Research Article / Araştırma Makalesi
doi: 10.18678/dtfd.1672720

Duzce Med J, 2025;27(2):208-213
Düzce Tıp Fak Derg, 2025;27(2):208-213

Bidirectional Association between Thyroid Function and Glycemic Status: A Cross-Sectional Study

Tiroid Fonksiyonu ve Glisemik Durum Arasındaki Çift Yönlü İlişki: Kesitsel Bir Çalışma

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Received / Geliş Tarihi : 09.04.2025
Accepted / Kabul Tarihi : 10.07.2025
Available Online / Çevrimiçi Yayın Tarihi : 09.08.2025

ABSTRACT

Aim: Diabetes and thyroid dysfunctions have similar mechanisms, and they may be overlooked or undiagnosed. This study aimed to evaluate the effect of thyroid hormone levels on glycosylated hemoglobin (HbA1c) and the thyroid-diabetes relationship.
Material and Methods: HbA1c, glucose, free T3 (fT3), free T4 (fT4), and thyroid-stimulating hormone (TSH) values measured in the same samples of patients aged 18 and 60 years were obtained. Normoglycemic individuals were divided into subgroups as normal, hypothyroidism, and hyperthyroidism according to their TSH levels (Model 1), and non-thyroid dysfunction patients were divided into normoglycemic, prediabetic, and diabetic subgroups according to their HbA1c levels (Model 2). Correlations and differences of the obtained data were analyzed.
Results: In Model 1, the median HbA1c level was 5.44 (range, 5.08-5.68) in the hyperthyroidism group, which was significantly higher than normal (5.32; range, 4.96-5.69) and hypothyroidism (5.33; range, 5.02-5.65) groups (p=0.021). In Model 2, fT3 levels were found significantly higher in normoglycemic patients (3.11; range 1.95-3.75 pg/ml) than prediabetic (3.01; range, 2.13-3.82 pg/ml), and diabetic (3.00; range, 2.02-3.69 pg/ml) patients (p=0.001), while fT4 levels in diabetic patients (1.29; range, 0.56-1.74 ng/dl) were significantly higher compared to normoglycemic (1.23; range 0.72-1.89 ng/dl), and prediabetic (1.24; range, 0.73-1.66 ng/dl) patients (p=0.003).
Conclusion: The results showed that HbA1c levels could be a marker for thyroid function in non-diabetic individuals. In diabetic patients, thyroid hormone balance and ratios are changing. For better glycemic control and the prevention of complications, regular thyroid function screenings are recommended, especially in individuals with a predisposition to diabetes.
Keywords: Glycemic control; hemoglobin A1c; thyroid dysfunction.

ÖZ

Amaç: Diyabet ve tiroid fonksiyon bozuklukları benzer mekanizmalara sahiptir ve gözden kaçabilir veya tanı konulamayabilir. Bu çalışmanın amacı, tiroid hormon düzeylerinin glikolize hemoglobin (HbA1c) üzerindeki etkisinin ve tiroid-diyabet ilişkisinin değerlendirilmesidir.
Gereç ve Yöntemler: Yaşları 18 ve 60 arasında olan hastaların aynı örneklerinde ölçülen HbA1c, glikoz, serbest T3 (fT3), serbest T4 (fT4) ve tiroid uyarıcı hormon (thyroid-stimulating hormone, TSH) değerleri elde edildi. Normoglisemik bireyler TSH düzeylerine göre normal, hipotiroidi ve hipertiroidi olarak alt gruplara ayrılırken (Model 1), tiroid fonksiyon bozukluğu olmayan hastalar HbA1c düzeylerine göre normoglisemik, prediyabetik ve diyabetik olarak alt gruplara ayrıldı (Model 2). Elde edilen verilerin korelasyonları ve farklılıkları analiz edildi.
Bulgular: Model 1'de hipertiroidi grubunda ortanca HbA1c düzeyi 5,44 (aralığı 5,08-5,68) olup normal (5,32; aralığı 4,96-5,69) ve hipotiroidizm (5,33; aralığı 5,02-5,65) gruplarından anlamlı derecede daha yüksekti (p=0,021). Model 2'de, fT3 düzeyleri normoglisemik hastalarda (3,11; aralığı 1,95-3,75 pg/ml), prediyabetik (3,01; aralık 2,13-3,82 pg/ml) ve diyabetik (3,00; aralık 2,02-3,69 pg/ml) hastalara kıyasla anlamlı derecede daha yüksek bulunurken (p=0,001), fT4 düzeyleri ise diyabetik hastalarda (1,29; aralık 0,56-1,74 ng/dl) normoglisemik (1,23; aralık 0,72-1,89 ng/dl) ve prediyabetik (1,24; aralık 0,73-1,66 ng/dl) hastalara kıyasla anlamlı derecede daha yüksekti (p=0,003).
Sonuç: Sonuçlar, HbA1c düzeylerinin diyabetik olmayan bireylerde tiroid fonksiyonları için bir belirteç olabileceğini göstermiştir. Diyabetik hastalarda tiroid hormon dengesi ve oranları değişmektedir. Daha iyi glisemik kontrol ve komplikasyonların önlenmesi için, özellikle diyabete yatkınlığı olan bireylerde düzenli tiroid fonksiyon taramaları önerilmektedir.
Anahtar kelimeler: Glisemik kontrol; hemoglobin A1c; tiroid disfonksiyonu.

INTRODUCTION

Thyroid hormones are produced by the iodination of the amino acid tyrosine. The thyroid primarily synthesizes thyroxine (T4), while triiodothyronine (T3) is the biologically active form. Continuous and regulated secretion of thyroid hormones is essential for maintaining metabolic processes in the body (1).

The most common endocrinological clinical diseases are diabetes mellitus (DM) and thyroid dysfunctions worldwide, and these two disorders may be related (2,3). Compared to the general population, the risk of developing thyroid dysfunction is much higher in diabetics. Thyroid dysfunction prevalence is higher due to the similar autoimmune origin with type 1 DM, which is characterized by the absence of insulin. However, recent studies show that the incidence of thyroid dysfunctions increases among type 2 DM patients, which is characterized by insulin resistance (4).

Thyroid hormones stimulate hepatic gluconeogenesis and glycogenolysis to increase plasma glucose levels, in contrast to the effect of insulin (5). Thyroid hormones directly affect pancreatic functions and carbohydrate metabolism, and DM may cause thyroid function tests to vary. This proves that thyroid dysfunction and DM show similar clinical features and give similar symptoms. If two endocrine disorders occur at the same time, diagnosis can be delayed or lead to misdiagnosis, causing the occurrence of various complications (4,6). There have been many studies examining the relationships between thyroid dysfunction and DM, but most of these are studies with low participants, without control groups, and not described through descriptive parameters.

Glycosylated hemoglobin (HbA1c) has been recognized as an important marker of long-term glycemic control in DM patients. In 2010, the American Diabetes Association recommended the use of HbA1c not only for control purposes but also as a diagnostic tool for prediabetes and diabetes (7). HbA1c levels come to the fore as a more reliable parameter in terms of showing chronic hyperglycemic status, the course of diabetes, and the patient's condition (8,9). However, HbA1c levels can vary with descriptive features such as race, age (10,11), and indifference to certain diseases such as anemia (12), acute coronary syndrome (13), and Graves' hyperthyroidism (14). Therefore, it is clear that large-scale studies are needed to examine the relationships between HbA1c and thyroid functions.

This study aimed to examine the relationships between glycemic status, HbA1c levels, and thyroid function tests in a general cross-sectional study, including baseline characteristics.

MATERIAL AND METHODS

Study Design

This single-center hospital-based study was conducted in Eskişehir Osmangazi University Hospital, Laboratory of Clinical Biochemistry, from April 2018 to April 2020. Approval was obtained from the non-interventional ethics committee at Eskişehir Osmangazi University (decision no: 12.05.2020, 02). Patients aged between 18 and 60 were included in the study. Pregnant women, patients with malignancies, chronic illnesses, pediatric patients, and those with a known history of diabetes or taking diabetes medication were excluded from the study.

Data Collection and Modeling

The HbA1c, glucose, free T3 (fT3), free T4 (fT4), and thyroid-stimulating hormone (TSH) levels measured in the same serum samples of 4104 adult patients were obtained. Thyroid hormones were measured according to the electrochemiluminescence immunoassay (ECLIA) sandwich method with appropriate commercial reagents on the Roche Cobas e 801 auto-analyzer device (Roche Diagnostic GmbH, Mannheim, Germany). Measurement of fasting glucose values of the participants was made on Roche Cobas c 702 auto analyzer using commercial kits, including reference spectrophotometric hexokinase method (15). HbA1c measurements of the patients were performed on the Roche Cobas c 502 auto-analyzer device with appropriate commercial kits (Tina-quant second and third-generation assays). The determination of HbA1c is based on the turbidimetric inhibition immunoassay (TINIA) test for whole blood samples (16). These adult patients were divided into the following subgroups according to the criteria examined.

Model 1: Patients with normal HbA1c levels (<5.7%) were divided into normal (TSH=0.27-4.2 μIU/ml, n=1614), hypothyroidism (TSH >4.2 μIU/ml, n=232), and hyperthyroidism (TSH <0.27 μIU/ml, n=100) groups (17).

Model 2: Patients with normal TSH levels (0.27-4.2 μIU/ml) were divided into normoglycemic (HbA1c <5.7%, n=1077), prediabetic (HbA1c=5.7-6.49%, n=512), and diabetic patient (HbA1c ≥6.50%, n=569) groups (18).

Patients with known diagnosed pituitary gland disorders or thyroid dysfunction were not included.

Statistical Analysis

Distributions of all parameters were examined with the Kolmogorov-Smirnov and Shapiro-Wilk normality tests. A chi-square test was used to compare the gender distribution between groups. The differences in laboratory values were investigated with the Kruskal-Wallis test since the data are not normally distributed. The Dunn test was used for multiple comparisons. Spearman's rho test was applied for correlation analysis. Data are expressed as median with 25^{th}-75^{th} percentiles, and minimum-maximum. A p-value below 0.05 was considered statistically significant. All statistical analyses were completed using GraphPad Prism version 8.4.2.

RESULTS

The Relationship between Glycemic Status and Thyroid Function Tests in the Non-Diabetic Group (Model 1)

A total of 1946 patients were included in this model, taking into account the specified criteria above. The demographic characteristics and laboratory values of the normal, hypothyroidism, and hyperthyroidism groups were summarized in Tables 1 and 2.

Females were found to be more dominant than males for all groups. The percentage of females in the normal group was 75.2% (n=1213), and in the groups with hypo and hyperthyroidism patients, it was 83.2% (n=193) and 81.0% (n=81), respectively. All thyroid function tests were significantly different between groups (p<0.001). According to the multiple comparison results, HbA1c and glucose levels showed a significant difference in the hyperthyroidism group compared to the normal and hypothyroidism groups, while fT3 and fT4 levels were significantly different between all three groups.

Table 1. Age and gender distribution of the model 1 subgroups

	Normal (n=1614)	Hypothyroidism (n=232)	Hyperthyroidism (n=100)	p
Age (years)	44 (34-52) [18-60]	45 (32-52) [18-60]	48 (38-54) [18-60]	0.380
Gender, n (%)				
Female	1213 (75.2)	193 (83.2)	81 (81.0)	**0.014***
Male	401 (24.8)	39 (16.8)	19 (19.0)	

Descriptive statistics were expressed as median (25^{th}-75^{th} percentiles) [minimum-maximum], *: significance in the hypothyroidism group compared to the normal group

Table 2. Laboratory values and multiple comparison results of the model 1 subgroups

	Normal (n=1614)	Hypothyroidism (n=232)	Hyperthyroidism (n=100)	p
HbA1c (%)	5.32 (5.11-5.51) [4.96-5.69]	5.33 (5.12-5.49) [5.02-5.65]	5.44 (5.19-5.53) [5.08-5.68]	**0.021**
Glucose (mg/dl)	90 (83-97) [72-100]	91 (85-98) [75-106]	93 (86-103) [73-110]	**0.020**
fT3 (pg/ml)	3.03 (2.74-3.34) [1.88-4.14]	2.84 (2.50-3.23) [1.66-4.95]	3.19 (2.92-3.47) [1.7-6.89]	**<0.001**
fT4 (ng/dl)	1.24 (1.11-1.39) [0.87-1.52]	1.18 (1.04-1.29) [0.56-1.87]	1.68 (1.42-1.86) [0.57-2.05]	**<0.001**

HbA1c: glycosylated hemoglobin, fT3: free T3, fT4: free T4, descriptive statistics were expressed as median (25^{th}-75^{th} percentiles) [minimum-maximum], according to the post hoc test, significant differences were found in HbA1c levels between the normal and hyperthyroidism (p=0.032), and hypothyroidism and hyperthyroidism (p=0.020) groups; in glucose levels between the normal and hyperthyroidism (p=0.022), and hypothyroidism and hyperthyroidism (p=0.013) groups; and in fT3 and fT4 levels between all groups (p<0.001 for all)

Glucose and HbA1c levels were positively correlated with fT4, and HbA1c levels were negatively correlated with TSH in these patients (Table 3).

The Relationship between Thyroid Function Tests and Diabetes Susceptibility in Normal TSH Group (Model 2)

In total, 2158 patients were included in this model, taking into account the specified criteria above. The demographic characteristics and laboratory values of the normoglycemic, prediabetic, and diabetic groups were summarized in Tables 4 and 5.

Table 3. Correlations between serum glucose, HbA1c, and thyroid function tests

	HbA1c		Glucose	
	r_s	p	r_s	p
fT3	-0.027	0.238	-0.023	0.300
fT4	0.066	**0.004**	0.135	**<0.001**
TSH	-0.048	**0.034**	-0.035	0.119

fT3: free T3, fT4: free T4, TSH: thyroid-stimulating hormone, r_s: Spearman's rho

While the percentage of females in the normoglycemic group and prediabetic patients was 69.6% (n=750) and 68.8% (n=352), respectively, it was 55.7% (n=317) in the group with diabetic patients. Glucose levels were found to be significantly different between all groups (p<0.001). When thyroid function tests were examined, fT4 levels were found to be significantly higher in the DM group compared to normoglycemic and prediabetics (p=0.003). However, fT3 levels were significantly lower in the prediabetic and DM groups compared to the normoglycemic group (p=0.001). TSH levels were higher in prediabetic and DM groups compared to the normoglycemic group, but not statistically significant (p=0.873).

DISCUSSION

Insulin and thyroid hormones have vital effects on metabolism, and one disruption in the secretion of any of them directly affects the other (19). This link has been the basis of many studies in the literature. However, these studies either did not include a control group, had a small population size, or included comorbidities. (20-22). This

Table 4. Age and gender distribution of the model 2 subgroups

	Normoglycemic (n=1077)	Prediabetic (n=512)	Diabetic (n=569)	p
Age (years)	42 (32-51) [18-60]	53 (46-57) [18-60]	52 (44-57) [18-60]	**0.030***
Gender, n (%)				
Female	750 (69.6)	352 (68.8)	317 (55.7)	**<0.001****
Male	327 (30.4)	160 (31.2)	252 (44.3)	

Descriptive statistics were expressed as median (25^{th}-75^{th} percentiles) [minimum-maximum], *: significant difference in the prediabetic and diabetic groups compared to the normoglycemic group, **: significant difference in the diabetic group compared to the normoglycemic and prediabetic groups

Table 5. Laboratory values and multiple comparison results of the model 2 subgroups

	Normoglycemic (n=1077)	Prediabetic (n=512)	Diabetic (n=569)	p
TSH (%)	1.89 (1.33-2.61) [1.10-2.98]	1.92 (1.32-2.66) [1.22-3.05]	1.97 (1.33-2.73) [1.13-3.18]	0.873
Glucose (mg/dl)	89 (82-97) [70-100]	104 (95-116) [86-122]	151 (122-194) [119-210]	**<0.001**
fT3 (pg/ml)	3.11 (2.80-3.40) [1.95-3.75]	3.01 (2.74-3.33) [2.13-3.82]	3.00 (2.65-3.30) [2.02-3.69]	**0.001**
fT4 (ng/dl)	1.23 (1.11-1.35) [0.72-1.89]	1.24 (1.12-1.38) [0.73-1.66]	1.29 (1.17-1.42) [0.56-1.74]	**0.003**

TSH: thyroid-stimulating hormone, fT3: free T3, fT4: free T4, descriptive statistics were expressed as median (25^{th}-75^{th} percentiles) [minimum-maximum], according to the post hoc test, significant differences were found in glucose levels between all groups (p<0.001 for all pairwise comparisons), in fT3 levels between the normoglycemic and prediabetic (p=0.002), and normoglycemic and diabetic (p=0.001) groups; and in fT4 levels between the normoglycemic and diabetic (p=0.002), and prediabetic and diabetic (p=0.002) groups

study, it was aimed to investigate the relationship between thyroid function tests, glycemic control, and HbA1c with a large sample size.

The prevalence of thyroid dysfunction varies between 10-15% in patients with DM worldwide (23). Studies in the literature revealed that the risk of developing thyroid dysfunction in females, especially with type 2 diabetes, is 3.8 times higher than in males (23,24). In our study, it is seen that the percentage of females is more dominant than males. Therefore, it can be said that the female gender is among the risk factors in the development of thyroid dysfunction and diabetes.

In our study, the relationship between glycemic status and thyroid function tests was examined in non-diabetic patients, firstly (Model 1). The HbA1c is one of the most important markers currently used in the glycemic control of diabetes. While HbA1c levels provide information about 8-12 weeks of glycemic levels, it also correlates with complications that may develop with diabetes (25). In our results, the highest and statistically different HbA1c and glucose levels among the groups were found in patients with hyperthyroidism. There is a close relationship between impaired lipid balance, metabolic syndrome, and thyroid dysfunction with insulin resistance (26). As a result of increased gluconeogenesis and glycogenolysis in patients with hyperthyroidism, insulin secretion is impaired, and insulin resistance may occur peripherally (27). This situation can also be explained by the increase in secretion and receptor numbers of glucagon in patients with hyperthyroidism and decreased glucose uptake in muscles. HbA1c levels are affected not only by the glycemic state but also by the life span of erythrocytes (28). Reduced erythropoiesis with hypothyroidism and increased red blood cell (RBC) turnover in a thyrotoxic condition can cause changes in HbA1c levels, which can lead patients to be considered prediabetic or diabetic (29). In this case, a decrease in HbA1c levels can be expected in patients with hyperthyroidism. In the literature, HbA1c levels were examined before and after treatment in patients with hyperthyroidism. HbA1c levels, which were at a high level before the treatment, showed a negative correlation with TSH and decreased to normal levels after the treatment (30). HbA1c showed a positive correlation with fT4, while it showed a negative correlation with TSH values in our results. Insulin resistance causes decreased TRH synthesis in the hypothalamus. High insulin levels enhance TSH turnover, which in turn inhibits hepatic T4-T3 conversion, leading to increased fT4 levels and decreased T3 levels. But also, these differences may be due to the medications of thyroid dysfunction patients (31). Since our study was retrospective, the medical records of the patients were examined, and test results were obtained, but the medications used by the patients could not be determined.

As the second step in our study, we evaluated thyroid functions according to HbA1c levels in participants without any other chronic illness in patients with normal TSH values (model 2). According to HbA1c levels, we divided participants into three subgroups as normoglycemic, prediabetic, and DM patients. TSH levels were not statistically significant between normoglycemic, prediabetic, and DM groups. But the prediabetic and DM groups compared to the normoglycemic group showed a significantly lower fT3 level, and fT4 levels were found to be significantly higher in the DM group compared to the normoglycemic and prediabetic groups. This difference observed between the fT3 and fT4 levels between the groups is similar to the relationship we found in model 1, and probably supports the reduction of peripheral T4-T3 transformation as glucose tolerance is impaired.

These results show that thyroid hormone levels are affected by diabetes predisposition. So, DM patients may tend to develop thyroid dysfunction. Here, it can be seen that thyroid dysfunction may be associated with high HbA1c levels. The studies conducted with type 2 diabetes patients in the literature showed that the patients with higher HbA1c levels had a seven percent higher thyroid dysfunction prevalence, while patients with normal HbA1c had normal thyroid function percentages (32-34).

The limitations of our study can be summarized as follows: due to the retrospective nature of the study, some demographic data, such as BMI and smoking, were not available. Again, due to the retrospective nature of the study, although there were exclusion criteria, it could not be determined whether the included patients were taking different medications. Comparisons with different inflammatory markers could not be made.

CONCLUSION

In our study, we showed that thyroid dysfunction is associated with glycemic status in non-diabetics, and also that diabetes affects thyroid hormone levels in those without thyroid dysfunction. In this case, we can say that these two disease groups do not have a one-way relationship, the interaction between them is bilateral, perhaps because the mechanisms of these diseases are common. Insulin resistance, diabetes, and thyroid dysfunctions are autoimmune diseases with common effects, which can cause frequent confounded or overlooked diagnoses. We think that both thyroid function tests in DM patients and HbA1c test in thyroid dysfunction patients should be monitored regularly to prevent possible complications caused by common mechanisms and to catch early diagnosis. Even if people with diabetes predisposition, insulin resistance, and DM are euthyroid, the relationship between HbA1c levels and their effects on thyroid hormone levels should be taken into consideration, and their treatment and follow-up approaches should be determined by regulating and reducing HbA1c values.

Ethics Committee Approval: The study was approved by the Non-interventional Ethics Committee of Eskişehir Osmangazi University (12.05.2020, 02).

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: Idea/Concept: EK; Design: EKar; Data Collection/Processing: EK, ZKK; Analysis/ Interpretation: EKar, EK, ZKK; Literature Review: EKar, EK; Drafting/Writing: EKar; Critical Review: EK, ZKK.

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