Prolonged QT dispersion in Subclinical Hypothyroid Females: A Study in University Teaching Hospital in Central Nepal

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ABSTRACT

Background

QT dispersion is a simple index derived from 12 lead ECG; its prolongation has been shown to be associated with increased arrhythmia risk. Increased cardiovascular risks, particularly occurrence of the malignant arrhythmias are a common finding in patients with subclinical hypothyroidism. This increased arrhythmia risk is found to be higher mainly in patients with TSH level more than 10 milli international unit per liter.

Objective

To assess QT dispersion among subclinical hypothyroid and euthyroid Nepalese females aged 20-59 years attending general practice out patient department of centrally located University Teaching Hospital from November 2016 to April 2017.

Method

Forty-three newly detected subclinical hypothyroid females and forty-one euthyroid females were enrolled. Resting electrocardiogram (ECG) was performed. QT dispersion was analyzed from ECG and corrected for heart rate using Framingham correction formula. Independent sample t-test was applied to compare mean QT dispersion between two groups. Pearson correlation test was used to examine the association between QT dispersion and TSH level.

Result

Mean QT dispersion for sub-clinical hypothyroid group was 75.35 ± 43.82 whereas mean QT dispersion for euthyroid group was 59.51 ± 22.13, with p value 0.041. A weak association between QT dispersion and TSH level was seen with correlation factor of 0.23.

Conclusion

The result showed prolongation of QT dispersion in sub-clinical hypothyroid group and weak positive correlation between TSH level and QT dispersion suggesting arrhythmia risk in subclinical hypothyroid females.

KEY WORDS

Arrhythmia risk, QT dispersion, Sub-clinical hypothyroidism

INTRODUCTION

Subclinical hypothyroidism is a highly prevalence condition in Nepal.[1-4] The prevalence in both sexes is higher in Nepal in comparison to Europe.[1-5] Females are more at risk to the occurrence of subclinical hypothyroidism in comparison to males. Prevalence is seen higher particularly in females in the age group of 20-40 years.[1-3] Thyroid disorders predominantly affect young females due to the effect of estrogen on thyroid hormone binding globulin.[6] Studies on association of subclinical hypothyroidism with cardiovascular risk are not very conclusive, however strong positive association is seen in patients with higher TSH level of more than 10 milli international unit per liter (mIU/liter).[7-13]

Early recognition of cardiovascular disease has been attempted by exploring different measures of electrocardiogram (ECG). QT interval and QT dispersion are among the few markers.[14,15] Prolongation of QT interval and QT dispersion in subclinical hypothyroid patients have been demonstrated by some studies outside Nepal.[15] However, there is gross scarcity of this data in Nepal. Hence, the present study was conducted with the aim of exploring whether subclinical hypothyroid patients have prolonged QT dispersion similar to the studies outside Nepal adding to the existing knowledge in the context of Nepal.

METHODS

A cross-sectional comparative study was conducted in the General Practice Outpatient Department (OPD) of a University Teaching Hospital located in Central Nepal. The study was conducted from November 2016 to April 2017 with ethical approval from Institutional Review Board of the hospital. Written informed consent was taken for all the participants. Confidentiality and anonymity of the participants was maintained throughout the study.

Study sample was selected from female patients aged 20 to 59 years attending 'Wellness clinic' in General Practice OPD of the Teaching Hospital; these patients had thyroid function test (TFT) done as a part of routine investigation. Majority of selected sample visited the hospital from locations around Kathmandu valley. Bearing in mind the high prevalence of thyroid disorder in young female subjects, female subjects in the age range of 20 to 59 years were selected for the study purpose. Samples were selected using purposive sampling due to strict inclusion criteria of only the newly diagnosed subclinical hypothyroid cases. Sample size was calculated using the formula for comparing means of two independent groups with quantitative end point.[16] Effect size was calculated using mean and standard deviation from the study conducted by Bakiner et al.[15] Total sample size came out to be 50 but anticipating 10% attrition and considering similar past studies elsewhere, sample size of 88 was included for the study.[16]

Exclusion criteria were applied and the sample was divided into two groups, one subclinical hypothyroid group and another euthyroid group. Females with thyroid stimulating hormone (TSH) level more than 4.5 mIU/liter with normal level of free triiodothyronine (T3) level (4.26 to 8.1 picomole/liter) and tetraiodothyronine (T4) level (10.2 to 28.2 picomole/liter) were included in subclinical hypothyroid group.[17,18] Age matched females attending the same clinic as assessed by the same clinician with normal level of T3, T4 and normal TSH level (0.46 to 4.5 milliIU/liter) were included in euthyroid group. Subjects with known cardiovascular disease, known diabetes, known thyroid disease with or without treatment, presenting with thyroid specific symptoms, current or past history of arrhythmia, hepatic failure, renal failure and electrolyte abnormalities, treatment with medications known to interfere with cardiac conduction, were excluded from the study.[19-21] Four participants (one subclinical hypothyroid and three euthyroid) were excluded due to ECG abnormalities. Forty-three subclinical hypothyroid females and forty-one euthyroid females were finally selected for the study.

Medical history, physical examination, vital signs and anthropometric measurement were obtained by the researcher and recorded in the data collection sheet manually.[22] Blood pressure was recorded by standard mercury manometer and pulse rate was examined for one minute. The researcher followed up reports of TFT. Subjects with other types of thyroid function abnormalities and subjects with abnormal serum electrolytes were excluded from the study.

All the participants of the study underwent standard 12 lead ECG using Nihon Kohden Cardiofax S-1250 ECG machine in the ECG department of TUTH. ECGs with arrhythmias were excluded. ECGs were either electronically transmitted to a storage device or were photocopied for record in order to calculate QT intervals and QT dispersion. Two medical personnel who had no direct involvement in the study calculated QT intervals and they were blinded for the group allocation of the participants. ECG magnifier was used to read ECG when necessary.

QT intervals were corrected for heart rate using Framingham correction formula manually.[23] QT intervals were measured from the start of Q wave to the end of T wave for each lead. QT intervals were measured for each lead averaging at least three consecutive beats. Leads with u wave and unclear T waves were excluded. All the 12 leads were included for QT interval measurement. Maximum QT interval (QTmax) and minimum QT interval (QTmin) were derived for each ECG. Both QT max and QT min that were calculated, were corrected for heart rate to obtain corrected maximum QT interval (QTc max) and corrected minimum QT interval (QTc min).[24]

Calculation of QT dispersion: QT dispersion was calculated as a different between QTc max and QTc min.[25] Corrected

QT interval of more than or equal to 460 milliseconds (ms) and QT dispersion of more than 50 ms was considered prolonged for the purpose of this study.[25,26]

All statistical analysis was performed using Statistical package for Social Sciences (SPSS) software version 20. Normality test for distribution of data was done using SPSS software. Pearson correlation test was used to check the relationship between TSH and QT dispersion. Independent sample t test was used to compare the means of subclinical hypothyroid group and euthyroid group. All the results were expressed as mean ± standard deviation. A p (calculated probability) value of less than 0.05 was considered statistically significant.

RESULTS

Anthropometric measurements and vital signs of all 84 participants including 43 subclinical hypothyroid and 41 euthyroid females were comparable. (Table 1, table 2)

Table 1. Baseline characteristics of the study groups

Parameters	Euthyroid group (n = 41)	Subclinical hypothyroid group (n = 43)	P value
Age in years	41.32 ± 11.26	42.12 ± 10.66	0.739
Weight in kilogram	59.37 ± 10.70	59.42 ± 9.76	0.981
Height in meter (m)	1.53 ± 0.04	1.52 ± 0.06	0.926
Body Mass Index (Kg/m^2)	25.24 ± 3.67	25.33 ± 3.36	0.903

Table 2. Resting blood pressure and pulse rate of participants

Parameters	Euthyroid group (n = 41)	Subclinical hypothyroid group (n = 43)	P value
Systolic blood pressure (mmHg)	116.00 ± 10.14	119.21 ± 9.23	0.133
Diastolic blood pressure (mmHg)	77.41 ± 7.46	76.47 ± 5.46	0.506
Pulse rate (beats/ minute)	72.88 ± 9.37	73.67 ± 12.51	0.743

Significant difference exists in TSH level between the participants in two groups. Majority of the participants in subclinical hypothyroid group had mild subclinical hypothyroidism with TSH level of < 10 mIU/liter (Table: 3).

Table 3. Comparison of TSH level between study groups

Parameters	Euthyroid group	Subclinical hypothyroid group	P value
TSH (milliIU/liter)	2.36 ± 1.06	7.67 ± 3.05	0.000

No notable difference is seen in QT intervals (corrected and uncorrected) between subclinical hypothyroid group and euthyroid group. However, significant prolongation of QT dispersion is seen in subclinical hypothyroid group in comparison to euthyroid group. (Table 4)

Table 4. Comparison of QT intervals, "corrected QT intervals" and QT dispersion between study groups.

Parameters	Euthyroid group	Subclinical hypothyroid group	P value
QT maximum (ms)	408.78 ± 36.34	413.02 ± 43.39	0.629
QT minimum (ms)	348.29 ± 28.62	337.67 ± 44.76	0.201
QTc maximum (ms)	408.80 ± 3 6.33	413.05 ± 43.39	0.629
QTc minimum (ms)	349.29 ± 28.30	337.70 ± 44.76	0.162
QT dispersion (ms)	59.51 ± 22.13	75.35 ± 43.82	0.041

Table 5. Results of Pearson Correlation test between TSH level and QT dispersion

Parameter 1	Parameter 2	Correlation factor	P value
TSH level	QT dispersion	0.234	0.032

A weak positive correlation between TSH level and QT dispersion with the correlation factor of 0.234 is demonstrated. (Table 5)

DISCUSSION

Our result of increased QT dispersion in subclinical hypothyroidism is in consistent with the findings of other studies around the world supporting the fact that subclinical hypothyroid patients have associated prolongation in QT dispersion.[15,27] However, our study fails to show significant difference in QT intervals (maximum, minimum and corrected QT intervals) between the two groups in contrary to the above studies.[15,27] Mild degree of subclinical hypothyroidism in the participants of our study with mean TSH level of 7.67 ± 3.05 probably might have been responsible for indifferent QT intervals unlike the previous studies.[15,27,36] Our study also demonstrates the weak positive correlation between TSH level and QT dispersion similar to the study done by Bakiner et al. in Turkey, Galetta et al. in Italy, Unal et al. in Turkey.[15,27,28]

Several ideas have been proposed for the exact cause for prolonged QT dispersion in hypothyroid state.[29-32] Prolonged QT intervals reflect prolonged ventricular repolarization and prolonged QT dispersion indicates inhomogeneous ventricular repolarization. Both these situation is found to exist in hypothyroid state. A review of the literature has revealed many cellular effects of thyroid hormone deficiency state.[30] Experimental studies have reported an increase (31 to 44%) in the duration of ventricular action potential and decrease in the amplitude of L type calcium current in the myocyte membrane of hypothyroid guinea pigs.[29] Delay in the ventricular membrane repolarization and decrease in the slow component of delayed rectifier K current (IKs) was claimed to be primarily responsible

for this situation.[30,31] In a recent trial, it has been demonstrated that subclinical hypothyroidism can alter autonomic modulation of heart rate and cause increased heterogeneity of ventricular recovery times.[31,32] This non-uniform repolarization in hypothyroid disorders predisposes patients to risk of malignant arrhythmias.[29,34] Therefore, there is substantial physiological basis for prolonged QT intervals and prolonged QT dispersion in subclinical hypothyroid state.[31-33] The increase in QT dispersion is closely associated with repetitive and life-threatening ventricular arrhythmias and has been shown to be an independent risk factor for sudden cardiac death.[35] Clinical usage of QT dispersion as an indicator of arrhythmia risk is still questionable as there are numerous factors that can affect QT dispersion such as age, gender, medication, electrolyte imbalance, medical condition such as diabetes, heart failure and myocardial infarction.[26,34] However, it can be used in combination with other factors of cardiovascular risk in the assessment of patients with arrhythmia risk such as those with hypothyroid disorders

CONCLUSION

The result of the study demonstrates the presence of prolonged QT dispersion in subclinical hypothyroid females with weak positive association between the level of TSH and QT dispersion.

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