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The Relationship between Thyroid Hormone Levels and Corrected QT Interval and QT Dispersion in Non-Diabetic Hemodialysis Patients

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Abstract

Background: Cardiovascular disease and sudden cardiac death are common in hemodialysis patients. These cardiac complications are often associated with prolonged QTc interval (QTc) and QTc dispersion (QTcd). Subclinical hypothyroidism (SH) can alter autonomic modulation of heart rate and cause increased inhomogeneity of ventricular recovery time. We aimed to evaluate the relationship between thyroid hormone levels and QTc and QTcd in non-diabetic hemodialysis patients. Methods: We enrolled 29 non-diabetic hemodialysis patients without thyroid disease. After each hemodialysis session, a 12-lead ECG was recorded. Before each hemodialysis session, routine laboratory tests and measurement of thyroid hormone levels were performed. Patients were divided into 2 groups according to QTc (group 1 QTc < 430 ms, group 2 QTc ≥ 430 ms). We examined the relationship between QTc or QTcd and thyroid hormone in the respective groups and then compared the results from the 2 groups. Results: The mean age was 54.06 ± 14.72 years and the means of QTc and QTcd were 433.82 ± 22.03 ms, 59.10 ± 28.29 ms, respectively. Homocysteine levels were significant higher in group 2 than group 1 ($p < 0.05$) and QTcd was comparable between groups. In group 1, QTc and QTcd were not significant correlated with TSH, T3, fT4 and biochemical parameters. In group 2, QTc was significant positively correlated with TSH ($p < 0.05$) and QTcd was not significant correlated with thyroid hormone levels. Conclusion: The results of this study showed that TSH is associated with prolonged QTc interval and hyperhomocysteinemia in non-diabetic hemodialysis patients. Moreover, we suggest that SH may be associated with prolonged QTc in non-diabetic hemodialysis patients. However, further studies are required to elucidate the role of the L-thyroxine doses and TSH target levels in hemodialysis patients.

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Keywords

Thyroid Hormone; Hemodialysis; Cardiovascular Disease

1. Introduction

Cardiovascular disease and sudden cardiac death are common in hemodialysis patients. The cause of cardiovascular death in advanced renal disease is variable. Acute myocardial infarction is relatively rare. More commonly, death is developed suddenly and due to progressive heart failure [1]. Therefore, determinants of sudden cardiac death such as arrhythmia, left ventricular hypertrophy, prolonged QTc interval (QTc) and increased QTc dispersion (QTcd) are of great importance.

Subclinical hypothyroidism (SH) is an asymptomatic condition defined by slightly increased serum thyrotrophin (thyroid stimulating hormone; TSH) concentrations, but normal serum free T3 (fT3) and free T4 (fT4) hormone levels. Altered serum lipid levels and abnormal vascular reactivity in patients with SH may confer a higher risk for cardiovascular disease [2] [3]. SH is associated with a risk of heart failure, other cardiovascular events, and death [4]. Clinical studies have shown that SH can influence autonomic modulation of the heart rate and cause increased inhomogeneity of ventricular recovery times in patients with normal renal function. These previous studies also reported that early L-thyroxine treatment may be recommended not only to prevent progression to overt hypothyroidism but also to improve abnormal cardiac autonomic function and ventricular repolarization inhomogeneity [5].

We hypothesized that SH may be associated with cardiovascular disease and sudden cardiac death in hemodialysis patients. In the present study, we aimed to evaluate the relationship between thyroid hormone levels and QTc and QTcd in non-diabetic hemodialysis patients.

2. Materials and Method

Total 29 hemodialysis patients (13 men and 16 women; mean age 54.06 ± 14.72 years) without thyroid disease were enrolled in this study. Dialysis was performed in a standard setting with synthetic membranes, for the duration of 180 to 240 minutes, for 3 times per week. All patients are under went by standard bicarbonate dialysis.

After each hemodialysis session, a simultaneous 12-lead ECG was recorded using a 12-channel electrocardiograph at a paper speed of 25mm/s. RR and QT intervals were measured with a magnifying ruler on the ECG tracing. QT interval was measured from the beginning of the QRS complex to the end of the downslope of the T wave (crossing of the isoelectric line). When T waves were inverted, the end was considered as the point where the trace returned to the isoelectric line. When U waves were present, the end of the T wave was considered as the nadir between the T and the U wave. If the end of the T wave was not clearly identifiable, the lead was not included in the analysis.

QT intervals were corrected for the previous cardiac cycle length according to Bazett's formula: QTc (ms) = QT/√RR. QTc was considered to be prolonged when it was >440 ms, in accordance with the criteria commonly used in the literature [6] [7].

QTcd was calculated as the maximum QT interval minus the minimum QT interval in any of the leads. As QTcd does not depend on the heart period unlike the QT interval, it was not corrected using Bazett's formula [8].

Before each hemodialysis session, routine laboratory tests (plasma concentration of potassium, sodium, magnesium, calcium, phosphorus, chloride, urea, creatinine, albumin, bicarbonate, cholesterol, and homocysteine) and measurement of TSH, fT4, and T3 levels were performed.

Patients were divided into 2 groups according to QTc (group 1: QTc < 430 ms; group 2: QTc ≥ 430 ms). We examined the relationship between QTc or QTcd and thyroid hormone in the respective groups and then compared the results from the 2 groups.

All data are expressed as mean ± S.D. and compared using the one-way analysis of variance (ANOVA) among groups. Linear correlation analysis was used to assess the relationships between variables. Differences were considered significant when $P < 0.05$.

3. Results

Of the 29 patients, 13 were men and 16 were women. The mean age was 54.06 ± 14.72 at commencement of the study. Underlying renal diseases included hypertension (HTN) (55.2%), glomerulonephritis (GN) (20.7%), ADPKD (10.3%), and unknown (13.7%). The mean hemodialysis duration, Kt/V, nPCR, and BMI were 63.72 ± 42.78 months, 1.48 ± 0.20, 0.88 ± 0.22 g/kg/d, and 23.03 ± 3.93 kg/m^2, respectively. Moreover, TSH, T3, and fT4 were 4.66 ± 10.85 uIU/mL, 1.09 ± 0.16 ng/mL, and 0.99 ± 0.83 ng/dL respectively in group 1. And 2.50 ± 2.52 uIU/mL, 1.06 ± 0.20 ng/mL, and 0.96 ± 0.16 ng/dL respectively in group 2. TSH levels were significantly higher in group 2 patients than in group 1 patients ($P < 0.05$), whereas T3 and fT4 were comparable between groups.

There were no significant differences between the two groups, except for homocysteine levels. The mean homocysteine levels were 14.70 ± 4.26 umol/L in group 1 and 18.47 ± 3.84 umol/L in group 2 (**Table 1**).

Table 1. Clinical characteristics and biochemical parameters of patients (N = 29).

	Total (N = 29)	Group 1 (N = 13)	Group 2 (N =1 6)
Age (years)	54.06 ± 14.72	53.23 ± 13.92	54.75 ± 15.02
Sex (M:F)	13:16	5:8	8:8
Cause of ESRD N (%)			
Hypertension	16 (55.2)	7 (53.8)	9 (56.3)
Chronic GN	6 (20.7)	5 (38.5)	1 (6.3)
Polycystic kidney	3 (10.3)	0	3 (18.8)
Unknown	4 (13.7)	1 (7.7)	3 (18.8)
BMI (kg/m2)	23.02 ± 3.93	22.37 ± 3.13	23.55 ± 3.80
Kt/V	1.48 ± 0.20	1.48 ± 0.21	1.48 ± 0.20
nPCR (g/kg/day)	0.88 ± 0.22	0.85 ± 0.24	0.90 ± 0.20
HD duration (months)	63.72± 42.78	70.15 ± 45.95	58.50 ± 40.78
CRP (mg/dL)	0.35 ± 0.46	0.35 ± 0.56	0.34 ± 0.38
Calcium (mg/dL)	9.26 ± 0.88	9.26 ± 0.64	9.27 ± 1.05
Phosphorus (mg/dL)	5.22 ± 1.44	5.33 ± 1.34	5.13 ± 1.55
Ca × P product	48.54 ± 14.52	49.58 ± 13.82	47.69 ± 15.46
Uric acid (mg/dL)	8.10 ± 1.73	7.87 ± 1.36	8.28 ± 2.02
Protein (mg/dL)	6.83 ± 0.47	6.73 ± 0.41	6.91 ± 0.51
Albumin (mg/dL)	3.94 ± 0.36	3.98 ± 0.42	3.91 ± 0.31
Pre-albumin (mg/dL)	27.20 ± 7.48	27.10 ± 7.28	27.27 ± 7.87
tCO_2 (mEq/L)	20.96 ± 2.43	20.70 ± 2.55	21.17 ± 2.40
Hemoglobin (g/dL)	9.61 ± 2.12	9.66 ± 2.49	9.56 ± 1.86
Total Chol. (mg/dL)	130.79 ± 37.69	137.23 ± 48.32	125.56 ± 26.81
Triglyceride (mg/dL)	100.48 ± 53.56	107.30 ± 59.98	94.93 ± 49.02
HDL-Chol. (mg/dL)	37.60 ± 8.57	37.62 ± 6.68	37.59 ± 10.07
LDL-Chol. (mg/dL)	75.17 ± 20.99	76.46 ± 21.16	74.12 ± 21.48
TSH (uIU/mL)	3.69 ± 8.18	2.50 ± 2.52	4.66 ± 10.85
fT4 (ng/dL)	0.97 ± 0.12	0.96 ± 0.16	0.99 ± 0.08
T3 (ng/mL)	1.08 ± 0.18	1.06 ± 0.20	1.09 ± 0.16
Homocysteine (umol/L)	16.78 ± 4.39	14.70 ± 4.26	18.47 ± 3.84*
HOMA-IR	6.58 ± 5.32	6.64 ± 7.48	6.54 ± 2.84
QTc (ms)	433.82 ± 22.03	414.46 ± 6.15	449.56 ± 16.93*
QTcd (ms)	59.10 ± 28.29	51.65 ± 28.08	65.15 ± 27.86

Mean ± SD, *$P < 0.05$ vs. group 1. *Abbreviations*: ESRD; end stage renal disease, GN; glomerular nephropathy, BMI; body mass index, HD; hemodialysis, nPCR; normalized protein catabolic rate, CRP; C-reactive protein, Chol.; cholesterol, HDL; high density lipoprotein, LDL; low density lipoprotein, TSH; thyroid stimulating hormone, HOMA-IR; homeostasis model assessment method of insulin resistance.

In group 1, QTc and QTcd were not significantly correlated with TSH, T3, or fT4 and biomedical parameters (data not shown). In group 2, QTc was significantly positively correlated with nPCR and TSH ($p < 0.05$) (**Table 2**), but was not significantly correlated with thyroid hormone levels (**Figure 1**).

4. Discussion

Cardiovascular disease is the leading cause of death in patients with progressive renal disease and is responsible for up to 50% of deaths among patients underlying hemodialysis [9]. The cardiovascular risk of patients with progressive renal disease is up to 20 times that of the general population, and cardiovascular mortality in patients underlying dialysis is up to 10 times that of the general population [10]. These cardiac complications are often associated with prolonged QTc and QTcd.

QTc reflects the total duration of ventricular depolarization and repolarization [5]. QTc is an index of inhomogeneity of ventricular repolarization [11]. Experimental and clinical studies have shown that increased QTcd and reduced heart rate variability correlate with an increased risk of ventricular arrhythmias and cardiac mortality [12]-[14]. In ESRD patients, many factors can contribute to QTc prolongation, such as electrolyte abnormalities, associated conditions (including diabetes, heart failure, left ventricular hypertrophy and autonomic neuropathy) and medications. SH has also been reported to influence autonomic modulation of the heart rate and cause increased inhomogeneity of ventricular recovery times [5].

In the present study, our results showed that TSH is associated with prolonged QTc in non-diabetic hemodialysis patients. Prolonged QTc has been reported to be corrected when TSH levels of >10 mIU/L returned to normal after L-thyroxine therapy [15]. We suggest that the administration of L-thyroxine may be decreases the death rate associated with cardiovascular disease in hemodialysis patients without hypothyroid symptoms who have prolonged QTc as assessed by EKG. Further studies are required to elucidate QTc criterion, L-thyroxine dose and TSH target level.

In the present study, QTcd was not significantly correlated with TSH, T3, or fT4. An increase in QTcd is associated with repetitive and life-threatening ventricular arrhythmias and has been shown to be an independent risk factor for sudden death [16]-[23]. Several factors can affect QTcd, such as age, gender, myocardial ischemia, cardiac failure, diabetes, hypertension, electrolyte imbalance, certain drugs, and the circadian pattern of QTcd making its clinical use difficult to assess. The relationship between SH and QTcd in non-diabetic dialysis patients remains controversial, and our results in this regard were inconclusive. In addition, because, our study did not include patients with a long QTcd of >80 ms, further research is needed involving this group of patients.

A high level of homocysteine (Hcys) has been proposed as an independent risk factor for cardiovascular dis-

Table 2. The correlation of QTc with other study parameters in group 2 (QTc ≥ 430 ms).

	Bivariate analysis (N = 16)	
	Correlation coefficient	P value
BMI (kg/m^2)	0.450	0.080
Kt/V	−0.375	0.152
nPCR (g/kg/day)	0.609	0.012*
CRP (mg/dL)	0.088	0.747
Albumin (mg/dL)	−0.001	0.996
Pre-albumin (mg/dL)	0.367	0.162
tCO_2 (mEq/L)	−0.166	0.538
TSH (uIU/mL)	0.505	0.046*
fT4 (ng/dL)	−0.338	0.201
T3 (ng/mL)	−0.172	0.523
Homocysteine (umol/L)	0.018	0.947
HOMA-IR	0.202	0.453

Abbreviations: BMI; body mass index, Kt/V; dialyzer clearance of urea × dialysis time/volume of distribution of urea, approximately equal to patient's total body water, nPCR; normalized protein catabolic rate, CRP; C-reactive protein, HOMA-IR; homeostasis model assessment method of insulin resistance.

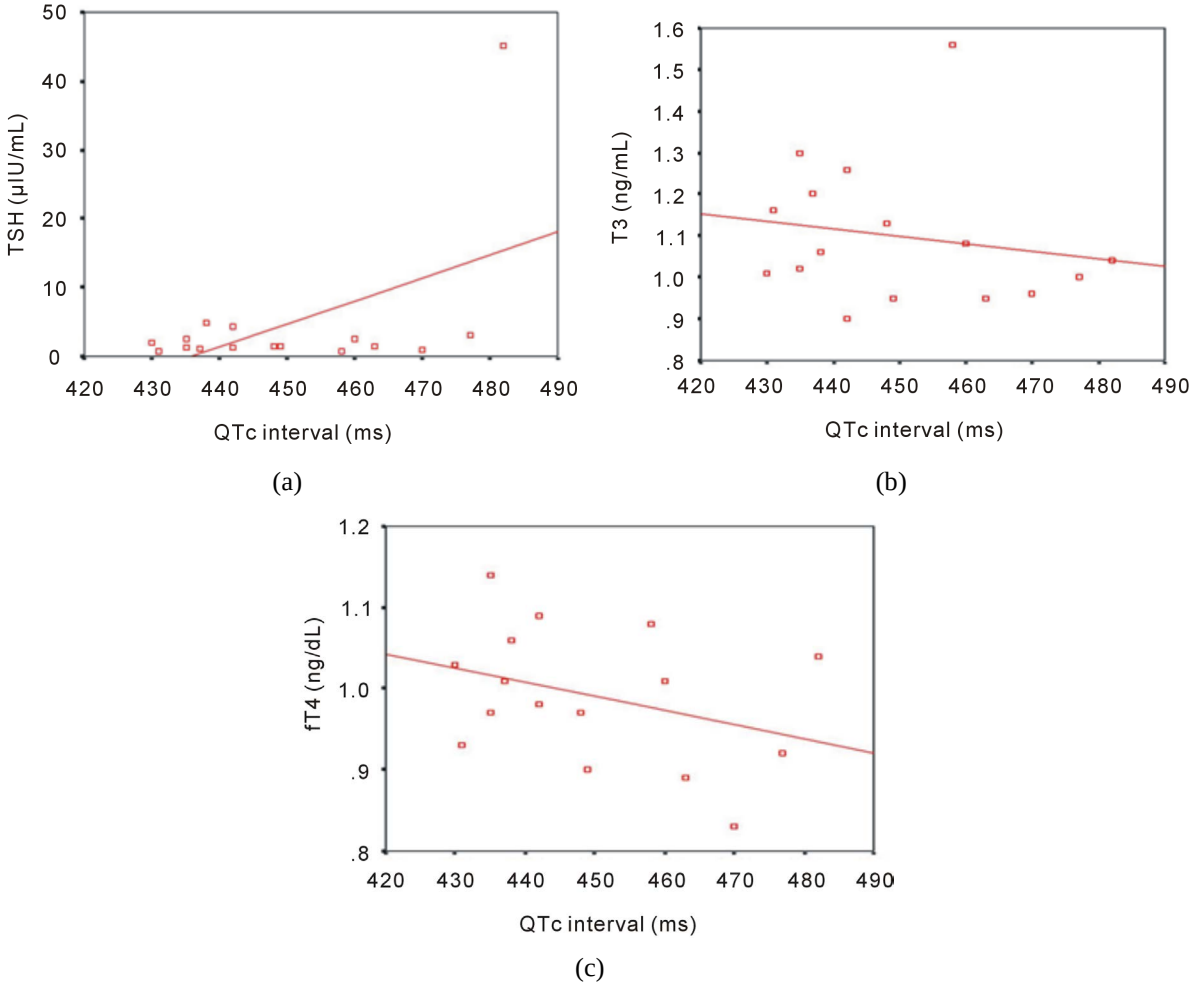

Figure 1. In group 2, QTc was significantly correlated with TSH (A) ($P < 0.05$), and not correlated with T3 (B) and fT4 (C) ($P > 0.05$).

ease. Plasma Hcys levels can be affected by several life-style and physiological factors and are elevated in renal failure [24]. There are consistent reports demonstrating that thyroid status is an important determinant of the plasma concentration of Hcys [25] [26]. Elevated plasma Hcys levels have been reported in overt hypothyroidism, and have been proposed as an independent risk factor for cardiovascular disease [27]. However, it remains unclear whether individuals with SH also have increased Hcys concentrations and whether this elevation can explain the increased prevalence of cardiovascular disease in this condition. A recent study reported that SH is not associated with hyperhomocysteinemia and Hcys does not appear to contribute to the increased risk for atherosclerotic disease in patients with SH [28] [29].

In contrast, in the present study, the SH group showed a higher plasma Hcys level than the control group. We suggest that the administration of L-thyroxine could prevent the development of cardiovascular disease in hemodialysis patients who have hyperhomocysteinemia and high TSH levels.

5. Conclusion

Prolonged QTc, QTcd and SH are reported to be associated with cardiovascular disease and sudden cardiac death. The results of this study showed that TSH is associated with prolonged QTc and hyperhomocysteinemia in non-diabetic hemodialysis patients. Moreover, we suggest that SH may be associated with prolonged QTc in non-diabetic hemodialysis patients. However, further studies are required to elucidate the role of the L-thyroxine doses and TSH target levels in hemodialysis patients.

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