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Relationship between T_{peak}-T_{end} (TPE), TPE/QT ratio and TPE dispersion in patients with subclinical hyperthyroidism

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ABSTRACT

Aims: Subclinical hyperthyroidism has been associated with an increased risk of cardiovascular events, including atrial fibrillation, heart failure, and cardiovascular mortality. Tpeak - Tend interval (TPE), TPE/QT ratio, and TPE dispersion have been suggested as potential electrocardiographic markers of ventricular repolarization abnormalities, which may be associated with an increased risk of arrhythmias and sudden cardiac death. However, the relationship between subclinical hyperthyroidism and these parameters remains unclear.

Methods: We conducted a cross-sectional study to investigate the relationship between subclinical hyperthyroidism and TPE, TPE/QT ratio, and TPE dispersion. A total of 106 patients were included in the study, with 42 patients diagnosed with subclinical hyperthyroidism group and 64 control group. Conventional echocardiographic and electrocardiographic parameters were measured and compared between the two groups.

Results: There are no significant differences in age (p=0.707) or gender (p=0.552) between the two groups. Patients in the subclinical hyperthyroidism group had significantly higher TPE, TPE/QT ratio, and TPE dispersion compared to the control group (p<0.001). However, there were no significant differences between the two groups in terms of conventional echocardiographic parameters, including left ventricular (LV) ejection fraction, LV end-diastolic diameter, LV end-systolic diameter, and right ventricular fractional area change.

Conclusion: Our results suggest that subclinical hyperthyroidism is associated with increased ventricular repolarization abnormalities, as evidenced by higher TPE, TPE/QT ratio, and TPE dispersion. These findings may have clinical implications for the management of patients with subclinical hyperthyroidism, particularly those with cardiovascular risk factors.

Keywords: Arrhythmia, subclinical hyperthyroidism, ventricular repolarization

INTRODUCTION

Subclinical hyperthyroidism, defined as low thyroid-stimulating hormone (TSH) levels and normal thyroid hormone levels, is a common condition affecting up to 10% of the population. Although often asymptomatic, recent studies have suggested an association between subclinical hyperthyroidism and an increased risk of cardiovascular disease (CVD).[1,2]

One potential mechanism for this increased risk is an alteration in the electrocardiographic (ECG) parameters that reflect cardiac repolarization. Specifically, previous research has shown that subclinical hyperthyroidism is associated with changes in the Tpeak - Tend (TPE) interval, which is a measure of the duration of ventricular repolarization.[3,4] In addition to the TPE interval, the TPE/QT ratio and TPE dispersion are also ECG parameters believed to reflect cardiac repolarization abnormalities. Studies have suggested alterations in these parameters among patients with subclinical hyperthyroidism, yet the relationship between these parameters and the TPE interval remains unclear.[5,6]

A recent study by Aweimer et al.[7] aimed to explore the relationship between TPE, TPE /QT ratio, and TPE dispersion in patients with subclinical hyperthyroidism. The study found that TPE interval was significantly increased in patients with subclinical hyperthyroidism compared to controls, and TPE dispersion was also increased. Additionally, the TPE/QT ratio was significantly higher in patients with subclinical hyperthyroidism than controls. These findings suggest that subclinical hyperthyroidism may be associated with alterations in ECG parameters that reflect cardiac repolarization abnormalities. However, further studies

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are needed to confirm these findings and determine the clinical implications of these changes.

This study aims to investigate the relationship between the TPE interval, TPE/QT ratio, and TPE dispersion as potential arrhythmia markers in the electrocardiograms of patients with subclinical hyperthyroidism.

METHODS

Ethics

The study was carried out with the permission of Fırat University Non-invasive Researches Ethics Committee (Date: 08.12.2016, Decision No: 16). The study was conducted in accordance with the Declaration of Helsinki and obtained ethical approval from the institutional review board. All participants provided informed consent before data collection.

Study Population

Participants were recruited from outpatient clinics at tertiary hospitals and endocrinology centers. Participants' demographic characteristics (age, gender, body mass index), medical history, and medication use history were recorded. Those with systemic illnesses or atherosclerosis risk factors were excluded from the study. The sample comprised 42 cases of subclinical hyperthyroidism and 64 euthyroid participants, matched for age and gender, all aged between 18 and 55 years. The study included patients diagnosed with subclinical hyperthyroidism based on clinical criteria, characterized by low TSH levels and normal thyroid hormone levels. Patients who were taking various drugs that could suppress TSH (such as dopamine, dopamine agonists, glucocorticoids, somatostatin, aspirin, fenofibrate, furosemide), or who were taking antiarrhythmic agents or agents that could cause arrhythmia (such as propranolol, terfenadine, amiodarone, erythromycin, clarithromycin, antidepressant agents, antipsychotic agents), those with structural heart disease detected by echocardiography, those with electrolyte imbalances, those with a BMI>30, those with psychiatric disorders or pregnancy, those with left or right bundle branch block detected in the baseline ECG, and those with poor ECG quality were excluded from the study.

Laboratory Measurements

Serum samples (6 cc for biochemistry, 5 cc for complete blood count, 5 cc for hormones) were collected in vacuum tubes containing 15% K3 EDTA. Hemoglobin, hematocrit, platelet count, and white blood cell count and types (neutrophil, lymphocyte, eosinophil, and monocyte) were determined using an automated hematology analyzer (Beckman Coulter LH 780) by the electrical impedance method. Glucose, urea, creatinine, total cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were measured using a Cobas-601 (Roche) automated analyzer by the chemiluminescence method. The serum levels of free thyroid hormones, free T3 (FT3), and free T4 (FT4) were determined using the chemiluminescent immunoassay method, while thyroid-stimulating hormone (TSH) levels were measured using the two-site chemiluminescent immunometric assay method with the Immulite 2000 (DPC) kit. The reference ranges for FT3, FT4, and TSH levels were 1.8-4.2 pg/ml, 0.80-1.80 ng/dL, and 0.40-4.0 mIU/ml, respectively.

Electrocardiogram (ECG) Recording and Analysis

Standard 12-lead ECG recordings were taken using a digital ECG device with a sampling rate of 1,000 Hz (Nihon Kohden, Tokyo). ECG recordings were taken while participants were lying in a supine position after a 10-minute rest period. The recordings were analyzed offline by two independent observers who were unaware of the study objectives and participant group assignments. Any differences between observers were resolved by a third observer. After scanning all ECGs, QT interval, corrected QT interval (QTc), and TPE interval were calculated using MATLAB (MathWorks, Natick, Massachusetts, USA.) software. The QT interval was defined as the distance from the onset of the QRS complex to the point of isoelectric descent of the T wave. For QTc interval, Bazzet's formula was applied: QTc (ms)=QT interval /√RR interval.8 TPE interval was defined as the time between the peak and the end of the T wave and was measured from each precordial derivation, with the longest value taken.[9] TPE/QT and TPE/QTc ratios were calculated after these measurements. TPE dispersion (TPEd) was obtained by calculating the difference between the maximum and minimum TPE intervals measured from each precordial derivation (one beat for each derivation).

Transthoracic Echocardiography (TTE)

M-mode and 2D ECHO were performed in the left lateral decubitus position using a 3.25 probe from the Vivid 3 ECHO echocardiography device, according to the American Society of Echocardiography criteria.[10] Parasternal short-long axis images and apical 4 and 2 chamber views, which are standard echocardiography positions, were used for measurements. Left ventricular wall thickness, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) were evaluated using M-mode method, and left ventricular ejection fraction (EF) was calculated using the Modified Simpson method.[11]

Data Analysis

ECG parameters (TPE interval, TPE/QT ratio, and TPE dispersion) were measured and analyzed for differences between the subclinical hyperthyroidism group and the control group.

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality of the data was evaluated using the Kolmogorov-Smirnov test. Numerical data with a normal distribution were presented as mean ± SD, while parameters with a non-normal distribution were presented as median (minimum-maximum) percentile, while categorical data were expressed as percentage. Student's t-test or Mann Whitney U test was used to compare unpaired samples as needed. Chi-square test was used to assess differences in categorical variables between groups. Multiple linear regression analyses using the stepwise method were performed to assess the independent variables affecting the dependent variable QTc. All independent variables in the multiple linear regression were tested for multicollinearity. If the variance inflation factor (VIF) exceeded 3.0, the variable was considered to be collinear. All reported confidence interval (CI) values are calculated at the 95% level. Statistical significance was defined as $p<0.05$ for a two-sided test.

RESULTS

The demographic and clinical characteristics of 42 subclinical hyperthyroidism patients and 64 control subjects included in the study are given in **Table 1**. The statistical analysis revealed that the age and gender distributions of the two groups, comprising individuals with normal thyroid function and subclinical hyperthyroidism, did not significantly differ from each other, with p-values of 0.707 and 0.552, respectively. Glucose and creatinine levels were found to be significantly higher in the subclinical hyperthyroidism group than in the control group ($p<0.001$). Potassium and calcium levels were also found to be significantly higher in the subclinical hyperthyroidism group compared to the normal group ($p=0.022$ and $p=0.009$, respectively). There were no significant differences between the two groups in terms of FT3, FT4, LDL, HDL, triglyceride, urea, sodium, hemoglobin, hematocrit, and WBC levels. TSH levels were found to be significantly higher in the control group compared to the subclinical hyperthyroidism group ($p<0.001$) (**Table 1**).

Comparison of conventional echocardiographic and electrocardiographic parameters between cardiac patients, parameters such as LVEF (%), LVEDD (mm), LVESD (mm), PW, IWS, RV-FAC (%), HR (beats/min), TPE, QTmax (msn), QTc (msn), TPE/QT, TPE/QTc, and TPEd (msn) were examined between the control group (n=64) and subclinical hyperthyroidism group (n=42). There was no significant difference observed between the control and subclinical hyperthyroidism groups in LVEF, LVEDD, and LVESD parameters ($p>0.05$). There was also no significant difference found in PW and IWS parameters between the control and subclinical hyperthyroidism groups ($p>0.05$). RV-FAC parameter also showed no significant difference ($p>0.05$). However, the subclinical hyperthyroidism group had significantly higher values in HR (beats/min), TPE, QTc, TPE/QT, TPE/QTc, and TPEd compared to the control group ($p<0.05$) (**Table 2**, **Figure**).

Table 1. Baseline characteristics and laboratory parameters of groups

Variables	Normal (n=64)	Subclinical hyperthyroidism (n=42)	p
Age, y (mean ± SD)	41.1±12.1	42.1±13.4	0.707
Female, n(%)	30 (47%)	23 (55%)	0.552
Glucose (mg/dL)	90.2±11.8	110.2±23.7	<0.001
LDL (mg/dl)	109.9±32.0	116.4±28.8	0.503
HDL (mg/dl)	44.0±8.4	49.0±15.6	0.110
Triglyceride (mg/dl)	129.5±46.8	128.3±63.4	0.942
Ure (mg/dl)	35.2±13.1	29.2±9.2	0.059
Creatinine (mg/dl)	0.8±0.2	0.6±0.1	<0.001
Sodium (mmol/L)	139.1±3.4	140.0±2.6	0.356
Potassium (mmol/L)	4.2±0.5	4.5±0.4	0.022
Calcium (mmol/L)	9.0± 0.6	9.5±0.7	0.009
Hemoglobin (g/dl)	14.1±1.7	13.8±1.6	0.403
Hematocrit (%)	42.3±5.1	41.7±6.7	0.648
WBC (10^3/uL)	8.1±2.7	7.5±1.5	0.246
TSH (uIU/ml)	0.9(0.0-11.1)	0.05(0.01-0.28)	<0.001
FT4 (mcg/dl)	0.9±0.3	3.1±1.4	<0.001
FT3 (mcg/dl)	2.2±1.1	10.7±4.8	<0.001

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell count, TSH: thyroid stimulating hormone, FT4: free T4, FT3: free T3

Table 2. Comparison of conventional echocardiographic and electrocardiographic parameters of patients

Variables	Normal (n=64)	Subclinic (n=42)	p
LVEF (%)	62.2±3.1	63.1±4.4	0.401
LVEDD (mm)	45.0±3.6	45.7±4.1	0.161
LVESD (mm)	29.8±3.8	30.3±4.0	0.231
PW	8.2±0.9	8.4±0.9	0.077
IWS	8.2±0.8	8.3±0.6	0.203
RV-FAC (%)	40.3±3.0	39.7±4.1	0.275
HR, beats/min	76.3±8.5	85.6±19.1	0.001
TpTe	65.2±4.3	82.3±12.9	<0.001
QTmax (msn)	344.9±16.8	340.6±36.6	0.412
QTc (msn)	388.0±20.5	399.4±19.9	0.006
TpTe/QT	0.18±0.01	0.24±0.03	<0.001
TpTe/QTc	0.16±0.01	0.20±0.03	<0.001
TpTed (msn)	13.0±5.0	24.4±7.6	<0.001

Abbreviations: LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESV, left ventricular end systolic diameter; PW, posterior wall; IWS, interventricular septum; RV-FAC, right ventricular fractional area change; HR, heart rate;QTc, corrected QT.

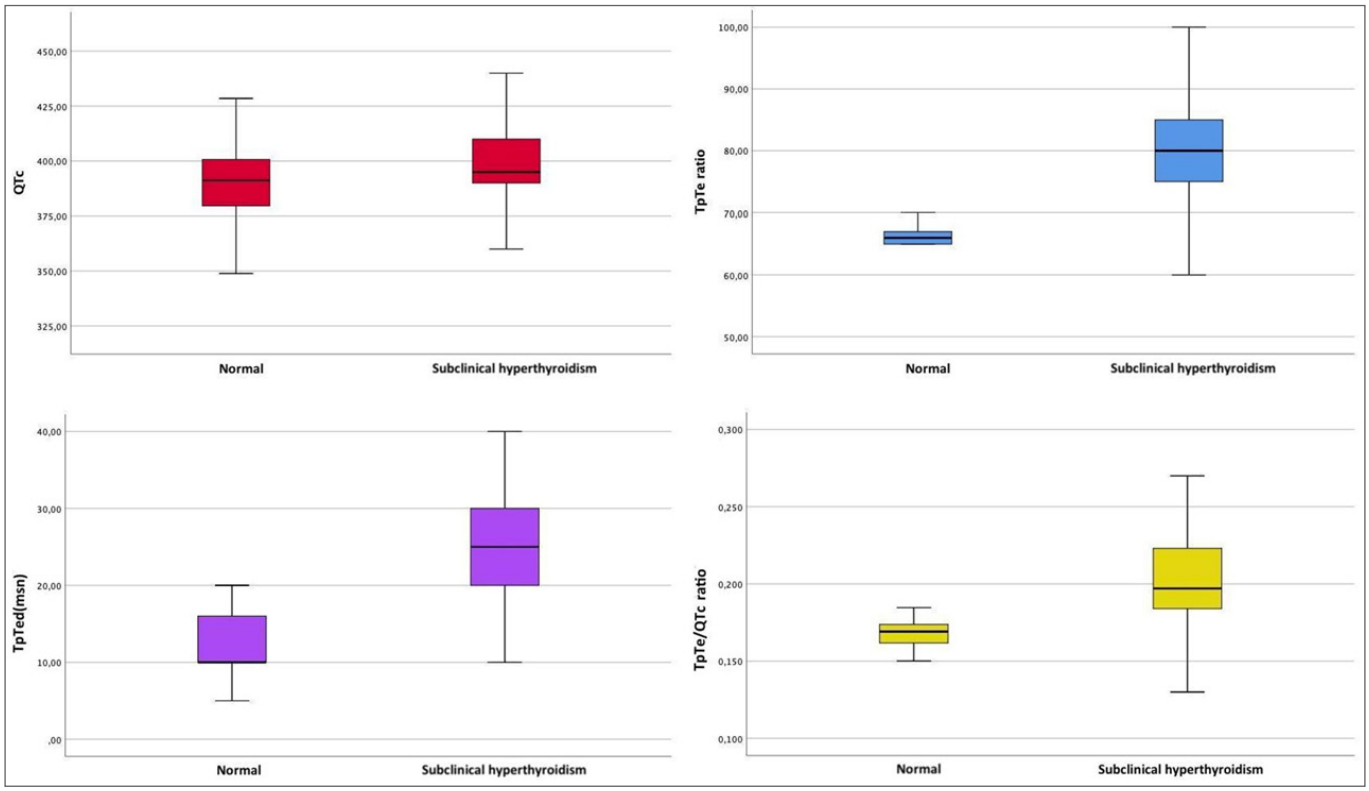

Figure. Comparison of QTc, Tpeak - Tend (TPE) interval, Tpeak - Tend dispersion, and TPE/QTc ratio in patients with subclinical hyperthyroidism and the control group

Factors affecting QTc were assessed using linear regression analysis, including both univariate and multivariate analyses. Primarily, statistically significant parameters and parameters likely to affect the QTc parameter were included in the model. Model fit R value was determined as 0.634 and R square was determined as 0.402. Heart rate, age, sodium and subclinical hyperthyroidism group were defined as an independent parameter of QTc in regression analysis (**Table 3**).

Table 3. Independent factors affecting QTc in subclinical hyperthyroidism patients in stepwise multiple linear regression analysis

Model	Unstandardized coefficients		Standardized coefficients	p value
	B	Std. Error	Beta	
(Constant)	293.081	81.455		0.001
Heart rate	-1.345	0.180	-0.665	<0.001
Age	-0.321	0.152	-0.188	0.038
Sodium	1.166	0.556	0.183	0.040
Subclinical hyperthyroidism group	10.650	5.091	0.187	0.040

DependentVariable: QTc
b. Correlates in the Model: (Constant), heart rate, age, sodium, subclinical hyperthyroidism group

DISCUSSION

The present study investigated the relationship between TPE, TPE/QT ratio, and TPEd in patients with subclinical hyperthyroidism. The findings indicate that patients with subclinical hyperthyroidism exhibit significantly higher TPE, TPE/QT ratio, and TPEd values compared to the control group.

Although subclinical hyperthyroidism was once considered a benign condition, recent studies have linked it to adverse cardiovascular outcomes.[4,12] The mechanisms underlying this relationship are not completely understood, but it has been suggested that subclinical hyperthyroidism may lead to various cardiovascular changes, including alterations in cardiac function and electrophysiology.[13] Several studies have investigated the association between subclinical hyperthyroidism and electrocardiographic (ECG) changes, and TPE interval and dispersion have been found to be increased in patients with subclinical hyperthyroidism.[14,15] TPE interval is a marker of ventricular repolarization, and an increase in this interval is associated with an increased risk of arrhythmia and sudden cardiac death.[16] TPE dispersion, which is the difference between the maximum and minimum TPE intervals across 12 leads, is also considered to be a marker of increased arrhythmic risk.[17]

Our findings align with previous studies that have shown an association between subclinical hyperthyroidism and elevated cardiovascular risk factors.[12,18] Several previous studies have demonstrated that TPE, TPE/QT ratio, and TPE dispersion are valuable markers of ventricular arrhythmias and sudden cardiac death.[14,16,19] Moreover, subclinical hyperthyroidism has been linked to an increased risk of cardiovascular events and mortality.[1,20] The TPE interval is a measure of the dispersion of repolarization in the heart,

which reflects the heterogeneity of ventricular recovery times and has been shown to be associated with increased risk of ventricular arrhythmias.[21] The TPE/QT ratio has been proposed as a marker of transmural dispersion of repolarization, which is an important determinant of the arrhythmogenic substrate.[22] In addition, TPE dispersion is an important parameter for assessing the heterogeneity of ventricular repolarization and has been shown to be a predictor of ventricular arrhythmias in various clinical conditions.[23,24] Our findings are consistent with these studies and provide further evidence that subclinical hyperthyroidism may increase the risk of ventricular arrhythmias.

The exact mechanisms linking subclinical hyperthyroidism and ventricular arrhythmias remain unclear. One proposed mechanism is the alteration of ion channels and intracellular calcium homeostasis, which can lead to an increase in early after depolarizations (EADs) and triggered activity.[25] In addition, subclinical hyperthyroidism may also increase sympathetic activity and induce hemodynamic changes that can further contribute to the development of arrhythmias.[26] The higher TPE, TPE/QT ratio, and TPE dispersion values observed in subclinical hyperthyroidism patients may be due to the effects of thyroid hormones on cardiac repolarization. Thyroid hormones have been shown to have direct effects on ion channels involved in cardiac repolarization, leading to changes in action potential duration and repolarization.[27] In addition, thyroid hormones can alter the expression of genes involved in cardiac ion channel regulation, which may also contribute to changes in cardiac repolarization.[28,29]

Limitations

The results of this study suggest that TPE, TPE/QT ratio, and TPE dispersion could serve as useful parameters for assessing cardiovascular risk in patients with subclinical hyperthyroidism. Although our study has several strengths, including the use of both conventional echocardiographic and electrocardiographic parameters and a well-defined study population, it also has some limitations. Firstly, the sample size was relatively small, which may limit the generalizability of our findings. Secondly, although we measured thyroid hormone levels, we did not investigate the specific mechanisms underlying the observed changes in electrocardiographic parameters.

CONCLUSION

Our study provides evidence that patients with subclinical hyperthyroidism have increased TPE, QTc, TPE/QT, TPE/QTc, and TPEd values, which may increase their risk of ventricular arrhythmias. Further studies with larger sample sizes and more comprehensive assessments of thyroid function are needed to confirm these findings and elucidate the underlying mechanisms. Clinicians should consider monitoring electrocardiographic parameters in patients with subclinical hyperthyroidism and implementing appropriate interventions to reduce the risk of adverse cardiovascular events.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Fırat University Non-invasive Researches Ethics Committee (Date: 08.12.2016, Decision No: 16).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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