RESEARCH ARTICLE

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The Effects of Pathophysiological Changes in Type-2 Diabetic Patients on Thyroid Dysfunction and Nodular Goiter Development in Turkey

ABSTRACT

Objective: The prevalence of thyroid dysfunction is higher in patients with diabetes, and its diagnosis couldenable a beter diabeticmanagement. The purpose of the present study is to examine the impact of pathophysiological changes in patients with Type-2 diabetes on the frequency of thyroid dysfunction, thyroid autoimmunity, thyroid nodule, and thyroid cancer in Turkey.

Method: The study was conducted on a total of 3.276 patients with Type-2 diabetes who underwent thyroid tests and thyroid ultrasonography (US). The demographic characteristics, biochemical and hormonal values, thyroid US reports, and histopathologic reports were collected from electronic records of the patients.

Results: Thyroid autoimmunity positive TPOab 15.9% (n = 524) and/orpositive TGab 9.9% (n = 327), the rate of positivity of both antibodies (TPOab + TGab) in the same patient, and total thyroid autoimmunity was found to be 32.57% (n=1067) in Type-2 diabeticpatients. Thyroid dysfunction wasdetected in 18.3% (n = 602) of these patients. The distribution of thyroid dysfunction was 9.09% (n = 298) subclinical hypothyroidism, 4.1% (n = 135) clinical hypothyroidism, 3.1% (n = 102) subclinical hyperthyroidism, 2.0% (n = 67) clinical hyperthyroidism. Also, 67.9% (n = 2225) thyroid nodules, and 5% (n = 164) thyroid cancer cases were detected.

Conclusion: Thyroid dysfunction was foundincreased in patients with Type-2 diabetes at significant levels.

Keywords: Type-2 Diabetes, Thyroid Dysfunction, Nodular Goiter, Thyroid Autoimmunity.

Türkiye'de Tip-2 Diyabetli Hastalarda Patofizyolojik Değişikliklerin Tiroid Disfonksiyonu Ve Nodüler Guatr Gelişimi Üzerine Etkileri

ÖZET

Amaç: Bu çalışmanın amacı, Türkiye'de Tip 2 diyabetli hastalardaki patofizyolojik değişikliklerin tiroid disfonksiyonu, tiroid otoimmünitesi, tiroid nodülü ve tiroid kanseri sıklığına etkisini incelemektir.

Gereç ve Yöntem: Çalışma, tiroid testleri ve tiroid ultrasonografisi (US) yapılan toplam 3.276 Tip-2 diyabetli hasta üzerinde yapıldı. Demografik özellikler, biyokimyasal ve hormonal değerler, tiroid US raporları ve histopatoloji raporları hastaların elektronik kayıtlarından toplandı.

Bulgular: Tiroid otoimmünite pozitif TPOab %15.9 (n = 524) ve/veya pozitif TGab %9.9 (n=327), aynı hastada her iki antikorun (TPOab + TGab) pozitiflik oranı ve total tiroid otoimmünitesi Tip-2 diyabetli hastalarda %32,57 (n=1067) olabilir. Bu hastaların %18,3'ünde (n=602) tiroid disfonksiyonu saptandı. Tiroid disfonksiyonu dağılımı %9.09 (n=298) subklinik hipotiroidi, %4.1 (n=135) klinik hipotiroidi, %3.1 (n=102) subklinik hipertiroidi, %2.0 (n=67) klinik hipertiroidi idi. Ayrıca %67.9 (n=2225) tiroid nodülü ve %5 (n=164) tiroid kanseri tespit edildi.

Sonuç: Tip-2 diyabetli hastalarda tiroid disfonksiyonunun anlamlı düzeyde arttığı bulundu.

Anahtar Kelimeler: Tip-2 Diyabet, Tiroid Disfonksiyonu, Nodüler Guatr, Tiroid Otoimmünitesi.

INTRODUCTION

Thyroid hormones are necessary for the carbohydrate metabolism (1). The effect of the secretion of insulin in excessive thyroid hormone may affect many aspects of carbohydrate metabolism over clearance. Thyroid hormone deficiency may prevent insulin secretion and metabolism, resulting in insulin resistance (2,3). Hyperglycemia may develop in dysfunction of the thyroid (4).

The thyroid dysfunction prevalence is higher in diabetic patients. Some organizations recommend that thyroid tests are performed for diabetic patients (5). Recognizing the presence of thyroid dysfunction in Type-2 diabetes patients results in a good management of diabetes (6). Also, some previous studies reported that thyroid nodule incidence is significantly higher in Type 2 diabetes patients compared to healthy subjects (7). In the present study, the purpose was to examine whether the pathophysiological changes in Type-2 diabetic patients hadimpacts on the frequency of thyroid dysfunction, thyroid autoimmunity, thyroid nodule, and thyroid cancer in our country, where a moderate level of iodine deficiency has been encountered.

MATERIAL AND METHODS

This study was performed on a total of 3.276 patients with Type-2 diabetes, followed up in the endocrinology and general surgery clinic between 2015-2021, and underwent thyroid tests and thyroid ultrasonography (US). The demographic characteristics, biochemical and hormonal values, thyroid US reports, and histopathology reports after their thyroid surgeries were collected from patient files and electronic records. The study was conducted with the approval of the Clinical Research Ethics Committee at Medicana International Samsun Hospital in line with the ethical rules (Date 16th April 2020-Issue Number: 07; (1):7123).

Pregnant women, those who were receiving antithyroid drugs or thyroid hormones, those using drugs that disrupt thyroid functions, or who had a radiation history to the head and neck area or who underwent thyroidectomy were excluded from the study. Type-2 diabetic patients over 18 were included in the study.

The Thyroid Function Evaluation Index was calculated by measuring free-T4 (cut-off level 4.6-11.2 µg / dL), free T3 (cut-off level 2.5-5 pg / mL), serum thyroid stimulating hormone (TSH, cut-off level 0.45-4.12 mU / L), thyroid peroxidase antibody (TPOab, cut-off level 0-35 IU / mL), and thyroglobulin antibody (TGab, cut-off level 0-40 IU / ml) levels with the immunochemiluminescent tests in an automated analyzer (Mindray CL-900i).The thyroid nodules and parenchyma of the participants were evaluated by the same endocrinologist by using the same US device (The *Philips* Affinity *70 ultrasound;* Philips North America Corporation 3000 Minuteman Road M/S 109 Andover, MA 01810, USA). The glycated hemoglobin Type A1c (HbA1c cut-off level ≥6.5%) and fasting plasma glucose (cut-off level 70-110 mg / dl) values of Type 2 diabetic patients were used in the study.

Statistical Analyses: The data were expressed as Mean ± Standard Deviation (SD). The categorical data were compared with the Chi-Square Test, and the continuous variables were compared with the Unpaired Student t-test. The One-way ANOVA and Multiple ***t***-tests were done to compare the biochemical and hormonal values. The Independent Samples ***t***-test was used to compare the differences in clinical characteristics and thyroid nodules. Statistically significant level was taken as $p < 0.05$. The data were analyzed with the SPSS software (Statistical Package for the Social Sciences, version 22.0, Chicago).

RESULTS

The data of 3.276 (1965 females, 1311 males) patients were examined for the study. The mean age of the patients was 56.8 ± 13.5 years. The demographic characteristics of the patients, their biochemical, hormonal values, thyroid nodules in thyroid US reports, and thyroid cancer data in histopathological reports after thyroid surgeries are given in Table 1. Also, it is seen in Table 1 that thyroid autoimmunity positive TPOab 15.9% (n = 524) and / or positive TGab 9.9% (n = 327), the rate of positivity of both antibodies (TPOab + TGab) in the same patient, and total thyroid autoimmunity was found to be 32.57% (n=1067) in Type-2 diabetic patients.

Table 1. Demographicandclinicalcharacteristics

Parameters	Type-2 Diabetes	P value
Age, years (mean ± SD	56.8±13.5	
Female gender, n (%)	1965 (%59.9)	
HbA1c,%, median (IQR)	8.1 (6.2–9.5)	**0.001**
Fasting blood glucose,mg/dL, (Mean ± SD)	185.7±24.6 (115-253)	**0.001**
Thyroid dysfunction, n (%)	602 (%18.3)	**0.001**
Thyroid autoimmunity, n (%)	1067 (%32.57)	**0.001**
Positive TPOAb, n (%)	524 (%15.9)	**0.001**
Positive TGAb, n (%)	327 (%9.9)	**0.001**
Positive TPOAb + TGAb n (%)*	216 (%6.5)	0.075
Thyroid nodule, n (%)	2225 (%67.9)	**0.001**
Thyroid cancer, n (%)	164 (%5)	0.064

TPOAb; thyroid peroxidase antibodies, TGAb; thyroglobulin antibodies, HbA1c; glycated hemoglobin, *Positive TPOAb + TGAb; patient with positivity of bothautoantibody tests

All of the 3.276 patients who were included in the study were diagnosed with Type-2 diabetes. Thyroid dysfunction was detected in 18.3% (n = 602) of these patients. The distribution of thyroid dysfunction was 9.09% (n = 298) subclinical hypothyroidism, 4.1% (n = 135) clinical hypothyroidism, 3.1% (n = 102) subclinical hyperthyroidism, 2.0% (n = 67) clinical hyperthyroidism. Also, 67.9% (n = 2225) thyroid nodules, and 5% (n = 164) thyroid cancer were detected. The thyroid dysfunctions, nodules, cancers, and thyroid hormonal values are shown in Table 2.

Table 2. Thyroid diseases and thyroid hormonal values in Tip-2 Diabeticpatients

Thyroid diseases	% (n)	P value	TSH	sT4	sT3
Clinical hyperthyroidism	%2.0 (n=67)	0.031	0.01	13.5±2.1	8.1±2.4
Subclinical hyperthyroidism	%3.1 (n=102)	0.025	0.12±0.2	9.4±1.1	4.1±0.8
Clinical hypothyroidism	%4.1 (n=135)	0.011	64.5±9.3	3.9±1.1	3.2±0.4
Subclinical hypothyroidism	%9.09 (n=298)	0.001	8.4±2.5	6.3±1.4	2.9±0.3
Thyroid nodüle	%67.9 (n=2225)	0.001	2.6±0.2	8.7±1.3	3.7±0.6
Thyroid cancer	%5 (n=164)	0.001	2.8±0.3	9.3±1.5	3.4±0.5

TSH; *Thyroid Stimulating Hormone*

DISCUSSION

The present study revealed that the thyroid dysfunction prevalence was 18.3% in Type-2 diabetespatients. Different reports were published in the past showing the relation between thyroid dysfunction and diabetes. The reported thyroid dysfunction prevalence ranged between 2.2% and 16% in diabetic patients (8,9,10). It was shown that thyroid dysfunction was between ~6.6%-13.7% in non-diabetic patients (11,12). Previous studies did not investigate the relation between Type 2 diabetes and thyroid disorders sufficiently. Generally, studies were conducted between Type 1 diabetes and thyroid (13). In the light of the findings of previous studies, it was reported that the thyroid dysfunction prevalence in patients with Type 2 diabetes was higher compared to the general population. The present study showed that the incidence rates of subclinical hypothyroidism, thyroid nodules, and autoimmune thyroiditis were significantly higher in Type-2 DM patients than in the normal population.

It was reported in previous studies that subclinical hypothyroidism in Type-2 diabetic patients was the most common thyroid dysfunction (4.8%-9.3%) (14,15). In the present study, it was found that the frequency of subclinical hypothyroidism was 9.0% as the most common thyroid dysfunction. This finding is supported by other studies that reported that subclinical hypothyroidism in Type-2 diabetic patients was the most common subtype of thyroid dysfunction. In the NHANES III study, the subclinical hypothyroidism prevalence was reported to be 5.8 % in women and 3.4 % in men (16). It was found in the present study that the subclinical hypothyroidism prevalence was 1.5-2.6 times higher in Type-2 diabetic patients compared to nondiabetic patients. Many studies showed that the clinical hypothyroidism prevalence varied between 0.2% and 4.8% (17). It was also shown that clinical hypothyroidism was detected at a rate of 1.9% in Type-2 diabetic patients (12). In the present study, it was found 4.1%.

Previous studies showed that the frequency of clinical and subclinical hyperthyroidism varied between 0.5% and 3% (16). Subclinical hyperthyroidism was found varied between 1% and 1.6% in patients with Type-2 diabetes(18,19). The presentstudy disclosed that the frequency of subclinical hyperthyroidism was 3.1%. Previous studies also showed that the clinical hyperthyroidism prevalence was 0.5%-1.5% in Type-2 diabetespatients (20,21). This study detected the frequency of clinical hyperthyroidism as 2.0%. The prevalence of hyperthyroidism is generally less in healthy non-diabetic individuals and Type-2 diabetic patients.

It was shown that thyroid autoimmunity was higher in Type-2 diabetic patients at significant levels. It was found in previous studies that 13%-14.7% positive TPOab, 1.7% positive TGAb, and 5.0% positivity for both autoantibodies (22,23). There are a limited number of studies comparing the thyroid autoantibodies prevalence in Type-2 diabetic patients. In the present study, it was found that 15.9% positive TPOab, 9.9% positive TGab, 6.5% both autoantibody positivity TPOab + TGab, and thyroid autoimmunity was 32.57%. In this context, it is possible to speculate that thyroid autoimmunity is higher in Type-2 diabetic patients than in the normal population.

In a meta-analysis of 9 studies conducted on the thyroid nodules prevalence in Type-2 diabetic patients, the prevalence was shown to be 60%, 50% in pre-diabetics, and 43% in non-diabetic population (24). The thyroid nodules prevalence in the general population was reported as 32.4% in China, 34.7% in France, 23.4% in Germany, and 17.0% in Brazil (25). In the present study, the thyroid nodules frequency was 67.9% in patients with Type-2 diabetes. It is very likely that diabetic patients develop thyroid nodules. A meta-analysis that included a 5-center prospective cohort study conducted in the USA and a retrospective cohort study conducted in Israel did not report any significant associations between diabetes and

thyroid cancer (26,27). The present study found that the incidence of thyroid cancer was 5% in Type-2 diabetic patients. In this respect, it is possible to speculate that although the thyroid nodules frequency increases in Type-2 diabetic patients, cancer incidence does not.

CONCLUSION

The results in the present study showed that thyroid dysfunction increased in patients with Type-2 diabetes at significant levels. Clinical and / or subclinical hypothyroidism has been the most common thyroid dysfunction prevalence detected in Turkey. It was confirmed in the present study that the autoimmune thyroiditis increased in diabetic patients. Moderate levels of iodine deficiency have been detected in Turkey. In this context, it was also found that iodine deficiency and Type-2 Diabetes increased the frequency of thyroid nodules at significant levels. The present study showed that there was no general relation between thyroid cancer and diabetes. When the relation between Type 2 diabetes and thyroid disorders is considered, efforts must be made to screen for thyroid diseases in Type 2 diabetic patients.

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