours PPG in 75 grams OGTT 7.8-11.0 mmol/L. Diabetes was diagnosed by FPG ≥7.0 mmol/L or 2 hours PPG in 75 grams OGTT ≥11.1 mmol/L. Diabetic patients were defined as participants meeting the above criteria or taking hypoglycemic medications. Dyslipidemia was defined by the International Diabetes Federation (IDF) as TG level ≥150 mg/dL (1.7 mmol/L) or patients receiving medical management for lipid abnormalities; and HDL-C <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females or patients receiving medical management. Obesity was diagnosed according to the International Diabetes Federation (IDF) 2006 guidelines as waist circumference ≥90 cm for men and ≥80 cm for women in the Chinese population. In China, obesity was specifically defined as BMI ≥25. Hyperuricemia was defined when the serum uric acid exceeded 7.0 mg/dL.

Statistics analysis

Categorical variables were analyzed using chi-square test or fisher's exact test. Numeric vari-

Table 2. Characteristics of the Study Population and Goiter

Variables	Positive rate of goiter		Variables	Positive rate of goiter	
	M/N (%)	*P value*		M/N (%)	*P value*
Education		0.077	Age (%)		<0.001
uneducated	23/219 (10.5)		<30	2/81 (2.5)	
elementary	67/682 (9.8)		~40	12/333 (3.6)	
middle school	117/1317 (8.9)		~50	60/758 (7.9)	
high school	54/642 (8.4)		~60	118/1026 (11.5)	
junior collage	7/160 (4.4))		~70	66/739 (8.9)	
undergraduate and above	1/64 (1.6)		≥70	11/147 (7.5)	
Marital status(%)		0.837	BMI		<0.001
married	267/3069 (8.7)		<25	36/975 (3.7)	
divorced or widowed	2/15 (13.3)		≥25	233/2109 (11.1)	
Parity		0.184	Seafood consumption		0.204
1	110/1420 (7.8)		never	44/448 (9.8)	
2 or 3	147/1550 (9.5)		occasional	212/2420 (8.8)	
≥4	12/112 (10.7)		frequent	11/198 (5.6)	
Menopause (%)		0.01	Hypertension (%)		<0.001
no	88/1236 (7.1)		no	114/1671 (6.8)	
yes	181/1848 (9.8)		yes	155/1413 (11.0)	
Alcohol consumption		0.307	Smoking history		0.314
never	259/2969 (8.7)		never	247/2897 (8.5)	
prior	3/16 (18.8)		prior	5/43 (11.6)	
active	7/99 (7.1)		active	17/144 (11.8)	
Waist curcumference		<0.001	Dyslipidemia (%)		0.004
<80	23/637 (3.6)		no	112/1541 (7.3)	
≥80	246/2447 (10.1)		yes	157/1543 (10.2)	
Hyperglycemia level		0.001	Salt intaking		0.194
normal	93/1351 (6.9)		mild	50/707 (7.1)	
prediabetes	93/1024 (9.1)		medium	135/1438 (9.4)	
diabetes	83/709 (11.7)		high	83/928 (8.9)	
Exercise intensity		0.299	Hyperuricemia (%)		0.426
high	0/19 (0.0)		no	254/2942 (8.6)	
medium	17/225 (7.6)		yes	15/142 (10.6)	
mild	242/2680 (9.0)				

M refers to the number of goiter in each subgroup, N refers to the total number of each subgroup.

ables were compared using t test if in normal distribution and Wilcoxon Rank-Sum test if not in normal distribution. Potential risk factors of TN and goiter were analyzed by logistic multiple stepwise regression with *P*-value at 0.1 of entry and remove variables. As stated earlier, these variables included age, parity, alcohol consumption, smoking, education, seafood intake, salt intake, hypertension, diabetes, menopause, dyslipidemia and BMI. In all tests, *P* value <0.05 was deemed statistically significant.

Results

Demographic data, life style and medical characteristics of the study population

Based on the criteria of inclusion and exclusion, a total of 3084 (out of 6323) subjects were analyzed by the study (**Table 1**). Demographic data included age, education and marital status. Within the study population, participants less than 30 years of age were 3%, near 40 were 11%, near 50 were 25%, near 60

Table 3. Relationship between WHR, BMI, TC, TG and Menopause with TN or Goiter

Parameters	Thyroid module			Goiter		
	TN	Non-TN	*P value*	Goiter	Non-goiter	*P value*
WHR	0.88±0.07	0.86±0.09	0.000	0.88±0.06	0.87±0.08	0.000
BMI (kg/m^2)	27.45±4.05	26.83±4.50	0.000	29.04±3.84	26.98±4.11	0.000
TC (mmol/L)	5.30±1.62	5.09±1.07	0.000	5.25±1.04	5.20±1.42	0.290
TG (mmol/L)	1.6±1.13	1.52±1.25	0.000	1.76±1.53	1.55±1.15	0.002
Menopause (age)	49.55±3.88	49.30±4.33	0.170	49.19±4.10	49.47±4.07	0.532

Table 4. Relationship of Medical Management of Comorbidities with TN or Goiter

Variables	Positive rate of TN		Positive rate of goiter	
	M/N (%)	*P value*	M/N (%)	*P value*
Hypertension (%)		0.015		0.157
treated	572/912 (56.1)		108/912 (11.8)	
untreated	281/501 (62.7)		47/501 (9.4)	
Diabetes (%)		0.649		0.593
treated	210/327 (64.2)		36/327 (11.0)	
untreated	239/382 (62.6)		47/382 (12.3)	
Dyslipidemia (%)		0.099		0.5664
treated	101/166 (60.8)		19/166 (11.5)	
untreated	745/1377 (54.1)		138/1377 (10.0)	
Menopause (%)		0.566		0.679
treated	4/9 (44.4)		0/9 (0.0)	
untreated	1039/1748 (59.4)		169/1748 (9.7)	

M refers to the number of goiter in each subgroup, N refers to the total number of each subgroup.

were 33%, near 70 were 24%, and older than 70 were 5%. The age showed a normal distribution with the median age being 52. In education, 7% participants received no formal education, 22% graduated from elementary school, 43% graduated from middle school, 21% graduated from high school, 5% graduated from junior college, and 2% completed undergraduate studies or above. Near 100% of the study population was currently married. The life style included drinking, smoking, seafood intake, exercise and salt intake. Of the study population, 96% denied drinking, 1% admitted prior drinking, and 3% was actively drinking. Compatible with this data, 94% participants denied smoking, 1% had prior smoking history, and 5% was smoking at present. In seafood consumption, 15% of the study population reported rarely, 79% occasionally, and 6% frequently had seafood in their diet. Excise was classified into high, modest and low intensities, for which the study population responded with 1%, 8% and 92%, respectively. Last in salt intake, 23% of the study group had low, 47% had medium, and 30% had high salt in their diet. Medical characteristics included parity, menopause, BMI, waist circumference, hypertension, hyperglycemia, dyslipidemia and hyperuricemia. 46% of the women had one child, 50% had two to three, and 4% had four children. 40% were actively menstruating, and 60% had reached their menopause. As stated earlier, obesity was defined as BMI ≥25 in China. In the study group, 32% participants were normal, and 68% were obese. This was consistent with another obesity parameter, waist circumference. Of the tested participants, 21% showed less than (normal) and 79% showed more than 80 cm (obese) in length.

Clinical and demographic features of TN and goiter

We next examined various clinical and demographical features of TN and goiter (**Tables 1** and **2**). For TN, we observed a significant relationship (P<0.05) with following variables: education level, age, parity, menopause, smoking, high salt intake, BMI, waist circumference, hypertension, hyperglycemia and dyslipidemia. The prevalence of TN increased with the number of parity, while declined with the educational level. We found no correlation with marital status, drinking, exercise and hyperuricemia. For goiter, we observed a significant association (P<0.05) with menopause, waist circumference, BMI, hypertension, dyslipidemia and hyperglycemia. Interestingly, age of the popula-

Table 5. Analysis of Risk Factors for TN or Goiter

Variables	TN		Variables	Goiter	
	OR (95% CI)	*P value*		OR (95% CI)	*P value*
Age		0.000	Age		0.003
unit = 1	1.034 (1.026, 1.042)		40-50 VS <40	1.871 (1.023, 3.423)	
unit = 5	1.183 (1.139, 1.229)		50-60 VS <40	2.531 (1.409, 4.544)	
unit = 10	1.399 (1.297, 1.509)		≥60 VS <40	1.706 (0.925, 3.148)	
Diabetes		0.003	BMI		0.000
yes VS no	1.328 (1.105, 1.597)		≥25 VS <25	2.859 (1.972, 4.145)	
Hypertension		0.003	Hypertension		0.065
yes VS no	1.277 (1.087, 1.500)		yes VS no	1.29 (0.984, 1.705)	
Salt intake		0.098			
medium VS mild	1.159 (0.962, 1.396)				
high VS mild	1.247 (1.018, 1.526)				

tion displayed a discordant correlation with goiter. At before or near 60 years of age, it showed a positive relationship, and after 60 a negative relationship. Other factors not relevant to goiter included education level, marital status, parity, drinking, smoking, sea food intake, salt intake, exercise and hyperuricemia. Taken together, the factors associated with both TN and goiter included menopause, waist circumference, BMI, hypertension, dyslipidemia, and hyperglycemia.

Obesity and dyslipidemia are associated with increased prevalence of TN and goiter

From the above analyses, we concluded that menopause, obesity, hypertension and dyslipidemia were significantly related to TN and goiter. To further determine the relationship, we directly compared the participants with or without TN or goiter, and their waist-hip ratio (WHR), BMI, TC, TG, and menopausal age (**Table 3**). Note that other metabolic parameters such as HDL and FPG were excluded from the analysis given that they showed large variations in our study. Shown in **Table 3**, WHR, BMI and TG had a significant association (P<0.01) with both TN and goiter, and TC only correlated (P<0.001) with TN. With this method, we did not observe statistical significance for median menopausal age (approximately 49 years of age).

The relationship of medical management of comorbidities with TN and goiter

Next we examined whether medical management of aforementioned comorbidities and risk factors could affect the prevalence of TN and goiter. We observed in our TN study group statistical significance (P<0.05) of anti-hypertensive therapy. Medical therapies in patients with diabetes and dyslipidemia, and estrogen supplementation in postmenopausal participants however had no statistical significant impact on either TN or goiter (**Table 4**).

Stratification of risk factors and comorbidities in TN and goiter

Last, we stratified the risk factors and identified significant comorbidities from our studies. Age directly associated with TN and goiter with statistical significance (P<0.001 and P<0.01, respectively). The risk of TN increased by 3% with age increased by every 1 year, by 18% with age increased by every 5 years, and by 30% with age increased by every 10 years (**Table 5**). Likewise, age over 40 was a strong predictor of goiter (odds ratio [OR] of age 40-50, 50-60, ≥60 VS <40 was 1.871, 2.531, and 1.706, respectively). Additionally, women with diabetes and hypertension had 1.33 and 1.28 times of risk in developing TN. Obesity, which was quantified by BMI also strongly predicted the likelihood of developing goiter (OR = 2.86).

Discussion

TN and goiter are frequent screening findings wherein patients may or may not present with clinical symptoms and abnormal laboratory tests. Given these two conditions are highly prevalent and associated with multiple thyroid pathologic conditions including cancer, it is per-

tinent to advocate routine thyroid examinations in the general population.

In this study, we conducted a large-scale observational study in the Chinese female population, aimed to further identify the risk factors of its pathogenesis. Our data suggest that menopause, waist circumference, BMI, hypertension, dyslipidemia and hyperglycemia are individual risk factors. This agrees with earlier studies performed in other populations [20, 22-24]. It is worth noting that most identified risk factors are components of the metabolic syndrome, a disorder of energy utilization and storage manifested as conditions such as hyperglycemia, dyslipidemia, arterial hypertension and obesity. Metabolic syndrome is a major health issue in western countries, with data estimating the prevalence in the United States to be 34% [25]. With the economic development and changes in life habits in recent years, it has become a growing concern in the Chinese population [26]. Recent survey shows that metabolic syndrome occurs in 12.7% in Chinese males and 14.2% in females, and the incidence of cardiovascular disease was high in an epidemiologic survey in 11 provinces in China [27]. It was long speculated that components of the metabolic syndrome may contribute to thyroid conditions including TN and goiter, yet the definitive conclusion could not be drawn due to the insufficiency of data. In one report, abdominal obesity associated with sick euthyroid syndrome in adult Nigerians [28]. In another study, prevalence of dyslipidemia increased accordingly to higher thyroid-stimulating hormone (TSH) concentrations [29]. In contrast to studying single metabolic disorder, our study included most components of the metabolic syndrome thereby providing one-step-further evidence in the strong correlation with the two disorders.

TN is more frequent in females than in males [14]. This has promoted us to choose Chinese women as the study population. In our study we observed a correlation between menopause and TN. We excluded estrogen and estrogen use based on the fact that few postmenopausal Chinese women take estrogen containing medications, even though the literature from another country indicated that estrogen contributed to the pathogenesis of TN [22]. Concerning age, our speculation is that advanced age contributes to the high rate of TN in postmenopausal females.

Nonetheless, there are other implicated factors that worth further investigation. For instance, smoking was known to precipitate metabolic syndrome [30] and some thyroid pathological conditions [31]. Our female study group was less engaged in smoking compared to the males of same demographic area. Further, Hyperuricemia is a known etiologic factor of gout. It has recently been recognized for its involvement in metabolic syndrome [32, 33]. In our survey however we did not identify a strong association with TN and goiter. Future work is needed to determine whether the characteristics of this study population were involved in generating this observational disagreement.

Together, our study is one of the first large-scale epidemiological studies of risk factors in the pathogenesis of TN and goiter in Chinese women. We propose that female patients in the Chinese population with advance age, menopause, obesity, and metabolic syndrome should be examined by physicians and imaging tests for TN and goiter. Patients with confirmed TN and goiter should be screened for age and obesity related disorders such as metabolic syndrome.

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Disclosure of conflict of interest

None.

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