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Impact of glycated hemoglobin (HbA_{1c}) on outcomes in differentiated thyroid cancer with type 2 diabetes mellitus

Merve Çatak[1], *Zeynep Çetin*[2], *Özden Özdemir Başer*[3], *Asım Kocabay*[4]

[1]*Department of Endocrinology and Metabolism, Faculty of Medicine, Tokat Gazıosmanpasa University, Tokat, Türkiye*
[2]*Tokat Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital, Department of Endocrinology and Metabolism, Faculty of Medicine, Amasya Şerefettin Sabuncuoğlu, Amasya, Türkiye*
[3]*Department of Endocrinology and Metabolism, Faculty of Medicine, Dokuz Eylul University, Izmir, Türkiye*
[4]*Department of General Surgery, Erbaa State Hospital, Tokat, Türkiye*

Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a frequent comorbidity in differentiated thyroid cancer (DTC). This study evaluated the impact of glycemic control, particularly glycated hemoglobin (HbA_{1c}) levels, on tumor characteristics and treatment outcomes.

Material and methods: We retrospectively analyzed 302 DTC patients, including 58 (19.2%) with T2DM. Baseline demographic, clinical, and pathological data were collected. Treatment response was assessed as per American Thyroid Association (ATA) guidelines. Logistic regression identified predictors of non-excellent response, and a subgroup analysis was performed among diabetic patients stratified by HbA_{1c} ($< 7\%$ *vs.* $\geq 7\%$).

Results: T2DM patients were older ($p < 0.001$), with more bilateral tumors ($p = 0.047$) and higher tumor foci ($p = 0.039$). Other tumor features were similar between groups. In multivariate analysis, both HbA_{1c} [odds ratio (OR): 1.307, 95% confidence interval (CI): 1.014–1.683, $p = 0.038$] and lymph node metastasis (OR: 3.932, 95% CI: 1.000–15.464, $p = 0.050$) independently predicted non-excellent response. Among diabetics, $HbA_{1c} \geq 7\%$ was associated with higher non-excellent response rates ($p = 0.030$).

Conclusion: Poor glycemic control, rather than T2DM itself, was linked to suboptimal treatment response. HbA_{1c} may serve as a simple prognostic marker in diabetic patients with DTC. **(Endokrynol Pol 2025; 76 (5): 507–515)**

Keywords: *type 2 diabetes mellitus; differentiated thyroid cancer; HbA_{1c}; tumor characteristics; treatment response*

Introduction

Thyroid cancer is the most common endocrine malignancy, and its incidence has been steadily increasing, largely due to the widespread use of thyroid ultrasonography and fine-needle aspiration biopsy [1]. Differentiated thyroid carcinomas (DTCs), including papillary and follicular subtypes, account for approximately 90–95% of all thyroid cancers [2]. Although the overall prognosis of DTC is generally excellent, recurrence occurs in approximately 10% of patients, often in the form of lymph node involvement or distant metastases, particularly to the lungs [3]. Established clinicopathological predictors of poor prognosis include extrathyroidal extension, vascular invasion, distant metastasis, and poor histological differentiation [3, 4].

The relationship between diabetes mellitus (DM) and thyroid cancer has been widely studied, but the findings remain inconsistent. While some studies suggest that DM increases the risk of thyroid cancer, others have found no significant association, or even a possible protective effect [5–8]. Several pathophysiological mechanisms have been proposed to underlie this potential relationship, including hyperinsulinemia, insulin resistance, chronic hyperglycemia, sustained elevations in thyroid-stimulating hormone (TSH), and the effects of various antidiabetic medications [9].

It has also been hypothesized that the pro-inflammatory and mitogenic effects of insulin and insulin-like growth factors may influence tumor initiation and progression in endocrine-related cancers [10, 11].

Moreover, there is growing interest in understanding whether DM not only contributes to cancer risk but also modifies tumor behavior and treatment outcomes [12]. In patients diagnosed with DTC, the presence of diabetes might impact tumor aggressiveness, response to radioiodine therapy, and recurrence risk [13, 14]. In particular, glycemic control — typically monitored through glycated hemoglobin (HbA_{1c}) — has emerged as a potentially relevant factor in cancer prognosis. However, whether this effect stems from DM itself or from the quality of glycemic control remains a subject of

Merve Çatak, M.D. Asst. Prof. Tokat Gazıosmanpasa University, Faculty of Medicine, Department of Endocrinology and Metabolism, Gaziosmanpaşa Üniversite Hastanesi, Kaleardı, 60030, Merkez, Tokat, Turkey; e-mail: merve.catak@gop.edu.tr

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debate [15, 16]. While the mere presence of diabetes has been variably associated with thyroid cancer outcomes, our study specifically focuses on the prognostic impact of glycemic control, as reflected by HbA_{1c}, rather than diabetes diagnosis.

Given the high prevalence of both type 2 diabetes mellitus (T2DM) and DTC in endocrine clinical practice, further investigation into their potential interaction is warranted. In this study, we aimed to evaluate the relationship between T2DM and the clinicopathological characteristics and short-term treatment outcomes in patients with DTC. Specifically, we examined the relationship between diabetes and various tumor characteristics and assessed whether baseline glycemic status was associated with treatment response in the early follow-up period.

Materials and methods

Study design

This retrospective study included 302 patients who underwent thyroid surgery between January 2013 and December 2020 and were diagnosed with DTC based on pathological evaluation. Patients were excluded if they had undifferentiated (anaplastic or poorly differentiated) thyroid carcinoma, a follow-up duration of less than one year after initial surgery, a history of previous thyroid surgery, were younger than 18 years of age at the time of diagnosis, or had missing data regarding pathology or diabetes status (e.g., missing HbA_{1c}).

Demographic and clinical variables recorded included age, sex, duration of diabetes, use of oral antidiabetic drugs or insulin, insulin dose, and the duration of follow-up for thyroid cancer. Histopathological features such as tumor size, localization, multifocality, number of tumor foci, histological type and variant, lymphocytic thyroiditis, capsular and vascular invasion, extrathyroidal extension (both microscopic and macroscopic), and lymph node metastasis were documented. Information regarding radioactive iodine (RAI) ablation therapy — including indication and dosage—was also collected, along with radiologic follow-up data (neck ultrasonography and whole-body iodine scans).

All patients underwent total thyroidectomy as the primary surgical approach. In cases where pathological lymph nodes were identified preoperatively in the central or lateral compartments via neck ultrasonography, corresponding central or lateral neck dissection was performed. Hemithyroidectomy was performed in patients with small, unilateral tumors, in accordance with current American Thyroid Association (ATA) guidelines. Patients who required completion thyroidectomy after initial hemithyroidectomy were included only if they had at least one year of follow-up following the second surgery.

RAI ablation was administered to patients with intermediate- or high-risk features for recurrence, as determined by histopathological and radiological criteria. The decision to administer RAI and the dose selection were made considering tumor size, lymph node involvement, and extrathyroidal extension.

Staging was performed according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification. For risk stratification and prognostic evaluation, patients were categorized as low, intermediate, or high risk based on the same ATA framework. Radiological and biochemical surveillance was conducted at regular intervals following the guideline-based follow-up protocols. At the final follow-up visit, response to treatment was assessed using the ATA response-to-therapy categories: excellent response, biochemical incomplete response, structural incomplete response, and indeterminate response, based on Tg levels and imaging findings.

Evaluation of treatment response

Treatment response was assessed according to the 2015 ATA response-to-therapy guidelines, with criteria tailored to the type of surgery and RAI treatment status.

For patients who received RAI ablation, an excellent response was defined as stimulated thyroglobulin (Tg) levels < 1 ng/mL or suppressed Tg levels < 0.2 ng/mL, with no clinical or imaging evidence of disease. A biochemical incomplete response was defined by a stimulated Tg ≥ 10 ng/mL, suppressed Tg ≥ 1 ng/mL, or a rising trend in anti-thyroglobulin antibody (TgAb) levels in the absence of structural disease. A structural incomplete response was assigned when structural disease was detected on imaging, regardless of Tg levels. An indeterminate response was defined by suppressed Tg levels between 0.2 and 1.0 ng/mL and nonspecific imaging findings.

For RAI-naïve patients, an excellent response was defined as suppressed Tg < 0.2 ng/mL, stimulated Tg < 2 ng/mL, and no structural disease on imaging, with stable or negative TgAb levels. A biochemical incomplete response was defined by suppressed Tg > 5 ng/mL or stimulated Tg > 10 ng/mL, regardless of imaging findings. An indeterminate response was characterized by suppressed Tg between 0.2 and 5 ng/mL and stimulated Tg between 2 and 10 ng/mL, accompanied by stable or nonspecific imaging findings. Structural incomplete response was assigned if any structural disease was identified on imaging, irrespective of Tg levels.

In patients who underwent unilateral thyroidectomy, an excellent response was defined as suppressed Tg < 30 ng/mL, absence of structural disease on imaging, and stable or declining TgAb levels. A biochemical incomplete response was identified by a rising trend in TgAb levels without imaging evidence of disease, whereas a structural incomplete response was diagnosed when structural disease was detected. An indeterminate response was defined by stable TgAb levels and nonspecific findings on imaging [17].

Patients who achieved an excellent response were considered to be in remission. After a minimum follow-up of one year, patients with biochemical or structural incomplete responses, as well as those who developed newly detected disease during follow-up, were classified as having persistent or recurrent disease.

Subgroup analysis was performed based on baseline HbA_{1c} levels among diabetic patients to evaluate the relationship between glycemic control and treatment response.

Biochemical evaluation

HbA_{1c} was measured only once at baseline (diagnosis), and this was used for analyses. Diabetes was defined according to the American Diabetes Association (ADA) Standards of Care 2023.

For biochemical evaluation, fasting blood glucose (FBG) and HbA_{1c} levels at the time of thyroid cancer diagnosis were recorded, in addition to preoperative TSH and free thyroxine (FT4) levels. Tg and TgAb levels at the last follow-up visit were also assessed. Patients were categorized into diabetic and non-diabetic groups based on the ADA criteria (FBG >125 mg/dL or HbA_{1c} > 6.5%).

Fasting plasma glucose was measured using the hexokinase enzymatic reference method. HbA_{1c} levels were determined via high-performance liquid chromatography (HPLC). TSH, serum Tg, and TgAb levels were measured using the electrochemiluminescence immunoassay (ECLIA) method on a Roche Cobas 6000 analyzer with the e601 module (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corporation, NY, USA). The normality of distribution for continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range,

IQR), depending on distribution. Categorical variables were presented as frequencies and percentages.

Comparisons between diabetic and non-diabetic groups were made using the independent samples t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed data. The Pearson chi-square test or Fisher's exact test was used for the analysis of categorical variables, as appropriate.

Subgroup analysis was performed based on baseline HbA_{1c} levels among diabetic patients to evaluate the relationship between glycemic control and treatment response.

Univariate logistic regression was first used to assess the association between each independent variable and remission status. Variables with $p < 0.25$ in the univariate analysis were included in the multivariate logistic regression model. Model adequacy was evaluated using the Hosmer–Lemeshow goodness-of-fit test.

Post hoc power analysis was performed for key subgroup comparisons (e.g., bilaterality and tumor multiplicity) to assess whether the sample size was adequate for detecting statistically significant differences.

A two-tailed p-value < 0.05 was considered statistically significant.

Results

The study included 302 patients DTC, of whom 58 (19.3%) had T2DM. Patients in the diabetic group were significantly older than their non-diabetic counterparts (54.9 ± 9.3 *vs*. 46.3 ± 12.2 years, $p < 0.001$). Although most patients in both groups were female, the proportion of males was higher among those with DM; however, this difference was not statistically significant ($p = 0.126$).

Other baseline biochemical and thyroid function parameters, including fasting glucose, HbA_{1c}, TSH levels, and thyroid status, are presented in Table 1.

The clinical characteristics and antidiabetic treatment profiles of diabetic patients are summarized in Table 2. Metformin was the most commonly prescribed agent, followed by sulfonylureas and dipeptidyl peptidase 4 (DPP-4) inhibitors. Approximately one-fourth of the diabetic patients were on sodium-glucose co-transporter 2 (SGLT-2) inhibitors, and insulin therapy was used in a subset, primarily via basal-bolus regimens. The mean duration of diabetes was six years, with a mean follow-up period of 39.8 months.

When tumor characteristics were compared between groups, the overall distribution of tumor size

Table 2. ***Clinical characteristics and antidiabetic treatment profiles of diabetic patients***

Parameter	Value
Age [years, mean ± SD]	54.9 ± 9.3
Gender	
Female (n, %)	44 (75.9%)
Male (n, %)	14 (24.1%)
Duration of T2DM [years, mean ± SD]	5.9 ± 5
Fasting blood glucose [mg/dL, mean ± SD]	158.1 ± 61.3
HbA_{1c} (%, mean ± SD)	7.8 ± 1.8
Metformin use (n, %)	53 (91.4%)
Sulfonylurea use (n, %)	15 (25.9%)
DPP-4 inhibitor use (n, %)	24 (41.4%)
SGLT-2 inhibitor use (n, %)	14 (24.1%)
GLP-1 receptor agonist use (n, %)	2 (3.5%)
Pioglitazone use (n, %)	1 (1.8%)
Insulin regimen	
Basal (n, %)	2 (10.5%)
Mixed (n, %)	3 (15.8%)
Basal bolus (n, %)	14 (73.7%)
Insulin dose (IU/day, mean ± SD)	69.7 ± 29.5
Follow-up duration (months, mean ± SD)	39.8 ± 17.7

Data are presented as n (%) for categorical variables, mean ± standard deviation (SD) for normally distributed continuous variables, and median (interquartile range, IQR) for non-normally distributed continuous variables. DM — diabetes mellitus; HbA_{1c}: glycated hemoglobin; DPP-4 — dipeptidyl peptidase-4; SGLT2 — sodium-glucose co-transporter 2; GLP-1 — glucagon-like peptide 1. Note: Subgroups with n < 5 should be interpreted carefully due to small sample size

Table 1. ***Baseline demographic, glycemic, and thyroid function characteristics of patients with and without type 2 diabetes mellitus***

	Non-diabetic (n = 244)	Diabetic (n = 58)	p-value
Age [years, mean ± SD]	46.3 ± 12.2	54.9 ± 9.3	< 0.001
Sex (n, % female)	208 (85.2%)	44 (75.9%)	0.126
Fasting glucose [mg/dL] (mean ± SD)	91.3 ± 8.4	158.1 ± 61.3	< 0.001
HbA_{1c} (%) (mean ± SD)	5.5 ± 0.4	7.8 ± 1.8	< 0.001
TSH [mIU/L] (mean ± SD)	1.7 ± 1.5	2.0 ± 2.3	0.206
Thyroid status			
Euthyroid	221 (90.6%)	46 (83.6%)	0.160
Hypothyroid	10 (4.1%)	4 (7.3%)	
Thyrotoxic	13 (5.3%)	5 (9.1%)	

SD — standard deviation; HbA_{1c} — glycated hemoglobin; TSH — thyroid-stimulating hormone

(microcarcinoma *vs*. macrocarcinoma), presence of capsular or vascular invasion, extrathyroidal extension, and lymph node metastasis did not significantly differ between diabetic and non-diabetic patients ($p > 0.05$ for all).

However, the number of tumor foci was significantly higher in diabetic patients (2.1 ± 1.4 *vs*. 1.7 ± 1.2, $p = 0.039$), and bilateral involvement was more frequent (36.8% *vs*. 24.0%, $p = 0.047$). Histological subtype distributions, including classical and follicular variant papillary thyroid carcinoma, were comparable between the groups. Detailed tumor characteristics are presented in Table 3. To evaluate the reliability of these findings, post hoc power analysis was performed. The power was 78.1% for tumor bilaterality and 81.4% for tumor multiplicity, indicating adequate statistical power for detecting these differences.

Tumor-node-metastases (TNM) staging, ATA risk classification, and the frequency of RAI therapy were comparable between diabetic and non-diabetic patients,

Table 3. *Tumor characteristics of diabetic and non-diabetic patients with differentiated thyroid cancer*

	Non-diabetic	Diabetic	p-value
Tumor size category			0.187
Microcarcinoma	137 (56.1%)	27 (46.6%)	
Macrocarcinoma	107 (43.9%)	31 (53.4%)	
Tumor size ([mm, median (IQR)]	9.0 (5.0–20.0)	12.0 (6.0–21.0)	0.211
Multicentricity			0.247
Unifocal	145 (59.4%)	29 (50.0%)	
Multifocal	99 (40.6%)	29 (50.0%)	
Number of tumor foci (mean ± SD)	1.7 ± 1.2	2.1 ± 1.4	0.039
Tumor location			0.193
Isthmus	30 (12.3%)	54 (94.7%)	
Non-isthmus	213 (87.7%)	3 (5.3%)	
Tumor laterality			0.047
Unilateral	184 (76.0%)	36 (63.2%)	
Bilateral	58 (24.0%)	21 (36.8%)	
Histological subtype			0.808
Minimally invasive FTC	6 (2.5%)	2 (3.4%)	
Widely invasive FTC	3 (1.2%)	1 (1.7%)	
Classical PTC	168 (68.9%)	42 (72.4%)	
Follicular variant PTC	46 (18.9%)	8 (13.8%)	
Oncocytic PTC	7 (2.9%)	0 (0%)	
Other PTC variants	14 (5.6%)	5 (8.7%)	
Capsular invasion			0.435
Absent	197 (80.7%)	50 (86.2%)	
Present	47 (19.3%)	8 (13.8%)	
Vascular invasion			0.211
Absent	228 (93.4%)	57 (98.3%)	
Present	16 (6.6%)	1 (1.7%)	
ETE			0.968
Absent	203 (83.2%)	49 (84.5%)	
Present	41 (16.8%)	9 (15.5%)	
Lymph node metastasis			0.645
Absent	222 (91.0%)	51 (87.9%)	
Present	22 (9.0%)	7 (12.1%)	

Data are presented as n (%) for categorical variables, mean ± standard deviation for normally distributed continuous variables, and median (interquartile range) for non-normally distributed continuous variables. PTC — papillary thyroid carcinoma; FTC — follicular thyroid carcinoma; ETE — extrathyroidal extension; SD — standard deviation; IQR — interquartile range

Table 4. *Staging, risk stratification, treatment characteristics, and response to therapy in diabetic and non-diabetic patients*

Parameter	Non-diabetic	Diabetic	p-value
Age [years, mean ± SD]	46.3 ± 12.2	54.9 ± 9.3	< 0.001
TNM Stage			0.199
Stage 1	228 (94.2%)	51 (87.9%)	
Stage 2	12 (5.0%)	7 (12.1%)	
Stage 3	2 (0.8%)	0 (0%)	
ATA Risk Category			0.600
Low	161 (66.0%)	37 (63.8%)	
Intermediate	79 (32.4%)	19 (32.8%)	
High	4 (1.6%)	2 (3.4%)	
Follow-up duration (months, mean ± SD)	37.1 ± 15	39.8 ± 17.7	0.292
RAI therapy			0.816
No	117 (54.4%)	32 (56.1%)	
Yes	98 (45.6%)	25 (43.9%)	
RAI dose [mCi] (mean ± SD)	93.7 ± 35.5	108.7 ± 30	0.060
Response to therapy			0.257
Excellent	194 (79.5%)	40 (69.0%)	
Structural Incomplete	2 (0.8%)	2 (3.4%)	
Indeterminate	39 (16.0%)	16 (27.6%)	
Biochemical Incomplete	9 (3.7%)	0 (0%)	
Final TSH [median (IQR)]	1.0 (0.2–4.1)	6.3 (1.4–33.0)	< 0.001
Final Tg [median (IQR)]	0.1 (0.0–0.4)	0.2 (0.0–0.8)	0.266
Final TgAb (mean ± SD)	14.6 ± 11.3	12.7 ± 5.5	0.234
Final TgAb [median (IQR)]	12.0 (10.0–16.0)	12.0 (9.0–16.0)	0.349

Data are presented as n (%) for categorical variables, mean ± standard deviation (SD) for normally distributed continuous variables, and median (interquartile range, IQR) for non-normally distributed continuous variables. TNM — tumor-node-metastasis staging; ATA — American Thyroid Association; RAI — radioactive iodine; TSH — thyroid-stimulating hormone; Tg — thyroglobulin; TgAb — anti-thyroglobulin antibody

as shown in Table 4 ($p > 0.05$ for all comparisons). Although the mean RAI dose was higher in diabetic patients, this difference was not statistically significant ($p = 0.060$). Treatment response rates were also similar between groups. However, final TSH levels were significantly higher in the diabetic group when evaluated using median values (6.3 [1.4–33.0] *vs*. 1.0 [0.2–4.1], $p < 0.001$), while other biochemical parameters, including Tg and TgAb, showed no significant differences.

In univariate logistic regression analyses, male sex, HbA_{1c}, lymph node metastasis, and RAI therapy were significantly associated with a non-excellent response. Variables with p-values < 0.25 in univariate analysis (HbA_{1c} and lymph node metastasis) were included in the multivariate model. In the adjusted model, HbA_{1c} (OR: 1.307, 95% CI: 1.014–1.683, $p = 0.038$) and lymph node metastasis (OR: 3.932, 95% CI: 1.000–15.464, $p = 0.050$) remained independently associated with a non-excellent response. The results of the univariate and multivariate logistic regression analyses for predictors of non-excellent response are summarized in Table 5**.** Model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit test. The test yielded a non-significant result ($\chi^2 = 6.84$, df = 8, $p = 0.553$), indicating an adequate fit of the logistic regression model to the observed data.

In the subgroup analysis limited to diabetic patients (n = 58), HbA_{1c} levels were further stratified based on a cut-off value of 7%. The proportion of patients with a non-excellent response was higher among those with $HbA_{1c} \geq 7\%$ compared to those with $HbA_{1c} < 7\%$. Additionally, mean HbA_{1c} levels were significantly higher in patients with a non-excellent response (8.62 ± 2.02%) compared to those with an excellent response (7.53 ± 1.55%) ($t = -2.221$, df = 56, $p = 0.030$).

However, due to the limited sample size in the diabetic subgroup, logistic regression analysis could not be reliably performed for this population. Therefore, only descriptive and univariate comparisons were conducted.

Table 5. *Logistic regression analysis for non-excellent response*

Variable	OR	Lower CI	Upper CI	p-value	OR (alt)	Lower CI (alt)	Upper CI (alt)	p-value (alt)
Sex (ref = Female)	2.330	1.209	4.492	0.012				
Age ≥ 55 years (ref = < 55)	1.152	0.644	2.061	0.633				
Diabetes (ref = No)	1.609	0.844	3.067	0.149				
HbA_{1c}	1.327	1.038	1.696	0.024	1.307	1.014	1.683	0.038
Tumor size (ref = Microcarcinoma)	1.113	0.646	1.917	0.700				
Extrathyroidal extension (ref = No)	1.131	0.554	2.311	0.735				
Lymph node metastasis (ref = No)	3.874	1.762	8.517	0.001	3.932	1.000	15.464	0.050
Laterality (ref = Unilateral)	1.691	0.938	3.046	0.080				
RAI (ref = No)	2.369	1.363	4.119	0.002				
Number of foci	1.079	0.876	1.330	0.473				

OR — odds ratio; CI — confidence interval; RAI — radioactive iodine; HbA_{1c} — glycated hemoglobin; DM — diabetes mellitus. Reference categories: Female for sex, age < 55 years, absence of DM, microcarcinoma for tumor size, no extrathyroidal extension, no lymph node metastasis, unilateral tumor, and no RAI therapy

Discussion

In this study, we found that patients with T2DM and DTC were older and more likely to have bilateral tumors compared to non-diabetic patients. Additionally, the number of tumor foci was significantly higher in diabetic individuals, indicating a greater overall tumor burden. Other tumor characteristics, including size, capsular or vascular invasion, extrathyroidal extension, and lymph node metastasis, were comparable between the groups. Importantly, although the presence of diabetes itself was not associated with non-excellent response in univariate analysis, elevated HbA_{1c} levels and lymph node metastasis were identified as significant predictors. In the multivariate logistic regression model, both HbA_{1c} and lymph node metastasis remained independently associated with a lower likelihood of achieving an excellent response. Furthermore, in a subgroup analysis limited to diabetic patients, those with HbA_{1c} levels ≥7% had a significantly higher rate of non-excellent response, and their mean HbA_{1c} was significantly higher compared to those with an excellent response. These findings indicate that glycemic regulation, rather than the mere presence of diabetes, is the key determinant of treatment outcomes in patients with DTC.

Previous studies have suggested that the prevalence of diabetes mellitus in thyroid cancer patients tends to be higher in younger individuals. For example, rates have been reported as approximately 18% in patients under 44 years of age, compared to 11% in those 45–65 years old [18]. In contrast, our study identified a higher prevalence of DM (19%) despite a mean patient age of 47 years. Additionally, diabetic patients in our cohort were significantly older than non-diabetic patients, while no statistically significant difference was observed in terms of gender distribution. However, it is noteworthy that the proportion of male patients was higher in the diabetic group. This may reflect underlying gender-related differences in metabolic risk or health-seeking behavior, although the association was not statistically significant. These findings may also reflect the unique features of our study population, including the requirement for a minimum one-year follow-up. It is also possible that older individuals with longstanding diabetes experience more pronounced metabolic alterations, which may contribute to the development or progression of DTC.

Although the study by Elbasan et al. did not assess DM, it reported that multifocality and bilaterality were associated with certain aggressive tumor features, such as larger tumor size and extrathyroidal extension. In particular, bilaterality was more common among patients with multiple tumor foci [19]. In our study, while the frequency of multifocal tumors was similar between diabetic and non-diabetic patients, the total number of tumor foci was higher in the diabetic group, and bilateral involvement was more frequent. Although this was not accompanied by other indicators of aggressive disease such as vascular invasion or lymph node metastasis, the broader tumor distribution may reflect metabolic influences on tumor architecture in T2DM. These findings support the notion that metabolic factors could influence structural tumor characteristics, and future studies should further investigate this potential association in DTC.

Numerous studies have explored the clinicopathological features of papillary thyroid cancer (PTC) in patients with DM, but findings remain inconsistent — likely due to heterogeneity in patient populations and insufficient adjustment for metabolic cofactors.

In a study by Shi *et al.*, DM was more prevalent in males under 55 years old and associated with a higher frequency of multifocal and extraglandular disease. Among older women, both DM and increased body mass index (BMI) were found to be independent risk factors for extrathyroidal extension (ETE), highlighting the compounded risk when obesity coexists with diabetes [20]. In contrast, a Turkish cohort of 865 PTC patients reported increased multifocality in diabetic patients but did not account for BMI, limiting interpretation of metabolic influence [21].

Similarly, a large earlier cohort study found that T2DM was associated with worse outcomes — including elevated thyroid cancer-specific mortality and a higher risk of secondary malignancies [22]. Notably, patients in that study also had higher BMI and more comorbidities, suggesting that adverse outcomes might reflect broader metabolic dysregulation rather than diabetes alone. Furthermore, it is important to note that this study was published over a decade ago, during which time substantial advances have been made in diabetes management. The introduction of novel antidiabetic agents, tighter glycemic targets, and improved cardiovascular and renal risk reduction strategies may have collectively mitigated the negative impact of diabetes on cancer prognosis in contemporary cohorts. These observations support the hypothesis that HbA1c and long-term glycemic control — rather than diabetes diagnosis itself — are more relevant to cancer-related outcomes.

Our study, although lacking BMI and insulin resistance data, adds to this growing body of evidence by showing that HbA_{1c}—an indicator of long-term glycemic control—was independently associated with non-excellent response in patients with DTC. In contrast, the presence of T2DM alone did not predict treatment outcomes. HbA_{1c} may also serve as a surrogate of subclinical inflammation, insulin resistance, and oxidative stress [23, 24], which could contribute to persistent disease or incomplete response, even in the absence of aggressive histopathologic features.

From a molecular perspective, chronic hyperglycemia can alter the tumor microenvironment through sustained production of pro-inflammatory cytokines, promotion of angiogenesis, and activation of proliferative signaling pathways [12, 25, 26]. Moreover, insulin and insulin-like growth factor-1 signaling — which are frequently elevated in patients with poor glycemic control — have been implicated in thyroid tumorigenesis and resistance to radioiodine therapy [12, 27, 28]. Taken together, these pathophysiological processes may contribute to impaired treatment response, supporting the clinical relevance of maintaining optimal HbA_{1c} levels in patients with DTC.

In our subgroup analysis limited to patients with T2DM, higher HbA_{1c} levels (≥ 7%) were associated with a significantly greater likelihood of a non-excellent response compared to those with better glycemic control (< 7%). This observation supports the hypothesis that inadequate glycemic control may negatively influence treatment outcomes in DTC, even in the absence of aggressive tumor features. Suboptimal glucose regulation has been linked to impaired immune surveillance, increased oxidative stress, and chronic low-grade inflammation, all of which may contribute to reduced treatment efficacy and persistence of disease [29]. Furthermore, $HbA_{1c} \geq 7\%$ is widely accepted as a clinical threshold for inadequate glycemic control, and our findings suggest that this level may also have prognostic relevance in thyroid cancer management [30].

In recent years, novel antidiabetic agents such as SGLT2 inhibitors and GLP-1 receptor agonists have been recognized not only for their metabolic and cardiovascular benefits but also for their potential influence on tumor biology [31, 32]. Although our study did not specifically evaluate these therapies, future research should investigate their possible effects on thyroid cancer outcomes.

Moreover, our findings are consistent with prior studies that have identified poor glycemic control as a predictor of adverse outcomes in thyroid cancer. Zhao *et al.* conducted a hospital-based cross-sectional study in China and demonstrated that DTC patients with HbA_{1c} levels ≥ 6.5% had a significantly higher frequency of lymph node metastasis and extrathyroidal invasion compared to those with better glycemic control, suggesting a more aggressive disease course in poorly regulated diabetics [33]. In addition, a recent meta-analysis including over 10,000 diabetic cancer patients showed that an HbA1c level of ≥ 7% was associated with a 68% increased risk of cancer recurrence and cancer-specific mortality [34]. These results are in line with our subgroup analysis showing worse response rates in patients with $HbA_{1c} \geq 7\%$, and they are further supported by recent studies. Wang *et al.* reported that elevated HbA_{1c} was significantly associated with decreased disease-free survival in papillary thyroid carcinoma [35]. Similarly, Lee *et al.* showed that poor glycemic control was linked to increased recurrence risk in a population-based cohort [36]. Chen *et al.* also demonstrated that preoperative HbA1c levels were predictive of recurrence in patients with differentiated thyroid cancer [37]. These findings emphasize the clinical utility of HbA_{1c} as a simple, accessible, and cost-effective biomarker for risk stratification in DTC.

Given these results, clinicians managing patients with DTC and diabetes should not only monitor thyroid-specific indicators, but also prioritize glycemic

optimization—particularly HbA_{1c} control. While recurrence rates did not significantly differ between diabetic and non-diabetic groups, the independent association between elevated HbA_{1c} and non-excellent response highlights a potentially modifiable prognostic factor. These findings underscore the importance of incorporating glycemic status into the risk stratification and follow-up strategies of DTC patients with comorbid diabetes.

Clinical implications

Based on our findings, several practical recommendations can be made:

— HbA_{1c} monitoring should be routinely considered in diabetic patients with DTC, as poor glycemic control is associated with a higher risk of suboptimal treatment response;
— metabolic optimization with a target $HbA_{1c} < 7\%$ may help improve treatment outcomes in diabetic DTC patients.
— future prospective studies with repeated HbA_{1c} measurements and larger diabetic cohorts are needed to validate these findings.

This study has several limitations that should be considered when interpreting the findings. First and foremost, its retrospective design may introduce selection bias and limits control over potential confounding factors. Second, our dataset lacked critical metabolic and inflammatory parameters such as body mass index, measures of insulin resistance [e.g., Homeostatic Model Assessment — Insulin Resistance (HOMA-IR)], and inflammatory markers (e.g., C-reactive protein), which could have provided further insight into the metabolic profile of patients and its potential influence on thyroid cancer outcomes. Third, tumor molecular profiling, including genetic alterations such as *BRAF*, *RAS*, or *TERT* promoter mutations, was not evaluated. These mutations are known to affect prognosis and treatment response in differentiated thyroid cancer and may act as confounders in assessing the independent impact of glycemic status. Additionally, although HbA_{1c} was used as a marker of glycemic control, it was only measured once during follow-up; repeated assessments would have offered a more comprehensive view of long-term glycemic trends. The relatively small sample size in the diabetic subgroup also limited the power of statistical analyses, particularly for evaluating independent predictors within that cohort. Finally, although all patients were followed for at least one year, longer follow-up would be necessary to evaluate late recurrences and the long-term impact of metabolic parameters on disease progression.

Conclusions

In conclusion, this study demonstrated that, although the presence of T2DM was not independently associated with treatment response or recurrence in patients with DTC, elevated HbA_{1c} levels were significantly linked to a non-excellent treatment response. Both HbA_{1c} and lymph node metastasis emerged as independent predictors of suboptimal therapeutic outcomes. Furthermore, subgroup analysis among diabetic patients revealed that HbA_{1c} levels $\geq 7\%$ were associated with significantly worse response rates, underscoring the potential prognostic value of glycemic control in this population. These findings suggest that long-term metabolic regulation, rather than the diagnosis of diabetes per se, plays a critical role in shaping DTC prognosis. Clinicians should therefore consider incorporating HbA_{1c} monitoring into routine risk stratification and follow-up protocols for diabetic patients with DTC. Since HbA_{1c} was independently associated with treatment response, prospective studies with larger diabetic cohorts, repeated glycemic assessments, and comprehensive metabolic profiling are warranted to validate its prognostic role and to further elucidate the underlying pathophysiological mechanisms.

Data availability statement

The data supporting the findings of this study are available within the article. The raw data that support the conclusions of this study are available upon request from the corresponding author.

Ethics statement

The study was approved by Tokat Gaziosmanpasa Univercity Ethics Committee Approval Number: 83116987-388 and approved on 28.03.2024 conducted in accordance with the Declaration of Helsinki.

Author contributions

M.Ç.: led the study, contributed to study design, data collection and processing, interpretation of findings, literature search, and manuscript preparation and writing; Z.Ç.: Contributed to study design, statistical analyzes, interpretation of results, and critical revision of the manuscript; Ö.Ö.B.: Statistical analyzes, interpretation of findings, and critical revision of the manuscript; A.K.: Data collection, interpretation of findings, and critical revision of the manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

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Supplementary material

Supplementary material including additional tables, figures, and methodological details can be found in the online version of this article (or available upon request).

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