RESEARCH ARTICLE

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Association of Inflammatory Indices with Thyroid Nodules in Type 1 Diabetes Mellitus

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Objective: Type 1 diabetes mellitus (T1DM) is associated with an increased risk of thyroid disorders. Identifying predictors of thyroid nodules in these patients may enable more appropriate management strategies. To the best of our knowledge, the relationship between thyroid nodules and inflammatory parameters is not fully investigated in patients with T1DM. The present study aimed to investigate the diagnostic value of several hematological inflammatory indices, such as systemic immune inflammation index (SII) in predicting the presence of thyroid nodules in patients with T1DM.

Materials and Methods: A total of 69 T1DM patients with thyroid nodules and 111 T1DM patients without were included. In patients with T1DM, logistic regression models were performed to assess the independent predictors for thyroid nodules. Receiver operating characteristics (ROC) curve analysis was performed to evaluate the diagnostic accuracy of SII in identifying T1DM patients with thyroid nodules.

Results: Patients with thyroid nodules had higher mean SII values than those without ($p<0.001$). There was no significant association between age, gender, disease duration, thyroid function tests, and thyroid nodules. The mean SII value was an independent predictor of thyroid nodules in univariate and multivariate logistic regression analyses ($p<0.001$).

Conclussion: Our findings suggest that inflammation may play an important role in the development of thyroid nodules in patients with T1DM and that SII value may be useful in determining the risk of thyroid nodules in these patients.

Key Words: *Systemic immune-inflammation index, Type 1 diabetes mellitus, thyroid nodule, thyroid ultrasonography*

Tip 1 Diyabetes Mellitus'ta İnflamatuar İndeksler ile Tiroid Nodüllerinin İlişkisi

Amaç: Tip 1 diabetes mellitus (T1DM), tiroid bozuklukları riskinin artmasıyla ilişkilidir. Bu hastalarda tiroid nodüllerinin öngörücülerini belirlemek, daha uygun yönetim stratejilerine olanak sağlayabilir. Bildiğimiz kadarıyla, T1DM'li hastalarda tiroid nodülleri ile inflamatuvar parametreler arasındaki ilişki tam olarak araştırılmamıştır. Mevcut çalışmanın amacı, T1DM'li hastalarda tiroid nodüllerinin varlığını tahmin etmede sistemik immün-inflamasyon indeksi (SII) gibi çeşitli hematolojik inflamatuvar indekslerin tanı değerini araştırmaktı.

Gereç ve Yöntem: Tiroid nodülü olan toplam 69 T1DM hastası ve olmayan 111 T1DM hastası çalışmaya dahil edildi. T1DM'li hastalarda tiroid nodüllerinin bağımsız öngörücülerini değerlendirmek amacıyla lojistik regresyon modelleri kullanıldı. Tiroid nodülü olan T1DM hastalarını belirlemede SII'nin tanısal doğruluğunu değerlendirmek için Receiver operating characteristics (ROC) eğrisi analizi yapıldı.

Bulgular: Tiroid nodülü olan hastaların ortalama SII değerleri, olmayanlara göre daha yüksekti ($p<0.001$). Yaş, cinsiyet, hastalık süresi ve tiroid fonksiyon testleri ile tiroid nodülleri arasında anlamlı bir ilişki yoktu. Ortalama SII değeri, tek değişkenli ve çok değişkenli lojistik regresyon analizlerde tiroid nodüllerinin bağımsız bir öngörücüsüydü ($p<0.001$).

Sonuç: Bulgularımız, inflamasyonun T1DM'li hastalarda tiroid nodüllerinin gelişiminde önemli bir rol oynayabileceğini ve SII değerinin bu hastalarda tiroid nodül riskini belirlemede yararlı olabileceğini düşündürmektedir.

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Introduction

Insulin-dependent Diabetes Mellitus (Type 1, T1DM) is a chronic disease that develops due to autoimmune destruction of pancreatic beta (β) cells in genetically predisposed individuals and leads to absolute insulin deficiency (1). It is well known that T1DM is associated with various thyroid diseases, including chronic autoimmune thyroiditis, and the frequency of autoimmune thyroid dysfunction in adults with T1DM varies between 17-30% (2,3). Studies investigating thyroid nodules and cancers in patients with DM have controversial results. Anıl et al. (4) showed that thyroid volume and thyroid nodule frequency were higher in patients with prediabetes and diabetes than in controls. Another study demonstrated that the frequency of thyroid nodules was

similar between patients with T1DM and non-diabetic controls and higher in patients with type 2 DM (T2DM) (5). Carstensen et al. (6) demonstrated an increased risk of thyroid cancer in women with T1DM compared with the general population. Consequently, there is currently insufficient and conflicting data on thyroid nodularity in adult T1DM patients, and it has become important to determine the presence of thyroid nodules in these patients.

The American Thyroid Association defines thyroid nodules as “lesions within the thyroid gland that appear radiologically distinct from the thyroid parenchyma” (7). It is thought that chronic inflammation caused by genetic and environmental factors leads to replication and hyperplasia of thyroid follicular cells and causes the development of thyroid nodules. Although 90% of thyroid nodules are benign, there is a 4-15% risk of thyroid carcinoma (8). The most important methods in evaluating the malignancy risk of thyroid nodules are thyroid ultrasonography (US) and histopathological examination (7). In places where these methods are not easily accessible, there is a need to investigate easily accessible, inexpensive, and simple tools that can be used to predict the presence of nodules and to evaluate nodule characteristics. In particular, systemic inflammatory indices, including the systemic immune-inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR) have been shown to have a significant influence on the clinicopathological features and prognosis of various disorders such as coronary artery disease and malignancies (9,10). In another study conducted by Cao et al.,(11) SII was found to be an independent predictor of the presence of thyroid nodules in patients with T2DM.

Although the relationship between inflammatory indices and various autoimmune disorders is well known, the relationship between thyroid nodules and inflammatory parameters is not fully elucidated in patients with T1DM. The present study aimed to evaluate the diagnostic value of various inflammatory indices, such as SII in predicting the presence of thyroid nodules in adult patients with T1DM.

Materials and Methods

Research and Publication Ethics: The study was conducted in accordance with the declaration of Helsinki and was approved by the Ethical Committee of our hospital (Approval no: 2024/ 573).

Study Population: Between October 2022 and May 2024, 841 consecutive patients with T1DM who applied to our outpatient clinic were retrospectively evaluated. After applying the exclusion criteria, 69 patients with thyroid nodules and 111 patients without thyroid nodules matched for age, gender, and body mass index (BMI, kg/m²) were included in the study. Exclusion criteria were as follows; age less than 18 years, T1DM duration of less than 5 years, incomplete data, pregnancy, hematological disorders, acute diabetic complications, infections or hospitalization within the last three months, thyrotoxicosis, hypothyroidism, history of thyroid surgery, head and neck irradiation, chronic liver diseases, renal failure (estimated glomerular filtration rate <60ml/min /1.73 m^2), malignancy, celiac disease, malabsorption, rheumatological, autoimmune, and inflammatory diseases, use of glucocorticoids, and alcohol abuse. Sociodemographic and clinical data such as age, gender, smoking, BMI, blood pressure (BP), comorbidities, medications, and laboratory measurements were obtained from medical records and the national health database system.

Biochemical parameters, such as complete blood count, plasma glucose, glycated hemoglobin A1c (HbA1c), albumin, creatinine, C-reactive protein (CRP), and liver function tests were measured with standard laboratory methods in all participants. Assessment of thyroid function included serum thyroid stimulating hormone (TSH), free-thyroxin (FT4), free-triiodothyronine (FT3), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb). Thyroid function tests were measured with the chemiluminescent immunoassay (Beckman Coulter, CA, USA). Reference ranges were defined as thyroid stimulating hormone (TSH): 0.38–5.33 uIU/mL, free thyroxine (fT4): 0.60–1.25 ng/dL, free triiodothyronine (fT3): 2.28–4 pg/mL. The SII developed by Hu et al. was calculated by the following formula: total platelet count x neutrophil count/lymphocyte count (12). The neutrophils to lymphocytes ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count (10,13). All the thyroid US examinations were performed by the same endocrinologists (B.C.H, E.Ç) using a 6–15 MHz/50mm linear probe (Logiqe 9, GE Medical Systems, WI, USA) who had at least five years of experience and were blinded to the clinical and biochemical data of the study population.

Statistical Analyses: Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY. The Kolmogorov-Smirnov test was used to evaluate the distribution pattern of numerical data. The continuous variables were compared using the Student’s t-test or Mann–Whitney U test where appropriate, and categorical variables were compared using the chi-square test. All data are expressed as numbers and percentages (%), medians (interquartile range, IQR), or means±standard deviation. The correlations between several parameters and thyroid nodules were evaluated using Spearman’s test. The receiver operating characteristic (ROC) curve analysis was also performed to determine the best cut-off value of the SII level in predicting the presence of thyroid nodules in patients with T1DM. To determine the independent predictors of the presence of thyroid nodules, univariate and multivariate logistic regression analyses were performed. Variables with *p*-value <0.25 in univariate logistic regression and variables of clinical significance were included in the multivariate logistic regression model. All statistical analyses were performed two-sided, and a *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 180 euthyroid patients with T1DM were included in the study; 69 of the patients had thyroid nodules. Patients with and without thyroid nodules were similar in terms of age, gender, and BMI. There were no significant differences between the two groups in terms of prevalence of HT, dyslipidemia, and chronic microvascular complications (p>0.05 for all). Baseline characteristics and biochemical parameters are shown in Table 1.

There was no significant correlation between the age, gender, BMI, and thyroid nodules (*rho*=0.123; p=0.099, *rho*=-0.123; p=0.099, *rho*=0.032; p=0.667, respectively). In addition, there was no significant correlation between thyroid nodules and serum TSH level, the presence of thyroid autoantibodies, and the presence of thyroiditis on US (*rho*=-0.061; p=0.419, *rho*=0.044; p=0.559, *rho*=0.025; p=0.735, respectively). The presence of thyroid nodules in patients with T1DM was positively correlated with the SII and NLR (*rho*=0.526; p<0.001, *rho*=0.373; p<0.001, respectively) (Table 2). While there was no significant correlation between the SII value and the number of nodules, there was a significant positive correlation between the SII value and the maximum nodule diameter (*rho*=0.087; p=0.475, *rho*=0.726; p<0.001, respectively).

Table 1. Demographic and clinical characteristics of the study population

	Thyroid nodule (+) (n=69)	**Thyroid nodule (-) (n=111)**	***p***
Age, (years)	29.95±5.45	28.82± 5.87	0.200
Gender, (male, n, %)	19 (27.5)	44 (39.6)	0.098
Duration of diabetes, (years)	13.5±4.77	12.92±4.95	0.440
BMI, kg/m²	23.95±2.90	23.69±2.58	0.539
Smoking, (n, %)	6 (8.7)	9 (8.1)	0.890
HT, (n,%)	9 (13)	9 (8.1)	0.283
Dyslipidemia, (n,%)	16 (23.2)	21 (18.9)	0.491
CVD, (n,%)	2 (2.9)	1 (0.9)	0.559
Neuropathy, (n,%)	25 (36.2)	27 (24.3)	0.087
Nephropathy, (n, %)	15 (21.7)	16 (14.4)	0.206
Retinopathy, (n,%)	4 (5.8)	2 (1.8)	0.205
Thyroiditis in the US, (n,%)	38 (55.1)	64 (57.7)	0.734
Number of nodules, (n)	1 (1-2)	-	-
Largest nodule diamater, mm	8 (3.25-9)	-	-
Glucose, (mg/dL)	145.97±47.91	150.59±45.75	0.519
HbA1c, (%)	8.48±1.5	8.74±1.67	0.284
GFR, ml/min/1.73 m²	113 (99-123.5)	115 (107-126)	0.098
TSH, (mIU/L)	2.0±0.89	2.07±0.77	0.576
FT4, (ng/dL)	1.21±0.17	1.16±0.19	0.137
FT3, (ng/dL)	2.83±0.35	2.81±0.39	0.749
TPOAb (+), (n,%)	26 (37.7)	50 (45)	0.331
TGAb, (+), (n,%)	19 (27.5)	36 (32.4)	0.488
Hemoglobin, (g/dL)	14.06±1.27	14.20±1.07	0.442
Platelet × 10³ /mL	304 (263.5-353.5)	267 (240-310)	**<0.001**
Neutrophil × 10³ /mL	4.71±0.99	4.09±1.05	**<0.001**
Lymphocyte × 10³ /mL	2.37 (2.03-2.67)	2.43 (2.03-3.04)	**0.111**
SII	629.23±176.41	443.27±124.02	**<0.001**
NLR	2.04±0.51	1.65±0.49	**<0.001**
CRP, (mg/L)	2.1 (0.86-3.24)	1.6 (0.88-2.57)	0.315

BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular diseases; FT3, free-triiodothyronine; FT4, free-thyroxin; GFR, glomerular filtration rate; HbA1c, glycolized hemoglobin; HT, hypertension; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune inflammation index; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; US, ultrasonography.

Results are expressed as percentages, mean ± standard deviation or median (interquartile range) according to the distribution pattern. Significant p values are in bold.

Table 2. Correlation analysis between several parameters and thyroid nodules in the study population

		Age	Gender	BMI	Duration of diabetes	HbA1c	TSH	FT4	SII	NLR
Thyroid nodule	*Rho*	0.123	-0.123	0.032	0.053	-0.069	-0.061	0.132	0.526	0.373
	P	0.099	0.099	0.667	0.483	0.356	0.419	0.077	**<0.001**	**<0.001**

BMI, body mass index; FT4, free-thyroxin; HbA1c, glycolized hemoglobin; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune inflammation index; TSH, thyroid stimulating hormone.
Significant p values are in bold.

Table 3. Univariate and multivariable logistic regression analysis showing independent predictors of thyroid nodules

	Univariate analysis				Multivariable analysis			
		95% CI				95% CI		
	OR	Lower	Upper	*p*	OR	Lower	Upper	*p*
Age	1.035	0.982	1.092	0.200	1.054	0.986	1.126	0.120
Gender	0.579	0.302	1.109	0.099	0.599	0.272	1.316	0.202
Duration of diabetes	1.025	0.963	1.090	0.438				
BMI	1.036	0.927	1.157	0.537				
Hba1c	0.902	0.746	1.089	0.283				
TSH	0.900	0.622	1.300	0.573				
FT4	3.424	0.673	17.422	0.138	3.949	0.559	27.889	0.169
SII	1.009	1.006	1.011	**<0.011**	1.009	1.006	1.012	**<0.001**

BMI, body mass index; FT4, free-thyroxin; HbA1c, glycolized hemoglobin; SII, systemic immune inflammation index; TSH, thyroid stimulating hormone.
Significant p values are in bold.

We performed univariate and multivariate logistic regression analyses to determine the independent predictors of the presence of thyroid nodules in patients with T1DM. In the multivariate model, only the SII value remained independently associated with the presence of thyroid nodules (p<0.001) (Table 3).

In the ROC analysis, the optimum cut-off value of the SII value for predicting patients with thyroid nodules was 498 x10^3 (AUC:0.812, CI 95%: 0.747 - 0.877, p<0.001, sensitivity 79.7% and specificity 68.5%) (Figure 1).

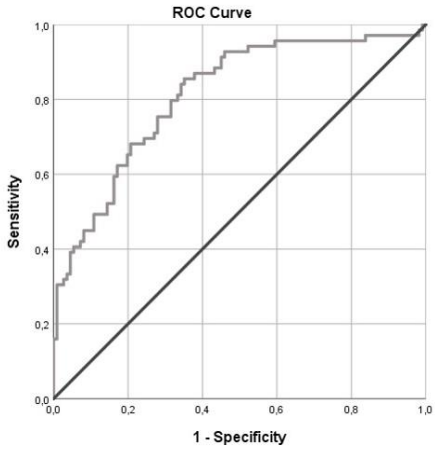

Figure 1. ROC curve of the ability of SII value to predict T1DM patients with thyroid nodules.

Discussion

In the present study, we found that T1DM patients with thyroid nodules had higher SII values compared to patients without and that the mean SII value was an independent predictor of thyroid nodules in patients with T1DM. To the best of our knowledge, this is the first study that demonstrates the association between SII level and thyroid nodules in patients with T1DM. Our findings support the potential role of systemic inflammation in the development of thyroid nodules in patients with T1DM.

The frequency of thyroid nodules has increased worldwide due to the increased use of neck US or other imaging modalities, and varies between 19% and 68%, depending on several factors such as age and gender (7). While most thyroid nodules are benign, thyroid cancer is detected in 4-15% of the nodules, depending on various factors, such as gender, radiation exposure, family history, chronic inflammation, genetic factors, and presence of autoimmune thyroiditis (7,8). There are insufficient and conflicting data on thyroid nodules and cancers in adult patients with T1DM. In a study conducted by Junik et al., (5) the frequency of thyroid nodules assessed by US was higher in patients with

T2DM compared to non-diabetic controls, while there was no significant difference between patients with T1DM and controls. Völzke et al. (14) demonstrated an increased risk of autoimmune thyroid disease and a decreased risk of goiter and thyroid nodules in adult patients with T1DM. In another study evaluating the risk of thyroid cancer in patients with T1DM with a mean follow-up of 35.3 years, the incidence of thyroid cancer in patients with T1DM was 2.4-fold higher than in controls (15). In the same study, there was a female predominance in control thyroid cancer patients, however, the risk was equal between genders in patients with T1DM. In addition, the largest tumor size and signs of invasion were more often in the control group than in patients with T1DM. The authors stated that this condition may be explained by early diagnosis in T1DM patients, regardless of gender, due to regular outpatient clinic visits. Consequently, it is important to evaluate the presence of thyroid nodules and it's predictors in chronic diseases such as T1DM, which affect the lives of patients from very young ages many years, where various genetic and environmental factors play a role.

One of the most important mechanisms underlying the development of thyroid nodules is increased replication and hyperplasia in thyroid follicular cells caused by the chronic inflammatory condition resulting from the interaction of genetic and environmental factors (16). Radiation exposure, smoking, several medications, iodine and selenium deficiency, insulin resistance, and various genetic mutations contribute to the formation of thyroid nodules and cancer (17). These factors activate various signaling pathways and transcription factors and increase the levels of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF), which may cause chronic inflammation and, subsequently, the development of thyroid cancer (18). Li et al. (19) argued that inflammation may play a major role in the formation and development of thyroid nodules through inhibiting thyroid hormone synthesis indirectly. In another study, it was shown that mean CRP level was positively correlated with number of thyroid nodules (19). The authors stated that their findings may indicate that inflammation is an important mechanism underlying thyroid nodule development. There is increasing evidence that inflammatory and autoimmune-mediated pathways play an important role in the development of T1DM, and the most accepted theory is that pancreatic beta cells are damaged by an inflammation called insulitis (20,21). In various autoimmune diseases, including T1DM, it has been shown that serum soluble IL2 receptor (sIL2Ra), a marker of activated helper T cells, is increased by the activation of the TNF-alpha system (22). Current knowledge supports that similar inflammatory pathways may play a role in the development of both T1DM and thyroid nodules. Therefore, we investigated whether several inflammatory parameters easily obtained from complete blood count are independent risk factors for thyroid nodules during routine outpatient clinic visits in patients with T1DM.

There is increasing evidence suggesting that several hematological parameters are gaining importance as potential biomarkers to diagnose various inflammatory conditions, including thyroid nodules and cancers. SII and NLR are biomarkers of inflammatory processes that are simply obtained from complete blood counts (9). It was shown that SII level was an independent predictor of the presence of thyroid nodules, in patients with T2DM, especially in males (11). Şenoymak et al. (23) demonstrated that NLR and SII levels were significantly higher in malignant thyroid nodules compared with benign thyroid nodules. Although the underlying mechanism of the development of thyroid nodules is not clear, it is known that inflammation can directly damage the thyroid tissue, leading to a further increase in thyroid tissue and cell proliferation (24). Neutrophils, the key cells of inflammation, are recruited to damaged tissue through various mediators and contribute to the production of various cytokines, leading to an increase in cell proliferation (25). In addition, an increase in platelet count and function is observed during inflammation, and increased platelets contribute to the formation of a favorable microenvironment for tumor development by secreting platelet-derived growth factors (26). There is lacking data to estimate the value of inflammatory parameters obtained from complete blood count in thyroid nodules in patients with T1DM. We investigated the predictive value of SII and NLR, which are easily obtained and reproducible tools in this patient group, and since there is a strong correlation between SII and NLR, we included only the SII level in the regression models. Consequently, we found that the SII value was a valuable marker in predicting the presence of thyroid nodules in patients with T1DM, supporting previous studies.

Type 1 diabetes mellitus is associated with several other autoimmune endocrine disorders. Autoimmune thyroid disease is one of the most prevalent concomitant autoimmune endocrinopathies occurring in T1DM (3). It has been argued that the pathogenesis of both diseases is due to the interaction of genetic and environmental factors and both are organ-specific T-cell mediated diseases resulting in dysfunction of the target organ (2,3). Although the association between autoimmune thyroiditis and T1DM has been clearly established, in the present study, we found no significant difference in the prevalence of positivity for thyroid autoantibodies or thyroiditis on US examination between patients with and without thyroid nodules. Based on our findings, it may be thought that other inflammatory pathways rather than autoimmune thyroiditis play a role in the etiology of thyroid nodule development in patients with T1DM.

Our study has several limitations. Firstly, the present study had a retrospective design and the sample size was relatively small. Due to the retrospective design and the inclusion of consecutive patients, the number of participants in the patient groups with and without thyroid nodules was not equal. In addition, cytokine levels such as TNF and IL, which are also associated with other complications of diabetes, were not measured due to the retrospective nature of the study. However, it is not possible to measure various inflammatory cytokines in routine outpatient controls unless there is a significant reason in our country. The strengths of this study were our strict inclusion criteria and exclusion of patients with

duration of T1DM <5 years, as autoimmune thyroiditis and thyroid nodules often develop years after the onset of T1DM.

In conclusion, we found that SII levels were higher in patients with T1DM with thyroid nodules compared to those without, suggesting the potential role of systemic inflammation in the development of thyroid nodules in patients with T1DM. Our findings suggest that the SII value, an easily measurable, inexpensive, and reproducible tool might be a useful marker in predicting the presence of thyroid nodules in T1DM. Further larger studies are needed to evaluate the predictors of the development of thyroid nodules in patients with T1DM.

Conflict of interest: The authors declare that they have no conflict of interest.

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