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CLINICAL RESEARCH

Association of thyroid-stimulating hormone with corrected QT interval variation: A prospective cohort study among patients with type 2 diabetes☆

Association de la TSH avec la durée de l'intervalle QTc et de sa variation : une étude de cohorte prospective chez des patients diabétiques de type 2

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Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; Cred-drugsTdP, drugs known to cause TdP according to the CredibleMeds website; *DIACART*, *Diabète et Calcification Arterielle*; *HbA1c*, *haemoglobin A1c* (glycated haemoglobin); IGF1, insulin-like growth factor 1; IQR, interquartile range; QTc, QT interval corrected for heart rate; *QTcB*, *Bazett's corrected QT interval*; QTcF, Fridericia's *corrected QT interval*; T2DM, type 2 diabetes mellitus; T3, triiodothyronine; T4, thyroxine; TdP, torsades-de-pointes; TSH, thyroid-stimulating hormone; VA, ventricular arrhythmia.

☆ Tweet: Serum TSH is associated with QTcF variation in euthyroid type 2 diabetics even after correction of QT prolonging drugs.

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KEYWORDS
Thyroid-stimulating hormone;
Electrocardiogram;
QT prolongation;
Arrhythmias;
Diabetes

Summary
Background. — Patients with type 2 diabetes mellitus (T2DM) have a prolonged QT interval and are at high risk of sudden cardiac death. A prolonged QT interval, indicative of impaired ventricular repolarization, is a risk factor for lethal ventricular arrhythmias, such as torsades-de-pointes (TdP).
Aims. — To identify key clinical and biochemical covariates associated with Fridericia's corrected QT interval (QTcF) among euthyroid patients with T2DM, and to describe the temporal relationship between these factors and QTcF.
Methods. — We performed prospective, clinical, biochemical and electrocardiographic measurements among patients with T2DM enrolled in the DIACART study at Pitié-Salpêtrière Hospital, at T1 (baseline) and T2 (follow-up), with a median interval of 2.55 years.
Results. — Mean age (63.9 ± 8.5 years), sex (22.35% women), drugs with known risk of TdP according to the CredibleMeds website (Cred-drugsTdP) and serum thyroid-stimulating hormone (TSH) concentrations correlated with QTcF in univariate analysis at both T1 and T2. In multivariable analysis, all these covariates except age were significantly associated with QTcF at both T1 (women: standardized $\beta = 0.24 \pm 0.07$, $P = 0.001$; Cred-drugsTdP: $\beta = 0.19 \pm 0.07$, $P = 0.007$; TSH concentration: $\beta = 0.18 \pm 0.07$, $P = 0.01$) and T2 (women: $\beta = 0.25 \pm 0.08$, $P = 0.002$; Cred-drugsTdP: $\beta = 0.25 \pm 0.08$, $P = 0.001$; TSH concentration: $\beta = 0.19 \pm 0.08$, $P = 0.01$). Furthermore, variation in QTcF over the years was associated with variation in TSH concentration ($r = 0.24$, $P = 0.007$) and changes in use of Cred-drugsTdP ($r = 0.2$, $P = 0.02$).
Conclusions. — Serum TSH concentration and its variation were associated with QTcF and its variation, even after correcting for the main determinants of QTcF. Interventional optimization of TSH concentration in T2DM warrants further investigation to establish its impact on the risk of TdP and sudden cardiac death.

MOTS CLÉS
Thyrotropine ;
Électrocardiogramme ;
Allongement de l'intervalle QT ;
Arythmies ;
Diabète

Résumé
Contexte. — Les patients atteints de diabète de type 2 (DT2) ont un intervalle QT prolongé et présentent un risque plus élevé de mort subite d'origine cardiaque versus la population générale. Un intervalle QT prolongé, indicatif d'une repolarisation ventriculaire altérée, est un facteur de risque d'une forme particulière d'arythmies ventriculaires potentiellement mortelles, appelées torsades de pointes (TdP).
Objectifs. — (1) Comprendre les principales covariables cliniques et biochimiques associées à l'intervalle QT corrigé pour la fréquence cardiaque par la méthode de Fridericia (QTcF) chez les patients atteints de DT2, (2) comprendre comment ces facteurs peuvent prédire une variation temporelle du QTcF.
Méthodes. — Nous avons effectué des mesures cliniques, biochimiques et électrocardiographiques prospectives chez 215 patients atteints de DT2 aux temps T1 (référence) et T2 (suivi), avec un intervalle médian de 2,55 ans (NCT02431234). L'analyse multivariée a été réalisée par analyse de covariance (ANCOVA).
Résultats. — L'âge ($63,9 \pm 8,5$ ans), le sexe (22,35 % de femmes), les médicaments à risque connu de TdP selon le site Web de Crediblemeds (Cred-drugsTdP) et les taux sériques de TSH étaient corrélés avec le QTcF en analyse univariée à T1 et à T2. En analyse multivariée, toutes ces covariables sauf l'âge étaient significativement associées au QTcF à T1 (femmes: $\beta = 0,24 \pm 0,07$, $p = 0,001$; Cred-drugsTdP: $\beta = 0,19 \pm 0,07$, $p = 0,007$ et taux de TSH: $\beta = 0,18 \pm 0,07$, $p = 0,01$) et à T2 (femmes: $\beta = 0,25 \pm 0,08$, $p = 0,002$, Cred-drugsTdP: $\beta = 0,25 \pm 0,08$, $p = 0,001$ et taux de TSH: $\beta = 0,19 \pm 0,08$, $p = 0,01$). De plus, la variation du QTcF au cours du temps était associée à une variation des taux de TSH ($r = 0,24$, $p = 0,007$) et aux changements dans l'utilisation de Cred-drugsTdP ($r = 0,2$, $p = 0,02$).

Conclusion. — Les taux sériques de TSH et sa variation étaient associés au QTcF et à sa variation, même après correction des principales covariables déterminantes du QTcF. L'optimisation interventionnelle des niveaux de TSH dans le DT2 mérite d'être évaluée plus avant pour établir son impact sur le risque de TdP et de mort subite.

Background

Patients with type 2 diabetes mellitus (T2DM) have a predilection for prolonged QTc duration, ventricular arrhythmias (VAs) and sudden cardiac death [1] compared with the general population. The QT interval corrected for heart rate (QTc) serves as an inexpensive and non-invasive modality by which clinicians can assess ventricular repolarization—heterogeneity of which may cause a particular form of VA, called torsades-de-pointes (TdP) [2]. Apart from an increased risk of VAs, prolonged QTc has also been shown to be a predictor of mortality among patients with T2DM [1].

The aetiologies for QTc prolongation and risk of VAs among patients with diabetes are complex, because of several concomitant conditions and hormonal fluctuations that can affect action potential duration. Conditions that are often prevalent in the diabetic population, such as systemic arterial hypertension, hypoglycaemia associated with autonomic dysfunction, left ventricular hypertrophy, conduction abnormalities and systolic dysfunction, have been previously shown to be associated with prolongation of QTc in T2DM [3]. Concomitant overt and subclinical thyroid disorders frequently observed among patients with diabetes may further increase the risk of QTc prolongation and VAs as a result of the effect of thyroid-stimulating hormone (TSH) on action potential duration [4]. In fact, changes observed in repolarization on electrocardiograms in patients with subclinical hypothyroidism (normal triiodothyronine [T3] or thyroxine [T4] concentrations and elevated TSH) are similar to those in patients with overt hypothyroidism, which suggests a direct role for TSH in the regulation of the cardiac conduction system and risk of TdP [5]. The temporal variations in these clinical and biochemical factors and in QTc duration, however, have not been fully elucidated.

We aimed to identify key clinical and biochemical covariates associated with Fridericia's corrected QT interval (QTcF) and their variation over time in a prospective cohort of patients with T2DM at high risk of cardiovascular disease.

Methods

Study design

Our work is ancillary to the *Diabète et Calcification Arterielle* (DIACART) study, a single-centre prospective observational cohort study among French patients with T2DM. The detailed protocol for our current study has been described elsewhere [6]. All patients provided written informed consent, and the study was approved by the institutional ethics committee. The DIACART study is registered at ClinicalTrials.gov (Identifier: NCT02431234).

Study population

Our study population consisted of a subset of patients who were recruited for the DIACART study; the selection of our study population from the DIACART study is outlined in Fig. 1. Over an 8-month period, 215 patients with T2DM aged $\geq$ 50 years (60 years for women), at high risk of cardiovascular disease (peripheral artery disease and heart failure), seen in the departments of cardiology and diabetology at the Pitié-Salpêtrière Hospital (Paris, France), were included in the DIACART study at times T1 (baseline) and T2 (follow-up). The main exclusion criteria were severe chronic kidney disease or end-stage renal failure (calculated as estimated glomerular filtration rate < 30 mL/min using the Modification of Diet in Renal Disease equation). As QTcF measurements are unreliable in patients with prolonged QRS (> 130 ms), multiple premature ventricular contractions, ventricular pacing and supraventricular tachycardia, patients with these conditions were excluded from this study (Fig. 1).

Clinical evaluation and laboratory tests

A detailed medical history was taken and a clinical examination was performed at the Centre d'Investigation Clinique-Paris Est (CIC-1901, Pitié-Salpêtrière Hospital, France). Medication history was obtained from the patients to identify those who were taking drugs known to increase the risk of TdP according to the CredibleMeds website (CreddrugsTdP) [7]. Urine and blood samples were collected after an overnight fast to perform routine biochemical tests, acquire lipid and thyroid profiles, measure blood glucose, haemoglobin A1c (HbA1c; glycated haemoglobin) and electrolytes and assess renal function.

Electrocardiography acquisition and QTc analysis

Electrocardiograms were recorded using a digital electrocardiograph (ELI 280, V1.02.01; Mortara Instrument, Inc., Milwaukee, WI, USA) by trained nurses, with a sampling rate of 1000 Hz and a filter of 150 Hz. The 12-lead 10-second resting triplicate electrocardiograms were analysed with the concatenation method: the three 10-second sequences of the triplicate electrocardiogram were used as a single 30-second electrocardiogram, followed by semiautomated QTc

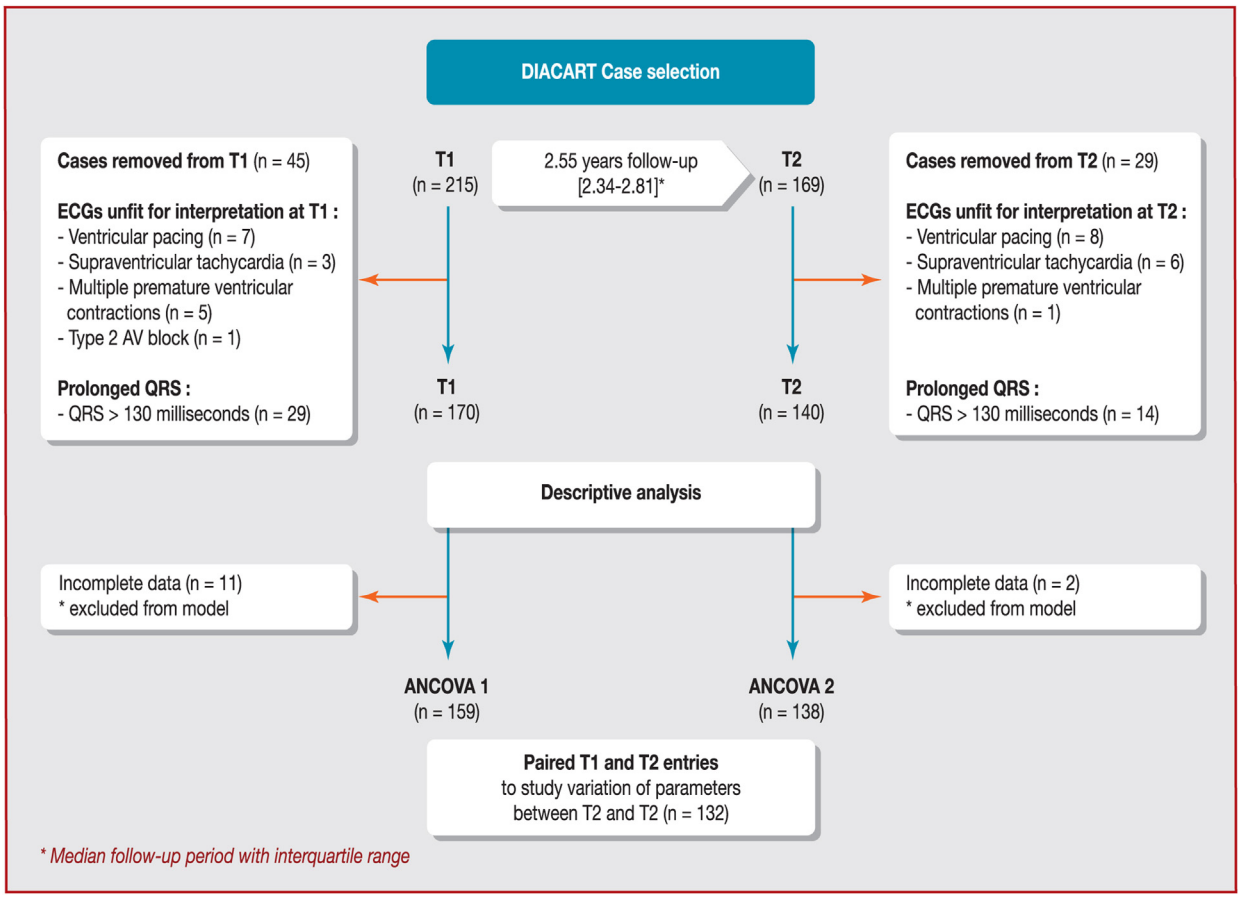

Figure 1. Flow chart of patient selection from the *Diabète et Calcification Arterielle* (DIACART) study. ANCOVA: analysis of covariance; AV: atrioventricular; ECG: electrocardiogram; T1: baseline; T2: follow-up; y: year. [a] Median follow-up period with interquartile range. [Publishers: * to be changed to [a] in figure.].

determination, using a unique superimposed median beat, by the overlap method (Fig. 2; CalECG® software; AMPS LLC, New York, NY, USA). In our centre, inter- and intraobserver variability assessment for QTc measurement using this method was performed, which has been detailed elsewhere [8]. The QT interval was corrected for heart rate by Fridericia's method. Although Bazett's method (QTcB) is most widely used, several studies have shown its inferiority compared with Fridericia's method, as QTcB tends to overcorrect the QT interval at low heart rate and undercorrect it at high heart rate in both sexes [9]. In addition, in a hospitalized setting, QTcF was a better predictor of 30-day and 1-year all-cause mortality than QTcB [9].

Statistical analyses

Data were analysed using the Statistical Package for Social Services, version 24 (IBM Corp. Armonk, NY, USA) and XLSTAT® (Addinsoft, Paris, France). Pearson's or Spearman's correlation coefficients and analysis of covariance (ANCOVA) were calculated to assess the associations between QTcF and patient characteristics, as appropriate. Studied variables were age, sex, homeostatic model assessment of insulin resistance, circulating concentrations of glucose, insulin, insulin-like growth factor1 (IGF1), albumin, creatinine, HbA1c, corrected calcium, potassium, TSH, T3, T4 and Cred-drugsTdP. A univariate correlation analysis between QTcF and patients' characteristics at both T1 and T2 was performed to select variables to be considered for the multivariable model. The multivariable models (ANCOVA at T1 and T2) were selected using a stringent criterion, i.e. the lowest Schwartz Bayesian criterion. Statistical analyses were two-tailed, with a P-value < 0.05 deemed significant.

Results

Baseline demographics and clinical and biochemical characteristics in patients with T2DM

Out of the 215 cases enrolled in DIACART, 169 returned for follow-up measurements. Forty-five cases at T1 and 29 at T2 with conditions that rendered QTcF measurements unreliable (prolonged QRS, supraventricular tachycardia, ventricular pacing and multiple premature ventricular contractions) were excluded from the study (Fig. 1).

The demographic, clinical and biochemical profiles of the 170 and 140 patients with T2DM ultimately included at times T1 and T2, respectively, are shown in Table 1. T1 and T2 were

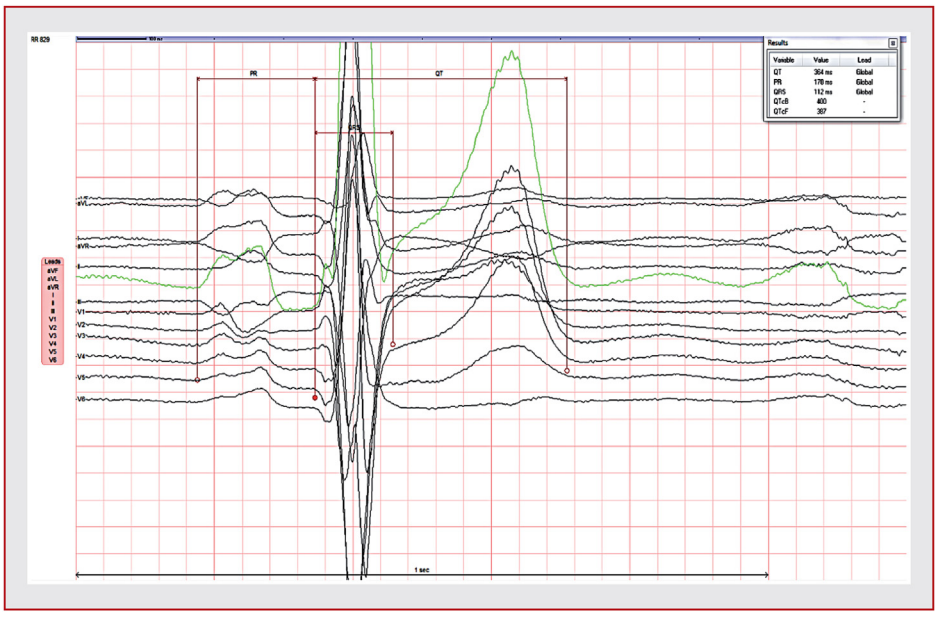

Figure 2. Example of QT measurement by the overlap method. *QTcB: Bazett's corrected QT interval;* QTcF: Fridericia's *corrected QT interval.*

separated by a median of 2.55 years [interquartile range (IQR) 2.34—2.81 years]. Mean age was 63.9 ± 8.5 years at the beginning of the study, and 38/170 (22.35%) patients were female. Median HbA1c was 7.50% (IQR 7.00—8.33) at T1 and 7.65% (IQR 6.9—8.30) at T2. Normal, borderline and prolonged QTcF were defined as QTcF < 430 ms, 430—450 ms and > 450 ms, respectively, in men, and 20 ms above these thresholds in women. A total of 20/170 (11.8%) and 26/140 (18.6%) participants had prolonged QT (borderline or prolonged QT) at T1 and T2, respectively. A total of 8/170 (4.7%) patients at T1 and 8/140 (5.7%) at T2 were taking Cred-drugsTdP [7]. A majority (88.8% at T1 and 91.4% at T2) of the study population were euthyroid, and only one patient had hypothyroidism at T1 (Table 1).

Clinical and hormonal correlations with QTcF in patients with T2DM

Results of the univariate association between QTcF and the tested clinical and hormono-metabolomic circulating concentrations in this T2DM cohort are shown in Table 2. The variables showing a significant univariate correlation with QTcF were then considered for multivariable analysis. Using multiple regression and analysis of covariance (Table 2), five covariates: sex (β = 0.24 ± 0.07 for females), Cred-drugsTdP (β = 0.19 ± 0.07), TSH concentration (β = 0.18 ± 0.07), triglyceride concentration (β = 0.16 ± 0.07) and potassium concentration (β = −0.19 ± 0.07) were associated with QTcF ($r = 0.48$, $P < 0.0001$) at T1. Similarly, at T2, four covariates: sex (β = 0.25 ± 0.08 for females), Cred-drugsTdP (β = 0.25 ± 0.08), TSH concentration (β = 0.19 ± 0.08) and hypertension (β = 0.2 ± 0.08), were associated with QTcF ($r = 0.46$, $P < 0.0001$). Compared with males, females had a 11.7 ms increase in QTcF at T1 ($P = 0.001$) and a 13.6 ms increase at T2 ($P = 0.002$). Patients taking Cred-drugsTdP had an 18.7 ms increase in QTcF at T1 ($P = 0.007$) and a 25.1 ms increase in QTcF duration at T2 ($P = 0.01$) versus those who were not taking Cred-drugsTdP. With every unit increase in normalized TSH concentration, there was a significant 3.2 ms increase in QTcF at T1 ($P = 0.01$) and a 3 ms increase in QTcF at T2 ($P = 0.01$). Of note, there was no significant correlation between QTcF and free T3 (T1: $r = 0.04$, $P = 0.6$; T2: $r = -0.1$, $P = 0.3$) or free T4 (T1: $r = 0.01$, $P = 0.9$; T2: $r = 0.1$, $P = 0.3$). IGF1 was associated with QTcF in univariate analysis at both T1 ($r = -0.17$, $P = 0.03$) and T2 ($r = -0.25$, $P = 0.003$), but was not retained in the stepwise variable selection model (Table 2).

Temporal variation in TSH and QTcF in patients with T2DM

There were 132 patients with paired values for T1 and T2, which were used to analyse the trends in QTcF over time and their relationship with variations in other covariates. There was a significant increase in mean QTcF from T1 to T2 (mean difference 3.60 ms, 95% confidence interval [CI] 0.42—6.77; $P = 0.03$) (Fig. 3). We studied the effects of variations in the covariates that were found to be significantly associated with QTcF at both T1 and T2 (use of Cred-drugsTdP and TSH) on the variation in QTcF (as given by values in T2 minus those in T1). Changes in TSH and in the patient's Cred-drugsTdP status were correlated with variation in QTcF ($r = 0.24$, $P = 0.007$, $n = 123$ and $r = 0.2$, $P = 0.02$, $n = 132$, respectively) (Fig. 4). Furthermore, as a sensitivity analysis, when excluding patients who were on a drug from the Cred-drugsTdP list either at T1 or T2, the significant association between change in TSH concentration and variation in QTcF persisted ($r = 0.19$, $P = 0.04$, $n = 113$).

Discussion

To the best of our knowledge, our study is the first to demonstrate an association between a change in QTcF over time

Table 1 Demographic, clinical, biochemical and electrocardiographic measurements at baseline.

	Measurement at T1	Measurement at T2
	(n = 170)	(n = 140)
General characteristics		
Age (years)	64 ± 8	67 ± 8
Male sex	132 (77.7)	112 (80.0)
Weight (kg)	83.4 ± 15.3	83.2 ± 15.7
Height (m)	1.7 ± 0.1	1.7 ± 0.1
Body mass index (kg/m^2)	28.9 ± 4.7	28.8 ± 4.9
History of coronary artery disease[a]	111 (65.3)	91 (65)
Hypertension	137 (80.6)	120 (85.7)
Metabolic biochemistry profile		
HbA1c (%)	7.5 (7.0–8.3)	7.7 (6.9–8.3)
Blood glucose (mmol/L)	8.2 ± 2.7	8.8 ± 2.7
Insulin (mIU/L)	12.3 (6.8–17.7) (n = 168)	10.4 (4.9–16.8) (n = 139)
IGF1 (ng/mL)	144.7 ± 52.8 (n = 169)	124.1 ± 39 (n = 139)
HOMA-IR	4.1 (2.1–6.7) (n = 168)	5.4 (1.6–7.2) (n = 139)
Triglycerides (mmol/L)	1.2 (0.9–2.0)	1.4 (0.9–2.0)
Total cholesterol (mmol/L)	3.8 ± 0.9	4.0 ± 0.9
HDL cholesterol (mmol/L)	1.1 ± 0.4	1.1 ± 1.1
LDL cholesterol (mmol/L)	1.9 (1.5–2.4)	1.9 (1.6–2.5)
QT-prolonging drugs		
Present[b]	8 (4.7)	8 (5.7)
Renal function		
Creatinine (mmol/L)	87.0 (76.0–105.8)	84.0 (74.0–101.0)
Albumin (g/L)	42.2 ± 3.7	42.6 ± 3.1 (n = 137)
Electrolytes		
Calcium (mmol/L)[c]	2.3 ± 0.1	2.3 ± 0.1 (n = 138)
Potassium (mmol/L)	4.7 ± 0.4	4.6 ± 0.4 (n = 138)
Thyroid function[d]		
TSH (mIU/L)	1.9 (1.3–2.6) (n = 160)	1.7 (1.2–2.5) (n = 139)
Free T3 (pmol/L)	5.0 ± 0.6 (n = 158)	4.9 ± 0.5 (n = 138)
Free T4 (pmol/L)	16.4 ± 2.7 (n = 155)	16.0 ± 2.5 (n = 138)
Thyroid status		
Euthyroid	142 (88.8)	127 (91.4)
Subclinical hypothyroid	10 (6.2)	4 (2.9)
Subclinical hyperthyroid	7 (4.4)	8 (5.8)
Overt	1 (0.6) (hypothyroidism)	None
Electrocardiogram variables		
Heart rate (beats/min)	69.7 ± 11.1	69.1 ± 11.8
QTcF (ms)	412.3 ± 21.2	415.8 ± 22.4
PR (ms)	171 ± 25.5	173.0 ± 28.7
QRS (ms)	107.1 ± 9.1	103.2 ± 10.7
Prolonged QTcF[e]		
Normal	150 (69.8)	114 (81.4)
Borderline	17 (7.9)	20 (14.3)
Abnormal	3 (1.4)	6 (4.3)
Treatments		
Levothyroxine supplementation	9 (5.3)	6 (4.3)

Data are expressed as mean ± standard deviation for normally distributed variables, median (interquartile range) for non-normally distributed variables and n (%) for categorical variables. HbA1c: haemoglobin A1c (glycated haemoglobin); HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; IGF1: insulin-like growth factor 1; LDL: low-density lipoprotein; QTcF: Fridericia's corrected QT interval; T1: baseline; T2: follow-up; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone.

[a] Coronary artery disease defined as history of myocardial infarction, coronary angioplasty or bypass grafting.

[b] Patients taking a drug at known risk of torsades-de-pointes (www.crediblemeds.org [7]): at T1, these drugs included amiodarone (n = 3), domperidone (n = 1), escitalopram (n = 1) and sotalol (n = 3); at T2, all eight patients were taking amiodarone.

[c] Corrected for albumin concentrations.

[d] Normal values for thyroid function: TSH, 0.45–4.49 mIU/L; free T4, 11–25 pmol/L [19].

[e] Normal values for QTcF were taken as: normal < 430 ms, borderline 430–450 ms, abnormal > 450 ms in males; and normal < 450 ms, borderline 450–470 ms, abnormal > 470 ms in females [19].

Table 2 Correlation and regression analyses with Fridericia's corrected QT interval as outcome variable at T1 and T2.

T1				T2			
Patient factor	Correlation coefficient[a]	Multiple regression analysis (ANCOVA)		Patient factor	Correlation coefficient[a]	Multiple regression analysis (ANCOVA)	
	r value	Standardized β value	*P*		*r* value	Standardized β value	*P*
Female sex	0.29	0.24 ± 0.07	0.001	Female sex	0.22	0.25 ± 0.08	0.002
Cred-drugsTdP[b]	0.22	0.19 ± 0.07	0.007	Cred-drugsTdP[b]	0.26	0.25 ± 0.08	0.001
TSH	0.30	0.18 ± 0.07[c]	0.01	TSH	0.18	0.19 ± 0.08[c]	0.01
Triglycerides	0.17	0.16 ± 0.07[c]	0.02	Hypertension	0.25	0.2 ± 0.08	0.01
Age	0.18	—	—	Age	0.28	—	—
IGF1	−0.17	—	—	IGF1	−0.25	—	—
Potassium	−0.23	−0.19 ± 0.07	0.007				
Calcium[d]	0.16	—	—				
Albumin	−0.17	—	—				

ANCOVA: analysis of covariance; IGF1: insulin-like growth factor 1; TdP: torsades-de-pointes; TSH: thyroid stimulating hormone.
[a] Univariate analysis with Pearson's coefficient for normally distributed variables, and Spearman's coefficient for non-normally distributed variables. Only variables with correlations with $P < 0.05$ with Fridericia's corrected QT interval are shown. Other tested variables include weight, height, body mass index, history of coronary artery disease, haemoglobin A1C (glycated haemoglobin), blood glucose, insulin, homeostatic model assessment of insulin resistance, total cholesterol, high density lipoprotein, low density lipoprotein, creatinine, creatinine clearance, free T3 and free T4.
[b] Patients taking a drug at known risk of TdP (www.crediblemeds.org [7]): at T1, these drugs included amiodarone ($n = 3$), domperidone ($n = 1$), escitalopram ($n = 1$) and sotalol ($n = 3$); at T2, all eight patients were taking amiodarone.
[c] Normalized before entering into multiple linear model.
[d] Corrected for albumin concentrations.

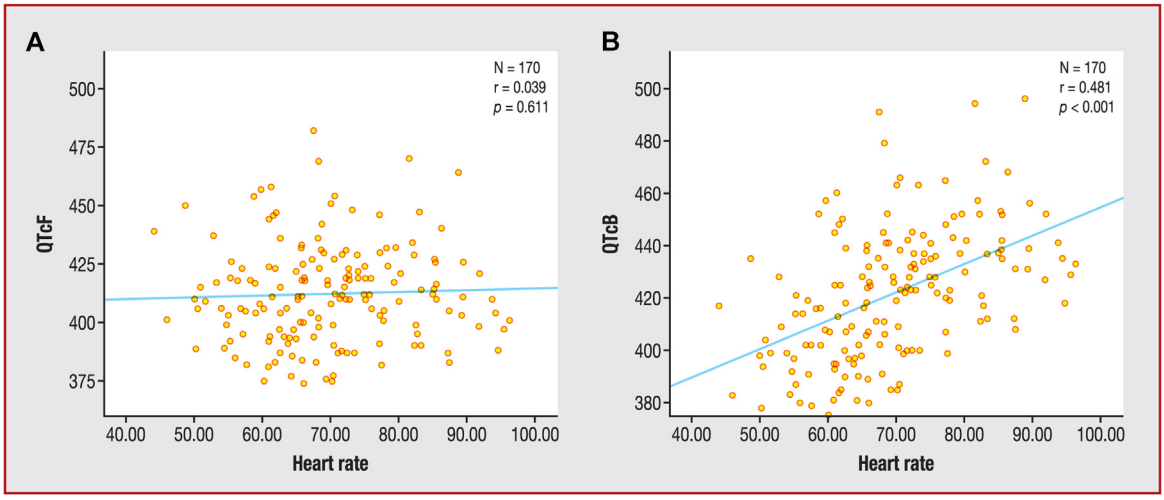

Figure 3. A. Correlation between heart rate and Fridericia's *corrected QT interval* (QTcF). B. Correlation between heart rate and Bazett's *corrected QT interval* (QTcB). QTc is measured in ms, and heart rate in beats per minute; measurements are at T1 with $n = 170$.

and a change in TSH concentration in euthyroid patients with T2DM, even after correction for well-established associations of female sex and Cred-drugsTdP use [7]. We also found a significant inverse correlation between prolonged QTcF and IGF1 at both T1 and T2 in univariate analysis.

TSH increase is associated with QTc prolongation

Temporal changes in TSH concentrations in the euthyroid patient with T2DM have been studied previously in large population groups. Among 17,061 patients without diabetes in South Korea undergoing routine yearly check-up visits and followed over a 4-year period, each 1 μIU/mL increase in TSH after multivariable adjustment was associated with a risk of developing diabetes. During the study follow-up period, among 956 patients with incident diabetes, TSH change rather than baseline TSH was found to be positively associated with a change in HbA1c and worsening metabolic risk factors, which included body mass index, body fat percentage and hyperlipidaemia. Compared with the remaining 16,105 patients who did not develop diabetes, TSH con-

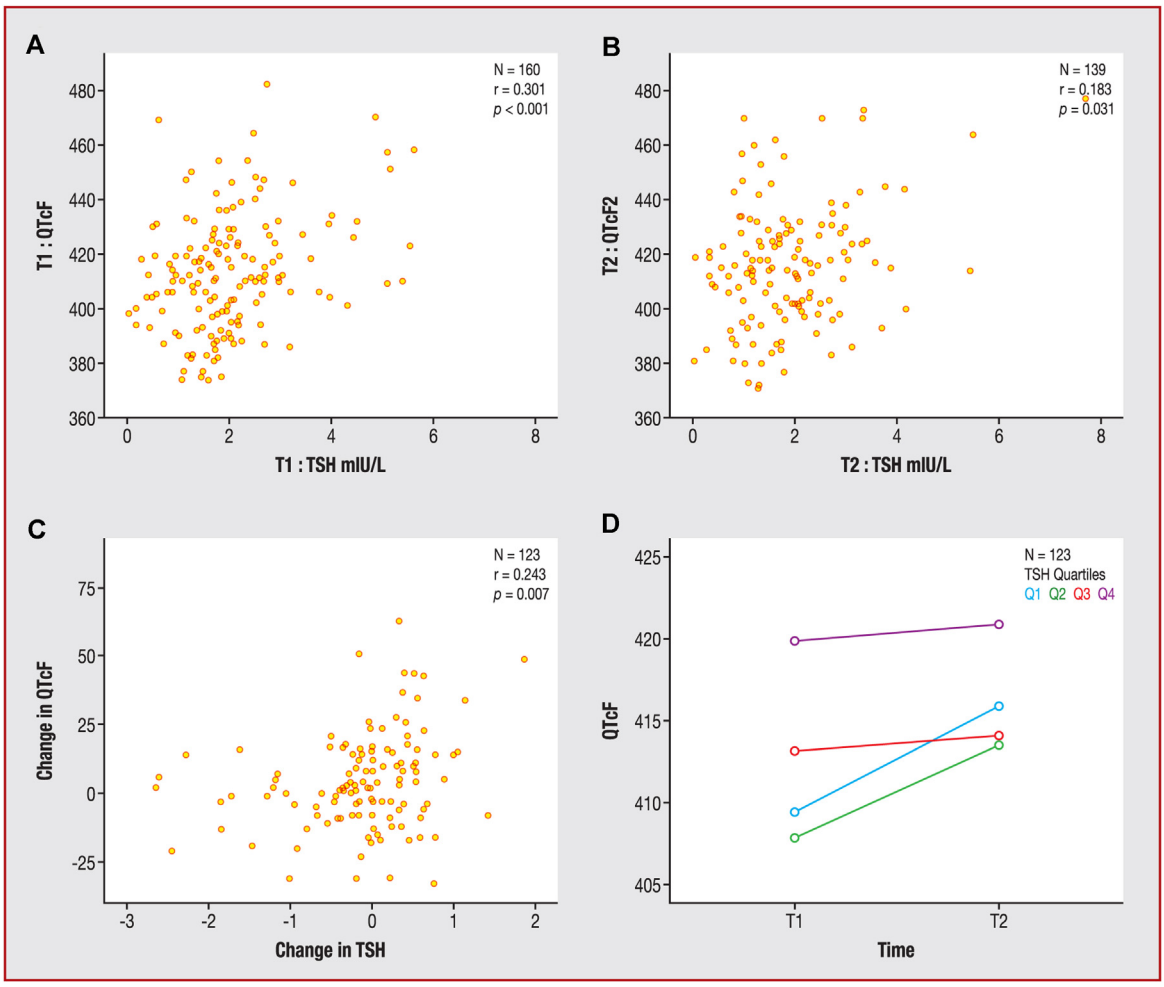

Figure 4. A. Correlation (Spearman's) between thyroid-stimulating hormone (TSH) (mUI/L) and Fridericia's *corrected QT interval* (QTcF) (ms) at T1 (baseline). B. Correlation (Spearman's) between TSH (mUI/L) and QTcF (ms) at T2 (follow-up). C. Correlation (Spearman's) between the variation in QTcF and the variation in TSH. Variations in QTcF over time between T1 and T2 by quartile of TSH concentration at T1.

centrations remained within normal limits [10]. In another retrospective cross-sectional population study in China that examined patients with previously diagnosed T2DM versus newly diagnosed T2DM, the T4/T3 ratio was increased in patients with previously diagnosed T2DM, but TSH was chronically suppressed in both groups [11]. These results were interpreted as a lower rate of peripheral T4 turnover in patients with a longer duration of diabetes and increased risk of development of euthyroid sick syndrome. The authors further suggested that frequent screening of thyroid hormones in euthyroid patients with T2DM may not be necessary as the peripheral turnover of thyroid hormones is dynamic in euthyroid sick syndrome.

In our study, there was a significant association between TSH and QTcF, with an incremental increase of ≈3 ms in QTcF with every log-normalized unit increase in TSH. We observed a significant positive correlation with the temporal variation (either an increase or a decrease) in TSH, which persisted even after exclusion of patients with a change in QT-prolonging drug status. This finding highlights the possibility of an association between TSH concentrations and QTcF. As the log-normalized TSH value unit ranged within 4 units for normal euthyroid values and 12 units for dysthyroid patients, this could result in a potential increase of up to 12 ms to 36 ms in QTc duration within euthyroid and dysthyroid values, respectively, which may create significant variability in QTc prolongation from normal to borderline, or from borderline to prolonged QTc categories. Although TSH may be within the euthyroid range, a significant temporal change in TSH should draw attention to the potential of QTc prolongation and risk of TdP. Based on our findings and previous studies that demonstrated a positive association between an increase in TSH and fasting blood glucose, HbA1c and metabolic risk factors [11], we propose the consideration of more periodic TSH monitoring in those with T2DM and additional metabolic risk factors, as they may be at increased risk of significant QTc prolongation and TdP.

Previous studies have demonstrated the effects of thyroid activity on electrolyte homeostasis, such that serum magnesium and potassium concentrations are elevated and decreased, respectively, in patients with hypothyroidism/elevated TSH [12]. Particularly among patients with T2DM, who may be at risk of diabetic ketoacidosis or hyperosmolar hyperglycaemia syndrome, hypokalaemia and hypomagnesaemia are typically prominent, and can further increase the risk of QTc prolongation and sudden cardiac

death [13]. Thus, in the previously euthyroid patient with T2DM who presents with TdP and QTc prolongation, in addition to ensuring normalization of potassium and magnesium concentrations, it would be prudent to evaluate thyroid activity using TSH concentration, and to correct with thyroid supplementation. The effects of levothyroxine treatment on electrocardiographic variables have not been studied on a large scale, but several case reports [14,15] have described the use of levothyroxine to correct QTc prolongation in rare presentations of TdP with severe hypothyroidism. A smaller patient population study by Unal et al. demonstrated that levothyroxine supplementation significantly decreased the QT interval (from 387.2 ± 10.8 ms to 345.6 ± 13 ms; $P < 0.001$) and QT dispersion (from 46.5 ± 5.3 ms to 30.7 ± 5.8 ms; $P < 0.001$) among 16 women with subclinical hypothyroidism, but had no effect on the RR, PR or QRS intervals [16]. In addition, a correlation analysis showed that QT dispersion was positively related to logarithmic TSH concentrations. Similar findings were observed in another small study in 18 patients from South Korea with primary hypothyroidism who were treated with levothyroxine [17]

Although several studies have examined the relationship between hyperthyroid and hypothyroid states and QTc prolongation, only a few cross-sectional studies have looked at the relationship between thyroid hormones and QTc duration in the euthyroid population [5,18—20], with conflicting results. Among these reports, the association between TSH and QTc duration was based on static TSH quintiles rather than temporal changes in TSH, as in our study. In the US Third National Health and Nutrition Examination Survey and The Rotterdam Study, with 5990 (100%) and 880 (93.72%) euthyroid individuals, respectively, there was no significant association between TSH quintiles/concentrations and QTc (by residual method and Bazett's formula, respectively), in fully adjusted multivariable models [19,20]. In contrast, the Study of Health in Pomerania, which included a representative sample of 3610 individuals, with 87.8% euthyroid patients, found a significant association between TSH (categorical concentrations) and Hodges linear function QTc, in a fully adjusted multivariable model, with depressed TSH concentrations associated with shorter QTc (odds ratio 0.73, 95% CI 0.55—0.97; $P < 0.001$) when compared with euthyroid controls [18]. Similarly, a large population registry-based study in Denmark, with 127,215 (95.86%) euthyroid patients, found a significant association between TSH (as a continuous covariate) and QTcB in an age- and sex-stratified linear model, among young and middle-aged (16—60 years) groups of both sexes [5].

In comparison with overt hypothyroid and hyperthyroid states, where T4 concentrations are correlated with QTc, there are limited studies on the correlations between T3 or T4 and QTc in the euthyroid individual. In our study, there was no association between free T3 or T4 and QTc, which contrasts with previous findings, and may result from the fact that hyperthyroid and euthyroid patients were grouped together in the correlation analyses [21]. Among the 880 (93.72%) euthyroid individuals in the Rotterdam Study, the highest quintile of free T4 in males was associated with a significant adjusted increase in QTc of 9.7 ms (95% CI 2.1—17.2), with a gradual increase ($P = 0.008$ for linear trend), as well as a significantly higher risk of a borderline QTc or QTc prolongation (adjusted odds ratio 2.12, 95% CI 1.02—4.40) compared with the first quintile ($P = 0.009$) [19]. However, the US Third National Health and Nutrition Survey among 5990 euthyroid individuals did not find a significant association between T4 and QTc duration after fully adjusted models, although they did observe that men in the > 95th percentile of total T4 had longer residual adjusted QT intervals than those in the < 5th percentile [20]. Given that our study sample size was comparatively smaller, our analysis may have been insufficiently sensitive to detect this association.

The genomic and non-genomic actions of T4 and its largely peripherally deiodinated counterpart T3 on the cardiovascular system, through modulation of expression of multiple cardiac genes affecting ion-channel transport, sympathetic responses and myocardial contractility, are well established. Particularly within the conduction system, prolonged repolarization observed in hypothyroid patients is largely a result of a reduction in the transient outward potassium current (I_{to}) and an increase in the L-type calcium current channel ($I_{Ca\text{-}L}$) [4]. After detection of the functional expression of the TSH receptor in murine and human cardiomyocytes, recent studies have also demonstrated the direct action of TSH in the modulation of cardiac ion channels [4,22].

In human cardiomyocytes, TSH reduced expression of the potassium-voltage gated channel subfamily D member 3 and subfamily Q member 1 (*KCND3* and *KCNQ1*, respectively), I_{to} and the delayed rectifier potassium current (I_{Ks}) encoding proteins [22]. Changes caused by TSH via protein kinase A signalling, consistent with that of primary hypothyroidism, resulted in characteristic early after depolarizations and subsequent arrythmias [22]. This was only seen during sympathetic/adrenergic stimulation suspected as a result of enhanced calcium accumulation within the sarcoplasmic reticulum and augmentation of the proarrhythmic sodium-calcium exchange (*NCX*) and $I_{Ca\text{-}L}$ stimulation [22]. Furthermore, in a genome-wide association study among 37,154 North American individuals of European ancestry, a weighted polygenic predictor for TSH, and not T3 or T4, was significantly associated with arrhythmias, particularly atrial fibrillation or flutter [23]. Taken together, this further highlights the important role of TSH in the homeostasis of electrical conductivity, and as a risk factor for arrhythmia vulnerability.

QTc duration and T2DM

Ventricular electrophysiological disturbances in patients with T2DM are thought to be caused by hyperglycaemia, autonomic neuropathy, ventricular inflammation and fibrotic changes [4]. Studies have shown that during episodes of severe hypoglycaemia, patients experience QTc prolongation and VAs suspected to be caused by autonomic dysfunction [24]. Increased variability in plasma fasting and postprandial glucose has also been associated with prolongation of QTc [24]. In our cohort, the included patients with T2DM were mostly well equilibrated, with HbA1c, glucose and insulin blood concentrations within normal or subnormal ranges; this may have blunted the association between the concentration of these hormones and QTc duration shown previously in patients with T2DM with more extreme values.

We observed a significant inverse correlation between prolonged QTcF and IGF1 at both T1 and T2 in univariate analysis, which is consistent with previous work in pooled subpopulations from the Study of Health in Pomerania and Rotterdam studies [25]. IGF1 concentrations demonstrate a U-shape association with insulin resistance, and both oversecretion, such as in acromegaly, and undersecretion of IGF1 are typically observed in patients with T2DM [26]. Altered IGF1 concentrations have been associated with increased cardiovascular morbidity as a result of heart failure and cardiac arrhythmias [27]. These observed effects on QTc duration and risk of VAs, have been speculated to be related to growth hormone itself, which regulates several cellular mechanisms, including metabolic pathways, sympathetic signalling and ion-channel activities, affecting cardiac conduction [27]. Direct effects of IGF1 on cardiac electrophysiological activity might also exist, as shown in a recent in vitro study where VAs were reversed by increasing connexin-43 expression in rat cardiomyocytes with IGF1 treatment and hepatocyte growth factor [28]. Given that low IGF1 concentrations are associated with T2DM [26], it may be of interest to explore IGF1 concentrations as a biomarker of VAs, especially in individuals with diabetes.

Study limitations

There are several limitations to our study. First, it was a single-centre institutional study, and extrinsic validation of our findings is required. Second, our regression analysis did not include the effects of various sex hormones on QTc. Our study was observational and cannot conclude for the causality of association between TSH concentrations and QTc variations. Interventional or preclinical mechanistic studies are required to further assess this point.

Conclusions

Serum TSH concentration and its variation was associated with QTcF and its variation, even after correcting for QTc prolonging drugs [29,30]. Optimization of TSH concentration in T2DM deserves further investigation to establish its impact on risk of TdP and sudden cardiac death.

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Disclosure of interest

The authors declare that they have no competing interest.

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