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Evaluation of Tp-E interval and Tp-E/Qtc ratios in patients with overt hypothyroidism and subclinical hypothyroidism

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Abstract. – OBJECTIVE: Tp-e interval and Tp-e/QTc are among the new-generation indicators used for predicting cardiac arrhythmia and ventricular repolarization. In this study, we aimed to evaluate Tp-e and Tp-e/QTc ratios in patients with overt hypothyroidism and subclinical hypothyroid patients.

PATIENTS AND METHODS: In this study, a total of 105 patients were included with 35 overt hypothyroidism, 35 subclinical hypothyroidism, and 35 healthy euthyroid patients. The anthropometric measurements, laboratory results, and electrocardiographic data of the patients were measured. The groups were compared in terms of Tp-e interval, Tp-e/QT and Tp-e QT/c ratios.

RESULTS: When the Tp-e interval and Tp-e/QTc values of the patients were compared, a significant difference was found ($p<0.001$). A positive correlation was found between thyroid stimulating hormone (TSH) with Tp-e interval and Tp-e/QT ratio.

CONCLUSIONS: Tp-e interval and Tp-e/QTc duration increased in overt hypothyroidism and subclinical hypothyroidism patients compared to euthyroid patients. We believe that regular use of levothyroxine therapy in overt hypothyroidism patients will decrease cardiac mortality. Cardiac risk factors should be considered to decide on levothyroxine therapy for subclinical hypothyroidism patients.

Key Words:
Hypothyroid, Tp-e interval, Tp-e/QTc ratio.

Introduction

The clinical course of thyroid gland-induced insufficient thyroid hormone synthesis and decreased metabolism related to insufficient thyroid hormone is called overt hypothyroidism. Patients affected by this disease experience high thyroid stimulating hormone (TSH) and low thyroxine (T4). Subclinical hypothyroidism (SH) is a condition, generally not accompanied by clinical findings, which shows high TSH levels in the serum while the free thyroid hormone levels are normal. There is no clear consensus on the time of initiation of treatment[1,2]. If hypothyroidism is not diagnosed early and without that an appropriate treatment is started, it can lead to pathologies regarding the autonomic regulation of the cardiovascular system and ventricular repolarization[3]. Similarly, similar cardiac pathologies were seen[4] for subclinical hypothyroidism.

Autonomic changes might impact ventricular repolarization[5]. In electrocardiography (ECG), ventricular repolarization is evaluated according to QT interval (QT), corrected QT interval (QTc) and transmural repolarization distribution. Tp-e interval (Tp-e) is the duration between the maximum amplitude of the T wave and the end of the T wave, and it is the indicator of Tp-e transmural repolarization. Prolonged Tp-e ventricular repolarization indicates an abnormal distribution and is related to ventricular arrhythmia[6]. Tp-e/QT and Tp-e/QTc ratio is among the new parameters used for predicting ventricular arrhythmia.

In previous studies[3,4,7], Tp-e, QT/Tp-e ratio, and ventricular repolarization changes were evaluated separately for hypothyroidism, overt hyperthyroidism, and subclinical hypothyroidism cases. For overt hyperthyroidism, the studies in the literature for Tp-e, Tp-e/QT ratio are limited. In this study, we aimed to evaluate Tp-e and QT/Tp-e ratio for patients with hypothyroidism, subclinical hypothyroidism and euthyroid under levothyroxine therapy in the same study.

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Patients and Methods

In this study, a total of 105 patients were included with 35 overt hypothyroidism, 35 subclinical hypothyroidism, and 35 euthyroid patients. The patients included in this study did not have coronary artery disease, diabetes mellitus and hyperlipidemia.

The electronic file system in the hospital was searched and the results of the patients followed in the Internal Medicine Outpatient Clinic were obtained. Patients were divided into 3 groups: overt hypothyroidism, subclinical hypothyroidism and euthyroid, based on their TSH and free T4 values measured from venous blood. Patients with high TSH due to central pathology were excluded.

Before measuring the ECG of the patients, arterial blood pressure was measured with a fixed manual blood pressure device after a 15-minute rest period. The pulse rates of all patients were measured from the radial artery for 1 minute. When the arterial blood pressure was <140/90 mmHg and pulse rates (pulse/minute) were <90, ECG measurements were started. For ECG measurement, a routine standard 12-lead body surface ECG (Nihon Kohden, Tokyo, Japan) at a paper speed of 50 mm/s was performed. Tp-e interval, QT and QTc interval, Tp-e/QT and Tp-e/QTc ratio, and QRS complex (QRS) were manually measured by 3 cardiologists. A special ECG reading scale was used for sensitive measurements. QT interval was measured in milliseconds from the first deflection of the QRS complex to the time the T wave reaches the isoelectric line. QTc interval was calculated using the Bazett formula ($QTc = QT/\sqrt{RR}$). Tp-e interval was calculated as the duration from the peak of the T wave until the intersection of the deflection line with the isoelectric line in terms of milliseconds. These measurements were undertaken in the most suitable precordial derivation for the measurement. Patients with distinct U wave or negative/biphasic T wave on surface ECG were excluded.

Statistical Analysis

The descriptive statistics of the numerical variables obtained in this study were indicated as mean±standard deviation (SD), while the descriptive statistics of the categorical variables were indicated as numerical and percentage values. Chi-square (Pearson Chi-square) was applied to compare intergroup categorical variables. The normal distribution of the continuous variables was evaluated with Kolmogorov-Smirnov test. Independent Samples *t*-test was applied to compare the variables in two groups that show normal distribution. The accepted significant level was selected as $p<0.05$ and all calculations were conducted with SPSS (PASW 18) software (SPSS Inc., Chicago, IL, USA).

Results

In this study, a total of 105 patients were included with 35 overt hypothyroidism, 35 subclinical hypothyroidism, and 35 healthy euthyroid patients. There was no statistically significant difference between anthropometric measurements such as age, gender, body mass index (BMI), and laboratory tests between the groups. The anthropometric measurements and laboratory results of the patients are given in Table I.

There was a statistically significant difference in TSH levels between the groups ($p<0.001$). T4 levels showed a statistically significant difference between the groups ($p<0.001$). This difference was due to T4 values between overt hypothyroid and euthyroid patient groups. While there was a statistically significant difference for Tp-e, Tp-e/QTc, Tp-e/QT between the groups ($p<0.005$), there was no statistically significant difference between QT and QTc. The thyroid function tests and ECG measurements of the patient groups are given in Table II.

Independent from the groups among patients, there was a positive correlation analysis between TSH values and Tp-e and Tp-e/QTc (r: 0.48 $p<0.001$, r: 0.42 $p<0.001$). Figures 1 and 2 show the TSH/Tp-e and TSH/Tp-e/QT correlation analysis.

Discussion

In this study, patients with overt hypothyroidism and patients with subclinical hypothyroidism were compared with the healthy euthyroid patient group, and a significant difference was found between Tp-e interval, Tp-e/QT and Tp-e/QTc ratios between the groups. The result of our study is important due to limited literature data on Tp-e interval and Tp-e/QT ratio for overt hypothyroidism patients and since there is no study in which these parameters were evaluated simultaneously in patients with primary hypothyroidism and subclinical hypothyroidism.

Table I. Demographic and biochemical data of the patients.

	Euthyroid	Subclinical hypothyroidism	Primary hypothyroidism	*p*-value
Age (years)	44.73±**14.6**	51.03±**14.97**	36±**11.26**	0.108
Gender (%, male)	30	34	32	0.563
BMI (kg/m²)	28±**2.1**	26±**2.2**	28±**3.2**	0.486
SBP (mmHg)	118±**14**	120±**17**	110±**12**	0.489
DBP (mmHg)	75±**7**	83±**8**	72±**5**	0.452
Hemoglobin (g/dl)	14±**1.8**	13.5±**1.5**	13.7±**1.4**	0.387
Creatine (mg/dl)	0.8±**0.1**	0.72±**0.15**	0.74±**0.2**	0.455
Urea (md/dl)	15±**3.1**	22±**4.6**	18±**3.2**	0,362
Glucose (mg/dl)	96±**25**	80±**12**	85±**18**	0.232
ALT (IU/L)	25±**5.2**	28±**4.3**	30±**3.4**	0.342
AST (IU/L)	20±**4.8**	32±**3.6**	28±**5.2**	0.319
T. Cholesterol (mg/dl)	172±**37**	185±**41**	201±**44**	0.162
LDL (mg/dl)	115±**28**	128±**31**	132±**34**	0.332
HDL (mg/dl)	57±**12**	54±**14**	56±**18**	0.214
Triglyceride (mg/dl)	155±**35**	165±**48**	170±**45**	0.184

SBP: Systolic blood pressure, DBP: diastolic blood pressure, ALT: alanine transaminase, AST: aspartate aminotransferase, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

Table II. Thyroid function tests and ECG measurements of the patients.

	Euthyroid	Subclinical hypothyroidism	Primary hypothyroidism	*p*-value
TSH (mU/L)	1.87±**1.16**	6.10±**3.05**	12.33±**49.13**	**<0.001**
T4 (ng/dl)	1.38±**0.22**	1.19±**0.16**	0.69±**0.21**	**<0.001**
TP-e (ms)	72.71±**10.02**	86.03±**23.78**	94.67±**19.21**	**0.005**
QT (ms)	365.96±**27.40**	377.16±**35.15**	380.33±**22.03**	0.370
QTc (ms)	401.02±**20.00**	412.16±**28.13**	415.33±**12.70**	0.121
TP-e/QT (ms)	0.198±**0.01**	0.22±**0.02**	0.250±**0.02**	**<0.001**
TP-e/QTc (ms)	0.181±**0.02**	0.208±**0.03**	0.226±**0.01**	**<0.001**

TSH: thyroid stimulant hormone, T4: thyroxine, QT: QT interval, QTc: corrected QT interval, Tp-e: Tp-e interval.

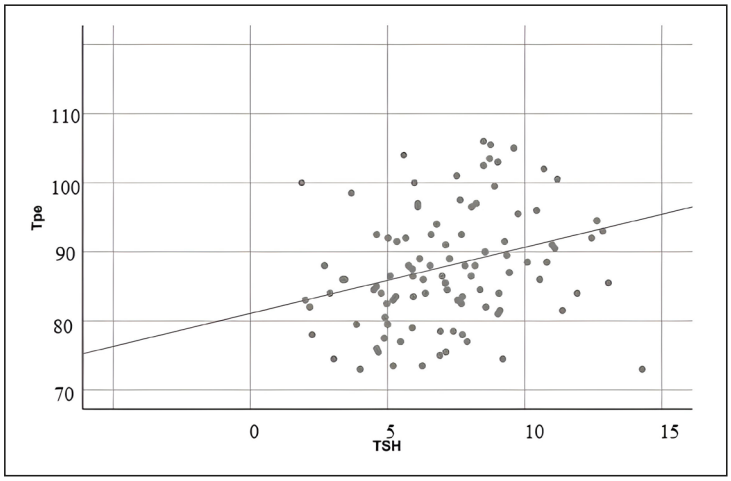

Figure 1. Correlation Between TSH and Tp-e.

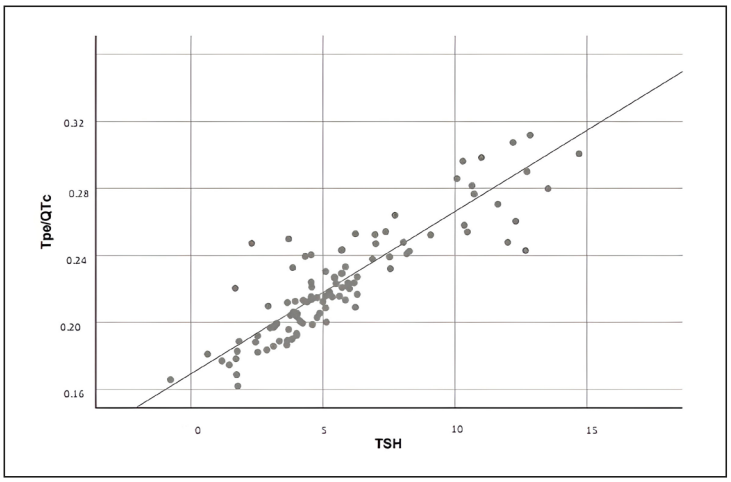

Figure 2. Correlation Between TSH and Tp-e/QTc.

One of the main targets of the thyroid hormone is the cardiovascular system. Beeckman et al[8] observed that patients with hypothyroidism experienced a decreased catecholamine sensitivity in vascular structures and a decreased binding to receptors on myocytes. Decreased cardiac contractility, decreased cardiac output, and electrophysical changes can be commonly seen in hypothyroidism[9,10]. In recent years, there have been numerous studies[4,11,12] on ventricular repolarization of hypothyroid patients.

In ECG, the distance from the beginning of QRS until the end of T wave is defined as QT, and it is accepted as one of the indicators of ventricular repolarization. Corrected QT is obtained by correcting the QT interval for heart rate[13]. Prolonged QT interval is related to ventricular arrhythmia and cardiac mortality. A study[14] with 8,455 healthy volunteers found that the average QT dispersion duration was 33 ms. Okin et al[15] indicated that when the QTD distance was above 58 ms, the cardiac mortality increased 2 times. Galetta et al[3] compared QT interval distribution of 42 hypothyroid patients with 32 euthyroid control group patients and found that QT distribution interval increased in the hypothyroid patient group. This was related to cardiac autonomic regulation problems and ventricular repolarization disorder due to overt hypothyroidism.

Although QT distance duration was generally higher for subclinical hypothyroidism patients compared to the control group, there are studies[4] with no significant difference. Unal et al[12] followed 16 female patients with subclinical hypothyroidism on levothyroxine treatment for 16 weeks and indicated that QT distributions decreased after the patients became euthyroid. Galetta et al[11] compared QT distributions between subclinical hypothyroidism patients and euthyroid control group and showed that the subclinical hypothyroidism patient group had a longer QT interval than the control group. A study by Gürdal et al[4] found no significant difference in QTc levels between subclinical hypothyroidism patients and healthy volunteers. In our study, there was no significant difference in QTc level for subclinical hypothyroidism patients compared to the euthyroid control group.

One of the ventricular repolarization markers whose prevalence has increased in the last decade is the Tp-e interval. Tp-e/QT and Tp-e/QTc ratios are among the new parameters used for predicting cardiac arrhythmia and these ratios have a significant relationship with cardiovascular mortality[16]. A study[17] on 60 healthy volunteers found that Tp-e interval was 40-110 ms (av. 76.1±1.7 ms), Tp-e/QT ratio as 0.15-0.25 (av. 0.21±0.003). Sicouri and Antzelevitch[18] showed prolonged Tp-e interval increased ventricular arrhythmia. It is shown that Tp-e/QT ratio significantly increases in organic health patients with prolonged QT, Brugada Syndrome and myocadiac infarcts. Gürdal et al[4] compared Tp-e/QT ratio between subclinical hypothyroidism patients and the control group and found statistically significant differences. The findings in our study support the findings in the literature.

In our study, statistically significant differences were found between Tp-e and Tp-e/QT durations between 3 groups (overt hypothyroidism, subclinical hypothyroidism, and euthyroid control group). In the previous studies[19,20], it was reported that ventricular repolarization abnormalities

developed due to impacts on the cardiac calcium canal related to serum T3 and T4 for patients with hypothyroidism. In our study, significant differences were found between groups when TSH levels were compared. It suggests that TSH level may have a significant effect on ventricular repolarization, such as Tp-e, Tp-e/QTC times, independent of T4. As expressed by Galetta et al[11], this supports that TSH concentration has a significant impact on cardiac sympathovagal imbalance.

Limitations

The most important limitation of this study is the limited number of patients and the retrospective nature of this study. Prospective and multi-central studies with a larger participant group that might reveal the reasons for arrhythmia and mortality over the long run are needed.

Conclusions

As a result, while a positive correlation between TSH levels and Tp-e, Tp-e/QTc was found, there was no statistically significant impact on QTc. Tp-e, Tp-e/QTc, which are among the new generation indicators, can be used for predicting ventricular repolarization and cardiac arrhythmia. In addition, we think that closely monitoring the efficiency and adequacy of LT4 therapy in patients with overt hypothyroidism is beneficial in reducing the development of arrhythmia and the risk of cardiovascular disease. Similarly, we believe that it is possible to recommend LT4 treatment which not only can help slow the hypothyroidism progression and decrease clinical symptoms for subclinical hypothyroidism patients, but also decrease TSH levels to protect the patient from cardiovascular risks.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Ethics Approval

The study was approved by the Ethics Committee of Afyonkarahisar Health Sciences University (date: 02.12.2022, meeting No.: 2022/16, approval number: 593).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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SA: Conceptualization, Writing - Original Draft, Writing - Review and Editing. DİE: Formal analysis, Writing - Review and Editing UA: Formal analysis, Writing - Review and Editing KC: Formal analysis, Writing - Review and Editing BE: Formal analysis, Writing - Review and Editing MA: Formal analysis, Writing - Review and Editing.

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