RESEARCH

Relation of prediabetes and type 2 diabetes mellitus to thyroid cancer

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Abstract

Objective: Patients with type 2 diabetes (T2DM) generally experience a higher incidence of cancer. However, the association between T2DM and thyroid cancer is inconclusive.
Methods: Case-control prospective study, where 722 patients were screened for T2DM and prediabetes (PDM) and underwent thyroid ultrasound and biochemical tests. The patients were assigned to groups of PDM ($n = 55$), T2DM ($n = 79$) or a non-diabetes group (NDM) ($n = 588$). Fine-needle aspiration biopsy was carried out in 263 patients. Histological examinations were done for 109 patients after surgery, with findings of 52 benign (BS) and 57 malignant tumors (MS).
Results: Thirty-three percent of patients with T2DM and especially PDM were newly diagnosed by our screening: 6.5% with T2DM and 72% with PDM, respectively. The percentage of thyroid cancers did not significantly differ between the groups (χ^2 test = 0.461; $P = 0.794$). Relevant positive thyroid predictors for T2DM (t-statistic = 25.87; $P < 0.01$) and PDM (21.69; $P < 0.01$) contrary to NDM (–26.9; $P < 0.01$) were thyroid volume (4.79; $P < 0.01$), thyroid nodule volume (3.25; $P < 0.01$) and multinodular thyroid gland (4.83; $P < 0.01$), while negative relevant predictors included the occurrence of autoimmune thyroid disease (AITD) (–2.01; $P < 0.05$).
Conclusion: In general, we did not observe an increased risk for thyroid cancer in the diabetic and prediabetic groups in comparison to controls, in spite of well-established increased risk for other malignancies. Structural and benign changes such as larger and multinodular thyroid glands, in comparison to autoimmune thyroid disease, are present more often in diabetics.

Key Words
- prediabetes
- type 2 diabetes mellitus
- insulin resistance
- obesity
- thyroid disease
- thyroid cancer

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Introduction

Thyroid cancer (TC) is a relatively rare cancer, with an incidence from 1 to 5.3% of all malignancies, but it represents the most common malignancy originating from the endocrine organs. The most common TCs are differentiated carcinomas, with majority being papillary carcinomas (PTC), especially micropapillary carcinoma (PMTC). TC is more frequent in women than in men and it is currently the third most common cancer in women under the age of 45 in highly developed countries (1, 2, 3). In spite of its striking increase of incidence in both men and women, the mortality rate for thyroid cancer has not changed and has remained low (women 3%; men 5%). Nevertheless, in some studies, mortality is increased in ≥40 years-old age groups, and annual mortality has increased by 1% in men by 3% for advanced PTC (1974–2013). An increase of larger TC tumors (>5 cm) has also been noted (4, 5).

TC differs from other tumors in age distribution, with the most-commonly affected group patients in the

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economic productive age of 24–60 years, while in other malignancies the risk of carcinoma increases continuously with age. Therefore, secondary causes of this increase in TC incidence have been suggested. They include, briefly: (1) ionizing radiation, which is dose dependent with the highest sensitivity in childhood; however, less than 5% of all TC are associated with radiotherapy (6). (2) Environmental factors, including endocrine disrupting chemicals affecting the endocrine system, though there is lack of direct evidence in humans (7). (3) Hormonal changes especially estrogens in the reproductive period of women contribute to the higher TC incidence in women. It should be emphasized that while women are diagnosed with TC more frequently than men, in autopsy studies the female/male ratio is the same (8). (4) Autoimmune thyroid disease (AITD). Studies have produced contradictory results and AITD can even be a protective factor in TC progression (9, 10). (5) Both iodine deficiency and overconsumption have been suggested to be risk factors for TC. Obviously, follicular thyroid cancer occurs predominantly in iodine-deficient countries in comparison with PTC in iodine-sufficient countries (11). (6) Familial non-medullary thyroid carcinoma, which with a 3–10% prevalence is more frequent in comparison with other tumors (12). (7) TC incidence may have also been increased due to better TC detection ('overdiagnosis') depending on the numbers of physicians providing ultrasound and ultrasound-guided fine-needle aspiration (6). Finally, and the topic of our study, (8) type 2 diabetes (T2DM), obesity and insulin resistance (IR) in the framework of the worldwide epidemic of diabetes and obesity. In general, patients with diabetes have an approximately 20–25% higher risk of cancer in comparison with patients without diabetes. Epidemiological studies have consistently reported that individuals who are either overweight or obese are at an increased risk of thyroid cancer, but the results are inconsistent for diabetic patients. Both obesity and type 2 diabetes are characterized by insulin resistance, hyperinsulinemia and the overproduction of other growth factors (13, 14). The relationship between T2DM and thyroid cancer is unclear, so in our study we explored whether the presence of diabetes affects the risk of thyroid cancer.

Materials and methods

The protocol of this study complies with the Declaration of Helsinki, and before entering the study, written informed consent was obtained from patients after they received both written and oral information. The study was approved by the ethical committee of Institute of Endocrinology. In our prospective case-control study, we included randomly 561 women and 161 men in a country with iodine sufficiency (15). The power of the sample size was established. The patients were recruited from October 2013 to February 2018. Patient history, ultrasound of neck (US), and biochemical testing were done at the Institute of Endocrinology and 2nd Department of Internal Medicine, University Hospital Kralovske Vinohrady (a secondary referral center). The patients were recruited into the study during the first appointment at the outpatient clinic (Fig. 1). These patients were recommended to our department from primary care mainly due to suspicions of thyropathy, other endocrinopathy or diabetes. Patients with negative history of prediabetes or diabetes were screened for diabetes following the standards of the American Diabetes Association and the European Association for the Study of Diabetes. Patients with prediabetes are defined by the presence of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and/or HbA1c 39–47 mmol/mol. IFG is defined as fasting plasma glucose (FPG) levels between 5.6 and 6.9 mmol/L and IGT as 2-h plasma glucose levels during a 75 g oral glucose tolerance test (OGTT) between 7.8 and 11.0 mmol/L. Diabetes may be diagnosed based on plasma glucose criteria, either using the FPG value or the 2-h plasma glucose (2-h PG) value during an OGTT, or A1C criteria. Criteria for the diagnosis of diabetes: FPG ≥7.0 mmol/L or 2-h PG ≥11.1 mmol/L during OGTT or A1C ≥6.5% (48 mmol/mol) or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥11.1 mmol/L (16, 17). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR = (fasting C-peptide (nmol/L) × fasting glucose (mmol/L)/22.5). The HOMA estimates steady state beta-cell function (%B; HOMA-B) and insulin sensitivity (%S; HOMA-S), as percentages of a normal reference population (18). Antidiabetic treatment data were not assessed in detail. However, the antidiabetic treatment was as follows: metformin 53%, intensive insulin therapy 15.2%, diet 12.1%, combination of insulin with peroral antidiabetics (PAD) 7.6%, combination of PAD 6.1%, GLP-1 analogs 3%, gliptins 1.5%, and sulfonylureas 1.5% patients.

The diagnosis of autoimmune thyroid disease (AITD) was based on positive thyroid autoantibodies and/or the hypoechogenic pattern typical for AITD during the US examination. Only 28 patients with Graves-Basedow disease were included in the study. Patients with hypo-

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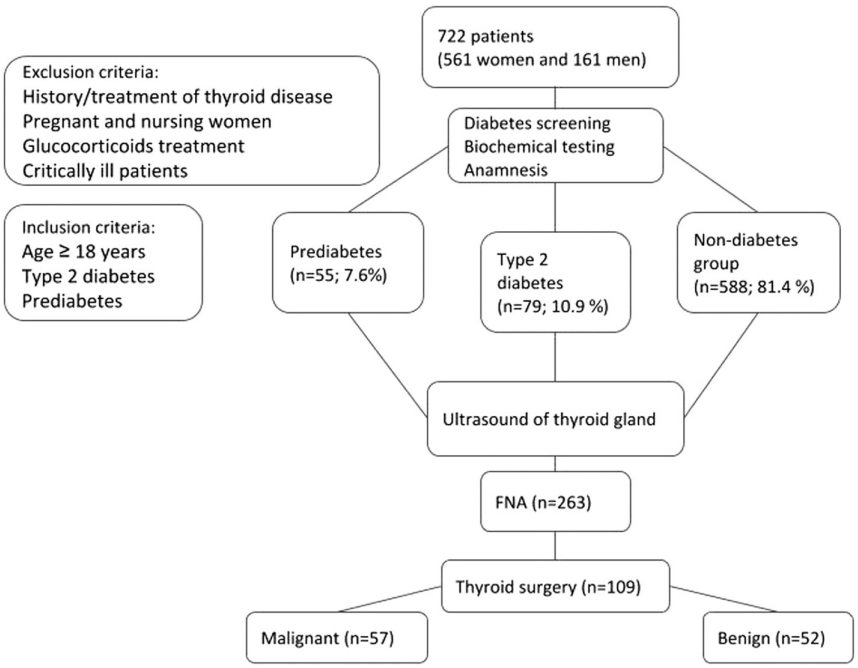

Figure 1
Flow chart of the study.

or hyperthyroidism were re-checked for glucose disorders after reaching a euthyroid state. Basal blood samples for the determination of TSH, fT4, fT3, anti-thyroid peroxidase antibodies (anti-TPO), anti-thyroglobulin (anti-Tg), thyrotropin receptor antibodies (TRAbs), calcitonin, glucose, C-peptide, and hemoglobin A1c (HbA1c) were taken.

The patients were sorted to groups of prediabetes (PDM) ($n=55$; 7.5%), type 2 diabetes (T2DM) ($n=79$; 10.9%) or a non-diabetic group (NDM) ($n=588$).

Fine-needle aspiration biopsy (FNA) was performed in 263 thyroid nodules using the pistol technique under US guidance. FNA was generally performed on thyroid nodules sized >1 cm. Thyroid nodules with suspicious US features such as hypoechogenicity, irregular or microlobulated margins, taller-than-wide, punctate echogenic foci and solid components were preferentially chosen for FNA. FNA was performed once for each thyroid nodule using a 20-gauge needle attached to a 20 mL syringe. Local anesthesia was not applied. In mixed nodules, solid areas were chosen. Aspirated material was expelled onto glass slides and sent for cytopathology examinations. May-Grünwald/Giemsa and hematoxylin and eosin stained specimens were evaluated by expert cytopathologists following the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) 2017: (1) nondiagnostic or unsatisfactory; (2) benign; (3) atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS); (4) follicular neoplasm or suspicious for a follicular neoplasm; (5) suspicious for malignancy; and (6) malignant (19). US was performed at a frequency of 12.5 MHz on a Phillips Epiq5.

By the end of the study, histological examinations had been done in 109 patients, with 57 findings being malignant (MS; 8.0%) and 52 benign (BS).

Serum TSH (0.270–4.200 mUI/L), fT4 (12.00–22.00 pmol/L), fT3 (3.10–6.80 pmol/L), TRAbs (0.30–1.75 IU/L), calcitonin (1.0–4.8 ng/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 that is certified by the NGSP (www.ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. 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.

Statistical significance was set for P-values <0.05. Two-way ANOVA consisting of factors and diagnostic group (NDM, PDM, and T2DM) as well as age group (45–59 vs >60 years of age) with interactions between these factors was used to evaluate the effects of status and age. Due to the non-Gaussian data distribution and non-constant variance in most variables, the original continuous variables were transformed by power transformations prior to further processing to attain data symmetry and homoscedasticity (20). The homogeneity and distribution

of transformed data were checked as described elsewhere (21, 22). Statistical software Statgraphics Centurion 18 from Statpoint (The Plains, VA, USA) was used for Box-Cox transformations and ANOVA testing. Kruskal–Wallis multiple comparisons with Bonferroni correction for multiplicity were used for comparisons between diagnostic groups and age groups. The importance of individual predictors to discriminate between individual groups was evaluated using multivariate regression with a reduction of dimensionality known as orthogonal projections to latent structure (OPLS) for one predicted (dependent) variable in the model (23, 24). The method is effective in coping with the problem of multicollinearity within the matrix of predictors (high intercorrelations) where ordinary multiple regression fails to correctly evaluate such data (25).

Results

The patients ($n=722$) were divided into groups of prediabetes (PDM) ($n=55$; 7.5%; age (years) medians with quartiles 67.4 (60.4–74.1), type 2 diabetes (T2DM) ($n=79$; 10.9%; age 71.8 (63–76.6) and a non-diabetes group (NDM) ($n=588$; age 48.3 (36.6–64.5), with a significant difference for age between study groups ($P<0.001$). The influence of age on the observed parameters and groups of PDM and T2DM in comparison to NDM was tested. BMI was significantly different between the study groups ($P<0.001$) and followed by a significant impact of age on BMI ($P=0.004$). Further, we observed a significant impact of age on TSH; especially, TSH level in NDM 2.02 (CI 95% 1.79–2.26) vs PDM 4.17 (CI 95% 2.5–6.91) ($P=0.028$).

In general, the PDM/T2DM group of patients had higher values of glycemia, Hb1Ac and HOMA-IR ($P < 0.001$). The patients with T2DM had larger thyroid gland volume ($P=0.007$) and higher fT4 ($P=0.011$) in comparison to NDM. In contrast, the NDM group tended to have higher levels of anti-Tg ($P=0.064$). The data are summarized in Table 1.

Thirty-three percent of patients with T2DM and especially PDM were newly diagnosed by our screening: 6.5% with T2DM and 72% with PDM, respectively. Thyroid nodule and/or multinodular thyroid gland (MNTG) were present in 66% PDM, 62% T2DM and 50% NDM patients. Fine-needle aspiration (FNA) was carried out in 263 patients. FNA Bethesda findings were: (1) ($n=20$; 9.1%), (2) ($n=170$; 76.9%), (3) ($n=12$; 5.4%), (4) ($n=7$; 3.2%), (5) ($n=6$; 2.7%), and (6) ($n=6$; 2.7%). Histological examination was done in 109 patients who underwent total thyroidectomy, with 57 findings malignant (8.0%): 43 papillary thyroid carcinomas (75.4%), 3 micromedullary thyroid carcinoma (MTC), 3 MTC, 2 anaplastic carcinoma, 1 follicular thyroid carcinoma, 1 oncocytic carcinoma, 1 metastasis and 3 poorly differentiated carcinoma. Malignant tumors according to diagnosis were 7/55 in PDM (12.7%), 9/79 in T2DM (11.4%), and 41/588 in NDM (7.0%). The percentage of malignant tumors did not significantly differ between the groups (χ^2 test = 0.461; $P=0.794$).

Relevant positive predictors for T2DM (t-statistic = 25.87; $P<0.01$) and PDM (21.69; $P<0.01$) contrary to NDM (–26.9; $P<0.01$) included thyroid volume (mL) (4.79; $P<0.01$), multinodular thyroid gland (MNTG) (4.83; $P<0.01$), thyroid nodule volume (mL) (3.25; $P<0.01$), BMI (22.47; $P<0.01$), age (16.98; $P<0.01$), smoking or history of smoking (2.61; $P<0.05$) and non-thyroid cancer (2.86; $P<0.05$), while negative relevant predictors included the occurrence of autoimmune thyroid disease (AITD) (–2.01; $P<0.05$), anti-TPO (–5.89; $P<0.01$), anti-Tg (–5.75; $P<0.01$) and fT3 (–2.86; $P<0.05$) (Table 2). Further, the relationships between the duration of PDM/T2DM and predictors were established. Due to the small number of patients in the PDM group, the PDM and T2DM groups were pooled for this analysis. Glycemia (2.67; $P<0.05$) and Hb1Ac (5.12; $P<0.01$) were positive relevant predictors for the duration of T2DM/PDM (4.52; $P<0.01$). C-peptide (–12.94; $P<0.01$), HOMA-IR (–7.85; $P<0.01$), smoking or history of smoking (–3.29; $P<0.01$) and AITD (–2.3; $P<0.05$) were negative relevant predictors for the duration of T2DM and PDM (4.52; $P<0.01$) (Table 3).

Next, the group of patients undergoing thyroid surgery was analyzed, comparing malignant ($n=57$; MS) to benign thyroid histology ($n=52$; BS). Relevant positive predictors for MS with explained variability 35.5% after cross-validation (t-statistic = 5.45; $P<0.01$) contrary to BS were TSH (4.35; $P<0.01$), anti-Tg (9.06; $P<0.01$) and FNA results (4.94; $P<0.01$), while negative relevant predictors were thyroid gland volume (–3.61; $P<0.01$) and thyroid nodule volume (–3.55; $P<0.01$). Differences between group of patients with benign and malignant thyroid tumors are described in more detail in Table 4.

The history of non-thyroid cancer (NTC) was also analyzed in the PDM, T2DM and NDM groups. Thirty percent of T2DM and 10% of PDM patients had a positive history for NTC in comparison to 8.4% of the NDM group excluding non-melanoma skin cancers. The most common types of cancers were colon, prostate, breast,

Table 1 Characteristics of the study groups. Dependence of parameters on age and status (retransformed means with 95% confidence limits).

Variable	Group			ANOVA
	NDM	PDM	T2DM	
BMI (kg/m^2)	26.2^{a,b} (25.7, 26.6)	30.4^{a} (28.4, 32.7)	31.7^{b} (30.4, 33.2)	Age: F = 3.5, *P* = 0.062, ηp2 = 0.0104; Group: F = 31.6, *P* < 0.001, ηp2 = 0.159; Age × Group F = 5.7, *P* = 0.004, ηp2 = 0.0327
Thyroid gland volume (mL)	11.7^{a} (11.1, 12.3)	12.4 (10.2, 15.5)	15^{a} (13.2, 17.2)	Age: F = 0.5, *P* = 0.477, ηp2 = 0.00123; Group: F = 5.1, *P* = 0.007, ηp2 = 0.024; Age × Group F = 0.1, *P* = 0.928, ηp2 = 0.000364
Thyroid nodule volume (mL)	0.5 (0.4, 0.7)	0.5 (0.1, 1.5)	1.0 (0.51, 2.0)	Age: F = 1.3, *P* = 0.262, ηp2 = 0.00301; Group: F = 1.1, *P* = 0.345, ηp2 = 0.00507; Age × Group F = 1, *P* = 0.37, ηp2 = 0.00475
TSH (mIU/L)	2.02^{a} (1.79, 2.26)	4.17^{a} (2.5, 6.91)	2.06 (1.57, 2.68)	Age: F = 8.5, *P* = 0.004, ηp2 = 0.0206; Group: F = 2.7, *P* = 0.066, ηp2 = 0.0134; Age × Group F = 3.6, *P* = 0.028, ηp2 = 0.0176
fT4 (pmol/l)	14.5^{a} (14.2, 14.7)	14.6 (13.4, 15.9)	15.6^{a} (15, 16.3)	Age: F = 0.5, *P* = 0.489, ηp2 = 0.00134; Group: F = 4.5, *P* = 0.011, ηp2 = 0.0247; Age × Group F = 0.1, *P* = 0.874, ηp2 = 0.000748
fT3 (pmol/l)	4.66 (4.58, 4.73)	4.74 (4.44, 5.05)	4.82 (4.62, 5.02)	Age: F = 4.1, *P* = 0.045, ηp2 = 0.0167; Group: F = 0.9, *P* = 0.406, ηp2 = 0.00753; Age × Group F = 0.8, *P* = 0.474, ηp2 = 0.00622
anti-TPO (IU/mL)	0.92 (0.77, 1.09)	0.68 (0.20, 1.39)	0.48 (0.22, 0.78)	Age: F = 0.3, *P* = 0.617, ηp2 = 0.0006; Group: F = 2.4, *P* = 0.09, ηp2 = 0.0115; Age × Group F = 0.5, *P* = 0.601, ηp2 = 0.00243
anti-Tg (IU/mL)	0.40^{a} (0.34, 0.48)	0.27 (0.05, 0.56)	0.19^{a} (0.08, 0.33)	Age: F = 0.8, *P* = 0.371, ηp2 = 0.00191; Group: F = 2.8, *P* = 0.064, ηp2 = 0.013; Age × Group: F = 0.3, *P* = 0.738, ηp2 = 0.00145
TRAbs (IU/L)	0.06 (0.05, 0.07)	0.08 (0.03, 0.16)	0.06 (0.04, 0.09)	Age: F = 1.1, *P* = 0.3, ηp2 = 0.00257; Group: F = 0.2, *P* = 0.844, ηp2 = 0.000814; Age × Group F = 0.8, *P* = 0.461, ηp2 = 0.0037
C peptide (pmol/L)	713 (646, 789)	817 (660, 1020)	886 (769, 1020)	Age: F = 0.4, P = 0.52, ηp2 = 0.00307; Group: F = 2.4, *P* = 0.095, ηp2 = 0.0343; Age × Group F = 0.4, *P* = 0.667, ηp2 = 0.00599
Glycaemia (3.9–5.6) (mmol/L)	5.06 (5.02, 5.11)	6.09 (5.83, 6.39)	7.6 (7.23, 8.06)	Age: F = 0, *P* = 0.868, ηp2 = 0.0000965; Group: F = 236.7, *P* < 0.001, ηp2 = 0.621; Age × Group F = 0.7, *P* = 0.508, ηp2 = 0.00468, P>C, D>P, D>C
HbA1c (20.0–42.0) (mmol/mol)	36.1^{a,b} (35.5, 36.6)	38.9^{b,c} (37.4, 40.7)	50.7^{a,c} (48.2, 53.8)	Age: F = 3.2, *P* = 0.074, ηp2 = 0.0166; Group: F = 98.8, *P* < 0.001, ηp2 = 0.509; Age × Group F = 1.8, *P* = 0.175, ηp2 = 0.0181
HOMA-IR	1.58^{a} (1.43, 1.73)	1.9 (1.54, 2.36)	2.37^{a} (2.05, 2.76)	Age: F = 1.6, *P* = 0.212, ηp2 = 0.0116; Group: F = 8.3, *P* < 0.001, ηp2 = 0.11; Age × Group F = 0.3, *P* = 0.724, ηp2 = 0.00481
HOMAB (%)	126^{a,b} (118, 133)	101^{a,c} (85.8, 116)	61^{b,c} (51.8, 70.4)	Age: F = 0.2, *P* = 0.658, ηp2 = 0.00152; Group: F = 41.2, *P* < 0.001, ηp2 = 0.388; Age × Group F = 2.2, *P* = 0.117, ηp2 = 0.0325
HOMAS (%)	63.8^{a} (57.8, 70.2)	52.8 (42.2, 65.2)	42^{a} (35.9, 48.7)	Age: F = 1.6, *P* = 0.212, ηp2 = 0.0116; Group: F = 8.3, *P* < 0.001, ηp2 = 0.11; Age × Group F = 0.3, *P* = 0.722, ηp2 = 0.00485

anti-Tg, anti-thyroglobulin antibodies; anti-TPO, anti-thyroid peroxidase antibodies; HOMA-B (%), steady state β cell function; HOMA-IR, the homeostatic model assessment of insulin resistance; HOMA-S (%), insulin sensitivity; NDM, non-diabetes group; PDM, prediabetes; T2DM, type 2 diabetes; TRAbs, TSH receptor autoantibodies.

Significance for multiple comparisons with Bonferroni correction (*P* < 0.05). Glycaemia (3.9–5.6) (mmol/L); 5.06^{a,b} (5.02, 5.11); 6.09^{b,c} (5.83, 6.39); 7.6^{a,c} (7.23, 8.06); Age: F = 0, *P* = 0.868, ηp2 = 0.0000965; Group: F = 236.7, *P* < 0.001, ηp2 = 0.621; Age × Group F = 0.7, *P* = 0.508, ηp2 = 0.00468.

melanoma and urothelial carcinoma. Four patients in the PDM/T2DM group had cancer duplicity. Relevant positive predictors for NTC with explained variability 9% after cross-validation (t-statistic 3.01; *P*<0.01) were T2DM (24.99; *P*<0.01), duration of PDM/T2DM (13.30; *P*<0.01), male gender (6.51; *P*<0.01), age (12.95; *P*<0.01), BMI (13.68; *P*<0.01), smoking or history of smoking (6.01; *P*<0.01), multinodular thyroid gland (12.00; *P*<0.01), thyroid nodule volume (6.78; *P*<0.01) and glycemia (21.13; *P*<0.01). In contrast, relevant negative predictors for NTC were anti-TPO (–3.90; *P*<0.01) and anti-Tg (–3.84; *P*<0.01).

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Table 2 Relationships between groups of patients with prediabetes (PDM), type 2 diabetes (T2DM), and a control group (non-diabetes group; NDM) and predictors for the first predictive component as evaluated by the O2PLS model (for details see Statistical analysis).

	Variable	Predictive component			
		Component loading	*t*-statistics	R^a	
Relevant predictors (matrix X)	Male	0.185	4.53	0.280	c
	Age	0.460	16.98	0.708	c
	BMI	0.388	22.47	0.604	c
	Smoking	0.079	2.61	0.112	b
	NTC	0.198	2.86	0.295	b
	MNTG	0.176	4.83	0.249	c
	Thyroid nodule volume	0.090	3.25	0.116	c
	Thyroid gland volume	0.135	4.79	0.201	c
	AITD	−0.056	−2.01	−0.076	b
	fT3	−0.071	−2.86	−0.114	b
	anti-TPO	−0.144	−5.89	−0.201	c
	anti-Tg	−0.132	−5.75	−0.180	c
	Glycaemia	0.655	52.63	0.885	c
(matrix Y)	T2DM	0.597	25.87	0.508	c
	PDM	0.355	21.69	0.255	c
	NDM	−0.721	−26.90	−0.583	c
Explained variability		22% (20.8% after cross-validation)			

AITD, autoimmune thyroid disease; anti-Tg, anti-thyroglobulin antibodies; anti-TPO, anti-thyroid peroxidase antibodies; MNTG, multinodular thyroid gland; NTC, non-thyroid cancer; Smoking or history of smoking.
[a]*R*, Component loadings expressed as correlation coefficients with predictive component, [b]$P < 0.05$, [c]$P < 0.01$.

Discussion

Generally, there is a higher prevalence of thyroid disorders among diabetic patients compared with the general population (10.8% vs 6.6%) (26). Epidemiological studies suggest that the incidence of thyroid cancer (TC) is dependent on modifiable risk factors such as environmental carcinogens, dietary habits, and lifestyle (27, 28). In our study, we focused on the links between prediabetes, type 2 diabetes and thyroid disease. Specifically, we concentrated on the risk of TC and the modifiable factors, diabetes, obesity and insulin resistance.

In our study, the typical patient with PDM or DM was an elderly, overweight or obese man with benign multinodular goiter. In addition, smoking or ex-smoking was a common history of these patients. On the other hand, the typical control proband was younger with a higher incidence of autoimmune thyroid disorder. Our findings are supported by other studies showing that type 2 diabetes is not convincingly associated with the prevalence of hypo- or hyperthyroidism or the presence

Table 3 Relationships between the duration of prediabetes (PDM) and type 2 diabetes (T2DM) and predictors for the first predictive component as evaluated by the O2PLS model (for details see the Statistical analysis section).

	Variable	Predictive component			
		Component loading	*t*-statistics	R^a	
Relevant predictors (matrix X)	AITD	−0.189	−2.30	−0.334	b
	Smoking	−0.140	−3.29	−0.249	c
	C-peptide	−0.497	−12.94	−0.889	c
	Glycemia	0.223	2.67	0.391	b
	HbA1c	0.254	5.12	0.427	c
	HOMA-IR	−0.442	−7.85	−0.793	c
	HOMA-B	−0.479	−8.85	−0.855	c
	HOMA-S	0.443	7.72	0.794	c
(matrix Y)	Duration of PDM/T2DM	1.000	4.52	0.529	c
Explained variability		27.9% (21.5% after cross-validation)			

AITD, autoimmune thyroid disease; HOMA-B, steady state beta cell function; HOMA-IR, the homeostatic model assessment of insulin resistance; HOMA-S, insulin sensitivity; Smoking or history of smoking.
[a]*R*, Component loadings expressed as correlation coefficients with predictive component, [b]$P < 0.05$, [c]$P < 0.01$.

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Table 4 Differences between group of patients with benign (BS) and malignant thyroid tumors (MS) for metric variables (Mann–Whitney *U*-test).

Variable	BS		MS		*P*-value
	Median (quartiles)	Mean (s.d.)	Median (quartiles)	Mean (s.d.)	
Age	47 (38.8, 65.3)	49.8 (15.9)	53 (39, 67)	53 (16.8)	0.402
BMI	25.2 (22.2, 29.9)	27 (6.61)	26.8 (22.5, 30.1)	26.7 (5.27)	0.786
TN	8.2 (2, 16.5)	12.8 (16.8)	1.8 (0.22, 7.3)	6.24 (14.4)	<0.001
TG	24.5 (16.6, 34.8)	32.8 (37.4)	17 (10.8, 27.4)	22.5 (17.5)	0.021
TSH	1.08 (0.117, 1.96)	1.23 (1.09)	2.14 (1.25, 3.37)	3.86 (7.75)	<0.001
fT4	15.7 (14.1, 18.4)	21.8 (16.4)	15.4 (14, 16.4)	15 (3.31)	0.145
fT3	5 (4.76, 5.79)	7.99 (8.53)	4.8 (4.5, 5.21)	4.83 (0.624)	0.071
anti-TPO	5.02 (1.88, 12)	31 (68.6)	6.1 (2.98, 144)	154 (317)	0.259
anti-Tg	0.86 (0.36, 3.55)	4.74 (9.61)	12.8 (1.63, 33.8)	284 (1330)	0.001
TRAbs	0.39 (0.3, 10.8)	5.77 (9.88)	0.32 (0.3, 0.6)	0.915 (1.82)	0.293
C-peptide	818 (598, 1110)	895 (516)	729 (434, 887)	866 (669)	0.484
Glycaemia	5.31 (4.87, 5.58)	5.62 (1.55)	5.2 (4.9, 5.58)	5.44 (1.1)	0.792
Hb1Ac	41 (36, 53)	48.9 (22.8)	36 (34.4, 38.2)	37.2 (7.14)	0.080
HOMA-IR	2.26 (1.61, 2.52)	2.39 (1.28)	1.61 (0.98, 2.35)	2 (1.58)	0.178
Calcitonin	2 (0.9, 3.35)	2.84 (2.67)	3.2 (1.3, 6.93)	20 (69.8)	0.184

anti-Tg, anti-thyroglobulin antibodies; anti-TPO, anti-thyroid peroxidase antibodies; HOMA-IR, the homeostatic model assessment of insulin resistance; TG, thyroid gland volume (mL); TN, thyroid nodule volume (mL); TRAbs, TSH receptor autoantibodies.

of anti-TPO positivity (29, 30, 31). After statistical analyses of PDM/T2DM duration on relevant predictors, we found that the typical course of PDM/T2DM is a gradual decline of insulin secretion, progression of hyperglycemia and worsening of glucose control as measured by Hb1Ac, with insulin sensitivity assessed by HOMA-S at a maximum. Finally, autoimmune thyroid disorder did not develop frequently during the course of prediabetes and type 2 diabetes.

In a multivariate analysis, insulin resistance, and not TSH, determines the thyroid nodules development and higher thyroid volume in comparison to non-insulin resistant controls (32, 33, 34). Our study brings similar findings, with the group of prediabetic and diabetic patients having both larger thyroid gland volume and larger thyroid nodule size. We have to emphasize that ageing is crucial in this pathogenesis. The key role of TSH signaling in thyroid carcinogenesis has been supported by large epidemiological studies showing a strong association between serum TSH levels and TC development and progression. On the other hand, it is known that TSH levels can be increased in differentiated thyroid carcinoma (DTC) compared to benign thyroid disease (BTD), but not in comparison to the background population. A lower TSH among patients with BTD may be due to co-existing functional nodular autonomy (35, 36, 37). This bias can lead to misinterpretations of a positive relation between higher TSH and risk of DTC. In our study, we did not observe any difference in TSH levels between the PDM, T2DM and NDM groups of patients. Our results are supported by a large population-based study that showed no convincing evidence that people with type 2 diabetes are at increased risk of hypothyroidism (29). However, we observed significantly higher levels of TSH in patients undergoing thyroid surgery with histologically proven malignancy in comparison to lower TSH levels in the benign group. Multinodular goiter, multinodular toxic goiter, toxic nodule and Graves-Basedow thyrotoxicosis were the reasons for our benign surgery results. Generally, toxic nodules have a very low risk of malignancy (6). This clearly explains the TSH level differences between the MS and BS groups, and TSH levels have not generally been helpful in the prediction of TC risk.

Additionally, we observed lower fT3 levels but higher fT4 levels in the normal range in PDM and T2DM patients. There are some studies supporting our findings. One explanation can be genetic polymorphism in the selenodeiodinases D2 in diabetic patients. The major role of D2 is to control the intracellular T3 concentration, its accessibility to the nucleus, and the saturation of the nuclear T3 receptor in target tissues. In some diabetic patients lower D2 activity is present, and therefore, intrinsic thyroid disease is expected with possible metabolic consequences (38, 39).

Case-control and cohort studies have confirmed an increased TC risk in approximately 20% in diabetic patients, independently of geographic region, study design, and quality analysis. Despite the high heterogeneity among studies, the observation that the risk is increased among diabetic women, but not among men, has been always

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confirmed. In addition, the TC risk associated with DM is more evident in geographic areas of the world with high rates of TC (40, 41, 42).

In our study, we did not observe any TC risk difference between PDM and T2DM in comparison to NDM similarly to other study published previously (43). We suppose that one of the explanations is the overdiagnosis of TC in diabetics. Diabetic patients are more prone to be screened for thyroid dysfunction, thus contributing to the increased detection of thyroid cancer in this population. Further, they have larger thyroid gland volume and larger thyroid nodule size, perhaps leading to earlier TC manifestation and detection. Generally, thyroid incidentalomas are very frequent findings (26). In our study, we used histologically proven results as the gold reference standard to compare patients with TC and control group. We believe that sample selection bias of the control group could be the reason for different study results in comparison to previous studies. Finally, in our study the patients with proven TC had a smaller thyroid volume and thyroid nodule volume, in contrast to diabetic patients with typical multinodular goiter.

As mentioned previously, we did not observe a higher incidence of TC in PDM/T2DM patients compared to NDM. In contrast, 30% of T2DM and 10% of PDM patients had a positive history for non-thyroid cancer (NTC) in comparison to 8.4% in NDM. Our study also supports the relation between diabetes and cancer. The incidence of NTC increases with the duration of PDM/T2DM. As previously described, the positivity of anti-TPO and/or anti-Tg were relevant negative predictors for both PDM/T2DM and NTC. Perhaps, patients with autoimmune thyroid disorder have a different background in comparison to diabetics and the NTC group of patients. Furthermore, multinodular thyroid gland and larger thyroid nodules were more often present in the NTC group. This may support the idea of the growth stimulation of various types of both benign and malignant tumors in diabetics.

Epidemiological studies, followed by the systematic review suggest that obesity is associated with an increased risk of thyroid cancer; however, the relationships between obesity and thyroid cancer stage or behavior are uncertain (44, 45). In our study, we did not observe higher BMI ($P=0.786$) or insulin resistance ($P=0.178$) in group of patients with thyroid carcinoma. In contrast, BMI was one of relevant positive predictors for non-thyroid cancers. We suppose that obesity is not significantly related to thyroid cancer compared to other malignancies.

Finally, we would like to emphasize that TC differs from other tumors in age distribution, with the most commonly affected group of patients in the economic productive age of 24–60 years, while in other malignancies the risk of carcinoma increases continuously with age. In contrast, in developed countries, more than half of the people with type 2 diabetes mellitus are older than 65 years and only 8% are less than 44 years of age (46).

One limitation of our study is the difference between the study groups in age – the PDM and T2DM group of patients were older in comparison to the NDM group. For that reason, we adjusted the data on age, but we did not observe significant interactions between age and the tested parameters except BMI and TSH. Another limitation is the small size of the prediabetic group. This may have been the reason why some significant results seen in T2DM were not significant for PDM. The number of patients with histologically proven thyroid tumors was limited; however, the sample size reached sufficient statistical power. Further, C-peptide levels were not available in all patients, but it was sufficient for the statistical analysis. However, a strength of our study is the prospective design with active screening for glucose disorders and the use of histology as the reference standard. It should be noted that in some previous studies the diagnosis of prediabetes/diabetes was ascertained by a self-administered questionnaire. In our study 72% patients with PDM and 6.5% with T2DM were diagnosed by our active screening. Self-reported PDM and T2DM can be quite misleading, with some studies supporting our findings of undiagnosed glucose disorders of up to 45.8% globally (47). Our study also includes prediabetes, and to our knowledge, limited data is available for this subgroup of patients. Taken together, we believe that our study can, to some extent, explain the inconsistencies in previously published studies focused on diabetes and links to thyroid cancer and other thyroid diseases.

Conclusions

In the most insulin-resistant subjects, the diabetic and prediabetic groups, we did not observe an increased risk for thyroid cancer, in spite of the well-established increased risk for other malignancies. Structural and benign changes such as larger and multinodular thyroid gland, in comparison to autoimmune thyroid disease, were present more often in patients with prediabetes and 2 type diabetes. Intrinsic thyroid disease cannot be ruled out even under euthyroidism in these patients.

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Reasons for this finding may simply be overdiagnosis and/or stimulation of tumor growth with earlier manifestations in pre/diabetics or other unknown reasons remaining to be clarified.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
Tereza Grimmichova conceived of the presented idea. Martin Haluzik and Karel Vondra supervised the findings of this work. Martin Hill and Petr Matucha analyzed the data. All authors discussed the results and contributed to the final manuscript.

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