



THE ASSOCIATION BETWEEN TYPE 2 DIABETES MELLITUS, HYPOTHYROIDISM, AND THYROID CANCER

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SUMMARY – This study aimed to investigate the association between type 2 diabetes mellitus (T2DM), antidiabetic therapy, hypothyroidism, and thyroid cancer. We analyzed data from 320 patients who underwent thyroid surgery for suspicion of cancer. The diagnosis of thyroid cancer was confirmed by histopathological analysis in 95 patients. No significant difference was found in the diagnosis of T2DM and hypothyroidism concerning the presence of thyroid cancer ($p=0.13$; $p=0.85$), nor in the gender of patients with T2DM and hypothyroidism with respect to the type of thyroid cancer ($p=0.19$; $p=0.25$). Patients with T2DM (Odds ratio [OR] 1.89; 95% CI, 0.856–4.163) and patients with hypothyroidism (OR, 1.05; 95% CI, 0.530–2.164) had higher prevalence of thyroid cancer, as did those who had both diagnoses combined ($p=0.37$; OR, 2.39; 95% CI, 0.333–17.278), compared with the patients who did not have those diagnoses. Men with T2DM (OR, 6.19; 95% CI, 1.180–32.513) had higher prevalence of thyroid cancer than women. Patients who were on oral antidiabetics (OR, 1.91; 95% CI, 0.804–4.512) had higher prevalence of thyroid cancer than those receiving insulin. According to the results of this study, we can conclude that there is an association between T2DM, hypothyroidism, oral antidiabetics, and thyroid cancer.

Key words: *type 2 diabetes mellitus; hypothyroidism; thyroid cancer*

Introduction

In a large number of people, all sorts of knots can occur in the thyroid gland throughout their lifetime, and can be smaller or larger, solitary or multiple, and with a much higher incidence in women than in men, with a ratio of 3–4:1¹. If we look at thyroid cancer exclusively, it is also more frequently diagnosed in women, with a ratio of 2–3:1¹. The thyroid gland is the commonest site of malignancy in the endocrine system². The most frequent malignant tumors of the thyroid

gland are papillary, follicular, and other differentiated carcinomas of the thyroid gland^{3–5}. Over the last few decades, there have been multiple increases in the incidence of thyroid cancer worldwide, including in Croatia^{6,7}. The incidence of thyroid cancer is increasing in Croatia, and according to the Croatian Institute of Public Health the incidence rate is highest (29/100 000) in women 55–59 years of age⁸. Higher thyroid cancer incidence can be partially explained as due to more diagnostic procedures in the purpose of detecting thyroid cancer, such as ultrasound, but these diagnostics cannot fully explain the higher incidence of newly developed thyroid malignomas^{9,10}.

Risk factors for thyroid cancer are not yet fully established. Only neck irradiation and iodine deficiency

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are well-known factors that increase the risk of thyroid cancer^{2,11,12}. The relationship between type 2 diabetes mellitus (T2DM) and several carcinomas is well-established, but the relationship between T2DM and thyroid cancer is still controversial. One prospective cohort study from 2011¹³ has shown that women with T2DM have a higher risk of thyroid cancer, and one meta-analysis from 2014¹⁴ clearly supported that claim and did indeed find that women have a greater risk of thyroid cancer if they have T2DM. The same meta-analysis did not establish a relationship between duration of T2DM and thyroid cancer but found that patients who had diabetes mellitus (DM) not longer than 5 years had significantly lower risk of developing thyroid cancer¹⁵. In contrast to previous studies that showed an association between T2DM and thyroid cancer, studies such as that of Luo *et al.*¹⁶ do not support the hypothesis that DM or antidiabetic medications are associated with a risk of thyroid cancer in women. Given the possible effects of medications that are being used in treating T2DM and occurrence of thyroid carcinoma, recent studies, such as the one by Cho *et al.*¹⁷, show that metformin facilitates apoptosis of thyroid cancer cells and can lower the risk of developing thyroid malignancy.

A meta-analysis of 61 studies by Han *et al.*¹⁸ showed a higher prevalence of subclinical hypothyroidism in patients with T2DM. The prevalence of hypothyroidism among patients with DM varies from 4.8 to 31.4%¹⁹. Since the association of T2DM and thyroid cancer has been suggested, a correlation between hypothyroidism and thyroid cancer has also been suggested, with a higher incidence of hypothyroidism in patients with T2DM. To our knowledge, there is no study in the literature examining the association of T2DM in combination with hypothyroidism and thyroid cancer.

This study aimed to investigate the association between T2DM, antidiabetic medication, hypothyroidism, and thyroid cancer. A secondary aim was to investigate whether T2DM and hypothyroidism affected the size of thyroid cancer.

Patients and methods

Patients

This retrospective study included data from the hospital records of 320 patients who underwent sur-

gery for suspicion of thyroid cancer from January 2018 to December 2019 at the Clinic for Otorhinolaryngology and Head and Neck Surgery in the Osijek Clinical Hospital Centre. The pathohistological diagnosis (PHD) confirmed thyroid cancer in 95 patients. The following data were analyzed: age, gender, diagnosis of hypothyroidism before surgery, diagnosis of T2DM, type of antidiabetic medication (insulin or peroral antidiabetic medications), the type of thyroid cancer according to PHD, and size of the cancer. The size of the cancer was divided into two groups according to the classification of the American Cancer Society: <2cm and >2cm. The exclusion criteria were as follows: diagnosis of type I diabetes mellitus and hyperthyroidism. All data were entered into a computer database, and the data were only available to the researcher. This study was approved by the Ethical Committee of our institution. Given that this was a retrospective study, the patients did not sign informed consent.

Statistical analysis

All the data were analyzed using SPSS (IBM Corp. Released in 2013. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. Differences of categorical variables were tested with the Chi-squared test and Fisher's exact test. Differences in numerical variables between the two independent groups were tested using the Mann-Whitney U test. Conditional logistic regression models were used to evaluate the effects of T2DM, antidiabetic medication, and hypothyroidism on thyroid cancer and the size of cancer. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated for each variable from the results of the logistic regression model. All P values were two-sided. The significance level was set at $\alpha = 0.05$.

Results

Out of 320 patients, 95 of them had thyroid cancer confirmed by pathohistological analysis. Papillary cancer was the type of thyroid cancer with the highest frequency (Table 1).

Out of 95 patients with thyroid cancer, 18 (18.9%) were men and 77 (81.1%) were women. The median age of all patients with thyroid cancer was 53.5 years (interquartile range, 42.5-64.2 years). There was no

significant difference in age regarding the gender of patients with thyroid cancer (Mann Whitney U test, $p=0.43$).

Out of 320 patients, 28 (8.8%) of them had T2DM, 5 (1.6%) patients were on insulin therapy, and 23 (7.2%) patients were on oral antidiabetics. Hypothyroidism before surgery was present in 42 (13.1%) out of 320 patients.

There was no significant difference in the number of patients with T2DM with respect to the number of patients with hypothyroidism (Fisher's exact test, $p=0.77$) and with the type of antidiabetic therapy with respect to the diagnosis of hypothyroidism (Fisher's exact test, $p=0.57$).

Table 1. Type of thyroid cancer according to pathohistological diagnosis

Diagnosis	Frequency	Percent
Papillary cancer	72	75.8
Micropapillary cancer	7	7.3
Papillary cancer with neck metastasis	5	5.3
Follicular cancer	5	5.3
Hurthle cell cancer	5	5.3
Medullary thyroid cancer	1	1
Total	95	100

There were 12 (12.6%) patients with T2DM and thyroid cancer; 7 of them were men, while 5 of them were women. No significant difference was found in the presence of T2DM diagnosis compared with the presence of thyroid cancer diagnosis (Fisher's exact test, $p=0.13$) or in the gender of patients with T2DM regarding the type of thyroid cancer (Chi-squared test, $p=0.19$).

There was no significant difference in the diagnosis of T2DM with respect to the type of thyroid cancer (Table 2).

There was no significant difference in the type of antidiabetic therapy with respect to the type of thyroid cancer (Table 3).

The total number of patients with hypothyroidism and thyroid cancer was 13 (13.7%), and 4 of them were men and 9 were women. There was no significant difference between the presence of a diagnosis of hypothyroidism and the presence of a thyroid cancer diagnosis (Fisher's exact test, $p=0.85$) or in the gender of patients with hypothyroidism with respect to the type of thyroid cancer (Chi-squared test, $p=0.25$).

There was no significant difference in the diagnosis of hypothyroidism regarding the type of thyroid cancer (Table 4).

In the group of cancers that were larger than 2 cm, the majority of them (17.9%) were papillary cancers.

Table 2. Diagnosis of type 2 diabetes mellitus with regard to the type of thyroid cancer

		Number (%) of patients with regard to the type of thyroid cancer						Total	P*
		Papillary cancer	Micro-papillary cancer	Papillary cancer with neck metastasis	Follicular cancer	Hurthle cell cancer	Medullary thyroid cancer		
T2DM	YES	10 (13.9)	0 (0)	0 (0)	1 (20)	1 (20)	0 (0)	12 (12.6)	0.78
	NO	62 (86.1)	7 (100)	5 (100)	4 (80)	4 (80)	1 (100)	83 (87.4)	
Total		72 (100)	7 (100)	5 (100)	5 (100)	5 (100)	1 (100)	95 (100)	

*Chi-squared test; T2DM: type 2 diabetes mellitus

Table 3. Type of antidiabetic therapy with regard to the type of thyroid cancer

Type of therapy	Number (%) with regard to the type of thyroid cancer			Total	P*
	Papillary cancer	Micropapillary cancer	Follicular cancer		
Insulin	2 (20)	0 (0)	0 (0)	2 (16.7)	0.78
Peroral antidiabetics	8 (80)	1 (100)	1 (100)	10 (83.3)	
Total	10 (100)	1 (100)	1 (100)	12 (100)	

*Chi-squared test

Table 4. The diagnosis of hypothyroidism before surgery with regard to type of thyroid cancer

Diagnosis of hypothyroidism		Number (%) of patients with regard to the type of thyroid cancer						Total	P*
		Papillary cancer	Micro-papillary cancer	Papillary cancer with neck metastasis	Follicular cancer	Hurthle cell cancer	Medullary thyroid cancer		
YES		11 (15.3)	1 (14.3)	0 (0)	1 (20)	0 (0)	0 (0)	13 (13.7)	0.84
NO		61 (84.7)	6 (85.7)	5 (100)	4 (80)	5 (100)	1 (100)	82 (86.3)	
Total		72 (100)	7 (100)	5 (100)	5 (100)	5 (100)	1 (100)	95 (100)	

*Chi-squared test

Table 5. Diagnosis of type 2 diabetes mellitus with regard to the cancer size

		Number (%) with regard to the cancer size		Total	P*
		< 2 cm	> 2 cm		
T2DM	YES	10 (14.1)	2 (8.3)	12 (12.6)	0.72
	NO	61 (85.9)	22 (91.7)	83 (87.4)	
Total		71 (100)	24 (100)	95 (100)	

*Fisher's exact test

Table 6. Diagnosis of hypothyroidism with regard to the cancer size

		Number (%) with regard to the cancer size		Total	P*
		< 2 cm	> 2 cm		
Hypo-thyroidism	YES	16 (22.5)	2 (8.3)	18 (18.9)	0.15
	NO	55 (77.5)	22 (91.7)	77 (81.1)	
Total		71 (100)	24 (100)	95 (100)	

*Fisher's exact test

Most of the patients (74.7%) had a cancer size of less than 2 cm. There was no significant difference in cancer size with respect to the type of thyroid cancer (Chi-squared test, $p=0.49$).

There was no significant difference between a diagnosis of T2DM, hypothyroidism, and cancer size (Tables 5 and 6).

Patients with T2DM ($p=0.11$; Odds ratio [OR] 1.89; 95% CI, 0.856–4.163) and patients with hypothyroidism ($p=0.84$; OR, 1.05; 95% CI, 0.530–2.164) had higher prevalence of thyroid cancer than patients without T2DM and hypothyroidism. Patients with T2DM and hypothyroidism also had higher prevalence of thyroid cancer ($p=0.37$; OR, 2.39; 95% CI,

0.333–17.278) than patients without those diagnoses. Patients who were on oral antidiabetics had higher prevalence of thyroid cancer ($p=0.13$; OR, 1.91; 95% CI, 0.804–4.512) than those receiving insulin ($p=0.63$; OR, 0.62; 95% CI, 0.068 – 5,620). Women had higher prevalence of thyroid cancer ($p=0.53$; OR, 1.20; 95% CI, 0.637–2.295) than men. Men with T2DM ($p=0.01$; OR, 6.19; 95% CI, 1.180–32.513) had higher prevalence of thyroid cancer than women with T2DM ($p=0.48$; OR, 1.41; 95% CI, 0.538–3.705). Patients with T2DM ($p=0.72$; OR, 0.82; 95% CI, 0.286 – 2.379) and hypothyroidism ($p=0.15$; OR, 0.53; 95% CI, 0.172–1.652) did not have higher prevalence of cancer sizes greater than 2 cm compared with those without T2DM and hypothyroidism.

Discussion

In this study, we investigated the association between T2DM, antidiabetic medication, hypothyroidism, and thyroid cancer. We also investigated the association between T2DM, hypothyroidism, and the size of the thyroid cancer. Diabetes mellitus and hypothyroidism diagnoses are associated with an increased risk of thyroid cancer^{20,21}. Two recent large-sized studies indicate that a history of DM may be a risk factor for thyroid cancer^{13,22}. In our study, 8.8% of subjects had T2DM, which is slightly higher than the prevalence in Europe. In 2010, the prevalence of DM in European regions including Russia was 8.5%, and the global prevalence was 6.6%²³. Hypothyroidism prior to surgery was present in 13.1% of patients, which is significantly higher than the prevalence in the US. In the National Health and Nutrition Examination Survey (NHANES III study), a survey of 17,353 subjects representing the US population, hypothyroidism was found in 4.6% of subjects²⁴. In their meta-analysis, Yeo

et al. indicated that T2DM was associated with a statistically significant increase in thyroid cancer risk of approximately 20% of overall study populations, with a 30% increase among women, but not among men¹⁴. Results of the updated meta-analysis indicated that patients with DM had a 20% increase in thyroid cancer incidence compared with those without DM. Furthermore, women with DM had an impact on the risk of thyroid cancer, and no significant difference was detected when pooling for men²¹. Our retrospective study showed that 39% of men with histopathologically proven thyroid malignancy also had T2DM, whereas in women with T2DM only 6.5% had malignant thyroid disease. Plausible biologic pathways linking diabetes to thyroid cancer risk include chronic thyroid-stimulating hormone (TSH) stimulation, insulin resistance, elevated circulating insulin levels, vitamin D deficiency in diabetics, and antidiabetic medication-mediated effects¹³.

The major weakness of our study was its retrospective design. We do not have data on how long patients had T2DM and hypothyroidism. Tseng et al.¹⁵ showed the lack of an overall association between diabetes and thyroid cancer. Patients with DM of duration of less than 5 years may have a significantly reduced risk¹⁵. Nevertheless, the present study had several strengths. We were able to conduct sex-specific analyses which suggested that men with T2DM had higher odds of thyroid cancer than women with T2DM.

Clinical hypothyroidism was found in around one-tenth of patients with T2DM, which is in agreement with a study by Nair et al.²⁵, where clinical hypothyroidism was observed in around one-tenth of Indian patients with type 2 diabetes. Subclinical hypothyroidism was found in another 5% of patients²⁵. In our study, hypothyroidism was present in 13 (13.7%) subjects with thyroid cancer. In their meta-analysis, Zheng et al.²⁶ addressed serum thyroid-stimulating hormone (TSH) and thyroid cancer risk. Their results indicate that patients with thyroid cancer have significantly increased levels of serum TSH. This hormone stimulates the production and release of thyroid hormones and promotes thyroid cancer growth as well as invasion and angiogenesis. TSH also has growth effects in thyroid cancer²⁶. There are differences in TSH levels between differentiated thyroid carcinoma and benign thyroid enlargement. Patients with high TSH levels have a higher risk of differentiated carcinoma than pa-

tients with low TSH levels. Thyroid-stimulating hormone levels are an independent predictor for the diagnosis of thyroid malignancies in patients with thyroid gland enlargement²⁷. The role of hyperthyroidism in the production of thyroid cancers is unclear. Nayci et al.²⁰ concluded that the rate of malignancy among patients with hyperthyroidism was significantly higher than those with hypothyroidism. On the other hand, the conclusion of the study by Rieger et al.²⁸ which included 1848 patients was that the rate of cancer is lower among patients with hyperthyroidism in regions endemic for goiter. There is no difference in glucose tolerance, insulin sensitivity, lipid profile, and glucoregulatory hormone levels between TSH-suppressed and euthyroid patients²⁹, which was also evident in the present study because there was no significant difference in the diagnosis of T2DM with respect to the diagnosis of hypothyroidism. Poor glycemic control is associated with a significantly elevated risk of subclinical hypothyroidism. The prevalence of subclinical hypothyroidism is similar between patients with T2DM and patients without T2DM³⁰. Mild hypothyroidism in T2DM confers a protective effect with respect to glucose tolerance, whereas the presence of overt hypothyroidism in T2DM has a deleterious effect. The increased incidence of subclinical hypothyroidism could be a repercussion of a physiological attempt by the body to mitigate the damage wrought by diabetes³¹. In our study, there was no significant difference in the diagnosis of diabetes regarding the type of thyroid cancer. Furthermore, there was no significant difference in the type of antidiabetic therapy with respect to the type of thyroid cancer and the diagnosis of hypothyroidism. Neither metformin nor any other anti-diabetes medication was statistically significantly associated with an altered relative thyroid cancer risk³². On the other hand, Seo et al. concluded that individuals who were taking medication for T2DM had higher risk of thyroid cancer compared with those individuals who were not taking T2DM medication³³. Among insulin users, those on Glargine (an insulin analog) may have an increased risk of cancer compared with those on human insulin¹³. In our study, patients who were on oral antidiabetics had higher prevalence of thyroid cancer than patients who were on insulin. According to our results, a diagnosis of diabetes or hypothyroidism does not affect the size of thyroid cancer.

Although there was no significant difference in the presence of the diagnosis of T2DM and hypothyroid-

ism or the type of antidiabetic therapy with respect to thyroid cancer, patients with T2DM as well as with hypothyroidism had a higher prevalence of thyroid cancer than patients who did not have those diagnoses. The highest prevalence of thyroid cancer was found in patients with T2DM and hypothyroidism in combination. There was therefore an association between T2DM, hypothyroidism, oral antidiabetics, and thyroid cancer, but those variables were not associated with the size of the thyroid cancer. Furthermore, the limitations of this study, such as the number of thyroid cancer patients who had T2DM and hypothyroidism as comorbidity and the retrospective structure of the study, should be taken into account when interpreting the results. Due to the sampling method and the relatively small sample size, the findings of this study are a preliminary representation of the association between T2DM, hypothyroidism, antidiabetic therapy, and thyroid cancer. In conclusion, this study provides preliminary evidence on the impact of T2DM, types of antidiabetic therapy, and hypothyroidism on thyroid cancer, and is a good basis for further research. However, future prospective studies with a larger number of patients are expected to achieve stronger statistical significance and confirmation of the obtained results.

Conflict of interest

The authors declare that there was no conflict of interest.

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Sažetak

POVEZANOST DIABETES MELLITUSA TIP 2, HIPOTIREOZE I KARCINOMA ŠTITNJAJE

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Cilj ove studije je bio ispitati povezanost diabetes mellitusa tip 2 (T2DM), antidijabetičke terapije, hipotireoze i karcinoma štitnjače. Analizirani su podaci od 320 pacijenata koji su operirani zbog sumnje na karcinom štitnjače. Dijagnoza karcinoma štitnjače je potvrđena patohistološkom analizom kod 95 pacijenata. Nije nađena značajna razlika u prisutnosti dijagnoze T2DM i hipotireoze u odnosu na prisutnost karcinoma štitnjače ($p=0.13$; $p=0.85$), kao niti u spolu ispitanika s T2DM i hipotireozom s obzirom na tip karcinoma štitnjače ($p=0.19$; $p=0.25$). Pacijenti s T2DM (Odds ratio [OR] 1.89; 95% CI, 0.856–4.163) i pacijenti s hipotireozom (OR, 1.05; 95% CI, 0.530–2.164) su imali veću vjerojatnost od karcinoma štitnjače, kao i ispitanici koji su imali obje dijagnoze u kombinaciji ($p=0.37$; OR, 2.39; 95% CI, 0.333–17.278), u odnosu na pacijente koji nemaju te dijagnoze. Muškarci s T2DM (OR, 6.19; 95% CI, 1.180–32.513) su imali veću vjerojatnost od karcinoma štitnjače od žena. Veću vjerojatnost od karcinoma štitnjače imali su pacijenti koji uzimaju peroralne antidijabetike (OR, 1.91; 95% CI, 0.804–4.512) u odnosu na one koji uzimaju inzulin. Prema rezultatima ove studije možemo zaključiti da postoji povezanost T2DM, hipotireoze, peroralnih antidijabetika i karcinoma štitnjače.

Ključne riječi: *diabetes mellitus tip 2; hipotireoza; karcinom štitnjače*