# Type 2 Diabetes, Obesity and Their Relation to the Risks of Thyroid Cancer

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**Summary**

Objective: patients with type 2 diabetes (T2DM) and obesity are generally known to have increased risk of various types of cancer, though studies addressing associations between T2DM/obesity and thyroid cancer are inconclusive. The aim of our study was to evaluate the risk of thyroid cancer focusing on diabetic patients under conditions of euthyroid status. A retrospective study in 184 patients was performed. Three cohorts were established according to tumor histology: malignant (M), benign (B) and low-risk carcinoma (MB). Fisher's exact test and Kruskal-Wallis one-way ANOVA of ranks were used for statistical analysis. The M (39.1 %), B (57.6 %) and MB (3.3 %) cohorts had comparable age (p=0.4), BMI (p=0.452), glycaemia (p=0.834), Hb1AC (p=0.157) and HOMA-IR (p=0.235). T2DM patients had larger thyroid gland volumes (28.8 vs 17.6 mL;p=0.001) compared to the cohort with normal glucose tolerance. Compared to women, men had more frequently present distal metastases (p=0.017), minimally invasive disease (p=0.027), more advanced staging (p=0.01) and positive pathogenic mutations in the TERT gene (p=0.009);these results were also significant for the diabetic male cohort (p=0.026). Type 2 diabetes and obesity are not risk factors for thyroid cancer, but a subgroup of males seems to have thyroid cancers of poorer prognosis. In general, diabetic patients with insulin resistance and hyperinsulinemia are also prone to have a goiter.

**Key words**

Thyroid cancer • Type 2 diabetes • Obesity • Thyroid nodule • Insulin resistance

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## Introduction

Cancer is a leading cause of mortality and morbidity, and the prevention of type 2 diabetes and obesity may also reduce the burden of cancer. Unfortunately, the relationships between T2DM, obesity and thyroid cancer are unclear. Thyroid cancer is a relatively rare cancer, with an incidence from 1-5.3 % of all malignancies. However, it represents the most common malignancy originating from the endocrine organs. Thyroid cancer is most frequently diagnosed among people aged 40-59 years old. Thyroid cancer incidence rates in the United States increased during the years 2000–2014, but declined from 2014–2018, especially for papillary thyroid cancers (PTC) [1]. Nevertheless, mortality due to thyroid cancer continued to increase, particularly for PTC >2 cm and for distant disease. These findings suggest that changes in practice patterns may have led to the overdiagnosis of small indolent tumors but have not affected the incidence of more advanced tumors [1].

Therefore, secondary causes of these trends in thyroid cancer have been suggested, in particular type 2 diabetes (T2DM) and obesity [2, 3]. Obesity is a major risk factor of T2DM in both sexes, and it is not surprising that the prevalence patterns of T2DM across regions resemble those of obesity. Obesity has rapidly become a global pandemic health problem, especially in the USA and Europe where 35 % and 20 % of the population, respectively, are obese [4]. The global prevalence of

diabetes in 2017 was 8.8 % with a further increase expected to 9.9 % by the year 2045, nearly 90 % of which was T2DM [5-7].

Epidemiological studies have consistently reported that individuals who are either overweight or obese are at an increased risk of thyroid cancer, but the results have been inconsistent for diabetic patients. However, patients with diabetes have an approximately 20-25 % higher risk of cancers in general. Both obesity and type 2 diabetes are characterized by insulin resistance, hyperinsulinemia and the overproduction of other growth factors [8, 9].

The prevalence of thyroid disease in diabetes mellitus has been estimated to be 10.8 %, compared to 6.6 % in non-diabetic populations. The evidence is even more clear for type 1 diabetes that is accompanied by autoimmune predispositions, with a prevalence of autoimmune thyroiditis in type 1 diabetes of up to 17-30 %. The situation is different for type 2 diabetics, with hypothyroidism the most common form of thyroid disease. In particular, subclinical hypothyroidism is higher (1.93-fold increase) in T2DM patients vs. healthy controls [10]. However, subclinical hypothyroidism might be overestimated [11]. The prevalence of hyperthyroidism in T2DM patients has also been found to be higher by 4.4 % than in the general population [10]. Toxic multinodular goiter is a more frequent cause of hyperthyroidism also due to the aging of the T2DM population. Regarding the effects of insulin on the thyroid gland, high circulating levels of insulin may induce increased thyroid proliferation with the development of larger thyroid volume and the formation of nodules [10-12].

The inconclusive evidence on relationships between diabetes and thyroid disease is reflected in the various recommendations by professional societies. The guidelines of the American Diabetes Association recommend screening thyroid function in patients with type 1 diabetes annually [13]. However, there is lack of definitive guidance on the screening of thyroid dysfunction in T2DM. The European Thyroid Association recommends thyrotropin hormone (TSH) measurement in case of inexplicable glucose excursions, while the American Thyroid Association proposes TSH level be assessed at the onset of T2DM and then repeated at 5-year intervals, and the American Diabetes Association suggests neck palpations in all diabetic patients and measurements of TSH in patients > 50 years old and with presented dyslipidemia [14-16]**.** However, current guidelines do not specifically address the screening of thyroid function in T2DM [10]. Furthermore, some authors recommend thyroid cancer screening in diabetics and obese patients due to more advanced thyroid cancers in this population [17]. And finally, screening for type 2 diabetes has been proposed for patients having undergone thyroidectomy for thyroid cancer, even at ages younger than 45 years, because subsequent thyroid-stimulating hormone suppression can have detrimental effects on glucose homeostasis [17, 18].

In our cohort retrospective study, we explored whether the presence of thyroid cancer compared to benign results confirmed by histology is more common in diabetic and/or obese patients. In other words, we asked if diabetic or obese patients are at a higher risk of developing thyroid cancer. A further objective of our study was to assess and characterize thyroid disease in patients with T2DM.

## Materials and Methods

The protocol of this retrospective cohort study complied with the Declaration of Helsinki and was approved by the ethical committee of the Institute of Endocrinology. 894 patients were enrolled with diagnosis codes ICD-10 E89.0 and C73. Of these, 710 patients were excluded due to non-fulfilment of the study criteria. The reasons for study exclusion were mostly incomplete patient's records and screening of diabetes was not done under euthyroid status. For more details see Figure 1.

Patient histories, neck ultrasounds (US), and biochemical and molecular testing were done at the Institute of Endocrinology and Internal Medicine Department, University Hospital Kralovske Vinohrady. The records of the 184 patients enrolled into the study were obtained from these two centers: an institutional and hospital database from 1997-2023. The lab testing was done before thyroid surgery, and glucose metabolism was only investigated during states of euthyroidism within the same year the thyroid surgery was performed. Patients with a negative history of prediabetes or diabetes were screened following the standards of the American Diabetes Association and the European Association for the Study of Diabetes [19]. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated in only 54 patients, because C-peptide levels were not available. The following formula was used: HOMA-IR=(fasting C-peptide (nmol/l)×fasting glucose (mmol/l)/22.5). The HOMA estimates steady state beta cell function ( % B;

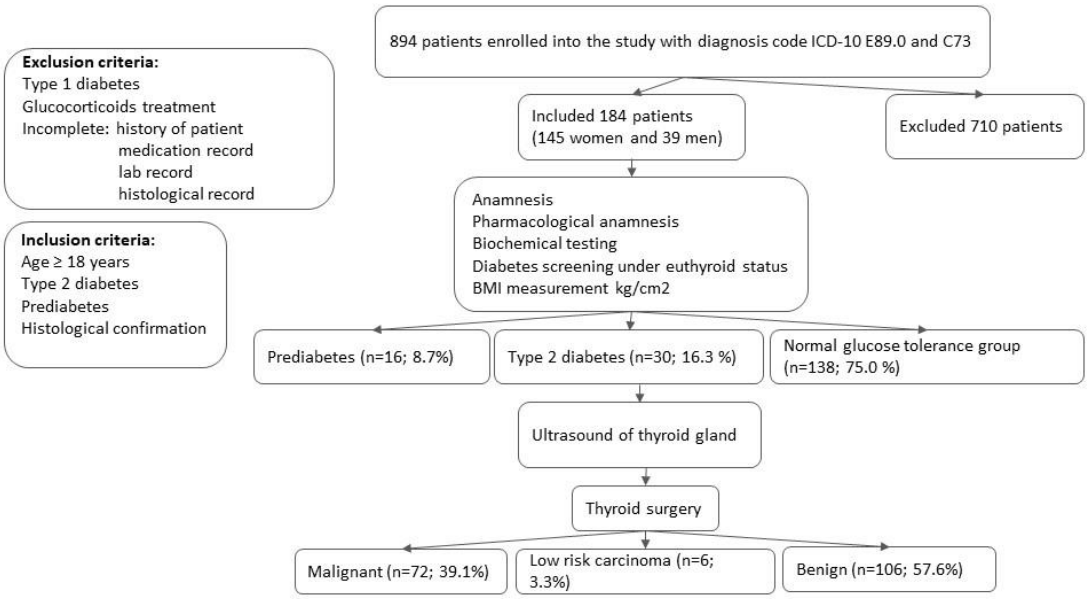


**Fig. 1.** Flow chart of the study.

HOMA-B) and insulin sensitivity ( %S;HOMA-S), as percentages of a normal reference population [20]. Antidiabetic treatment data were not assessed. The body mass index (BMI), calculated as the ratio of weight in kilograms to height in meters squared (kg/m$^2$), was categorized as follows: normal weight (BMI ≤ 24.9 kg/m$^2$), overweight (BMI 25.0– 29.9 kg/m$^2$), and obese (BMI ≥ 30.0 kg/m$^2$). Diagnosis of autoimmune thyroid disease (AITD) was based on positive thyroid autoantibodies and/or the hypoechogenic pattern typical for AITD during the ultrasound examination.

Ultrasound of the thyroid was performed in all patients (frequency of 12.5 MHz on a Phillips Epiq5) and if indicated fine needle aspiration biopsy (FNA) was performed. DNA and RNA molecular testing from FNA samples were done in 33 patients. More details on the procedure are described in our previous study [21]. Over time, we established testing procedures mainly in samples evaluated as Bethesda categories III and above. First, we analyzed DNA for the most common mutation *V600E* in the *BRAF* gene using allele specific Real Time PCR (LC480, Roche). *BRAF*-positive samples were screened for *TERT* mutations using direct sequencing (CEQ 8000, Beckman Coulter). *BRAF*-negative samples were analyzed by next generation sequencing using the Thyro-ID panel (MiSeq, Illumina, San Diego, CA, USA) examining other 12 genes (*BRAF, HRAS, KRAS, NRAS, TERT, AKT1, EGFR, TP53, PTEN, PIK3CA, CDKN2A, NOTCH,* and *CTNNB1)*. The samples that were negative in the NGS panel were subjected to detection of 23 fusion genes including *ALK*, *BRAF*, *GLIS*, *NTRK1*, *NTRK3*, *PPARG* and *RET* genes.

All 184 patients underwent thyroid surgery, and according to histology were divided into cohorts of benign (B), malignant (M), and low-risk (MB) carcinomas. Basal blood samples were taken, and serum thyrotropin (standard range 0.270-4.200 mUI/L), fT4 (12.00-22.00 pmol/l), fT3 (3.10-6.80 pmol/l) and C-peptide (268-1274 pmol/L) concentrations were measured using the ECLIA method (Roche). The HbA1C (20.0-42.0 mmol/mol) test was performed using an ion exchange HPLC method. Serum anti-Tg (0.01-120 IU/mL) and anti-TPO (0.01-40 IU/mL) were measured by ELISA (Aeskulisa). Glucose (3.9-5.6 mmol/L) was measured by a spectrophotometry (UV)-hexokinase method.

Kruskal-Wallis One-Way ANOVA on Ranks with medians and their 95 % confidence intervals (95 % CI) was used to compare measurements across cohorts. Due to the small number of probands, prediabetic and diabetic patients were merged for the statistical analysis, and the same method was used to compare this prediabetic/2 type diabetic group with the normal glucose tolerance group. Fisher's Exact 2-Sided test was performed to determine if there were any non-random associations between two categorical variables. NCSS 2019 Statistical Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss was used, with statistical significance set for p-values <0.05.

## Results

The study included 184 patients (145 women and 39 men) who were divided into the following cohorts: 72 patients (M;39.1 %) were malignant, 6 patients (MB;3.3 %) had a low-risk carcinoma, and 106 patients (B;57.6 %) were benign. The age of probands was comparable between cohorts M, B and MB: median age 53 years in cohort M, 53 years in cohort B, and 46 years in cohort MB (p=0.4). Papillary thyroid carcinoma (PTC) was the most common histotype in 55 patients (76.4 %), follow by 5 medullary thyroid carcinomas, 4 oncocytic carcinomas, 3 anaplastic carcinomas, 2 follicular carcinomas, 2 poorly differentiated carcinomas and 1 metastasis of a fibrous carcinoma. In the group of PTC ten incidentalomas were identified with a maximum diameter of 7 mm;6/10 incidentalomas were detected in the prediabetes/type 2 diabetes group (PDM/T2DM)(p=0.024). In the low risk-carcinoma group there were 3 thyroid tumors of uncertain malignant potential, 2 non-invasive follicular thyroid neoplasms with papillary-like nuclear features, and 1 hyperplasia of C-cells.

Prediabetes was present in 16 patients and type 2 diabetes in 30 patients. Thyroid cancer was detected in 20 PDM/T2DM patients in comparison to 52 in normal glucose tolerance group (20/46 vs. 52/138;p=0.637);with a majority being low-risk carcinoma (stage I (n=15);stage II (n=1);stage III (n=0), stage IV (n=4)) in PDM/T2DM.

Multinodular thyroid gland (MNG) was present in 89 patients (48.4 %) and autoimmune thyroid disease (ATD) in 73 patients (39.7 %). There were not any significant differences in the incidence of MNG (p=0.156) and ATD (p=0.746) between the M, B and MB cohorts. MNG was present more often in men (p=0.042) and we did not observe any significant difference between diabetic and non-diabetic cohorts (p=0.263). More detailed characteristics of the cohorts with medians are given in Table 1.

**Table 1** Detailed characteristics of the benign (B), malignant (M) and low-risk carcinoma (MB) cohorts.

| Variable | B | M | MB | p-value all cohorts | p-value benign vs. malignant |
|---|---|---|---|---|---|
| | 107 | 71 | 6 | | |
| *Women/Men* | 86/21 | 51/20 | 5/1 | | |
| *Age (years)* | 53 (43, 63.5) | 53 (39, 65.5) | 46 (40.5, 47) | 0.400 | 0.832 |
| *Thyroid nodule size (mL)* | 2.8 (0.8, 15.1) | 1.9 (0.19, 8.63) | 2.36 (0.68, 4.71) | 0.073 | 0.026 |
| *Thyroid size (mL)* | 20.2 (13.3, 34.8) | 18.9 (12, 31.5) | 15.1 (12.9, 18.3) | 0.324 | 0.297 |
| *Thyrotropin (mUI/L)* | 0.95 (0.07, 2.21) | 1.86 (1.12, 2.87) | 1.27 (0.91, 1.94) | <0.001 | <0.001 |
| *Free thyroxine (pmol/L)* | 16.3 (14, 20.2) | 15.2 (14, 17.3) | 14.8 (13.9, 16.9) | 0.076 | 0.028 |
| *anti-tpo (mUI/L)* | 28 (4.14, 63.3) | 28 (5.98, 193) | 38 (36, 153) | 0.259 | 0.318 |
| *anti-tgl (mUI/L)* | 12 (1.26, 23.1) | 15.4 (5.21, 35.1) | 14.8 (8.05, 14.9) | 0.134 | 0.059 |
| *Glucose (mmol/L)* | 5.3 (4.95, 5.61) | 5.3 (4.9, 5.6) | 5.18 (5, 5.31) | 0.834 | 0.652 |
| *C-peptide (pmol/L)* | 830 (703, 1200) | 810 (471, 1120) | 325 (262, 552) | 0.130 | 0.562 |
| *Hb1AC (mmol/mol)* | 39 (35.8, 43.1) | 37 (34, 39) | 47.5 (39.8, 55.3) | 0.157 | 0.052 |
| *HOMA- IR* | 1.96 (1.57, 2.74) | 1.8 (1.14, 2.5) | 0.71 (0.58, 1.46) | 0.235 | 0.682 |
| *HOMA B%* | 118 (93.2, 131) | 104 (83.4, 138) | 49.5 (42.1, 63.1) | 0.039 | 0.936 |
| *HOMA S%* | 51.3 (36.4, 64) | 55.8 (40, 91.4) | 140 (92.8, 182) | 0.216 | 0.532 |
| *BMI (kg/m$^2$)* | 26.4 (23.3, 31) | 26.5 (22.8, 30) | 23.9 (23.3, 25.3) | 0.452 | 0.391 |

Statistics was determined by Kruskal-Wallis One-Way ANOVA on Ranks with medians (CI 95 %);statistical significance was set for p-values <0.05. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated in only 54 patients, because C-peptide levels were not available.

**Table 2.** Detailed characteristics of the cohorts of prediabetes (PDM) and type 2 diabetes (T2DM) compared to normal glucose tolerance group (NGT).

| Variable | NGT | PDM+T2DM | p-value |
|---|---|---|---|
| | 138 | 46 | |
| *Men/Women* | 26/112 | 16/30 | 0.472 |
| *Age (years)* | 48 (38.3, 59) | 63.5 (56.3, 69.8) | <0.001 |
| *Thyroid nodule size (mL)* | 2.17 (0.5, 8.68) | 6.15 (0.575, 16.9) | 0.070 |
| *Thyroid size (mL)* | 17.6 (12.4, 27.4) | 28.8 (16.4, 46.4) | 0.001 |
| *Thyrotropin (mUI/L)* | 1.36 (0.418, 2.44) | 1.58 (0.709, 2.38) | 0.342 |
| *Free thyroxine (pmol/L)* | 15.8 (14.1, 19) | 15.5 (13.7, 18.4) | 0.458 |
| *anti-tpo (mUI/L)* | 28 (5.03, 90.3) | 17.6 (4.38, 39.8) | 0.250 |
| *anti-tgl (mUI/L)* | 15 (2.18, 50) | 9.02 (1.2, 19.3) | 0.059 |
| *Glucose (mmol/L)* | 5.2 (4.8, 5.32) | 6.2 (5.9, 7.23) | <0.001 |
| *C-peptide (pmol/L)* | 700 (443, 831) | 1140 (795, 1450) | <0.001 |
| *Hb1AC (mmol/mol)* | 36 (34, 39.3) | 41.5 (36.9, 46.1) | <0.001 |
| *HOMA- IR* | 1.55 (1.01, 1.8) | 2.66 (2.17, 3.54) | <0.001 |
| *HOMA B%* | 110 (82.6, 136) | 106 (85, 132) | 0.767 |
| *HOMA S%* | 64.9 (55.8, 101) | 37.6 (28.4, 46.2) | <0.001 |
| *BMI (kg/m$^2$)* | 24.5 (22.5, 28.6) | 30.7 (28.1, 35.6) | <0.001 |

Statistics was determined by Kruskal-Wallis One-Way ANOVA on Ranks with medians (CI 95 %);statistical significance was set for p-values <0.05.

TSH levels were lower in the B cohort in comparison to the M and MB cohorts, respectively 0.95 vs. 1.86, 1.27 mUI/L (p<0.001). Glucose, C-peptide, HOMA-IR and HOMA-S were not different between cohorts, but HOMA-B was higher in the B cohort in comparison to other cohorts (p=0.039). As mentioned above, HOMA-IR was calculated for just 54 patients (34 in cohort B, 17 in M and 3 in MB) due to the lack of C-peptide data. Hb1ac was slightly higher in the B cohort compared to the M cohort, but this difference was not significant (39 vs. 37 mmol/mol;p=0.052). Patients in cohorts M and B had non-significantly higher BMI compared to the MB cohort (26.5 kg/m², 26.4 kg/m² and 23.9 kg/m²;p=0.452).PDM/T2DM patients were significantly older and had higher BMI values than patients with normal glucose tolerance (NGT) (age 63.5 vs. 48 years;p<0.001;BMI 30.7 vs. 24.5 kg/m²;p<0.001). PDM/T2DM patients had a larger thyroid volume compared to NGT patients (28.8 vs. 17.6 ml;p=0.001), and conversely tended to have lower levels of anti-Tg autoantibodies (p=0.059), and larger thyroid nodules (6.15 vs. 2.17 ml;p=0.07). Thyrotropin levels were comparable between PDM/T2DM and NGT patients (p=0.342). As expected, the two cohorts differed significantly in parameters of glucose metabolism. For more details see Table 2.

Compared to women, men had higher insulin resistance calculated by HOMA-IR (p=0.033), higher fasting glucose and C-peptide levels (p=0.044 and p=0.041), but glycated hemoglobin (Hb1ac) levels were comparable (p=0.159). Compared to women, men were more likely to have goiter (p<0.001), distal metastases (p=0.017), minimally invasive disease (p=0.027), advanced thyroid cancer (p=0.01), and positive TERT gene mutations (p=0.009);this was particularly true for men with PDM/T2DM (p=0.026). Males tended to be diagnosed with multinodular thyroid (p=0.053). Neck lymphadenopathy, macroscopic extrathyroidal expansion, angioinvasion and other pathological molecular investigations did not differ between males and females. For more details see Table 3.

Molecular testing revealed 37 pathological mutations in 33 available FNA samples. The most frequent mutation was the V600E mutation in the BRAF gene (n=17), followed by the C228T mutation in the TERT gene (n=4), the Q61R mutation in the NRAS gene (n=3), the Q61R mutation in the HRAS gene (n=1), the Q245 mutation in the PTEN gene (n=2), the G13D mutation in the KRAS gene (n=1), as well as mutations in the RET

**Table 3.** Detailed characteristics of women and men.

| Variable | Women | Men | p-value women vs. men |
|---|---|---|---|
| | 142 | 42 | |
| *Age (years)* | 53 (41, 63.8) | 52.5 (42, 65.5) | 0.739 |
| *Thyroid nodule size (mL)* | 2.17 (0.5, 8.63) | 4.1 (0.475, 28) | 0.063 |
| *Thyroid size (mL)* | 17.8 (10.8, 28.5) | 30 (16.3, 47.1) | <0.001 |
| *Thyrotropin (mUL/l)* | 1.35 (0.513, 2.44) | 1.64 (0.572, 2.38) | 0.996 |
| *Free thyroxine (pmol/L)* | 15.9 (14.1, 18.8) | 15.2 (13.4, 19.3) | 0.458 |
| *anti-tpo (mUI/L)* | 28 (3.58, 95.2) | 28 (18, 52) | 0.204 |
| *anti-tgl (mUI/L)* | 15 (2.29, 39.4) | 15 (1.3, 22.5) | 0.581 |
| *Glucose (mmol/L)* | 5.26 (4.91, 5.54) | 5.32 (5.15, 6.23) | 0.044 |
| *C-peptide (pmol/L)* | 756 (516, 1120) | 937 (747, 1660) | 0.041 |
| *Hb1AC (mmol/mol)* | 38 (34, 41) | 38 (36.5, 44) | 0.159 |
| *HOMA- IR* | 1.77 (1.18, 2.51) | 2.32 (1.73, 4.15) | 0.033 |
| *HOMA B%* | 114 (81.9, 134) | 98.8 (91.5, 133) | 0.875 |
| *HOMA S%* | 58.9 (39.8, 89.4) | 43.3 (24.1, 57.9) | 0.026 |
| *BMI (kg/m$^2$)* | 25.6 (22.6, 30.1) | 27.6 (25, 30) | 0.052 |

Statistics was determined by Kruskal-Wallis One-Way ANOVA on Ranks with medians (CI 95 %);statistical significance was set for p-values <0.05.

(n=2), and AKT1 (n=1) genes. Several gene rearrangements were also detected, namely TPM3/NTRK1 (n=1), RET/PTC1 (n=2), EML4/ALK (n=1), ETV6/NTRK3 (n=2). Two mutations were detected in two patients (TERT+BRAF;TERT+RAS), and three mutations or rearrangements were detected in two patients (TERT+BRAF+AKT1;KRAS+NRAS+RET/PTC1).

## Discussion

In our study, we did not find evidence that patients with T2DM and/or obesity are at higher risk of being diagnosed with thyroid cancer. However, we did find that T2DM patients are at risk of developing a goiter, probably due to the disorder of glucose metabolism itself and not thyrotropin stimulation. In general, men are diagnosed with more advanced thyroid cancer compared to women, and these males with poorer prognosis regarding thyroid cancer tend to also have diabetes.

In the period from 1998 to 2014, rapid increases in the incidence of thyroid cancer have been observed, especially for papillary thyroid cancer, which is more likely to be found in a subclinical form and therefore detected by intense scrutiny of the thyroid gland [22]. This is supported by autopsy studies that have found the presence of differentiated thyroid carcinomas ("incidentaloma") in 8.5 % of patients [23]. For this reason, we believe that it is crucial to compare benign and malignant tumors confirmed by histology. In our study, incidentalomas, especially papillary microcarcinoma with maximum diameter 7 mm, were identified in 13.8 % of all thyroid cancers, and 60 % of incidentalomas were significantly detected in PDM/T2DM patients.

There is evidence of a robust association between patients with type 2 diabetes and an increased risk of common cancers, i.e. pancreatic, endometrial, breast, colorectal, and hepatocellular [24, 25, 26], with the risk of all cancers 16 % higher than the expected cancer incidence in the general population [27]. The analysis of Goto *et al.* 2020 provided evidence that the genetic mechanisms responsible for T2DM may not play major roles in cancer development [28]. Nevertheless, plausible biologic pathways linking diabetes to thyroid cancer risk include: 1) chronic thyrotropin stimulation;2) hyperinsulinemia and insulin resistance;(3) antidiabetic medication;4) concomitant increased body mass index (BMI) in the majority of diabetics, which has been in general associated with increased risk for malignancies, and (5) chronic glucose exposure [29, 30].

Rapp *et al.* 2006 performed a population-based prospective cohort study investigating relationships between fasting blood glucose and the incidence of cancer. Slightly positive associations with glucose values >5.3 mmol/l were noted for thyroid cancer;HRs of 1.34 (95 %

CI 0.66-2.72) in women and 1.24 (0.65-2.37) in men. Surprisingly, several cancers were also positively associated with low fasting blood glucose levels (2.2–4.1 mmol/l), including thyroid cancers in women;however, estimates were not statistically significant [31]. In our study, the B, M and MB cohorts were comparable in glucose levels;respectively 5.3, 5.3 and 5.18 mmol/L (p=0.834).

There have been many studies, mostly large-scale and employing meta-analyses, addressing the issue of diabetes and the risk of developing thyroid cancer. These studies have very conflicting results, with limited statistical significance between differentiated thyroid cancer risk and diabetes. Further, these studies have contrasting results in female and male populations. Although thyroid cancer typically occurs about three times more frequently in women than in men in the United States, rates of diabetes in men and women in the United States are similar [32-34]. The increased thyroid cancer risk varies even among patients with different kinds of diabetes mellitus, being 34 %, 30 %, and 51 % in patients with type 1 diabetes, gestational diabetes, and T2DM, respectively [35]. In addition, these analyses are considerably limited by the reliance on self-reported data. In our previous study, 33 % of patients with T2DM and especially PDM were newly diagnosed by our screening [36]. Data from the US has clearly shown that diabetes mellitus may be frequently undiagnosed;35 % of adults >20 years of age and 50 % of those >65 years of age may have prediabetes [37]. The study by Fang et al 2018 examined cancer risks for a total of 51,324 registered cancer-free individuals that had been newly diagnosed with T2DM. Within 1 year following the onset of diabetes onset, women with T2DM had a higher risk of thyroid cancer. The results suggest that T2DM patients are at a higher risk of certain cancers;this risk particularly increases shortly after diabetes diagnosis, which is likely due to detection bias caused by increased visits to medical institutions [38]. Our study results concur with these conclusions: PDM/T2DM were present in 25 % of all patients, which is higher than in the general population.

We did not observe an increased risk of thyroid cancer in our diabetic patients. Further, the cohort of prediabetic and diabetic patients are those with the most expressed insulin resistance and hyperinsulinemia, and thus have larger thyroid glands and tendency to have larger thyroid nodules, which could lead to earlier thyroid cancer manifestation and detection. In contrast, the cohort with proven thyroid cancer had smaller thyroid nodules compared to diabetic patients with typical goiter.

We also observed larger thyroid glands and a tendency to have larger thyroid nodules in men compared to women. Furthermore, men tended to be diagnosed with more advanced thyroid cancer, often characterized by unfavorable mutations such as in TERT. These males with high-risk thyroid carcinoma had more often diabetes. We have to emphasize that the sample size was very small, making definitive conclusions impossible.

Insulin resistance with hyperinsulinemia likely leads to thyroid growth, and we suppose that the thyroid growth trigger is general to thyroid tissue and not just to single thyroid nodules. We do not suggest, however, that chronic thyrotropin stimulation is the crucial cause of goitrogenesis. This is even though our B cohort had significantly lower TSH levels (p<0.001) than the M cohort, as TSH values were on average in the normal range in all cohorts and the B cohort had even larger thyroid nodules (p=0.026).

We also focused attention on assessing any glucose disorders during euthyroidism, because both hypo and hyperthyroidism have detrimental effects on optimal glucose tolerance. A recent study by Roh *et al.* 2022 showed that patients with thyroid cancer who underwent thyroidectomy were more likely to develop T2DM than the matched controls. There was a U-shaped dose-dependent relationship between the levothyroxine dosage and T2DM risk. TSH levels were not accessible in Roh *et al.* 2022 study, but it can be hypothesized that these patients could be over or underdosed [16].

Patients with insulin resistance have a higher prevalence of thyroid nodules. A study by Rezzónico et al 2009 showed that patients with thyroid cancer are more insulin resistant (p<0.001) with a positive association between insulin resistance and BMI. Those results could have been influenced by TSH suppressive medication, and only 40 probands were involved in the study [39]. We were able to calculate insulin sensitivity by the HOMA-IR index just in 54 patients, with glucose metabolism testing done under euthyroidism. We did not observe any significant differences between HOMA-IR and HOMA S % parameters between our B, M and MB cohorts, except for lower HOMA B % in the MB cohort (p=0.039). HOMA B % expresses the beta cell secretory capacity, and the higher the value, the more insulin the beta cells have to secrete to respond to blood glucose levels. Our MB cohort was younger and more insulin sensitive than the B and M cohorts, which explains the lower HOMA B % levels in the MB cohort. We must also emphasize that the number

of patients in our MB cohort was very small.

More than half of diabetic subjects are middle aged, and the incidence rises with increasing age in both sexes [40]. In contrast, new cases of thyroid cancer represent just 2.2 % of all new cancer cases, with a median age at diagnosis of 51 years, peaking at age of 45-54 (21.6 %) https://seer.cancer.gov/statfacts/html/thyro.html). From this point of view, we suggest that trends of T2DM incidence compared to thyroid cancer are diverged. Also, in our study the age of patients diagnosed with thyroid cancer peaked at 53 years in comparison to T2DM at 63.5 years old.

An extensive review published a few years ago estimated that 20 % of all cancers might be caused by obesity [41]. The prevalence patterns of obesity resemble those of T2DM. In addition to cancer risk, obesity is associated with more aggressive pathological tumor features and worse outcomes in patients with breast, ovarian, prostate, and colorectal cancers [42]. The relationship between obesity and thyroid cancer is uncertain, however. Although a positive association between obesity and thyroid cancer risk has been observed in women in several case–control and prospective studies [43, 44], not all studies have agreed, and the results are even less consistent in men [45]. In a study by Dieringer *et al.* 2015 in an age-related subgroup analysis, a higher BMI was correlated with more lymph node involvement ($p = 0.004$), lymphatic invasion ($p = 0.003$) and tumor multiplicity ($p = 0.008$) in patients ≥45 years of age. Interestingly, when the patients were stratified according to age, those 45 years old or older showed a significant relationship between BMI and clinicopathological features, but those younger than 45 years did not [17]. Another meta-analysis on 35,237 patients supported those results, with more pronounced associations as BMI increased [46]. However, in the case of thyroid cancer, great heterogeneity exists between studies regarding potential associations between obesity and clinicopathological characteristics. In our study we did not observe any significant differences in BMI between the B, M and MB cohorts ($p=0.452$). As we already mentioned, diabetic males seem to present with more advanced thyroid cancer, and these males are on average obese.

To the best of our knowledge, there are no similar studies comparing benign, malignant, and low-risk thyroid tumors regarding prediabetes, type 2 diabetes and obesity as the risk factors. We can not compete with the large-scale studies in sample size, but there are often biases in the way information is obtained and recorded in comparison to small trials [47]. In our retrospective cohort study, we devoted great attention to collecting all available data and at the same time point from medical, pharmacological and laboratory reports. Therefore, the benefits of our study are detailed medical histories combined with laboratory testing including molecular genetics and screening of diabetes, along with the gold standard of histological confirmation. Furthermore, glucose metabolism was determined under euthyroidism, so we could exclude the undesirable effects of hypo/hyperthyroidism. We did not use any questionnaires and/or self-reported data due to their lower reliability. Considering the limitations of our study, the retrospective design could have introduced some biases in data collection. The risk of selection bias was reduced by collecting data from two centers and the patients were chosen randomly regarding available glucose metabolism data. Further there was just a small sample of patients for evaluating HOMA-IR due to the low availability of C-peptide levels. Similarly, molecular testing was not performed in all patients according to Bethesda cytological groups, because FNA samples for molecular testing were not accessible in all cases.

## Conclusions

In conclusion, while aging increases the chance of becoming diabetic and/or obese, our data generally do not support the hypothesis that patients with prediabetes/type 2 diabetes and obesity are at a higher risk of thyroid cancer. However, these patients are at higher risk to have a goiter. In contrast, it seems that a subgroup of males with type 2 diabetes are at risk of being diagnosed with more progressive thyroid cancer. Insulin resistance with hyperinsulinemia could be a more potent candidate for thyroid growth stimulation compared to stimulation by thyrotropin or autoimmune thyroid disease in these patients. We suppose that particular attention should be given to males with metabolic disturbances. Further studies are needed to confirm our results, but we believe that our study can partly explain the heterogeneity found in previous studies.

## Conflict of Interest

There is no conflict of interest.

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