Original article:

Effects of L-Thyroxine treatment on QTc interval of overt hypothyroid female patients

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Abstract:

Introduction-In overt hypothyroid patients mostly the left ventricular dysfunction is seen, which is due to slowed myocardial relaxation. Also the ECG finding includes QTc interval prolongation, which is an index of the inhomogeneity of ventricular repolarization. Many previous studies concluded that prolongation in ventricular repolarization time is due to decreased serum T3 and elevated serum TSH levels in overt hypothyroid patients. Thus, the aim of this study was to test the hypothesis that L-Thyroxine treatment changes the QTc interval of overt hypothyroid patients.

Material and Methods-The study included newly diagnosed 38 female volunteers of overt hypothyroidism. All patients were checked with a lead-II ECG before and after 3 months of L-thyroxine treatment and QTc interval was noted.

Results-There was significantly improvement in the thyroid profile and QTc interval after L-Thyroxine treatment in overt hypothyroid patients.

Conclusion-In overt hypothyroid patients, decrease in thyroid hormone level leads to ventricular inhomogeneity, but subsequent replacement of L-thyroxine therapy may reduce risk of ventricular arrhythmias.

Introduction:

Over the past decade there has been increasing awareness of the role of endocrinal disorders like altered thyroid status in cardiac dysfunctions. The most consistent cardiac abnormality observed in overt hypothyroid patients is left ventricular diastolic dysfunction, characterized byslowed myocardial relaxation and impaired early ventricular filling.[1] Overt hypothyroid patients usually have abnormal standard ECG, including QT interval lengthening and flattening or inversion of the T wave.[2]QT interval corrected for heart rate (QTc) is an index of the inhomogeneity of ventricular repolarization.[3]

Previous studies have detected increase in ventricular repolarization time in patients of overt hypothyroidism, which may predispose to the risk of ventricular arrhythmia. Also they concluded that in overt hypothyroidism decreased serum T3 (Tri-iodothyronine) and elevated serum TSH levels prolong ventricular repolarization.[1,2,4]In view of the above conclusion and to test the hypothesis that L-Thyroxine treatment changes the QTc interval of overt hypothyroid patients, this study was undertaken.

Aim and Objectives:

The aim of present study was to evaluate the effect of L-Thyroxine treatment on QTc interval of overt hypothyroid patients.

Material and Methods:

The synopsis of this analytical study protocol was submitted to the institutional ethics committee and it was approved. This study included 38 female volunteerswith age ranging from 30 to 45 years

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from the patients attending medicine OPD. Newly diagnosed female patients of overt hypothyroidism, those who were not taking any treatment or medicines for thyroid disorder were included. Also those patients having other diseases which could alter autonomic reactivity like diabetes, electrolyte imbalance cardiovascular disorders, arrhythmia, hypertension, hepatic or renal failure or consumption of any medication that might alter cardiac conductibility were excluded.Diagnosis of overt hypothyroidism was based on both clinical and biochemical criteria (Thyroid hormone profile).[5]Those patients having low total T3, low total T4 and high TSH were grouped in overt hypothyroid.

Table 1: Thyroid Hormone profile, Laboratory reference range by ELISA test.

Tests (Parameters)	Expected normal Value
Total T3	56 to 188 ng/dl
Total T4	4.87-11.72 µg/dl
TSH	0.4-4.0µIU/ml

In the study all the participants were explained verbally in detail about the purpose and every step in the study. Adequate opportunity was given to discuss their queries. A written consent was obtained from all the participants. The detailed medical history was taken and clinical examination was done. Then all the participants were asked to come in the morning at 8 am. All the patients were checked with thyroid profile and ECG lead- II before and after 3 months of L-Thyroxine treatment. 5ml fasting blood sample was obtained under all aseptic precautions. Serum was separated and serum total T3, T4 and TSH was estimated by using Enzyme linked immunosorbent assay (ELISA) method. The subject were advised to avoid tea or coffee at breakfast and to attend the physiology department laboratory between 9:00 to 11:00 a.m. on the day of examination.

Resting ECG (Electrocardiogram) was recorded in lead- II after a 15 minutes rest in supine position and baseline heart rate of patients was measured. Patients having heart rate in between 60-90 beats/min were included. Blood pressure was measured in supine position with a standard mercury manometer. QT intervals were measured in lead II from onset of QRS complex to the end of T wave. Three consecutive QT intervals were measured and average was taken. QT interval was corrected (QTc) by Bazett's formula (QTc = QT/square root of R-R interval) for heart rate.[6]

Statistical analysis:

The data was presented as mean ± standard deviation. Comparisons were performed using paired t test. Then Co-efficient of correlation in bivariate relationships was obtained using the Pearson's correlation test. A ''p'' value of less than 0.05 was considered as statistically significant and "p" value of less than 0.001 as statistically highly significant. Statistical software namely Graphpad Prism for windows, version 5.01 was used.

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Results:

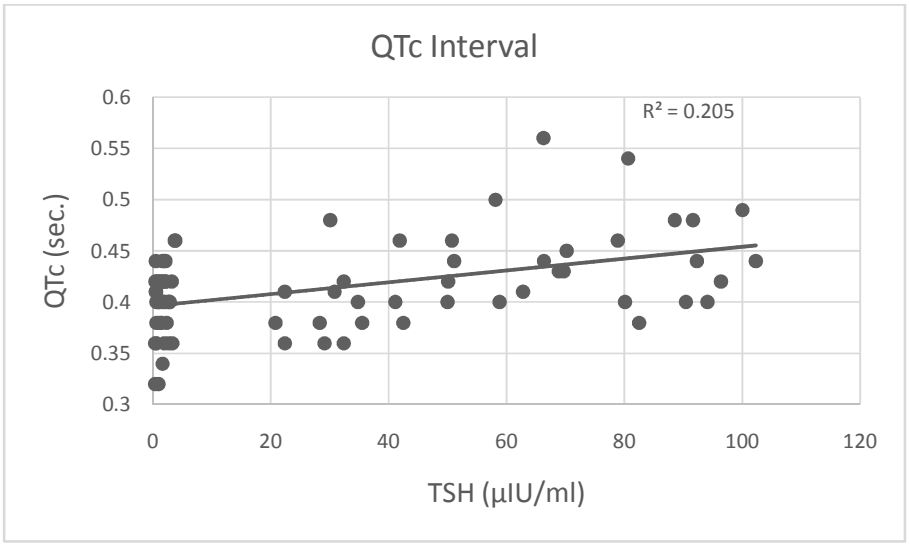
The mean age of 38 overt hypothyroid patients was 36.52 ± 4.84 years.

Table 2: Showing comparison of biochemical and clinical parameters before and after L-Thyroxine treatment.

Groups / Parameters (Mean±SD) (normal range)	Before treatment	After treatment	p value
Total T3 (56 to 188 ng/dl)	39.76 ± 9.00	82.84 ± 14.65	<0.05
Total T4 (4.87 to 11.72 µg/dl)	2.65 ± 0.91	06.57 ± 1.66	<0.001
TSH (0.4 to 4.0 µIU/ml)	59.08 ± 25.40	1.61 ± 0.97	<0.001
QTc (seconds)	0.42 ± 0.04	0.40 ± 0.03	< 0.001

p<0.05 = statistically significant, p<0.001 = statistically highly significant, SD= standard deviation.

Graph 1: Showing correlation between TSH levels and QTc interval for all patients and control subjects.



Graph 1 shows positive correlation between TSH levels and QTc intervals of 76 subjects (r = 0.45, p<0.001).

Table 2shows comparison between the mean values of total T3 (Tri-iodothyronine), total T4 (thyroxine), TSH (thyroid stimulating hormone) levels and QTc interval before and after 3 months L-Thyroxine treatment in overt hypothyroid patients.

There was statistically significant improvement in all the parameters in overt hypothyroid patients after L-Thyroxine treatment.Total T3 was

significantly increased ($p<0.05$) and total T4 level was highly significantly increased ($p<0.001$),while TSH level wasstatistically significantly decreased ($p<0.001$) after treatment of overt hypothyroid patients. QTc interval was statistically significantly decreased ($p<0.001$) after treatment of overt hypothyroid patients.

Discussion:

The clinical presentation of overt hypothyroidism is not obvious and most patients have few symptoms and signs. Bradycardia and systemic hypertension, with narrow pulse pressure and slightly increased mean arterial pressure, and some degree of exercise impairment are the most common findings in patients with overt hypothyroidism.Many patients with overt hypothyroidism have abnormal standard ECG, including QT interval lengthening and flattening or inversion of the T wave, which reflects the prolonged cardiac action potential.[2]In addition, overt hypothyroid patients are more prone to ventricular arrhythmias, particularly in the presence of an underlying ischemic heart disease, due to increased electrical dispersion in the myocardium.[2,7]QT interval reflects the total duration of ventricular myocardial depolarization and repolarization. It can be corrected for heart rate by commonly used Bazett's formula where QTc = QT /√RR interval. The QTc (corrected QT interval) effectively is the QT interval estimated at a rate of 60/minute.[6]

In the present study we found significantlyincrease in serum total T3 (82.84 ± 14.65 ng/dl) and total T4 (06.57 ± 1.66 µg/dl), while TSH level was significantly decreased (1.61 ± 0.97 µIU/ml) after L-Thyroxine treatment in overt hypothyroid patients. (Table 2)In our study, after treatment of L-Thyroxine for 3 months, overt hypothyroid patients returned to euthyroid state.

TheQTc interval (seconds) before L-Thyroxine treatment was 0.42 ± 0.04 in overt hypothyroid patients, while after treatment it was 0.40 ± 0.03.After treatment there was significantly decrease in QTc interval. (Table 2) Thus, all the parameters were normalised after achieving euthyroid state.Our results were compatible with previous studies.[2,8,9]Schenck JB et al and Fredlund B et al stated that the syndrome of torsade de pointes with a long QT interval and ventricular tachycardia can occur with hypothyroidism and can be resolved with T4 (L-Thyroxine) treatment alone.[7,10]

Also we found positive correlation between TSH levels and QTc intervals. (Graph 1)Nathaniel et al. reported that significant prolongation of the QTc interval occurred in inadequately treated hypothyroidism and the degree of the QTc prolongation was directly related to the severity of hypothyroidism.[11]Altun et al. showed that QT prolongation and increased QTdispersion (QTd) were directly related to the TSH levels in hypothyroidism. [12]

Increased QTc interval i.e. prolonged repolarization time may be due to an increase in the depolarizing currents or to a decrease in repolarizing currents. Bakiner O et al andWickenden AD et al proved that overt hypothyroidism reduces some cardiac repolarizing K^+ currents such as the transient outward potassium current (I_{to}) and increases the L-type calcium current (Ica-L).[13,14] In overt hypothyroidism most of the repolarization abnormalities found are due to a reduction of the I_{to}, and an increase in the I_{Ca}-L.[15,16,17]T3 regulates the I_{Ca}-L calcium current at transcriptional and posttranscriptional level.[2]This explain, decreased T3 in overt hypothyroid could increase theI_{Ca}-L current.

Thus, decreased serum T3 and elevated TSH level prolongs ventricular repolarization in overt hypothyroidism and after L-thyroxine treatment it reverts back to normal.

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Conclusion and Summery:

The aim of the present study was to test the hypothesis that L-Thyroxine treatment changes the QTc interval of overt hypothyroid patients. Our results showed improvement in QTc interval after L-Thyroxine treatment in overt hypothyroid patients.Thus the present study concludes that in overt hypothyroid patients, decrease in thyroid hormone level leads to ventricular inhomogeneity, but subsequent replacement of L-thyroxine therapy may reduce risk of ventricular arrhythmias.

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