Int J Clin Exp Med 2015;8(10):19332-19338
www.ijcem.com /ISSN:1940-5901/IJCEM0013281

Original Article

Observations on factors that influence thyroid nodules in diabetic and non-diabetic patients in the Zhejiang province of China

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Received July 22, 2015; Accepted September 28, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Background: To determine the incidence of diabetes and thyroid nodules and factors influencing them. Methods: A questionnaire was used for the epidemiological investigation of metabolic disorders, especially diabetes. Thyroid hormones and other indicator levels as well as ultrasound examinations were performed. Results: Of 842 cases, 43 had diabetes, with an incidence rate of 5.1%, while 799 cases were non-diabetic, accounting for 94.9%. The incidence rate of thyroid nodules was 81.4% (35/43) in diabetic patients and 70.7% (565/799) in non-diabetic patients. Statistical analysis showed that the pathogenesis of thyroid was not obviously associated with diabetes. A further analysis of clinical features and thyroid nodules in diabetic patients revealed that the morbidity of thyroid nodules was correlated with age but had no relation to gender. The incidence of thyroid nodules was 92.9% in patients > 60 years. The morbidity of thyroid nodules was not only associated with age but also gender in non-diabetic patients, with a relatively high probability in female patients > 60 years. Logistic regression analysis revealed that follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and glutamate pyruvate transaminase (GPT) were risk factors for developing thyroid nodules in all subjects; for males aged > 60 years, TSH and thyroxine were risk factors; for female subjects, FSH, TSH and GPT were the main factors. Conclusions: Diabetes is not a risk factor for thyroid nodules but an age > 60 years is an important factor for high morbidity of thyroid nodules.

Keywords: Diabetes, thyroid nodule, morbidity

Introduction

Type 2 diabetes is recognized as one of the world's most common chronic medical conditions and represents a major threat to global health. By 2011, the International Diabetes Federation estimated that 336 million people worldwide will have type 2 diabetes. This disease kills approximately 4.6 million people every year, which equates to 1 death every 7 seconds. The incidence of type 2 diabetes is not confined to the western world but is now widespread in developing countries. Most cases of type 2 diabetes are strongly associated with a lifestyle devoid of significant physical activity, obesity, adoption of a western-type diet, and as a consequence of aging. A person who contracts diabetes has an increased risk of developing heart disease, stroke, and vascular disorders, which may lead to blindness, renal failure, and peripheral neuropathy. Long-term hyperglycemia and a series of associated metabolic disorders will give rise to multi-systemic damage in a person who contracts diabetes, with an increased risk of developing heart disease, stroke, and vascular disorders, which may lead to blindness, renal failure, and peripheral neuropathy. This disease may require insulin therapy or other pharmacological agents to optimally control the blood glucose level within recommended limits [1]. One alarming statistic is that about 80% of patients with diabetes die from cardiovascular complications (stroke, heart attack, cerebrovascular and peripheral vascular disease, etc.). Thyroid nodule is a common endocrine disease with a complicated etiology, associated among other factors with exposure to radiation, autoimmunity, heredity and iodine uptake. Currently, several studies have demonstrated an increased prevalence of thyroid nodules in type 2 diabetic patients [2, 3]. The relationship between diabetes and thyroid nodule has raised concern, and some scholars have argued that there is a common heredity and immunological basis between them. Research has indicated that insulin resistance [4], hyperinsulinemia [5] and advanced glycosylation end products [6] are probably involved in the pathogenesis of thyroid nodules. Nevertheless, it still remains to be established unequivocally what the relationship is between diabetes and the factors involved in the development of thyroid nodules.

In the present study, a cross-sectional analysis of the morbidity of thyroid nodules in patients in the Zhejiang province of China, from was performed to explore the factors influencing the development of thyroid nodules in patients with type 2 diabetes, with a view to providing evidence for the prevention of their development.

Methods

Subjects

Between February 2014 and June 2014 a total of 3500 residents aged 25-75 years old, living in the Zhejiang province of China were screened for FBG and HbA1c and subjected to various physical examinations, according to the defined inclusion and exclusion criteria (*vide infra*). All participants read and then signed an informed consent form and their personal details were recorded.

Inclusion criteria

The inclusion criteria were: (1) individuals who fitted the guidelines for the diagnosis of type 2 diabetes in China, issued in 2010; (2) those who did not have a previous clinical history of thyroid disease.

Exclusion criteria

The exclusion criteria were: (1) individuals diagnosed with diabetes; 2) those who were suffered from level-three hypertension with DBP ≥ 110 mmHg and/or SBP ≥ 180 mmHg, or those who were regularly taking anti-hypertensive drugs with SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg; (3) individuals who had heart and renal failure, confirmed angina, coronary artery bypass grafting (CABG) surgery, percutaneous coronary intervention (PCI), myocardial infarction, stroke, transient ischemic attack (TIA), and other cardiovascular and cerebrovascular events; (4) patients who presented with serious diseases, including malignant tumors, severe arrhythmia, nervous-mental disease, and drug or alcohol addiction; (5) those who had a significantly abnormal liver function or a history of the following liver diseases, i.e. AST or ALT twice the normal upper limit value, a hepatic encephalopathy history, an esophageal varices history, or a portal vein shunting history; (6) individuals who had renal function damage or a history of the following; serum creatinine 1.5 times the normal upper limit, dialysis or nephritic syndrome history; (7) those who had a pregnancy plan or were pregnant and also breast feeding women; (8) subjects who had limb deficiencies or other diseases which prevented the individual from completing the required general physical activities, such as brisk walking, running, and others. Finally, a total of 842 individuals were included in the study for our epidemiological investigation of metabolic disorders, with a special emphasis on type 2 diabetes.

Clinical observation items and indicators

The compulsory detection indicators were: (1) a personal medical and family history, education level, smoking and drinking, physical activity, diet, medication use, and various risk factors for developing metabolic syndrome, all obtained using a questionnaire; (2) height, weight, waistline, hip circumference, blood pressure taken by a nationally standardized method (3 times), heart rate, heart rhythm through palpation of the pulse, and an electrocardiogram; (3) related laboratory measurements to diagnose metabolic disorder including FBG, TC, TG, HDL-c and LDL-c; Safety of participants was ensured by also making routine blood and urine measurements, liver and renal function tests, urine pregnancy test and HbAlc. The ideal detection indicators were: (1) correlated laboratory examination of metabolic disorders, such as insulin and blood uric acid (2) important metabolic indicators in the serum, such as adiponectin and C-reactive protein.

Detection method of the thyroid function

After overnight fasting for 12 h, the morning fasting elbow venous blood was taken and

Table 1. Analysis of the population baseline and the hormones in patients with thyroid nodules and no nodules among the diabetic and non-diabetic participants

Influencing factors	Diabetic patients (*n* = 43)			Non-diabetic patients (*n* = 799)		
	Non-thyroid nodule patients (*n* = 8)	Thyroid nodule patients (*n* = 35)	P	Non thyroid nodule patients (*n* = 234)	Thyroid nodule patients (*n* = 565)	P
Age						
< 60 years old	6 (40.0)	9 (60.0)	0.0083	144 (33.2)	290 (66.8)	0.0084
≥ 60 years old	2 (7.1)	26 (92.9)		90 (24.7)	275 (75.3)	
Gender						
Male	4 (33.3)	8 (66.7)	0.1225	108 (37.4)	181 (62.6)	0.0002
Female	4 (12.9)	27 (87.1)		126 (24.7)	384 (75.3)	
25-hydroxyvitamin D	37.46 ± 8.96	36.48 ± 10.01	0.8007	38.45 ± 10.96	39.14 ± 11.06	0.4235
LH	15.76 ± 12.2	18.63 ± 12.41	0.5580	11.57 ± 11.42	16.17 ± 13.29	< 0.0001
FSH	35.35 ± 33.13	45.51 ± 28.08	0.3766	25.46 ± 28.61	37.47 ± 33.2	< 0.0001
Testosterone	6.99 ± 7.02	4.96 ± 8.96	0.5530	7.84 ± 8.6	5.76 ± 7.98	0.0011
Estradiol	123.94 ± 70.33	92.3 ± 34.01	0.2513	169.92 ± 248.8	161.79 ± 221.74	0.6649
TSH	2.65 ± 0.62	2.18 ± 1.14	0.2644	2.78 ± 1.94	2.4 ± 1.49	0.0071
Thyroxine	104.23 ± 18.97	117.7 ± 19.87	0.0888	106.04 ± 20.91	109.37 ± 20.37	0.0372
T3	1.31 ± 0.24	1.39 ± 0.22	0.3849	1.44 ± 0.27	1.42 ± 0.23	0.2107
Creatinine	67.25 ± 8.15	71.23 ± 36.22	0.5598	67.33 ± 11.14	65.04 ± 11.64	0.0103
GOT	29.13 ± 11.14	26.51 ± 12.46	0.5895	28.8 ± 15.56	25.31 ± 12.17	0.0023
GPT	41.75 ± 30.27	25.31 ± 17.01	0.1762	26.91 ± 21.21	21.98 ± 14.66	0.0013
Insulin	58.39 ± 45.08	68.48 ± 64.74	0.6792	46.76 ± 43.12	40.14 ± 28.7	0.0316

Table 2. Comparison of the influencing factors in male diabetic and non-diabetic patients with complications of thyroid nodules

Influencing factors	Diabetic patients			Non-diabetic patients		
	Non-thyroid nodule patients	Thyroid nodule patients	P	Non-thyroid nodule patients	Thyroid nodule patients	P
25-hydroxyvitamin D	36.88 ± 6.73	38.69 ± 13.39	0.8075	41.72 ± 12.52	43.23 ± 12	0.3115
LH	5.33 ± 3.01	10.19 ± 6.81	0.2106	5.55 ± 3.08	6.84 ± 4.86	0.0062
FSH	6.78 ± 3.66	19.6 ± 17.58	0.0826	9.19 ± 5.88	11.44 ± 10.56	0.0208
Testosterone	13.38 ± 2.51	19.29 ± 9.26	0.2477	16.13 ± 5.68	16.49 ± 5.42	0.5943
Estradiol	170.43 ± 75.57	98.6 ± 27.5	0.1519	103.88 ± 38.07	112.15 ± 45.44	0.0982
TSH	2.14 ± 0.27	1.57 ± 0.84	0.2242	2.49 ± 1.96	2.04 ± 1.13	0.0295
Thyroxine	107.7 ± 16.64	121.55 ± 23.67	0.3240	100.18 ± 18.83	107.08 ± 22.01	0.0070
T3	1.48 ± 0.14	1.31 ± 0.26	0.2648	1.43 ± 0.21	1.43 ± 0.24	0.9954
Creatinine	71.75 ± 8.46	101.25 ± 67.95	0.2636	75.33 ± 9.29	75.48 ± 9.8	0.9036
GOT	33.25 ± 14.36	36.13 ± 14.54	0.7526	31.04 ± 14.99	28.04 ± 13.46	0.0808
GPT	55 ± 37.9	33.38 ± 19.37	0.2096	29.68 ± 25.18	25.92 ± 17.46	0.1739
Insulin	39.33 ± 8.1	42.1 ± 31.06	0.8181	45.66 ± 48.21	34.46 ± 27.24	0.0285

stored at -20°C for preservation, after separation of the serum. Radioimmunoassay (RIA) was used for serum FT3 and FT4 detection using kits (Roche Diagnostics GmbH, Mannheim, Germany). The normal reference ranges of FT3 and FT4 were 2.5-5.8 pmol/L and 11.5-23.0 pmol/L, respectively. Immunofluorometric analysis (IFMA) was utilized for serum TSH detection (Xiehe Pharmaceutical Science and Technology Ltd, Tianjing City). The reference range of TSH was 0.25-4.0 mIU/L. RIA was adopted for thyroid peroxide antibody (TPOAb) and thyrotropin receptor antibody (TRAb) determinations with commercial kits (RSR Limited, Cardiff, UK). The reference ranges of TPOAb and TRAb were 0-15 IU/mL and 1-10 IU/L, respectively. The coefficient of variation of the above indicators within a batch and

Table 3. Comparison of various indicators in thyroid and non-thyroid nodule patients among female diabetic and non-diabetic patients

Influencing factors	Diabetic patients			Non diabetic patients		
	Non-thyroid nodule patients	Thyroid nodule patients	P	Non-thyroid nodule patients	Thyroid nodule patients	P
Insulin	38.04 ± 11.89	35.83 ± 8.98	0.6610	35.65 ± 8.53	37.21 ± 10.05	0.0893
25-hydroxyvitamin D	26.2 ± 6.89	21.13 ± 12.66	0.4436	16.73 ± 13.29	20.58 ± 13.73	0.0062
LH	63.93 ± 19.26	53.19 ± 26.08	0.4376	39.4 ± 32.74	49.74 ± 33.17	0.0024
FSH	0.6 ± 0	0.71 ± 0.25	0.0283	0.74 ± 0.32	0.71 ± 0.26	0.3577
Testosterone	77.45 ± 8.3	90.44 ± 35.96	0.1214	226.53 ± 327.33	185.19 ± 264.04	0.1998
Estradiol	3.17 ± 0.33	2.36 ± 1.17	0.1844	3.02 ± 1.89	2.56 ± 1.61	0.0151
TSH	100.75 ± 23.04	116.56 ± 18.97	0.1397	111.05 ± 21.36	110.45 ± 19.48	0.7671
Thyroxine	1.14 ± 0.18	1.41 ± 0.21	0.0204	1.45 ± 0.32	1.41 ± 0.23	0.1733
T3	62.75 ± 5.44	62.33 ± 10.62	0.9398	60.48 ± 7.41	60.11 ± 8.86	0.6516
Creatinine	25 ± 6.16	23.67 ± 10.46	0.8071	26.89 ± 15.83	24.02 ± 11.3	0.0615
GOT	28.5 ± 15.29	22.93 ± 15.86	0.5155	24.53 ± 16.84	20.13 ± 12.75	0.0078
GPT	77.45 ± 60.89	76.3 ± 70.32	0.9755	47.7 ± 38.39	42.81 ± 29.01	0.1910

Table 4. Multi-factor logistic regression model of the risk factors of thyroid nodules in all subjects

Influencing factors	Predicative value	SD	OR (95% CI)
All subjects			
FSH	0.0130	0.00278	1.01 (1.01-1.02)
TSH	-0.1623	0.0482	0.85 (0.77-0.93)
GPT	-0.0149	0.00447	0.99 (0.98-0.99)
Male subjects			
Age ≥ 60 years old	0.7890	0.2543	2.20 (1.34-3.62)
TSH	-0.2451	0.1032	0.78 (0.64-0.96)
Thyroxine	0.0148	0.00604	1.02 (1.00-1.03)
Female subjects			
FSH	0.00972	0.00333	1.01 (1.00-1.02)
TSH	-0.1488	0.0580	0.86 (0.77-0.97)
GPT	-0.0195	0.00697	0.98 (0.97-0.99)

between batches was less than 10%. Ultrasound physicians performed thyroid ultrasound examinations of all patients using a HDI5000 Color Doppler Ultrasonic Diagnosis Apparatus (Philips/ATL, Washington, USA) with a transducer frequency of 5-12 MHz. A supine position was taken and the neck was fully exposed. A routine exploration of the bilateral glands and isthmus in the thyroid was performed to observe the internal echo. If a nodule was present, the size was measured and the nature of the nodule was evaluated. The diagnosis and treatment guidelines for thyroid nodules and differentiated thyroid carcinoma were used as a reference for the diagnostic criteria of thyroid nodules.

Statistical analysis

Statistical tests were performed using SAS™ 9.3 software (SAS Institute Inc, Cary, NC, USA). Demographical characteristics, hormones and other influencing factors between thyroid and non-thyroid nodule participants were compared using chi-square tests for categorical variables and student's t-test for continuous variables. Adjusted odds ratios (ORs) were calculated for all participants and separately for female and male participants, building logistic models first by adjusting for the factors achieved $P < 0.20$ in the univariate analysis, and then limiting final multivariate models with stepwise regression to risk factors or confounders that were statistically significant in the overall and gender-specific analyses. All statistical tests were conducted based on 2-tailed alternatives with significance set at the $P < 0.05$ level.

Results

Morbidity of thyroid nodules in diabetic and non-diabetic patients in the Zhejiang province

Among the 842 cases, 43 had diabetes with an incidence rate of 5.1%, while 799 cases were non-diabetic, accounting for 94.9%. The incidence rate of thyroid nodules was 81.4% (35/43) in diabetic patients and 70.7% (565/799) in non-diabetic patients. A statistical analysis showed that the pathogenesis of thyroid was not obviously associated with diabetes and that diabetes was not a risk factor for developing thyroid nodules in our cohort of patients.

Analysis of the population baseline and hormones in patients with thyroid nodules and non-nodules in diabetic and non-diabetic participants

The results showed that the morbidity of thyroid nodules was correlated with age but had no relation to gender in diabetic patients. Among these patients, the incidence of thyroid nodules was 92.9% in patients > 60 years old, far greater than that in patients < 60 years old (60%); the morbidity of thyroid nodules was not only associated with age but also gender in non-diabetic patients, with a relatively high probability in female patients > 60 years old.

In diabetic patients, there were no significant differences in the levels of vitamin D, sex hormones (LH, FSH, testosterone, estradiol), thyroid hormones (TSH, thyroxine, T3), creatinine, GOT, GPT and insulin between thyroid nodule and non-thyroid nodule patients (P > 0.05). In contrast, in non-diabetic patients, comparisons of the levels of LH, FSH, testosterone, TSH, thyroxine, creatinine, GOT, GPT and insulin between thyroid nodule and non-thyroid nodule patients were significantly different (P < 0.05). Therefore, the patients were checked to determine whether they were diabetic when the above indicators were used to diagnose thyroid nodules (**Table 1**).

Comparison of the influencing factors in diabetic and non-diabetic patients of different gender and complications of thyroid nodules

Comparisons of the levels of vitamin D, sex hormones and thyroid hormones between thyroid nodule and non-thyroid nodule patients among male and female diabetic and non-diabetic patients showed that among the male diabetic patients with the same configuration as all subjects, there was not a significant difference in any of the indicators between thyroid nodule and non-thyroid nodule patients. Among male non-diabetic patients, LH, FSH and thyroxine levels in the thyroid nodule patients were significantly enhanced compared with those in non-thyroid nodule patients (P < 0.05), but it is noteworthy that TSH and insulin levels were significantly reduced (P < 0.05, **Table 2**).

Among female diabetic patients, the levels of T3 in thyroid nodule patients were significantly higher than in non-thyroid nodule patients and the comparison of other indicators between the two groups was not significantly different. However, among female non-diabetic patients, LH and FSH levels in the thyroid nodule patients were significantly elevated compared to non-thyroid nodule patients; interestingly, TSH and GPT levels were significantly reduced (**Table 3**).

Multi-factor logistic regression model of the risk factors for thyroid nodules in all subjects

The above results showed that among diabetic patients, there was no significant difference between the indicators measured in thyroid nodule *vs* non-thyroid nodule patients; therefore, a further study was conducted to explore the risk factors that may be responsible for the development of thyroid nodules in all subjects (**Table 4**). A logistic multivariate regression analysis demonstrated that FSH (OR = 1.01, 95% *CI* = 1.01-1.02, P < 0.05), TSH (OR = 0.85, 95% *CI* = 0.77-0.93, P < 0.05), and GPT (OR = 0.99, 95% *CI* = 0.98-0.99, P < 0.05) were associated with the pathogenesis of thyroid nodules and were the independent risk factors for developing thyroid nodules in the general population. However, for male subjects, an age > 60 years old, TSH and thyroxine levels were the risk factors, while for female subjects, FSH, TSH and GPT levels were the main independent risk factors.

Discussion

Diabetes is a systemic metabolic disorder caused by multiple factors that result in an abnormal secretion of various hormones, including insulin and thyroid hormones. It has been reported in many previously published articles that there is an increased prevalence of thyroid disease in diabetic patients [3]. The results of our study showed that among the 842 cases studied in the Zhejiang province, the incidence of diabetes (5.1%) was lower than in other regions of China (20%), while 799 cases were non-diabetic, accounting for 94.9%. The incidence of thyroid nodules was 81.4% (35/43) in diabetic patients and 70.7% (565/799) in non-diabetic patients. A statistical analysis showed that the pathogenesis of thyroid was not obviously associated with diabetes. Previous studies have indicated that in the general population, thyroid nodules are preferentially found in females and that morbidity gradually increases with increasing age [7]. Therefore, in the present study, it was obvious that among the non-diabetic patients, the incidence of thyroid nodules in female patients (75.3%) was significantly higher than in male patients (62.6%) ($P < 0.001$); however, among the diabetic patients, the incidence of thyroid nodules in female patients (87.1%) appeared to be higher than in male patients (66.7%), but the comparison was not statistically significantly different ($P = 0.1225$), probably reflecting too few samples in the study. Accordingly, it will be important to conduct a large scale study to determine unequivocally whether there is a significant difference of morbidity of thyroid nodules between controls and the male and female diabetic patients.

Diabetes can give rise to an abnormal secretion of thyroid hormones. Insulin can induce the growth and proliferation of various cells, including thyroid cells, to trigger an abnormal thyroid structure and function [8, 9], while insulin-resistance can promote the development of thyroid nodules. Rezzonico et al. [5] argued that there is a higher prevalence of thyroid nodules in insulin-resistance patients and that the insulin-like growth factor 1 signaling pathway is involved in the proliferation of thyroid cells, an effect mediated by TSH. Insulin-resistance itself can promote the development of thyroid nodules [10]. This phenomenon only appeared in male non-diabetic patients in our study, among which the serum insulin level (34.46 ± 27.24, $n = 565$) was significantly reduced in patients with thyroid nodules ($P < 0.05$). However, among diabetic patients, insulin levels in thyroid nodule patients were slightly elevated, but the comparison between the thyroid nodule and non-thyroid nodule patients was not significantly different. There was a significant difference in the morbidity of thyroid nodules between patients < 65 years old and patients > than 65 years old ($P < 0.01$). The increased prevalence of thyroid nodules was associated with aging, with the incidence rate being significantly elevated in patients > 65 years old. It is believed that the increased morbidity of thyroid nodules with increasing age was associated with changes in the thyroid that accompany aging. These age-related changes include degeneration of thyroid cells associated with fibrosis, inflammatory cell infiltration, thyroid follicle alteration, and the formation of nodules [11]. Therefore, it is important to screen the thyroid for nodules in female and elderly individuals, especially if they are diabetic.

Multiple studies have demonstrated that diabetic patients are susceptible to the complications of hypothyroidism [12-14], which can induce an elevation of TSH levels. TSH has an important effect on the thyroid in that it can trigger a strengthened synthesis of nucleic acids and proteins in the epithelial cells of thyroid acini and thus stimulate proliferation of thyroid cells and a subsequent enlargement of the glands. Moreover, TSH, as a survival factor influencing thyroid cells, can protect them from apoptosis and plays a vital role in the formation of thyroid nodules. The results in the present study revealed that there was no significant difference in TSH and thyroid hormone levels in thyroid nodule and non-thyroid nodule patients, among male diabetic patients. However, among male non-diabetic patients, LH, FSH and thyroxine levels in thyroid nodule patients were significantly increased compared with those in non-thyroid nodule patients ($P < 0.05$). In contrast, TSH and insulin levels were significantly reduced ($P < 0.05$), findings in accordance with previously cited research (*vide supra*).

It has been suggested that the raised prevalence of thyroid nodules in females is associated with the female endocrine periodical change, and that increased levels of thyroxine are required during pregnancy and the menstrual cycle [15], among female diabetic patients, the levels of T3 in thyroid nodule patients was significantly higher than in non-thyroid nodule patients, but comparisons of other indicators between the two groups were not significantly different. However, among female non-diabetic patients, LH and FSH levels in thyroid nodule patients were significantly higher than in non-thyroid nodule patients. Therefore, it is argued that the thyroid nodules in female patients are probably associated with periodic female endocrine hormone secretion levels. To our best knowledge, no papers have been published on the relationship between GPT and thyroid nodules; thus, further extensive research is required into this important topic.

Conclusion

In conclusion, in the present study, diabetes was shown not to be a risk factor for the development of thyroid nodules, but that patients > 60 years old are likely to suffer from thyroid nodules. For male non-diabetic patients, TSH and thyroxine can be used as the detection indicators, while for female patients, changes in FSH, TSH and GPT levels can serve as useful diagnostic criteria.

Disclosure conflict of interest

None.

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