The Connection Between Thyroid Nodules and Diabetes Mellitus

Marwa Ahmed Salah Ahmed
Lecturer of Internal Medicine, Endocrine Division, Faculty of Medicine, Alexandria University

Introduction

Diabetes mellitus (DM) and thyroid disease are the two most prevalent pathological conditions in the endocrine system and they appear to coexist in high frequency (1).

It is well-established that thyroid hormones have effects on glucose and lipid metabolism (2).

Thyroid dysfunctions including both hypo- and hyperthyroidism have been shown to be related to IR (3, 4) and some researches have revealed thyroid dysfunction as a comorbid disorder of type 2 diabetes mellitus (T2DM), with a frequency of up to 11% (5,6).

Thyroid nodule is one of the most common benign thyroid disorders. A number of well-known factors are involved in nodule formation including iodine deficiency, gender, age, smoking, and genetic factors (7, 8). The global rate of diabetes is steadily rising, according to the International Diabetes Federation (IDF). Thyroid nodule incidence was also increasing in a similar manner. As a result, there may be a link between an elevated risk and T2DM characteristics such as insulin resistance. Recently, investigating the relationship between IR and thyroid morphology has become an interesting area of research. It has been documented that thyroid nodule occurrence was observed in patients with IR (9,10).

These results beg the question of whether thyroid nodule formation is impacted by T2DM resulting from IR (10, 11). There is less information about the correlation between type 2 diabetes and thyroid nodule formation, despite reports indicating people with pre-diabetes and diabetes had larger thyroid volumes and an increased risk of thyroid nodule formation (12).

Prevalence of Thyroid Nodule in T2DM, Prediabetes

The International Diabetes Federation (IDF) announced a continual increase in the rate of diabetes around the world. Similarly, the incidence of thyroid nodules was also rising. Thyroid volume was positively correlated with hyperglycemia in patients with impaired glucose metabolism, and larger thyroid volumes and higher nodule prevalence were noted in T2DM patients in certain cases (13,14).

In a review by Hong-Mei Zhang et al, they reported that thyroid nodules occurred more frequently in T2DM and pre-diabetes than in the normal glucose tolerance controls. The proportion of thyroid nodules 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. The prevalence of thyroid nodules was 60% for T2DM patients, 50% for pre-diabetes patients, and 43% for controls. Patients with T2DM are nearly two-fold more likely to develop thyroid nodules as compared with non-diabetes subjects (15).

Although many studies have investigated the relationship between type 1 diabetes mellitus (T1DM) and thyroid diseases, few studies have conducted a morphological evaluation of the thyroid gland in T1DM. A cross-

sectional study included 119 patients with T1DM and 105 healthy controls. No significant difference was found between the control group and the T1DM group in terms of thyroid function tests, thyroid volume, and the presence of thyroid nodules. As a result of regression analysis, ICA positivity in the T1DM group increased threefold the risk of having thyroid nodules. Thus, cases with ICA positivity may have a higher probability of nodules in the thyroid gland, and neck examinations should be performed more frequently (16).

A few population studies have focused on thyroid nodularity in patients with T1DM without AITD. Moreover, knowledge of T1DM and thyroid nodularity in adults is limited, as most studies included children and adolescents. To date, available data demonstrated inconsistent results about thyroid morphology in patients with T1DM (17,18).

Insulin resistance and thyroid nodules

Uncertainty surrounds the mechanisms responsible for a higher thyroid nodule prevalence in impaired glucose tolerance status, particularly in diabetics. Some studies have reported that IR, hyperinsulinemia, and advanced glycosylation end products are involved in the mechanism of thyroid nodule formation (10,19). 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. On the other hand, insulin plays an indirect role in tumorigenesis by modulating the insulin-like growth factor (IGF) system. High serum insulin levels cause increased IGF-1 levels. Results from basic research illustrated that insulin and IGF1 could induce thyroid proliferation. The insulin/ IGF-1 signaling pathway modulates the regulation of thyroid gene expression and may be regarded as a major factor in thyrocyte proliferation and differentiation (20,23).

It was reported that TSH interacts with insulin or IGF-1 to stimulate cell cycle progression and proliferation in cultured thyroid cell lines (24). Progression of the thyroid cell cycle depends on the combined activity of TSH and insulin/IGF-1, acting as co-mitogenic factors (25). Data have shown that increased insulin and/or glucose may lead to thyroid cell proliferation by affecting cellular energy metabolism (26), uncontrolled hyperglycemia is associated with thyroid morphology change and could lead to thyroid nodule formation in T2DM (27).

Yunzhao Tang et al investigated the correlation between IR and thyroid nodules in T2DM, they included patients newly diagnosed with T2DM, 201 patients with thyroid nodule disease, and 308 patients without thyroid nodules. Regression analysis showed that age, sex, FT4, and HOMA-IR were positive factors for thyroid nodules. The volume and size of the thyroid nodule were positively correlated with HOMA-IR (28).

Effect of Metformin Therapy on Thyroid Nodules

Metformin is an antidiabetic drug and is recommended to patients with IR. Studies have shown that metformin has an anti-goitrogenic effect [29]. Few studies revealed the potential effects of metformin on treating thyroid-related characteristics, such as the inhibitory effect of metformin on the growth of human thyroid cells (30), and thyroid cancer (31). However, the effect of metformin on benign thyroid nodules in subjects with IR remains unclear. Recently, a couple of randomized controlled trials

(RCTs) and non-randomized controlled trials were performed to estimate the association between IR and thyroid nodules. A systematic review and meta-analysis were performed to evaluate the effectiveness of metformin on benign thyroid nodules in subjects with IR. They included 7 studies (3 RCTs and 4 prospective self-controlled studies) with 240 patients. The results of the meta-analysis indicated that the volume of thyroid nodules decreased significantly after metformin therapy (SMD −0.62, 95% CI −0.98 ~ −0.27). They concluded that metformin was safe and useful in shrinking benign thyroid nodule volume and improving thyroid function and IR. A large number of high-quality prospective studies still need to be carried out (32).

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