CLINICAL STUDY

Metformin inhibits goitrogenous effects of type 2 diabetes

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Abstract

Objective: Data on the association between type 2 diabetes mellitus (T2DM) and thyroid volume are sparse. An experimental study demonstrated an inhibitory effect of metformin on the growth of human thyroid cells. So far no study on humans has investigated potentially modulating effects of metformin on the association between T2DM and thyroid volume. Therefore, we investigated these effects in a population-based cohort study.

Design and methods: We used data from the Study of Health in Pomerania and included 2570 individuals for cross-sectional and 1088 individuals for longitudinal analyses. T2DM was defined by physician-diagnosed self-report or intake of antidiabetic medication.

Results: In the cross-sectional data, females with T2DM treated with antidiabetic medication other than metformin had a larger thyroid volume ($\beta = 4.69$; 95% CI 1.87 to 7.50) and a higher odds ratio (OR) for goiter (OR $= 1.71$; 95% CI 1.05 to 2.79) than females without T2DM, whereas in males, no such association was detected. In females or males treated with metformin, T2DM was not associated with thyroid volume or goiter. In longitudinal analyses, incident T2DM not treated with metformin was significantly associated with a higher risk for incident goiter in the total population (incidence rate ratio (IRR) $= 1.70$; 95% CI 1.10 to 2.91). Individuals with T2DM having changed from metformin to other antidiabetic agents during follow-up also had a higher risk for incident goiter than individuals without T2DM (IRR $= 2.71$; 95% CI 1.74 to 4.20).

Conclusions: We demonstrate an inhibitory effect of metformin on prevalent and incident goiter. Anti-goitrogenous effects of metformin add to the general benefits of metformin treatment of T2DM.

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Introduction

Metformin is an antidiabetic drug, which is frequently prescribed and recommended in patients with type 2 diabetes mellitus (T2DM), obesity, insulin resistance, hyperinsulinemia, and without kidney disease (1). Metformin reduces more than one third of the total glucose production in T2DM (2) via inhibition of glucose production in the liver (3). Moreover, previous studies demonstrated that all-cause mortality (4, 5) is lower in patients with T2DM taking metformin than in those taking other antidiabetic agents. Likewise, it has been shown that metformin decreases lipid levels and does not increase body weight (3, 6). Although there are many benefits of metformin treatment, unintended side effects have to be considered. Particularly, metformin is associated with a higher risk for gastrointestinal events such as diarrhea (7, 8).

Recently, a few studies revealed possible effects of metformin treatment on thyroid-related characteristics. While three studies in patients with hypothyroidism and/or levothyroxine treatment showed a reduction of serum TSH levels under metformin treatment (9, 10, 11), a retrospective study demonstrated significantly higher serum TSH levels in euthyroid patients with T2DM treated with metformin compared with those treated with other diabetic agents (12). However, in that study, metformin use was not associated with serum TSH levels after adjustment for several potential confounding factors of which goiter was the only significant one (12). Thus, goiter might explain the difference in serum TSH levels between patients treated with and without metformin, which vice versa might argue for metformin as an independent protective factor for goiter in T2DM.

Data on the association between T2DM and thyroid volume are sparse. A current case–control study with 111 women reported a positive association between insulin resistance and thyroid volume (13). However, that study (13) did not explicitly focus on T2DM and also did not consider antidiabetic drug intake. Focusing on the relationship between metformin and thyroid volume, a recent experimental study (14) demonstrated an inhibitory effect of metformin on the growth of

human thyroid cells. Thus, it is intriguing to hypothesize that an association between T2DM and goiter, if existent, might be modulated by metformin use. Supporting this note, a study on 66 females with insulin resistance demonstrated a reduction of thyroid nodule size after treatment with metformin (15). So far no study has investigated potentially modulating effects of metformin on the association of T2DM with thyroid volume in the general population. Therefore, we aim to investigate these effects using data from a population-based German cohort study, in which T2DM was not only defined by physician-diagnosed self-report and medication but also by HbA1c levels.

Materials and methods

Study population

The Study of Health in Pomerania (SHIP) is a population-based cohort study conducted in West Pomerania (16). As with the whole of Germany, the region was formerly iodine deficient until the mid-1990s, when an iodine fortification program became effective (17). Particularly among older persons, goiter prevalence is still high (18).

A sample from the population aged 20–79 years was drawn from population registries comprising 6267 eligible subjects. Examinations were performed between 1997 and 2001. The baseline SHIP population (SHIP-0) included 4308 Caucasian participants (response 68.8%). Between 2002 and 2006, all participants were re-invited for an examination follow-up (SHIP-1), in which 3300 subjects took part (1589 men and 1711 women; 83.5% of all eligible subjects). The median follow-up time was 5.0 years (minimum, 4.4 years; maximum, 8.6 years; 17 315 person-years). Exclusion criteria for the present analyses are presented in Fig. 1.
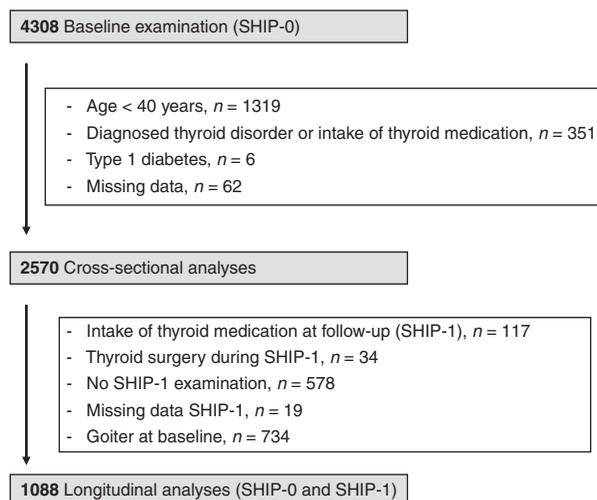

4308 Baseline examination (SHIP-0)

- Age < 40 years, $n = 1319$
- Diagnosed thyroid disorder or intake of thyroid medication, $n = 351$
- Type 1 diabetes, $n = 6$
- Missing data, $n = 62$

2570 Cross-sectional analyses

- Intake of thyroid medication at follow-up (SHIP-1), $n = 117$
- Thyroid surgery during SHIP-1, $n = 34$
- No SHIP-1 examination, $n = 578$
- Missing data SHIP-1, $n = 19$
- Goiter at baseline, $n = 734$

1088 Longitudinal analyses (SHIP-0 and SHIP-1)

Figure 1 Flow diagram for selection of our study population.

All participants gave informed written consent. The study followed the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

Assessments

Age, sex, smoking status, drug intake, and T2DM were assessed by computer-assisted personal interviews performed by certified staff. Smoking status was categorized into the three categories: current smokers, former smokers, and never smokers. Former smokers were individuals who had smoked during their lifetime but not in the last 12 months before the time of examination. All participants were asked to bring all medications taken 7 days before the time of examination. Medication data were obtained online using the IDOM program (online drug database led medication assessment) and categorized according to the Anatomical Therapeutical Chemical (ATC) classification index. Thyroid medication was defined by the ATC code H03, antidiabetic medication by the ATC code A10, and metformin intake by the ATC code A10BA02. T2DM was defined by self-reported diabetes in the interview or intake of antidiabetic medication. Individuals with T2DM were further categorized into the two groups: 'metformin intake' and 'no metformin intake'. For the longitudinal analyses, we defined a T2DM variable with seven levels: 1) no T2DM in SHIP-0 and SHIP-1; 2) no T2DM in SHIP-0, but T2DM not treated with metformin in SHIP-1; 3) no T2DM in SHIP-0, but T2DM treated with metformin in SHIP-1; 4) T2DM not treated with metformin in SHIP-0 and SHIP-1; 5) T2DM not treated with metformin in SHIP-0, but treated with metformin in SHIP-1; 6) T2DM treated with metformin in SHIP-0, but not treated with metformin in SHIP-1; and 7) T2DM treated with metformin in SHIP-0 and SHIP-1).

Examinations at baseline and follow-up included anthropometry, thyroid ultrasonography, and laboratory measurements. Height and weight were measured for calculation of the BMI: BMI = weight (kg)/height^2 (m^2). In SHIP-0 and SHIP-1, thyroid ultrasonography was performed with an ultrasound VST-Gateway with a 5 MHz linear array transducer (Diasonics, Santa Clara, CA, USA). Thyroid volume was calculated as length × width × depth × 0.479 (ml) for each lobe (19). Intra- and inter-observer reliabilities were assessed before the start of SHIP and afterward annually. All measurements of the thyroid volume showed Spearman correlation coefficients of > 0.85 and mean differences (±2 S.D.) of the mean bias < 5% (< 25%) between the examiners. Goiter was defined as a thyroid volume of > 18 ml in women and of > 25 ml in men (20). These cutoff values appear rather high but are appropriate given that West Pomerania suffered from iodine deficiency until the mid-1990s (21). Furthermore, we have kept this procedure constant over all publications for more than 10 years (22).

Although a more modern definition would also be possible, we have not introduced this so far to avoid the impression that goiter is arbitrarily defined across different SHIP publications.

Individuals were classified as having thyroid nodules if at least one thyroid nodule was detected in the right or the left lobe of the thyroid. Serum TSH levels were measured by immunochemiluminescent procedures (SHIP-0: LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany; SHIP-1: Immulite 2000, Third generation, Diagnostic Products Corporation, DPC, Los Angeles, USA). HbA1c levels were measured by HPLC (ClinRep HbA1c, Recipe Chemicals + Instruments GmbH, Munich, Germany) with a coefficient of variation of 1.5% during SHIP-0.

Statistical analysis

Data on quantitative characteristics are expressed as median and interquartile range; data on qualitative characteristics are expressed as percentages and absolute numbers. Group comparisons were done by Kruskal–Wallis test (continuous data) and χ^2 test (categorical data). Baseline T2DM treated with and without metformin was associated with baseline thyroid volume by linear regression and with prevalent goiter by logistic regression, both adjusted for age, sex, smoking status, and BMI. Analyses were repeated stratified by sex. Furthermore, we repeated the cross-sectional analyses in a population excluding individuals with dietary treatment of T2DM and individuals having no diagnosed T2DM but HbA1c levels $\geq 6.5\%$.

Change in T2DM and antidiabetic medication during follow-up was associated with incident goiter by Poisson regression with robust standard errors weighted for loss to follow-up and adjusted for baseline values of age, sex, smoking status, and BMI and for the log-transformed time between baseline and follow-up. Results of linear regressions are expressed as adjusted means and 95% CIs, results of the logistic regressions as odds ratio (OR) and 95% CI, and results of the Poisson regressions as incidence rate ratios (IRR) and 95% CI. $P < 0.05$ was considered as statistically significant. All analyses were performed using Stata 12.1 (Stata Corporation, College Station, TX, USA).

Results

Cross-sectional results

There were 278 individuals with T2DM in SHIP-0 (11.0%) of which 83 subjects (29.2%) were treated with metformin. The proportion of males was significantly higher among individuals with T2DM compared with individuals without T2DM (Table 1). Furthermore, individuals with T2DM were older and had a higher BMI and higher serum glucose and HbA1c levels than individuals without T2DM. Age at T2DM onset was comparable between groups of T2DM treated with and without metformin. Thyroid volume and goiter prevalence were the highest in the group of individuals with T2DM not treated with metformin. These differences were more pronounced among females than among males (Table 2). Thyroid nodules were more prevalent in individuals with T2DM, but the prevalence did not differ between individuals with and without metformin treatment (Table 1). Serum TSH levels were similar among individuals with and without T2DM.

Multivariable regression analyses adjusted for age, sex, smoking status, and BMI revealed that females with T2DM not treated with metformin had significantly larger thyroid volumes and a significantly higher risk for goiter than females without T2DM (Table 3). In contrast, females with T2DM treated with metformin

Table 1 Characteristics of the SHIP-0 population stratified by T2DM defined by self-report and medication intake. Data are expressed as median and interquartile range for continuous data and as total numbers and percentages for categorical data.

	No T2DM ($n=2292$)	**T2DM and no metformin intake** ($n=195$)	**T2DM and metformin intake** ($n=83$)	P^{a}
Males	1227 (53.5%)	120 (61.5%)	45 (54.2%)	0.098
Age (years)	57 (48; 67)	67 (60; 74)	64 (57; 71)	<0.001
BMI (kg/m^2)	27.6 (24.8; 30.5)	29.1 (26.6; 32.3)	30.0 (27.5; 34.8)	<0.001
Smoking status				
Former	886 (38.7%)	100 (51.3%)	39 (47.0%)	<0.001
Current	575 (25.1%)	23 (11.8%)	9 (10.8%)	
Glucose (mmol/l)	5.4 (5.0; 5.9)	7.8 (6.2; 10.4)	8.6 (5.9; 10.4)	<0.001
HbA1c (%)	5.4 (5.0; 5.8)	7.0 (6.1; 7.9)	6.9 (6.6; 8.3)	<0.001
Diabetic medication	–	143 (73.3%)	83 (100.0%)	<0.001
Age of T2DM onset	–	55 (48; 64)	54 (48; 60)	0.356
Thyroid volume (ml)	19.7 (14.9; 27.0)	23.1 (16.4; 29.4)	21.0 (15.6; 28.4)	0.003
Goiter	953 (41.6%)	101 (51.8%)	35 (42.2%)	0.021
At least one thyroid nodule	575 (25.1%)	63 (32.3%)	27 (32.5)	0.033
TSH (mIU/l) (SHIP-0)	0.62 (0.42; 0.87)	0.61 (0.40; 0.89)	0.69 (0.49; 0.88)	0.359
TSH (mIU/l) (SHIP-1)	0.73 (0.50; 1.09)	0.79 (0.57; 1.14)	0.80 (0.60; 1.10)	0.302

T2DM, type 2 diabetes mellitus.
$^{\mathrm{a}}$Kruskal–Wallis test (continuous data) and χ^2 test (categorical data).

Table 2 Characteristics of the SHIP-0 population stratified by sex and by T2DM defined by self-report and medication intake. Data are expressed as median and interquartile range for continuous data and as total numbers and percentages for categorical data.

	No T2DM ($n=2292$)	T2DM and no metformin intake ($n=195$)	T2DM and metformin intake ($n=83$)	P^a
Age (years)				
Males	59 (49; 68)	67 (61; 75)	63 (56; 69)	<0.001
Females	56 (47; 65)	68 (59; 73)	66 (59; 72)	<0.001
BMI (kg/m^2)				
Males	27.9 (25.5; 30.2)	29.1 (26.7; 31.6)	30.0 (27.4; 34.1)	<0.001
Females	27.2 (24.0; 30.7)	29.8 (26.1; 33.1)	30.0 (27.7; 35.5)	<0.001
Current smokers				
Males	350 (28.5%)	16 (13.3%)	7 (15.6%)	<0.001
Females	225 (21.1%)	7 (9.3%)	2 (5.3%)	0.011
Former smokers				
Males	643 (52.4%)	85 (70.8%)	29 (64.4%)	<0.001
Females	243 (22.8%)	15 (20.0%)	10 (26.3%)	0.480
Glucose (mmol/l)				
Males	5.5 (5.1; 6.0)	8.1 (6.4; 10.3)	8.5 (5.9; 10.5)	<0.001
Females	5.3 (4.9; 5.7)	7.6 (5.8; 10.4)	8.7 (6.6; 10.3)	<0.001
HbA1c (%)				
Males	5.4 (5.1; 5.9)	7.0 (6.1; 8.1)	6.9 (6.4; 8.3)	<0.001
Females	5.3 (4.9; 5.7)	6.9 (6.1; 7.9)	7.0 (6.8; 8.2)	<0.001
Diabetic medication				
Males	–	87 (72.5%)	45 (100.0%)	<0.001
Females	–	56 (74.7%)	38 (100.0%)	<0.001
Thyroid volume (ml)				
Males	23.7 (18.4; 30.9)	24.8 (18.7; 30.5)	24.4 (19.0; 29.2)	0.869
Females	16.3 (12.4; 20.7)	19.7 (12.8; 26.8)	16.6 (13.7; 26.9)	0.016
Goiter				
Males	546 (44.5%)	59 (49.2%)	18 (40.0%)	0.499
Females	407 (38.2%)	42 (56.0%)	17 (44.7%)	0.008

T2DM, type 2 diabetes mellitus.
[a]Kruskal–Wallis test (continuous data) and χ^2 test (categorical data).

had no significantly higher thyroid volumes and no significantly higher risk for goiter than females without T2DM. In males with and without T2DM, no significant differences in thyroid volume or goiter prevalence were detected.

After exclusion of individuals with T2DM treated only by diet, females with T2DM not treated with metformin still had a significantly larger thyroid volume ($\beta=4.58$; 95% CI 1.47 to 7.68; $P=0.004$) and a significantly higher OR for goiter (OR$=2.25$; 95% CI 1.27 to 3.99; $P=0.005$) than females without T2DM, whereas females with T2DM treated with metformin had no significantly larger thyroid volume ($\beta=0.77$; 95% CI -3.02 to 4.55; $P=0.690$) and no significantly higher OR for goiter (OR$=1.09$; 95% CI 0.55 to 2.16) than

females without T2DM. Similar to the whole male population, no associations were detected between T2DM and thyroid size.

Further exclusion of individuals with an HbA1c $\geq 6.5\%$ who were not aware of their T2DM ($n=103$; 70 males) increased the effect sizes in the group with T2DM not treated with metformin. In women, the effect sizes were $\beta=4.65$ (95% CI 1.53 to 7.78; $P=0.004$) for thyroid volume and OR$=2.32$ (95% CI 1.31 to 4.11; $P=0.004$) for prevalent goiter. Males with T2DM not treated with metformin had no significant larger thyroid volume ($\beta=0.34$; 95% CI -2.28 to 2.96; $P=0.800$) and no significant higher OR for goiter (OR$=1.32$; 95% CI 0.84 to 2.07; $P=0.236$) than males without T2DM, but effect sizes were higher than in the main analyses.

Table 3 Association between baseline T2DM (defined by self-report and medication intake) with and without metformin intake and baseline thyroid volume. Linear regression for thyroid volume and logistic regression for goiter adjusted for age, sex, smoking status, and BMI.

	Thyroid volume (ml) (adjusted means (95% CI))			Goiter (odds ratio (95% CI))		
	No T2DM	T2DM and no metformin intake	T2DM and metformin intake	No T2DM	T2DM and no metformin intake	T2DM and metformin intake
All	22.5 (22.1; 23.0)	24.2 (22.5; 25.9)	22.2 (19.6; 24.7)	Reference	1.35 (1.00; 1.83)	0.89 (0.57; 1.41)
Males	26.0 (25.4; 26.7)	25.8 (23.7; 27.9)	24.8 (21.4; 28.2)	Reference	1.16 (0.79; 1.71)	0.76 (0.41; 1.41)
Females	18.4 (17.7; 19.1)	23.1[†] (20.4; 25.8)	19.0 (15.2; 22.7)	Reference	1.71* (1.05; 2.79)	1.03 (0.52; 2.02)

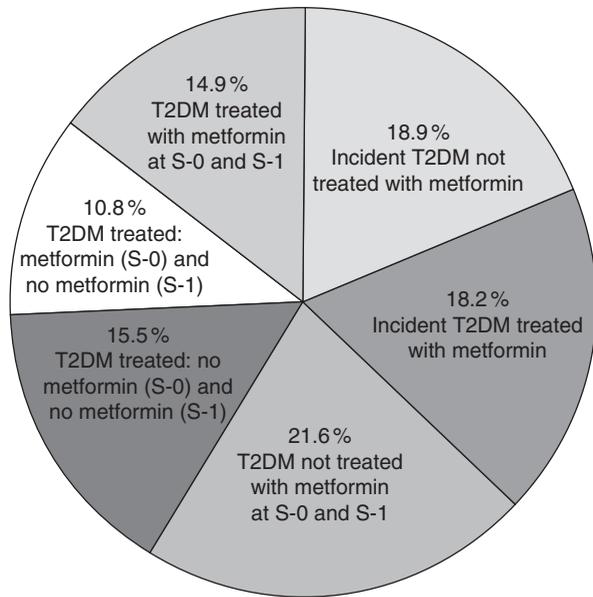T2DM, type 2 diabetes mellitus. *$P<0.05$; [†]$P<0.001$.

Figure 2 Individuals with type 2 diabetes mellitus (T2DM) at follow-up stratified by metformin treatment at baseline and follow-up.

Longitudinal results

Thyroid volume increased in median by 1.3 ml (interquartile range = −0.9 to 4.0) between SHIP-0 and SHIP-1. Incidence of goiter was 22.4%. Fifty-five individuals developed T2DM during SHIP-1 corresponding to an incidence of 5.5%. Incidence of T2DM was higher in males than in females (6.5 vs 4.5%). In total, there were 148 individuals with T2DM at SHIP-1 (13.6%). Proportions of metformin treatment in individuals with T2DM at SHIP-1 are shown in Fig. 2.

In multivariable Poisson regression, incident T2DM not treated with metformin was positively associated with incident goiter ($P=0.020$; Fig. 3). Moreover, individuals with T2DM at SHIP-0 and SHIP-1 switching from metformin to other antidiabetic agents during follow-up had a higher risk for incident goiter than individuals without T2DM at SHIP-0 and SHIP-1 ($P<0.001$). Because of the relatively low numbers included in our longitudinal analyses, it was not useful to perform sex-stratified analyses.

Discussion

In our cross-sectional data, we demonstrated a significant association between T2DM and thyroid volume in women not treated with metformin. This association was still present after exclusion of all women whose T2DM was treated with diet. These findings are in agreement with a small study from Argentina conducted in 133 women (13), in which insulin resistance was associated with thyroid volume, independently of obesity. Our study not only confirms the results of that study

(13) but also enhances recent knowledge by adding evidence that the association between T2DM and thyroid volume is not only present in selected volunteers but also in a general population from Central Europe. Furthermore, Northeast Germany is a region with former mild-to-moderate iodine deficiency (21), while the Argentinian study (13) was conducted in a region with sufficient iodine supply (23). The fact that two studies from regions with different iodine supplies came to similar conclusions may argue for a real association between T2DM and thyroid volume.

While thyroid volume was larger in females with T2DM treated with diet or medication other than metformin, there was no such association in females with T2DM treated with metformin. This finding is in good agreement with the results of an experimental study (14), in which an inhibitory effect of metformin on the growth of thyroid cells derived from nodular goiters was demonstrated. Metformin directly inhibits thyroid growth by activation of the AMPK/mammalian target of rapamycin (mTOR) pathway and antagonized the growth-stimulatory effect of insulin by inhibition of the MAPK pathway (14). Furthermore, in T2DM, metformin reduces insulin resistance and in turn hyperinsulinemia mainly by decreasing gluconeogenesis in the liver (24). This contributes to a diminished growth stimulation of the thyroid gland.

In contrast to our results in females, there was no association between T2DM and thyroid volume in males not treated with metformin. The reason for this discrepancy might be referred to a misclassification of T2DM in males. Females consult physicians more frequently and earlier than males (25), which might have led to a higher detection rate of T2DM in females. As a consequence, we might have underestimated the total number of males with T2DM in our cross-sectional population because T2DM was defined as a self-reported
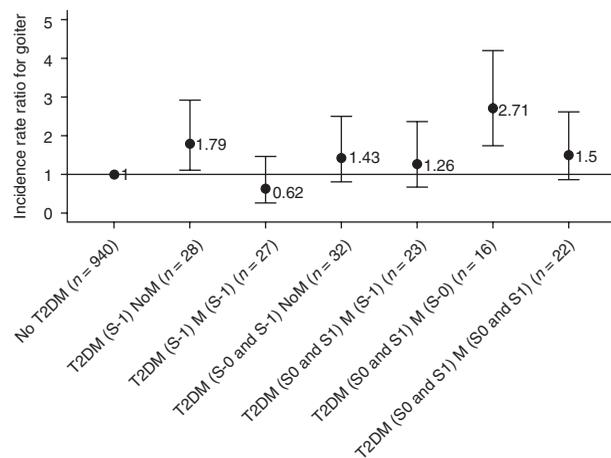

Figure 3 Association of change in incident type 2 diabetes mellitus (T2DM) and antidiabetic treatment with incident goiter. NoM, no metformin treatment; M, metformin treatment; S-0, baseline examination; S-1, follow-up examination.

diagnosis by a physician. Indeed, the frequency of HbA1c levels $\geq 6.5\%$, a threshold for T2DM according to guidelines of the American Diabetes Association in 2010 (25, 26), was significantly higher in males than in females after excluding individuals with self-reported T2DM. Furthermore, the association between T2DM not treated with metformin and thyroid volume was stronger when individuals without previous self-reported T2DM but an HbA1c $\geq 6.5\%$ were excluded from analyses. Thus, the group of males without diagnosed T2DM might be more heterogeneous than the respective group of females, which might partly explain the conflicting results between the sexes.

Another explanation for the different results between the sexes might have resulted from different smoking habits in males and females. In SHIP, the frequency of former smokers was higher in males with T2DM than in those without, while this was not the case for females (27). Furthermore, we have shown that smoking was positively associated with prevalent goiter in SHIP (28). Thus, smoking might have diminished the protective effect of metformin on the association between T2DM and goiter, particularly in males.

In agreement with the results of our cross-sectional data, individuals with T2DM not treated with metformin had a higher risk for incident goiter than individuals without T2DM, whereas this was not the case for individuals with T2DM treated with metformin. This finding provides further evidence that metformin inhibits thyroid growth and indicates that patients with T2DM and concomitant goiter should be preferably treated with metformin. Future randomized controlled trials should address the protective effect of metformin against the development of goiter.

Strengths of our study are its population-based design and the standardized protocol of thyroid ultrasonography, which was certified regularly during the study. A further strength of our study is that T2DM was not only defined by self-report but also by HbA1c levels. A limitation of our study is that some groups in the longitudinal analyses had relatively low numbers, so that it was not possible to perform sex-stratified analyses and it might be that we do not have sufficient power to demonstrate significant effects for risk ratios of 1.5. A further limitation of our study is the lack of information on insulin resistance.

We demonstrate an inhibitory effect of metformin on prevalent and incident goiter. Anti-goitrogenous effects of metformin add to the general benefits of metformin treatment in T2DM. This is of particular relevance for populations from regions with current or former iodine deficiency, where goiter is a highly prevalent finding.

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.

Funding

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