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ORIGINAL ARTICLE

Impaired central sensitivity to triiodothyronine is associated with gestational diabetes mellitus

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Abstract

Background Thyroid hormones play an important role in the regulation of glucose metabolism. Recently, some studies determined the relationship between diabetes and abnormality of indices of thyroid hormone sensitivity. Thyroid dysfunction may play a role in the etiology of gestational diabetes mellitus (GDM).

Objective In the present study, we aim to determine central and peripheral thyroid hormone resistance by evaluating indices of thyroid hormone sensitivity and thyroid function tests and to investigate its effect on the etiology of GDM.

Methods A total of 1416 euthyroid pregnant women were included in this study. Of these, 241 (17%) had GDM and 1175 (83%) did not have GDM. We evaluated the association of indices of sensitivity to thyroid hormones including $TFQI_{FT4}$, $TFQI_{FT3}$, TSHI, TT4RI, and FT3/FT4, with GDM in pregnant euthyroid women.

Results We found higher FT3, $TFQI_{FT3}$, and FT3/FT4 ratio in the GDM group. The present study also showed that significantly increased FT3 and $TFQI_{FT3}$ levels were associated with a higher risk of GDM after adjustment for potential confounding factors such as age and body mass index (BMI).

Conclusions FT3 and $TFQI_{FT3}$ were independently associated with the risk of GDM. The results of the present study may shed light on future studies by providing new information on the association of FT3 at the first antenatal visit with GDM.

Keywords Triiodothyronine · Indices of thyroid hormone sensitivity · Gestational diabetes mellitus

Introduction

Gestational diabetes mellitus (GDM) is the most common disease among pregnant women. According to the International Diabetes Federation (IDF) 2021 data, the prevalence of GDM was 14% during pregnancy [1]. GDM is associated with both adverse maternal and fetal outcomes [2]; therefore, the diagnosis of GDM in the early stages of pregnancy may significantly reduce perinatal complications.

During pregnancy, the thyroid gland enlarges and the production of thyroxine (T4) and triiodothyronine (T3) increases by 50% [3]. Increased human chorionic gonadotropin stimulates the secretion of thyroid hormones (THs) and reduces thyroid stimulating hormone (TSH) in the first trimester. The incidence of thyroid dysfunction, including subclinical and clinical hyperthyroidism or hypothyroidism, and autoantibody positivity in pregnant women is approximately 10–15% [3]. It is well established that thyroid dysfunction during pregnancy is associated with an increased risk of adverse pregnancy outcomes, including intrauterine fetal death, hypertension, and GDM [4]. Although many studies have found an association between thyroid disorders and the risk of GDM [5], there have been no other studies [6]. Changes in THs and TSH levels during pregnancy may also contribute to this controversy.

The hypothalamus-pituitary-thyroid (HPT) axis regulates THs owing to a negative feedback loop, which means that THs and TSH are inversely correlated [7]. An abnormal

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setting of the HPT axis may cause metabolic syndrome or diabetes [8]. Impaired HPT sensitivity to THs may also be related to diabetes [9]. The Thyroid Feedback Quantile-based Index (TFQI) is a newly suggested index to reflect the pituitary response to THs, i.e., the central sensitivity to the thyroid hormone, which is calculated simply by FT4 or FT3 and TSH levels [9, 10]. The relationship between reduced sensitivity to thyroid hormones and metabolic abnormalities is noteworthy. Laclaustra et al. recently showed that elevated values in indices of resistance to thyroid hormone, including TFQI, are associated with metabolic syndrome and diabetes in general and even in patients with normal thyroid hormone levels [9]. Peripheral thyroid hormone sensitivity is assessed by the FT3/FT4 ratio, which is a proxy for deiodinase activity [10]. T3 is an active metabolic form of thyroid hormone that induces endogenous glycemic activity [11]. Thyroid hormone indices have been also studied in relation to the risk of non-alcoholic fatty liver disease (NAFLD). In 2021, Lai et al. demonstrated that $TFQI_{FT3}$ and FT3/FT4 levels were positively associated with the risk of hyperlipidemia and NAFLD [12]. Some studies have also investigated the associations of FT3 or FT3/FT4 with the risk of GDM [13]. The thyroid hormone sensitivity indices calculated instead of THs and TSH may provide more integrated results in assessing the role of thyroid function in the development of GDM. Therefore, in this cross-sectional study, we aimed to investigate the association of central sensitivity to thyroid hormone assessed by $TFQI_{FT4}$, $TFQI_{FT3}$, TSHI, and TT4RI and peripheral sensitivity to thyroid hormone assessed by FT3/FT4 with GDM in euthyroid pregnant women.

Materials and methods

Study design

This retrospective cohort study was conducted between September 2016 and January 2022 at the University of Health Science, Gülhane Training and Research Hospital. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Gülhane Training and Research Hospital (Date 06.04.2022/No 2022/35).

Pregnant women aged 18–45 years were enrolled during the first antenatal visit to the outpatient clinic between 10 and 20 weeks of gestation. Pregnant women with a history of thyroid surgery, intake of any thyroid drugs and radioactive iodine, a history of diabetes before pregnancy, and a history of cancer were excluded. Finally, we reviewed the electronic medical records of 1416 pregnant women with euthyroid status in the last 6 months. Forty-four patients with a previous history of GDM were also included in the study. Sixty-six percent of the participants were in primigravida. Thyroid function tests of all pregnant women were evaluated at the first antenatal visit and oral glucose tolerance test (OGTT) was performed at 24–28 weeks of gestation. All pregnant women underwent a two-step standardized OGTT. The 50-g OGTT, cutoff value was 140 mg/dL. The diagnosis of GDM is made when at least two high values after 100-g OGTT were observed, according to Carpenter and Coustan criteria (fasting blood glucose 95 mg/dL, 1-h blood glucose 180 mg/dL, 2-h blood glucose 155 mg/dL, 3-h blood glucose 140 mg/dL) [14].

Laboratory tests

Serum levels of thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were measured with automated immunochemiluminescent assay (ICMA) kits (Roche GmbH, Mannheim, Germany). The coefficients of variation for these thyroid profile assays were all below 10%. Interassay CV and limit of detection were 1.88% and 0.5 ng/dL for FT4 and 2.84% and 0.6 ng/dL for FT3, respectively. The reference ranges of TSH, FT4, and FT3 were 0.38–5.33 mIU/L, 0.58–1.38 ng/dL, and 2.0–4.4 pg/mL, respectively. Euthyroidism was defined as having TSH, FT4, and FT3 within the reference ranges and no history of thyroid disorders. Fasting, 1-h, 2-h, and 3-h glucose concentrations were determined using the enzymatic colorimetric method with glucose oxidase.

Indices of thyroid hormone sensitivity

Indices of thyroid hormone sensitivity were checked between 10 and 20 weeks of gestation during the first antenatal visit. The central indices of thyroid hormone sensitivity included the Thyroid Feedback Quantile-based Index ($TFQI_{FT4}$ and $TFQI_{FT3}$), TSH Index (TSHI), and Thyrotroph T4 Resistance Index (TT4RI). $TFQI_{FT4}$ was calculated using the algorithm $TFQI = cdfFT4 - (1 - cdfTSH)$ developed by Laclaustra et al. [9]. The index range is ± 1. Negative values indicate that the HPT axis is more sensitive to changes in thyroid hormones, whereas positive values indicated lower sensitivity to thyroid hormones. To investigate the role of FT3 in this index, we replaced FT4 in the $TFQI_{FT4}$ formulas with FT3 to obtain $TFQI_{FT3}$ [12]. TSHI and TT4RI were defined as $\ln \text{TSH (mU/L)} + 0.1345 \times \text{FT4 (pmol/L)}$ and $\text{FT4 (pmol/L)} \times \text{TSH (mU/L)}$, respectively [15]. An increased TSHI and TT4RI indicated reduced central sensitivity to thyroid hormones. The FT3/FT4 ratio was calculated to evaluate peripheral thyroid hormone sensitivity, and an increased FT3/FT4 ratio indicated increased peripheral thyroid hormone sensitivity.

Statistical analysis

Statistical analysis was performed using IBM SPSS for Windows version 21.0. Continuous variables with normal distributions are expressed as mean ± standard deviation (SD). Categorical variables are presented as frequencies (%). Normality was tested using the Kolmogorov–Smirnov test. We used independent samples *t*-tests to compare continuous variables between participants with and without GDM. Chi-square tests were used to compare categorical variables. Using one-way analysis of variance, we compared baseline characteristics between the $TFQI_{FT4}$ and $TFQI_{FT3}$ quartiles for comparison of means. Multivariable logistic regression was applied to estimate the crude and full-adjusted odds ratios (ORs) of GDM by quartiles of FT3, FT4, TSH, FT3/FT4, TSHI, TT4RI, $TFQI_{FT4}$, and $TFQI_{FT3}$, respectively. Tests of linear trend were performed using the median of each quartile as a continuous variable in the regression models. Thyroid variables were further standardized to estimate GDM risk with one SD change. To evaluate the performance of the indices, we examined the receiver operating characteristics curves (ROC), which plot sensitivity against 1 − specificity. $p \leq 0.05$ was taken to indicate a significant difference.

Table 1 Baseline characteristics of participants with GDM and non-GDM

Parameters	GDM group ($n=241$)	Non-GDM group ($n=1175$)	*p* values
Age (year)	31.13 ± 5.51	28.83 ± 5.17	< 0.001
BMI (kg/m^2)	26.84 ± 2.56	23.51 ± 3.02	< 0.001
FPG (mg/dL)	91.71 ± 12.58	86.74 ± 10.72	< 0.001
TSH (mIU/L)	1.95 ± 1.02	1.89 ± 0.95	0.345
FT4 (pmol/L)	11.19 ± 2.57	11.39 ± 2.75	0.318
FT3 (pmol/L)	4.99 ± 0.64	4.78 ± 0.78	0.006
TSHI	2.03 ± 0.64	2.03 ± 0.63	0.937
TT4RI	21.95 ± 12.97	21.40 ± 11.93	0.520
$TFQI_{FT4}$	− 0.43 ± 0.31	− 0.41 ± 0.31	0.488
$TFQI_{FT3}$	− 0.33 ± 0.25	− 0.42 ± 0.28	0.001
FT3/FT4	0.45 ± 0.12	0.42 ± 0.13	0.036

Abbreviations: *BMI* body mass index, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid-stimulating hormone, *TSHI* TSH Index, *TT4RI* Thyrotroph T4 Resistance Index, $TFQI_{FT4}$ Thyroid Feedback Quantile-based Index calculated by FT4, $TFQI_{FT3}$ Thyroid Feedback Quantile-based Index calculated by FT3

Results

The baseline characteristics of pregnant women are presented in Table 1. Out of 1416 pregnant women, 241 (17%) were diagnosed with GDM, and 1175 (83%) were in the non-GDM group. Compared with the non-GDM group, participants in the GDM group had significantly higher ages and BMI (Table 1). The 668 patients had measurements of FT3 and compared with the non-GDM group, GDM patients tended to have a higher rate of plasma FT3, FT3/FT4 ratio, and $TFQI_{FT3}$ (Table 1). Moreover, higher fasting plasma glucose was observed in the GDM group. Baseline characteristics of the study population based on the $TFQI_{FT4}$ and $TFQI_{FT3}$ quartiles are presented in Tables 2 and 3, respectively. Table 4 shows the quartile distribution of $TFQI_{FT4}$ and $TFQI_{FT3}$ in both groups. The percentages of Q3 and Q4 for $TFQI_{FT3}$ were statistically significantly higher than the percentages of Q1 for $TFQI_{FT3}$ in the GDM group ($p=0.001$ and $p=0.002$, respectively).

To analyze whether TSHI, TT4RI, $TFQI_{FT4}$, $TFQI_{FT3}$, FT3/FT4, and FT3 have the capability to discriminate patients with GDM, ROC curve analyses were performed

Table 2 Baseline characteristic of the study population based on $TFQI_{FT4}$ quartile

Variables	$TFQI_{FT4}$				*p* values
	1st quartile (≤ − 0.69)	2nd quartile (> − 0.69, ≤ −0.49)	3rd quartile (> − 0.49, ≤ −0.13)	4th quartile (> − 0.13)	
Age (year)	29.55 ± 5.33	29.04 ± 5.38	29.06 ± 5.25	29.26 ± 5.22	0.545
BMI (kg/m^2)	23.80 ± 3.29	23.93 ± 3.31	24.30 ± 3.10	24.17 ± 2.98	0.173
FPG (mg/dL)	87.11 ± 11.37	88.55 ± 12.52	88.33 ± 11.39	87.58 ± 10.31	0.518
TSH (mIU/L)	1.48 ± 0.63	2.06 ± 0.97	2.02 ± 1.04	2.05 ± 1.02	< 0.001
FT4 (pmol/L)	8.51 ± 0.64	9.74 ± 0.86	12.02 ± 1.09	15.16 ± 1.31	< 0.001
FT3 (pmol/L)	4.81 ± 0.82	4.98 ± 0.78	4.87 ± 0.80	4.70 ± 0.67	0.008
TSHI	1.43 ± 0.44	1.91 ± 0.45	2.17 ± 0.49	2.62 ± 0.49	< 0.001
TT4RI	12.43 ± 4.91	19.44 ± 7.85	23.57 ± 10.83	30.56 ± 14.56	< 0.001
FT3/FT4	0.56 ± 0.10	0.51 ± 0.09	0.40 ± 0.07	0.32 ± 0.04	< 0.001

Abbreviations: *BMI* body mass index, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid-stimulating hormone, *TSHI* TSH Index, *TT4RI* Thyrotroph T4 Resistance Index, $TFQI_{FT4}$ Thyroid Feedback Quantile-based Index calculated by FT4, $TFQI_{FT3}$ Thyroid Feedback Quantile-based Index calculated by FT3

Table 3 Baseline characteristics of the study population based on $TFQI_{FT3}$ quartile

Variables	$TFQI_{FT3}$				*p* values
	1st quartile (≤−0.63)	2nd quartile (>−0.63, ≤−0.41)	3rd quartile (>−0.41, ≤−0.17)	4th quartile (>−0.17)	
Age (year)	29.63 ± 5.24	30.24 ± 5.37	29.46 ± 5.06	28.77 ± 5.32	0.098
BMI (kg/m^2)	23.92 ± 2.44	24.49 ± 2.14	26.17 ± 2.50	26.74 ± 2.72	< 0.001
FPG (mg/dL)	86.99 ± 11.01	87.17 ± 12.31	87.61 ± 10.83	88.29 ± 12.35	0.779
TSH (mIU/L)	1.61 ± 0.68	2.02 ± 0.95	1.98 ± 0.95	2.08 ± 1.07	< 0.001
FT4 (pmol/L)	12.01 ± 2.88	11.57 ± 2.81	12.45 ± 2.82	11.43 ± 2.73	0.005
FT3 (pmol/L)	3.97 ± 0.49	4.54 ± 0.23	5.00 ± 0.22	5.79 ± 0.47	< 0.001
TSHI	1.99 ± 0.59	2.14 ± 0.61	2.23 ± 0.64	2.12 ± 0.65	0.010
TT4RI	19.32 ± 9.48	23.37 ± 12.29	24.74 ± 13.81	23.58 ± 13.77	0.001
FT3/FT4	0.35 ± 0.09	0.41 ± 0.10	0.42 ± 0.10	0.53 ± 0.13	< 0.001

Abbreviations: *BMI* body mass index, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid-stimulating hormone, *TSHI* TSH Index, *TT4RI* Thyrotroph T4 Resistance Index, $TFQI_{FT4}$ Thyroid Feedback Quantile-based Index calculated by FT4, $TFQI_{FT3}$ Thyroid Feedback Quantile-based Index calculated by FT3

Table 4 The quartile distribution of $TFQI_{FT4}$ and $TFQI_{FT3}$

Variable	Quartile	GDM group	Non-GDM group	*p* values
$TFQI_{FT4}$	Q1	60 (24.9%)	294 (25%)	0.522
	Q2	68 (28.2%)	286 (24.4%)	
	Q3	60 (24.9%)	293 (25%)	
	Q4	53 (22.0%)	301 (25.6%)	
$TFQI_{FT3}$	Q1	16 (12.8%)[a,b]	143 (27.9%)	0.004
	Q2	32 (25.6%)	128 (25.0%)	
	Q3	39 (31.2%)	122 (23.8%)	
	Q4	38 (30.4%)[b]	120 (23.4%)	

Different letters show significant differences at $p < 0.05$

[a] *p* value between Q1 and Q3 = 0.001

[b] *p* value between Q1 and Q4 = 0.002

(Fig. 1). An AUC value of 0.591 (95% confidence interval [CI]: 0.539–0.644; $p = 0.001$) for $TFQI_{FT3}$ was better than that of other potential biomarkers for distinguishing GDM from non-GDM patients. FT3 followed $TFQI_{FT3}$ (AUC = 0.590; 95% confidence interval [CI]: 0.537–0.642; $p = 0.001$).

Compared with the lowest quartile of FT3 and $TFQI_{FT3}$, the third quartile group had a significantly increased risk of GDM by 108% (OR: 2.08; 95% CI: 1.10–3.96; *p* trend = 0.034) for FT3 and 164% (OR: 2.64; 95% CI: 1.36–5.11; *p* trend = 0.016) for $TFQI_{FT3}$. Similarly, compared with the lowest quartile of FT3 and $TFQI_{FT3}$, the highest quartile group had a significantly increased risk of GDM by 134% (OR: 2.34; 95% CI: 1.07–3.98; *p* trend = 0.034) for FT3 and 160% (OR: 2.60; 95% CI: 1.31–5.15; *p* trend = 0.016) for $TFQI_{FT3}$. In addition, the second quartile group had a significantly increased risk of GDM compared with the lowest quartile of $TFQI_{FT3}$ (OR: 2.06; 95% CI: 1.07–3.97). Pregnant women with one standard deviation increase in FT3 and $TFQI_{FT3}$ were significantly associated with an increased risk of GDM by 27% (OR: 1.27; 95% CI: 1.02–1.58) and 32% (OR: 1.32; 95% CI: 1.05–1.65), respectively (Table 5).

The current status of glucose metabolism was also recorded in 182 of 241 patients with GDM at a mean follow-up period of 16.92 ± 4.91 months. Of the 182 patients, 132 were normoglycemic, 43 were prediabetic, and 6 were diabetic. No correlations were observed between the indices of thyroid hormone sensitivity that were evaluated at the first antenatal visit and the eventual status of glucose metabolism in these patients.

Discussion

In this study, we evaluated the association of the indices of sensitivity to thyroid hormones, including $TFQI_{FT4}$, $TFQI_{FT3}$, TSHI, TT4RI, and FT3/FT4, with GDM in euthyroid pregnant women. We found that higher levels of FT3, $TFQI_{FT3}$, and the FT3/FT4 ratio in GDM as well as conspicuously increased levels of FT3 and $TFQI_{FT3}$ were associated with a greater GDM risk after adjusting for potential confounders, including age and BMI.

Thyroid hormones have significant effects on the regulation of glucose metabolism. Numerous studies have found that both hypothyroidism and hyperthyroidism are remarkably associated with impaired glucose metabolism [16, 17]. Considering the role of thyroid hormones in glucose metabolism, it has been proposed that thyroid dysfunction plays a role in the etiology of GDM. However, the available evidence is conflicting. Milovanovic et al. reported that the prevalence of TSH > 2.5 μIU/mL in the first trimester was 42.2% in the GDM group, in contrast to the lower number of GDM (17.8%) diagnosed with subclinical hypothyroidism

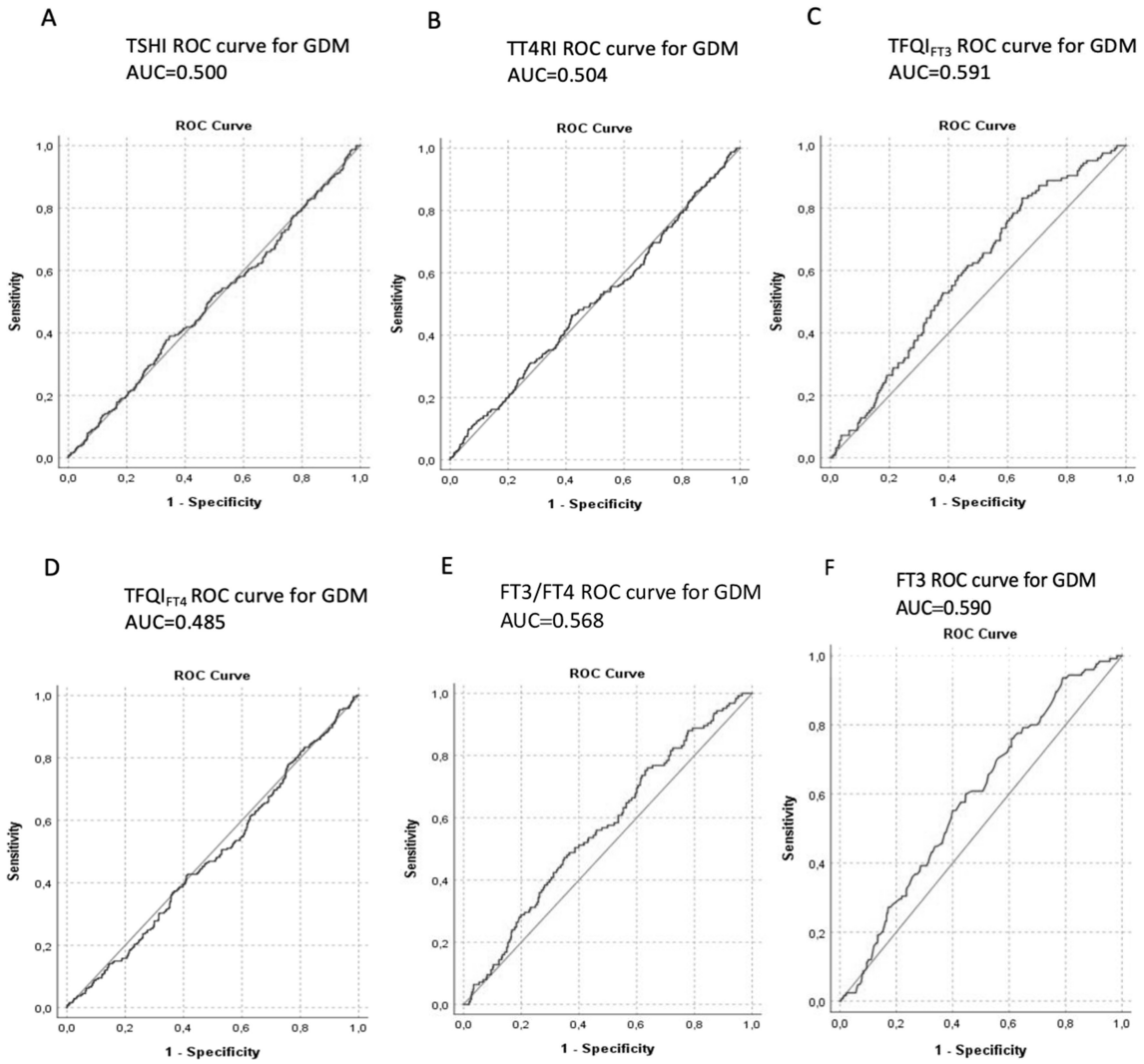

Fig. 1 ROC curve for GDM from TSHI, TT4RI, TFQI$_{FT3}$, TFQI$_{FT4}$, FT3/FT4, and FT3. Abbreviations: ROC, receiver operating characteristics; AUC, area under the curve; GDM, gestational diabetes mellitus; FT3, free triiodothyronine; FT4, free thyroxine; TSHI, TSH Index; TT4RI, Thyrotroph T4 Resistance Index; TFQI$_{FT4}$, Thyroid Feedback Quantile-based Index calculated by FT4; TFQI$_{FT3}$, Thyroid Feedback Quantile-based Index calculated by FT3

(SCH) using the criterion TSH > 4 μIU/mL in that study [18]. Alba et al. also showed that pregnant women with SCH defined TSH > 4.72 mIU/L as a significantly greater risk for GDM compared with euthyroid pregnant women (OR: 1.85; 95% CI: 1.36–2.52) [19]. In contrast, a meta-analysis by Maraka et al. reported no association between SCH and the risk for GDM [6]. That inconsistency in their results may be explained by the different cut-off points used to define SCH between 2.5 and 5 mIU/L. Furthermore, differences in study design and sample size may explain these conflicting data in the literature. In 2017, the new American Thyroid Association (ATA) guideline updated the cut-off TSH values above 4.0 μIU/mL for SCH during pregnancy [3]. According to the new ATA guideline, Rawal et al. found that TSH levels were similar between GDM and non-GDM groups [13]. Similarly, in our study, there were no differences in TSH levels, which were within the normal reference range (0.38 to 5.33 mIU/L) between the GDM and non-GDM groups.

In the literature, compared with TSH, fewer studies have examined the associations between FT3, FT4, and glucose metabolism in pregnant women. A large prospective cohort study by Yang et al. evaluated the correlations between different levels of thyroid hormones, except for FT3, during early pregnancy and the incidence of GDM and reported an inverse association between FT4 and GDM [20]. The authors speculated that low FT4 levels may indicate increased conversion from FT4 to FT3 or increased deiodinase (DIO) activity in patients with GDM [20]. The FT3/FT4 ratio, which is a marker of the conversion of FT4 to FT3, may be considered an indicator of peripheral deiodinase (DIO)

Table 5 Odds ratios (ORs) and 95% confidence intervals (CIs) of GDM by quartiles and per SD increment of thyroid function tests and central and peripheral indices of thyroid hormone sensitivity during early pregnancy

Thyroid hormones (min–max)		Crude OR (95% CI)	Adjusted OR (95% CI)	Per SD OR (95% CI)
FT3 (pmol/L)	Q1 (< 4.30)	1	1	1.37 (1.12–1.68)
	Q2 (4.31–4.79)	1.61 (0.85–3.04)	1.45 (0.76–2.77)	
	Q3 (4.80–5.27)	2.32 (1.26–4.29)	2.08 (1.10–3.96)	
	Q4 (> 5.28)	2.29 (1.24–4.22)	2.34 (1.07–3.98)	
	p for trend	0.006	0.034	
FT4 (pmol/L)	Q1 (< 9.00)	1	1	0.94 (0.81–1.08)
	Q2 (9.01–10.68)	1.24 (0.83–1.85)	1.23 (0.77–1.95)	
	Q3 (10.69–13.51)	1.09 (0.73–1.64)	0.95 (0.60–1.51)	
	Q4 (> 13.52)	0.82 (0.54–1.26)	0.76 (0.47–1.22)	
	p for trend	0.318	0.240	
TSH (mIU/L)	Q1 (< 1.19)	1	1	1.10 (0.96–1.26)
	Q2 (1.20–1.74)	1.02 (0.69–1.51)	0.98 (0.63–1.52)	
	Q3 (1.75–2.47)	0.96 (0.64–1.42)	0.87 (0.56–1.36)	
	Q4 (> 2.48)	1.08 (0.73–1.59)	0.92 (0.60–1.43)	
	p for trend	0.345	0.799	
Peripheral thyroid resistance index				
FT3/FT4	Q1 (< 0.33)	1	1	1.26 (1.04–1.53)
	Q2 (0.34–0.42)	1.56 (0.84–2.89)	1.38 (0.73–2.60)	
	Q3 (0.43–0.52)	1.63 (0.89–2.99)	1.59 (0.86–2.94)	
	Q4 (> 0.53)	2.23 (1.24–3.98)	2.06 (1.13–3.76)	
	p for trend	0.036	0.065	
Central thyroid resistance indices				
TSHI	Q1 (< 1.59)	1	1	1.04 (0.90–1.19)
	Q2 (1.60–2.07)	0.79 (0.53–1.18)	0.84 (0.53–1.32)	
	Q3 (2.08–2.46)	0.99 (0.67–1.45)	0.98 (0.63–1.53)	
	Q4 (> 2.47)	0.95 (0.64–1.40)	0.85 (0.55–1.32)	
	p for trend	0.937	0.548	
TT4RI	Q1 (< 12.63)	1	1	1.07 (0.993–1.23)
	Q2 (12.64–19.27)	0.96 (0.65–1.42)	0.98 (0.63–1.53)	
	Q3 (19.28–27.82)	0.94 (0.64–1.40)	0.99 (0.63–1.55)	
	Q4 (> 27.83)	1.04 (0.71–1.53)	0.91 (0.59–1.42)	
	p for trend	0.519	0.905	
$TFQI_{FT4}$	Q1 (< − 0.69)	1	1	0.96 (0.84–1.11)
	Q2 (− 0.68 to − 0.49)	1.23 (0.83–1.82)	1.29 (0.83–2.00)	
	Q3 (− 0.48 to − 0.13)	1.05 (0.71–1.57)	0.97 (0.62–1.51)	
	Q4 (> − 0.12)	0.90 (0.60–1.36)	0.86 (0.55–1.35)	
	p for trend	0.487	0.309	
$TFQI_{FT3}$	Q1 (< − 0.63)	1	1	1.41 (1.15–1.73)
	Q2 (− 0.62 to − 0.41)	2.17 (1.13–4.16)	2.06 (1.07–3.97)	
	Q3 (− 0.40 to − 0.17)	2.98 (1.58–5.64)	2.64 (1.36–5.11)	
	Q4 (> − 0.16)	3.08 (1.62–5.84)	2.60 (1.31–5.15)	
	p for trend	0.002	0.016	

Univariate and multivariable logistic regressions were used for statistical analyses with the adjusted variable including maternal age (year) and BMI. Abbreviations: *GDM*, gestational diabetes mellitus; *BMI*, body mass index; *FT3*, free triiodothyronine; *FT4*, free thyroxine; *TSH*, thyroid-stimulating hormone; *TSHI*, TSH Index; *TT4RI*, Thyrotroph T4 Resistance Index; $TFQI_{FT4}$, Thyroid Feedback Quantile-based Index calculated by FT4; $TFQI_{FT3}$, Thyroid Feedback Quantile-based Index calculated by FT3

activity [21]. A few studies have noted that the levels of FT3 and/or the FT3/FT4 ratio are related to the risk of GDM [13, 22]. Rawal et al. found that the level of FT3 and FT3/FT4 ratio were significantly and positively associated with GDM risk in both the first and second trimesters [13]. Another study by Zhu et al. [22] demonstrated that levels of FT3

and FT3/FT4 ratio in the first and second trimesters were positively associated with the risk of GDM among 2723 individuals. Similarly, in our study, we identified higher FT3 levels and FT3/FT4 ratio among women with GDM; however, the association was not significant for FT3/FT4 after adjusting for potential confounders, including age and BMI.

Thyroid hormone levels alone may be insufficient to explain the relationship between thyroid status and GDM. Indeed, TSH, FT4, and FT3 are all tightly influenced by each other, and circulating thyroid hormones are regulated by the HPT axis through a negative feedback loop. Therefore, new indices can estimate thyroid hormone homeostasis. Recently, Laclaustra et al. suggested that TFQI is a new central sensitivity to the thyroid hormone index [9]. They showed that TFQI values are related to diabetes and diabetes-related mortality. Impaired HPT sensitivity to thyroid hormones has also been suggested to be associated with adverse clinical outcomes, such as obesity [23] and type 2 diabetes [9]. A recent cross-sectional study suggested that the new TFQI index is the most relevant indicator of decreased thyroid hormone sensitivity for diabetes and hypertension in euthyroid subjects [15]. However, a study of a Chinese population showed that decreased sensitivity to thyroid hormones (increased TSHI, TT4RI, and parametric TFQI) is associated with a lower risk of prediabetes and has a protective effect [24]. Although contradictory results have been obtained from the aforementioned studies, these findings suggest the potential role of sensitivity to thyroid hormones in the regulation of glucose metabolism. To the best of our knowledge, there have been few studies focusing on the association between sensitivity to thyroid hormones and the risk of GDM. Thus, in the present study, we investigated the correlation between both central and peripheral sensitivity to thyroid hormone indices and GDM. We showed higher levels of $TFQI_{FT3}$ and FT3/FT4 in patients with GDM; however, the other indices were similar between groups. $TFQI_{FT3}$ and FT3/FT4 performed better than the other indices on ROC analyses for GDM prediction. After adjustment for age and BMI, only $TFQI_{FT3}$ was independently associated with the risk of GDM. A recent study reported that lower central resistance indices ($TFQI_{FT4}$, TSHI, and TT4RI) and higher levels of FT3 and FT3/FT4 were associated with an increased risk of GDM in pregnant women with or without euthyroidism [25]. In contrast, $TFQI_{FT4}$, TT4RI, and TSHI were not associated with the risk of GDM in our study.

Several mechanisms may explain the observed association between central and peripheral resistance to thyroid hormones and glucose metabolism. T3 is a biologically active thyroid hormone that stimulates gluconeogenesis [7] and levels of FT3 are positively associated with insulin secretion and hyperinsulinemia [26]. In addition, T3 has an important effect on the control of energy expenditure. For instance, T3 can increase glucose uptake in skeletal muscle cells by increasing GLUT4 expression [27]. Approximately 80% of circulating T3 levels are derived from T4 [28], suggesting that the FT3/FT4 ratio is a significant marker for glucose homeostasis. Elevated FT3 levels and FT3/FT4 ratio can be observed as an adaptive mechanism for increased energy expenditure during pregnancy. Only a few studies have investigated the association between the FT3/FT4 ratio and the risk of GDM.

In addition to peripheral pathways, cross-talk between the HPT axis and glucose metabolism can also be achieved through hormonal regulation, particularly leptin. Leptin is a hormone secreted from the adipose tissue and placenta [7]. Leptin stimulates TRH neurons by inducing signal transducer and activator of transcription (STAT) 3 phosphorylation [7], and it upregulates the expression of DIO1 in peripheral tissues [29]. While both leptin and thyroid hormones regulate energy metabolism, data on the relationship between leptin levels and thyroid disorders are conflicting. A systematic review and meta-analysis by Hosseini et al. recently showed that higher maternal levels of leptin are associated with an increased risk of GDM [30]. Although the exact mechanism between central sensitivity to thyroid hormones and the leptin pathway remains unclear, increased leptin levels during early pregnancy may contribute to the development of GDM by increasing the central effects of T3.

Some limitations of the present study should be recognized. Thyroid indices were assessed only at the first antenatal visit. It should be noted, however, that changes in insulin and insulin sensitivity during pregnancy may have an impact on thyroid indices. Future prospective studies evaluating the dynamic pregnancy process should investigate the pathogenetic relationship between insulin sensitivity, thyroid hormones, and related indices. Second, we did not measure total T3 and free hormone assays may have limitations due to the method of measurement. Third, the indices of thyroid hormone sensitivity were not validated in Turkish population. Lastly, we have no subgroups for patients who were managed by only diet and those who required insulin treatment. Since the follow-up period was short in our patients with GDM, we could not predict long-term glucose metabolism disorders. However, maternal and fetal complications can be reduced by early detection of GDM.

Although TSH and T4 levels are routinely measured in early pregnancy, T3 measurement is neglected. In addition, the ATA guideline recommends trimester-specific cut-off values for TSH in pregnancy to prevent adverse pregnancy outcomes, including GDM. However, FT3 and $TFQI_{FT3}$ were independently associated with the risk of GDM in this study. Indices of thyroid sensitivity are a more systemic view and provide important complementary information about the integrity of the feedback relationship between thyroid hormones and TSH in the pituitary. Our findings extend the classical concept of individually measuring thyroid markers

and add new quantitative dimensions to assess thyroid homeostasis in pregnant women.

Conclusion

Our present study demonstrates that increased FT3 and $TFQI_{FT3}$ in the first antenatal visit of pregnancy may predict GDM. Taken together, these findings suggest that higher levels of FT3 are related to the pathophysiology of GDM. Future studies evaluating insulin resistance as well as dynamic changes in thyroid hormone levels during pregnancy may help to explain the current findings.

Author contribution Nese Ersoz Gulcelik and Safak Akin designed the study. Safak Akin, Pinar Ulgen, Busra Sen Yildirim, and Ozhan Ozdemir contributed to data collection. Safak Akin and Eda Karaismailoglu performed statistical analysis. Safak Akin contributed to data analysis and writing the paper. Nese Ersoz Gulcelik provided lots of useful comments in this work. All authors read and approved the final manuscript.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Gülhane Training and Research Hospital (Date 06.04.2022/ No 2022/35).

Consent to participate Written informed consent was obtained from each participant before the measurement.

Consent for publication Authors are responsible for correctness of the statements provided in the manuscript.

Conflict of interest The authors declare no competing interests.

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