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Thyroid Nodules in Type 2 Diabetes Mellitus*

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Summary: The present analysis aims to investigate the prevalence of thyroid nodules in type 2 diabetes mellitus (T2DM) population. We searched PubMed, EMBASE, and Web of Science from inception to the March 1, 2018. The studies were selected to estimate the prevalence of thyroid nodules in T2DM subjects and to compare the prevalence of thyroid nodules in different glucose tolerance status. The random effects model was used, and the outcome was presented as a pooled prevalence proportion with 95% confidence interval (95% CI) or a summary odds ratio (OR) with 95% CI. In the end, 9 studies met the inclusion criteria and were included in the analysis. The pooled prevalence of thyroid nodules was 60% (95% CI: 0.52, 0.68) for T2DM 2 diabetes patients, 50% (95% CI: 0.48, 0.51) for pre-diabetes, and 43% (95% CI: 0.34, 0.52) for normal glucose tolerance population. Compared with patients without diabetes, diabetes subjects are more likely to develop thyroid nodules, adjusted OR for thyroid nodule was 1.78 (95% CI: 1.25, 2.55). Insulin resistance might be involved in thyroid nodule development.
Key words: thyroid nodule; diabetes; insulin resistance

Diabetes mellitus (DM) and thyroid disease are the two most common pathological status in the endocrine system and they seem to coexist in high frequency[1]. It is well established that thyroid hormones have effects on glucose and lipid metabolism[2]. Thyroid hormones are positively associated with insulin resistance (IR)[3]. Moreover, IR is also associated with thyroid disorders[4, 5]. Thyroid dysfunctions including both hypo- and hyperthyroidism have been shown to be related to IR and likely accompanied by impaired glucose tolerance or diabetes[4, 6–8], and some researches have revealed thyroid dysfunction as a comorbid disorder of type 2 diabetes mellitus (T2DM), with the frequency up to 11%[9, 10]. Diabetes, *per se* is related to thyroid dysfunction in some clinical conditions[11, 12].

Thyroid nodule is one of the most common benign thyroid disorders. The etiologic factors which influence thyroid goiter and nodule formation are multiple[13]. Recently, investigating the relationship between IR and abnormal thyroid function and morphology has become an interesting area of research. It has been reported that enlarged thyroid and nodule occurrence were observed in patients with IR[14, 15]. There are also other studies that revealed the constant association of IR with thyroid morphological changes. These findings raise the question of whether T2DM, as the result of IR, affects the formation of thyroid nodules[15, 16]. It has been reported that patients with pre-diabetes and diabetes have increased thyroid volumes and elevated risk of thyroid nodule formation[17], however, evidence on the association between T2DM and thyroid nodule is still sparse. Thus, in the present study, we performed a systematic review and meta-analysis to investigate the prevalence of thyroid nodules in T2DM patients.

1 MATERIALS AND METHODS

1.1 Search Strategy

A comprehensive search strategy was developed in consultation with a university librarian to search for articles online using PubMed, EMBASE, and Web of Science from inception to March 1, 2018. The search strategies were as follows: diabetes (Title/Abstract) OR hyperglycemia (Title/Abstract) AND thyroid neoplasms (Title/Abstract) OR goiter nodular (Title/Abstract) OR thyroid nodule (Title/Abstract]) OR thyroid tumor (Title/Abstract). In order to avoid missing any related study, we also reviewed relevant reference lists to find additional studies. We attempted to get in touch with the authors of the identified

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papers for the information which was not provided in the original publications. The present systematic review was reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[18]. There were no language restrictions. Ethical approval was not necessary.

1.2 Study Selection

The study inclusion criteria were as follows: (1) The study design needed to be observational; (2) All the subjects included were individuals with T2DM who had been evaluated for thyroid nodule by ultrasound; (3) The outcome of interest was thyroid nodule prevalence in T2DM patients; (4) The studies had sufficient data for a pooled prevalence or odds ratio analysis; (5) When more than one article from the same population was found, the most detailed article was included.

On the contrary, the exclusion criteria were as follows: (1) case reports, reviews, letters, editorials, or expert opinions; (2) lacking detailed information such as age; (3) subjects who were pregnant or had chronic organ dysfunction; (4) subjects who were diagnosed with type 1 diabetes or unspecified conditions; (5) the articles not clearly recording the diagnostic criteria of thyroid nodule; (6) the articles not clearly distinguishing thyroid nodule from other thyroid structural abnormality; (7) the articles only reporting thyroid nodule in T2DM with no controls; (8) the control group was type 1 diabetes; (9) the control group overlapped or had similar characteristics with T2DM such as obesity or metabolic syndrome.

1.3 Data Extraction and Quality Assessment

The systematic literature search, study selection, data extraction, and quality assessment were carried out by two investigators independently (HZ, QF). Any discrepancies were resolved by a third author (XW). For all included studies, data on the first author's name, publication year, age, gender, body mass index (BMI), location, the prevalence of thyroid nodules in T2DM group, impaired fasting glucose group or normal glucose tolerance group were extracted. Prevalence of thyroid nodule in each group was extracted as a total number of thyroid nodule cases divided by the number of total subjects. If the article reported an adjusted OR for thyroid nodule, then we also extracted the adjusted OR and the 95% confidence interval. If there was information on thyroid nodule in pre-diabetes like impaired fasting glucose or impaired glucose tolerance in addition to T2DM, the data of pre-diabetes were also extracted. We used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of case-control and cohort studies. And Agency for Healthcare Research and Quality (AHRQ) was used for cross-sectional studies.

1.4 Statistical Analysis

All analyses were finished using STATA software (version 13.0, Stata Corp LP, USA). We pooled the prevalence of thyroid nodules in abnormal glucose metabolism (T2DM, pre-diabetes) and normal glucose tolerance controls, and results were expressed as proportion and 95% CI. Moreover, we also pooled the results of studies in which adjusted OR for thyroid nodule was reported. The degree of heterogeneity among studies was calculated using the I^2 index. The effect estimates were pooled with the random-effects model. Because of the limited number of included studies, we did not examine the publication bias.

2 RESULTS

2.1 Description of Studies

Of the 817 citations identified in the primary search, 583 remained for title and abstract screening after duplicates were removed. Title and abstract screening removed 561 studies which were non-human studies or not laboratory studies (n=61), type 1 diabetes or other irrelevant records (n=402), case reports or reviews (n=98). Twenty-two full articles were reviewed for relevance. We tried to make contact with 5 authors of the identified papers for the information which was not provided in the original publications, only one responded. In the end, 9 articles (23 275 subjects) meeting the eligibility criteria were included in the review (fig. 1). Of the 9 included studies, one was cohort study[19], 3 were case-control studies[16, 17, 20], and 5 were cross-sectional studies[21–25]. Four studies compared the prevalence of thyroid nodules in T2DM patients with that of non-diabetes patients[16, 20, 21, 23]. Four studies compared the prevalence of thyroid nodules among T2DM, pre-diabetes (all were impaired fasting glucose) and non-diabetes[17, 22, 24, 25]. Four studies provided adjusted OR for thyroid nodule[16, 17, 19, 24]. Study characteristics of the included studies are presented in table 1.

2.2 Prevalence of Thyroid Nodule in T2DM, Pre-diabetes, and Controls

Results from 8 studies were pooled to assess the proportion of thyroid nodule in T2DM and results from 4 studies were pooled to assess the proportion of thyroid nodule in pre-diabetes (mainly impaired fasting glucose). The pooled proportion of thyroid nodule was 60% (95% CI: 0.52, 0.68) in T2DM, 50% (95% CI: 0.48, 0.51) in pre-diabetes, and 43% (95% CI: 0.34, 0.52) in normal glucose tolerance controls (fig. 2). There was significant heterogeneity among the selected studies for T2DM analysis (I^2=87.2%; P<0.001). But there was no heterogeneity among the selected studies for pre-diabetes (I^2<0.001%; P=0.847). The patients with T2DM were more likely to develop thyroid nodule than those with normal glucose tolerance, and adjusted OR was 1.78 (95% CI: 1.25, 2.55). The heterogeneity among the 4 included studies was 83%, P=0.001 (fig. 3).

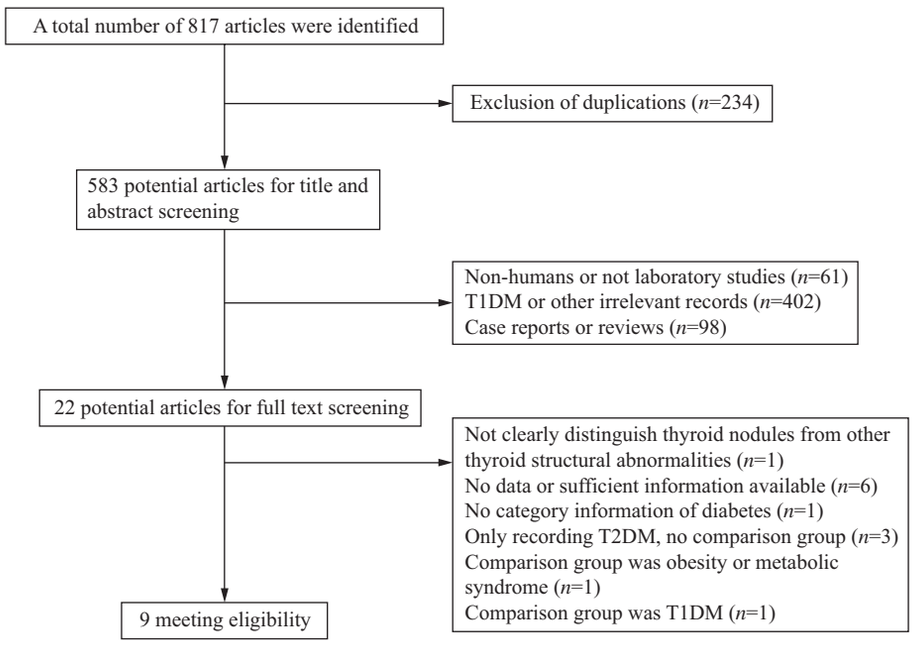

Fig. 1 Flow diagram of literature search

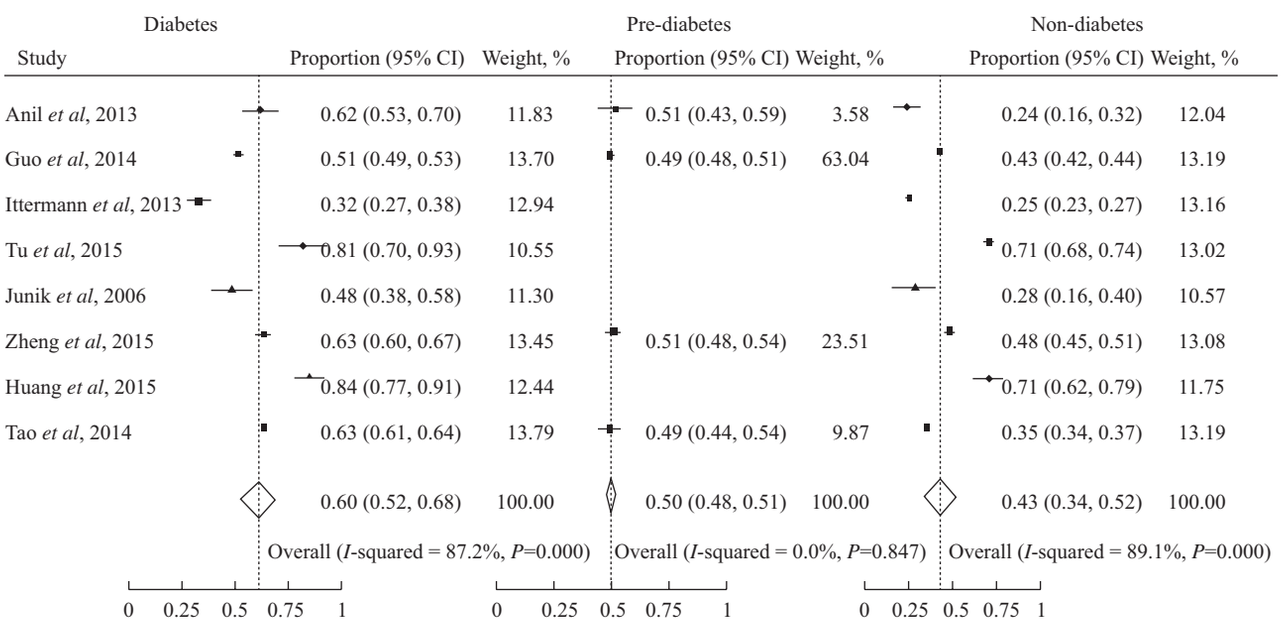

Fig. 2 Prevalence of thyroid nodules in T2DM, pre-DM, and non-DM

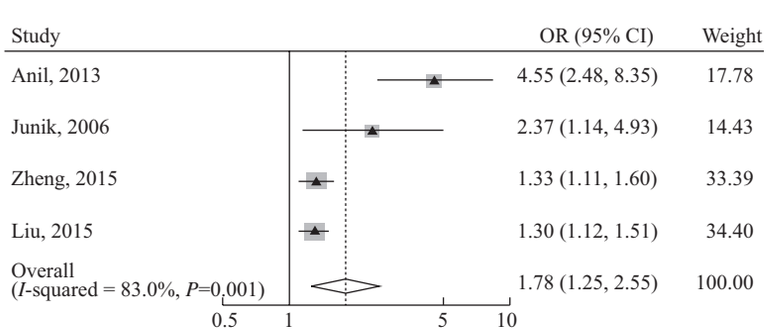

Fig. 3 Adjusted odds ratio for thyroid nodules in T2DM

Table 1 Induced-sputum characteristics[#]

Paper ID	First author	Publication year	Country City/ Region	Age (Mean, Year)	Gender Male/Female	BMI	Case (*n*)	Total (*n*)	Prevalence (%)	Adjusted OR (DM/NGT) 95% CI	Research type	Quality score
1	Anil C[17]	2013	Turkey/ Ankara	DM 54.6±6.85 IFG 53.1±7.3 NGT 52.5±7.2	43/80 51/105 31/83	31.9±4.9 31±5.3 27.4±5.2	DM 76 IFG 80 NGT 24	DM 123 IFG 156 NGT 114	DM 61.8 IFG 51.3 NGT 23.7	4.55 (2.48–8.43)	CC	5
2	Guo HW[22]	2014	China/ Nanjing	All >40	378/687 411/947 552/1464	Not in detail	DM 1065 IFG 1358 NGT 2018	DM 2093 IFG 2746 NGT 4693	DM 50.9 IFG 49.4 NGT 43.0		CS	6
3	Ittermann T[21]	2013	Germany/ Pomerania	DM1 67 (60, 74) DM2 64 (57, 71) NGT 57 (48, 67)	45/38 120/75 1227/1065	29.1 (26.6; 32.3) 30.0 (27.5; 34.8) 27.6 (24.8; 30.5)	DM 90 NGT 575	DM 278 NGT 2292	DM 32.4 NGT 25.1		CS	11
4	Tu WP[23]	2015	China/ Zhejiang	All 25-75	12/31 289/519	Not in detail	DM 35 NGT 565	DM 43 NGT 799	DM 81.4 NGT 70.7		CS	6
5	Junik R[16]	2006	Poland/ Bydgoszcz	DM 60 (55, 66) NGT 56 (48, 65)	54/44 29/21	Not in detail	DM 47 NGT 14	DM 98 NGT 50	DM 48 NGT 28	2.37 (1.14–4.93)	CC	5
6	Zheng L[24]	2015	China/ Beijing	All >18 All Female	Not in detail	Not in detail	DM 449 IFG 520 NGT 649	DM 709 IFG 1024 NGT 1351	DM 63.3 IFG 50.8 NGT 48	1.328 (1.105–1.597)	CS	5
7	Huang XQ[20]	2015	China / Shanghai	DM 84.09±3.43 NGT 84.12±3.09	84/19 81/22	24.27±4.50 23.47±4.99	DM 87 NGT 72	DM 103 NGT 103	DM 84.47 NGT 70.59		CC	5
8	Liu YX[19]	2015	China / Shandong	DM 57.87±14.3 NGT 46.66±3.84	840/274 9016/5398	F 25.95±3.67 M 26.54±3.15 F 23.39±3.33 M 25.51±3.12		DM 1114 NGT 14414		1.299 (1.118–1.510)	C	5
9	Tao YH[25]	2014	China / Tangshan	All 24-79	Not in detail	Not in detail	DM 272 IFG 211 NGT 2001	DM 434 IFG 430 NGT 5036	DM 62.7 IFG 49.1 NGT 35.5		CS	4

DM: diabetes mellitus; NGT: normal glucose tolerance; IFG: impaired fasting glucose; CC: case-control; CS: cross-sectional; C: cohort; F: female; M: male

3 DISCUSSION

In this review, we reported that thyroid nodule occurred more frequently in T2DM and pre-diabetes than in the normal glucose tolerance controls. The pooled prevalence of thyroid nodule was 60% for T2DM patients, 50% for pre-diabetes patients, and 43% for normal controls. As compared with non-diabetes subjects, the patients with T2DM are nearly two-fold more likely to develop thyroid nodules.

The mechanisms underlying higher thyroid nodule prevalence in abnormal glucose tolerance status, especially in diabetes patients is uncertain. Some researchers have reported that IR[14], hyperinsulinemia[15] and advanced glycosylation end products[26] are possibly involved in the pathogenesis of thyroid nodules. IR may be the major link between T2DM and thyroid nodule. Research has shown the association between IR and thyroid goiter and high frequency of thyroid nodules[15]. As a final consequence of IR, T2DM is a key factor in the pathogenic process of thyroid nodule. Some mechanisms have been proposed about how IR causes increased cellular proliferation. Under IR, the mitogen-activated protein kinase (MAPK) pathway will be activated to promote cell proliferation[27]. On the other hand, insulin plays an indirect role in tumorigenesis by modulating the insulin-like growth factor (IGF) system[28]. High serum insulin levels cause increased IGF-1 levels. Results from basic research illustrated that insulin and IGF-1 could induce thyroid proliferation[29, 30]. The insulin/IGF-1 signaling pathway modulates regulation of thyroid gene expression and may be regarded as a major factor in thyrocyte proliferation and differentiation[31].

Thyroid stimulating hormone (TSH) functions as an important regulator of the growth and differentiation of thyroid cells[32]. It was reported that TSH cooperates with insulin or IGF-1 to stimulate cell cycle progression and proliferation in a variety of cultured thyroid cell lines[33]. Progression of the thyroid cell cycle relies on combined activity of TSH and insulin/IGF-1, all of which act as co-mitogenic factors[34]. Some researches have shown that TSH levels were higher in patients with T2DM than in non-diabetes patients[17].

Experimental data have shown that increased insulin and/or glucose may lead to thyroid cell proliferation by affecting cellular energy metabolism[35], worse glucose control is associated with thyroid morphology alteration and could be a threat for thyroid nodule formation and thyroid tissue growth in T2DM[36]. Also, there are studies in rodents revealing that high glucose levels enhance thyroid oxidative stress enzymes which are well known to be associated with elevated cell proliferation rate[37]. Taken together, higher circulating glucose levels, increased insulin/IGF-1 levels, and elevated TSH levels may all play a role in thyroid nodule formation in T2DM.

The prevalence of diabetes is rising globally[38] and with increasing resolution of modern ultrasound equipment, thyroid nodule is commonly seen in diabetes patients. Our work further confirms that the prevalence of thyroid nodule in T2DM is significantly higher than in non-diabetes people. The main reason may be attributed to the insulin resistance. So in clinical practice, the treatment of T2DM should focus on the improvement of IR. Studies have shown that metformin has an anti-goitrogenic effect[21]. Also, metformin has been shown to decrease TSH levels in hypothyroidism. Therefore, antidiabetic agents which can improve IR such as metformin should have priority in the treatment of T2DM to prevent goiter and thyroid nodule formation.

The present review has several limitations. Firstly, this meta-analysis was based on the observational studies without high quality, so the estimates may be not completely reliable. Secondly, the pooled data showed high heterogeneity which might be attributed to the different study designs and poor quality of the recruited studies. Thirdly, we were unable to assess publication bias given that the number of enrolled studies was limited. The limitations warrant large-scale population-based prospective studies.

In summary, this meta-analysis shows that thyroid nodules are more prevalent in T2DM. IR might be involved in the development of thyroid nodule. Improvement of IR might slow the growth, or reduce the volume and size of the thyroid nodules and should be prioritized when treating T2DM.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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