International Urology and Nephrology (2022) 54:1399–1408
https://doi.org/10.1007/s11255-021-03016-0

NEPHROLOGY - ORIGINAL PAPER

Prolongation of QTc interval at the beginning and during dialysis is associated with hypervolemia and calcium and magnesium change in the first 2 h

I. Bozaci[1] · **E. Tatar**[1]

Received: 14 December 2020 / Accepted: 4 October 2021 / Published online: 19 October 2021

Abstract

Background and aims High rates of sudden cardiac death are mostly attributed to ventricular arrhythmias including QTc prolongation in hemodialysis patients. We aimed to investigate the correlation of electrolyte and volume changes with QTc interval prolongation in hemodialysis patients.

Study design The present study is designed as a cross-sectional study.

Methods The study was conducted at the hemodialysis unit of a training and research hospital and its' satellite dialysis unit. Patients were divided into three groups. Group-1: with normal QTc interval both at the beginning and during dialysis session; group-2: with prolonged QTc interval at the beginning and remained prolonged during dialysis session; group-3: with normal QTc interval at the beginning but prolonged during the dialysis session. In addition, patients were evaluated in terms of QTc change between the beginning and 2nd hour (delta-QTc-1) and between 2nd hour and 4th hour (delta-QTc-2), respectively, and defined as 'patients with increased QTc interval' and 'patients without increased QTc interval'.

Results A total of 45 prevalent hemodialysis patients were enrolled in the study. 14 patients (31.1%) had normal QTc interval (group-1), 13 patients (28.9%) had prolonged QTc interval at the beginning and remained prolonged during dialysis session (group-2) and 18 patients (40%) had normal QTc interval at the beginning but prolonged during dialysis session (group-3). There was no statistically significant difference between groups in terms of baseline electrolyte levels. Calcium change in the first 2 h was lower in patients with QTc prolongation from the start or during the dialysis session (group-2 and group-3). In addition, systolic blood pressure (SBP) levels at the beginning of the session (118 ± 15 mmHg vs 124 ± 28 mmHg vs138 ± 24 mmHg; $p = 0.04$) and intradialytic ultrafiltration (UF) rate were higher (1.96 ± 0.6 L/4 h vs 2.6 ± 1.0 L/4 h vs 2.8 ± 0.9 L/4 h; $p = 0.03$) in group-2 and group-3 compared to patients in group-1. Increase in QTc interval was found higher in patients with less calcium increase (Rho: − 0.36; $p = 0.01$) and with greater magnesium decrease in the first 2 h (Rho: 0.31; $p = 0.04$).

Conclusion QTc interval prolongation is common among hemodialysis patients. High intradialytic UF rates, change in serum magnesium and calcium levels in the first 2 h were found associated with QTc prolongation. However, QTc prolongation was found independently associated only with UF volume and calcium change in the first 2 h.

Keywords QTc prolongation · Hemodialysis · Delta calcium · Delta magnesium

Introduction

Sudden cardiac death (SCD) is the leading cause of mortality in hemodialysis (HD) patients [1]. Echocardiography and electrocardiography (ECG) are recommended to every patient at the beginning of dialysis and annually afterwards [2]. Compared with the general population, silent myocardial ischemia and atypical symptoms in terms of cardiovascular disease are common in HD patients [3]. On the other hand, patients with chronic kidney disease (CKD) are more

✉ I. Bozaci
ilterbozaci@gmail.com

E. Tatar
etatar@hotmail.com

[1] Department of Nephrology, University of Health Sciences Bozyaka Training and Research Hospital, Saim Cikrikci Street, No:59Karabaglar, 35360 Izmir, Turkey

likely to present with acute myocardial infarction (AMI), that is less likely to have ST elevation, than with stable angina as the initial manifestation of coronary heart disease (CHD) [3]. In a study in the literature, age, diabetes mellitus (DM), cardiovascular diseases, low serum creatinine and elevated alkaline phosphatase were found to predict high risk for SCD [4]. High rates of SCD are mostly attributed to ventricular arrhythmias instead of atherosclerotic risk factors in HD patients [5]. Arrhythmias can often occur shortly after the start of a dialysis session or at any time during the session [6]. Calcium, potassium and magnesium alterations were shown to contribute to the development of arrhythmias during hemodialysis [7]. Prolonged QTc interval was found associated with an increased risk of mortality in hemodialysis patients [8–10]. A rapid decrease in serum calcium or potassium can result in prolonged QTc interval and increased QTc dispersion [7, 11, 12]. Risk factors related to dialysis prescription in terms of sudden cardiac arrest (SCA) were identified in two large cohorts such as low potassium dialysate (< 2 mEq/L), a treatment time < 3.5 h, ultrafiltration (UF) volume > 5.7 percent of post-dialysis weight and low dialysate calcium [13, 14]. It is thought that changes in plasma volume and electrolytes may further increase cardiovascular stress during HD [8, 15]. Besides, hypomagnesemia was also found to be associated with ventricular arrhythmias including QTc prolongation [16–18].

In the present study, we aimed to investigate the correlation of electrolyte and volume changes with QTc interval prolongation which is known to be associated with increased mortality in maintenance HD patients.

Material and methods

Study design and population

The study was conducted at the hemodialysis unit of a training and research hospital and its' satellite dialysis unit. Participants were recruited from prevalent HD patients (HD time for over 6 months) who were older than 18 years old. Patients who had a pacemaker or automatic implantable cardiac defibrillator, who had detectable atrial fibrillation by electrocardiography (ECG) and whose ECG assessments were either incomplete or uninterpretable were excluded from the study.

First, patients were divided into three groups. Group-1 was composed of patients who has normal QTc interval both at the beginning and during the dialysis session. Group-2 was composed of patients who has prolonged QTc interval at the beginning and remained prolonged during the dialysis session. Group-3 was composed of patients who has normal QTc interval at the beginning but prolonged during the dialysis session.

Secondly, patients were also evaluated according to the QTc interval change in the first 2 h and between 2nd hour and 4th hour defined as 'delta QTc-1 and delta QTc-2'. Delta QTc-1 was calculated by the following formula: (QTc at 2nd hour-QTc at the beginning) whereas, delta-QTc-2 was, that was calculated by the following formula: (QTc at 4th hour–QTc at 2nd hour). In terms of delta QTc-1 and delta QTc-2, patients were also grouped as 'patients with increased QTc interval' and 'patients without increased QTc interval'.

Data collection

The patients were evaluated during routine monthly dialysis evaluations. All of the patients in the study were underwent hemodialysis three times a week for 4 h. Cardiac evaluations were conducted on a dialysis day and included ECG and blood pressure assessments by trained study staff. The patients underwent 12-lead ECG at the beginning (0. hour); in the middle (2nd hour) and at the end (4th hour) of the dialysis session using ECG machines from Fukuda Denshi (Tokyo, Japan). The QT and RR intervals were measured based on the automated algorithms. Bazett formula ($QTc = QT/\sqrt{RR}$) was used for the calculation of QTc interval. QTc prolongation was defined as QTc interval ≥ 450 msn in males and ≥ 460 msn in females [19]. Serum calcium levels used were corrected according to the formula: corrected calcium (mg/dl) = measured total calcium (mg/dl) + 0.8 (4.0- serum albumin (g/dL), and corrected calcium levels are used in the study. Venous blood samples were drawn immediately before (0. hour); in the middle (2nd hour) and at the end (4th hour) of the dialysis session. Serum calcium, magnesium, phosphorus and parathormone (PTH) levels were examined simultaneously with ECG at baseline, 2nd hour and 4th hour whereas serum potassium levels were examined at baseline and 4th hour. QTc intervals of patients were measured at the beginning, at 2nd hour, and 4th hour. The differences of the levels of calcium, magnesium, phosphorus, PTH and potassium between the beginning, 2nd and 4th hours were expressed as delta values. The differences between beginning and 2nd hour were expressed as delta.1; differences between 2nd and 4th hours were expressed as delta.2; differences between the beginning and 4th hour were expressed as delta.3. While delta.1, delta.2 and delta.3 values were measured in terms of calcium, magnesium, phosphorus, PTH; only delta.3 values were measured in terms of potassium and delta.1 and delta.2 values were measured in terms of QTc interval. Patients were also separated into two groups as prolonged QTc group and stable QTc group in terms of QTc interval change in the first 2 h (delta QTc-1). From the medical records on the day when ECG examination was undertaken, the following variables were also obtained: blood pressure assessments simultaneously with

ECG at baseline, 2nd hour and 4th hour; UF volume, demographic variables included age and gender and medication information of participants.

Statistical analysis

All of the parameters were expressed as the means ± SD. *P* value less than 0.05 was considered statistically significant. Comparisons between two groups were assessed by chi-squared and independent *t* test analysis. Differences between more than two groups were analyzed by ANOVA (Bonferroni test was used for equal variances; Dunnett's T3 test was used for unequal variances.) Statistically significant difference between Group-1 and Group-2 is defined with the marker *; statistically significant difference between Group-1 and Group-3 is defined with the marker **; statistically significant difference between Group-2 and Group-3 is defined with the marker ***. Pearson analysis was used for univariate correlations between delta QT and delta calcium, magnesium, other variables. Binary logistic regression analysis was used to identify the independent associations with QTc prolongation. All statistical analyses were performed using SPSS 20.0 (Chicago, IL USA).

Results

45 prevalent hemodialysis patients were enrolled in the study. Thirteen patients (29%) were with QTc prolongation at the beginning of the session. Eighteen of remained 32 patients revealed QTc prolongation during the hemodialysis session. 14 patients (31%) were in group-1; 13 patients (29%) were in group-2 and 18 patients (40%) were in group-3. The etiologies of CKD were as follows: 17 patients (38%) with type-2 diabetes mellitus; 14 patients (32%) with essential hypertension; five patients (11%) with glomerulonephritis; three patients (6%) with obstructive uropathy; two patients (4%) with autosomal dominant polycystic kidney disease and four patients (9%) with unknown etiology.

There was no statistically significant difference between group-1, group-2 and group-3 in terms of age (53 ± 20 years vs 65 ± 19 years vs 55 ± 12 years; $p = 0.14$) and gender (36 (F/M) (%) vs 38 (F/M) (%) vs 50 (F/M) (%); $p = 0.69$). On the other hand, patients with QTc prolongation from the beginning were relatively older and with lower calcium levels at the beginning and at 2nd hour. UF volumes (1.96 ± 0.6 L/4 h vs 2.6 ± 1.0 L/4 h vs 2.8 ± 0.9 L/4 h; $p = 0.03$) and SBP at the beginning of the dialysis session (118 ± 15 mm/Hg vs 124 ± 28 mm/Hg vs 138 ± 24 mm/Hg; $p = 0.04$) were found higher in group-2 and group-3 compared to group-1.

Serum calcium levels at 2nd hour (9.8 ± 0.8 vs 9.0 ± 0.6 vs 9.3 ± 0.7; $p = 0.02$) and calcium change between the beginning and 2nd hour (delta calcium-1) (0.3 ± 0.5 vs 0.5 ± 0.8 vs 0.9 ± 0.6; $p = 0.046$) were found lower and statistically significantly different in group-2 and group-3 compared to group-1. There was no statistically significant difference between groups in terms of other electrolyte (magnesium, potassium, phosphorus) and PTH levels and changings (delta values).

In terms of dialysate calcium (2/12/0 (1.25 mmol/L, 1.5 mmol/l, 1.75 mmol/L, *n*) vs 3/10/0 (1.25 mmol/L, 1.5 mmol/l, 1.75 mmol/L, *n*) vs 4/13/1 (1.25 mmol/L, 1.5 mmol/l, 1.75 mmol/L, *n*); p = 0.87) and potassium (6/8 (2.0 mmol/L, 3.0 mmol/L, *n*) vs 5/8 (2.0 mmol/L, 3.0 mmol/L, *n*) vs 10/8 (2.0 mmol/L, 3.0 mmol/L, *n*); $p = 0.62$), there was no statistically significant between group-1, group-2 and group-3, respectively. These results are presented at Tables 1 and 2.

Evaluation of patients with increased QTc interval and patients without increased QTc interval in terms of QTc change in the first 2 h (delta QT-1) and between 2nd hour and 4th hour(delta QT-2) revealed no statistically significant difference in terms of dialysate calcium (7/23/0 (1.25 mmol/L, 1.5 mmol/l, 1.75 mmol/L, *n*) vs 2/12/1 (1.25 mmol/L, 1.5 mmol/l, 1.75 mmol/L, *n*); $p = 0.23$) and dialysate potassium (15/15 (2.0 mmol/L, 3.0 mmol/L, *n* vs 6/9 (2.0 mmol/L, 3.0 mmol/L, *n*); $p = 0.53$) and (5/15/1 (1.25 mmol/L, 1.5 mmol/l, 1.75 mmol/L, *n*) vs 4/20/0 (1.25 mmol/L, 1.5 mmol/l, 1.75 mmol/L, *n*); $p = 0.23$) and dialysate potassium (11/10 (2.0 mmol/L, 3.0 mmol/L, *n* vs 10/14 (2.0 mmol/L, 3.0 mmol/L, *n*); $p = 0.56$), respectively.

In terms of QTc change in the first 2 h (delta QT-1), 30 patients were with increased QTc interval which was higher compared to patients with increased QTc interval between 2nd hour and 4th hour (delta QT-2) ($n = 21$). There was a statistically significant difference between patients with increased QTc interval and patients without increased QTc interval in terms of QTc interval at 2nd hour (471 ± 27 mm vs 432 ± 23 mm; $p < 0.01$).

We found higher levels of magnesium at the beginning (2.4 ± 0.4 mg/dl vs 2.02 ± 0.2 mg/dl; $p = 0.01$) and higher levels of magnesium change between the beginning and 2nd hour (delta magnesium-1) (0.4 ± 0.4 vs 0.04 ± 0.3; $p = 0.01$); and higher levels of magnesium change between the beginning and 4th hour (delta magensium-3) (0.5 ± 0.4 vs 0.06 ± 0.2; $p = 0.001$) in patients with increased QTc interval compared to patients without increased QTc interval in terms of QTc interval change between the beginning and 2nd hour.

Calcium change between the beginning and 2nd hour (delta calcium-1) was found lower in patients with increased QTc interval compared to patients without increased QTc interval (0.4 ± 0.6 vs 0.9 ± 0.7; $p = 0.01$) in terms of QTc interval change between the beginning and 2nd hour. The laboratory parameters of patient groups based on delta QTc are presented at Table 3.

Table 1 Demographical and laboratory results of group-1, group-2 and group-3

	Group-1 (QT interval normal) ($n=14$)	Group-2 (Prolonged baseline QT interval) ($n=13$)	Group-3 (QT interval prolongation during dialysis) ($n=18$)	p
Age (years)	53 ± 20	65 ± 19	55 ± 12	0.14
Gender (F/M)(%)	36	38	50	0.69
Sodium 0.h mmol/L	135 ± 3.1	135 ± 2.7	135 ± 3.1	0.88
Glucose 0.h (mg/dL)	116 ± 54	142 ± 71	138 ± 84	0.60
Albumin 0.h (g/dL)	3.7 ± 0.4	3.6 ± 0.4	3.7 ± 0.3	0.78
Uric Acid 0.h (mg/dl)	6.2 ± 1.3	5.7 ± 1.2	5.5 ± 0.7	0.23
ALP 0.h (U/L)	131 ± 72	159 ± 132	146 ± 39	0.68
kt/V	1.76 ± 0.17	1.58 ± 0.20	1.68 ± 0.25	0.11
URR (%)	76 ± 8.1	76 ± 6.8	74 ± 6.0	0.59
UF Volume (L/4 h)	1.96 ± 0.6	2.6 ± 1.0	2.8 ± 0.9	**0.03***,**
CVD (%)	29	46	33	0.63
DM (%)	21	15	28	0.72
Dialysate Ca (n) 1.25/1.50/1.75 mmol/L	2/12/0	3/10/0	4/13/1	0.87
Dialysate K (n) 2.0/3.0 mmol/L	6/8	5/8	10/8	0.62
HD Duration (months)	65 ± 45	61 ± 52	43 ± 36	0.33
HCO_3 0.h (mmol/L)	20 ± 1.7	21 ± 2.8	22 ± 2.0	0.23
Hemoglobin 0.h (g/dL)	11 ± 1.2	10 ± 2.1	11 ± 1.4	0.24

Bold value indicates statistically significance $p < 0.05$

Notification: Statistically significant difference between Group-1 and Group-2 is defined with the marker ($p=0.04$) *; statistically significant difference between Group-1 and Group-3 is defined with the marker ($p=0.02$) **; statistically significant difference between Group-2 and Group-3 is defined with the marker ***

F Female; *M* Male; *ALP* Alkaline Phosphatase; *URR* Urea Reduction Ratio; *UF Volume* Ultrafiltration volume; *CVD* Cardiovascular Disease; *DM* Diabetes Mellitus; *HCO_3* Bicarbonate; *SBP* Systolic Blood Pressure; *DBP* Diastolic Blood Pressure

We found that QTc prolongation in the first 2 hs (delta QTc-1) was negatively correlated with calcium change (delta calcium-1) (Rho: − 0.36; $p=0.01$) and positively correlated with magnesium change in the first 2 h (delta magnesium-1) (Rho: 0.31; $p=0.04$). Correlation analysis of delta QT and delta calcium between the beginning and 2nd hour (delta calcium-1) is presented in Fig. 1; correlation analysis of delta QT and delta magnesium between the beginning and 2nd hour (delta magnesium-1) is presented in Fig. 2.

In Binary logistic regression analysis (variables: age, CVD, UF volume, delta calcium-1, delta magnesium-1) QTc prolongation was found independently associated with UF volume (Exp(B): 1.001 (CI 1.001–1.002); $p=0.04$) and delta calcium-1 (Exp(B): 0.190 (CI 0.047–0.763); $p=0.01$).

Twenty-one patients were with increased QTc interval and 24 patients were without increased QTc interval in terms of QTc change between 2nd hour and 4th hour (delta QT-2). There was no statistically significant difference between patients with increased QTc interval and patients without increased QTc interval between 2nd hour and 4th hour (delta QT-2) in terms of serum electrolyte levels and changes.

Discussion

SCD in HD patients is largely attributed to arrhythmias including QTc prolongation instead of coronary events and atherosclerotic risk factors. Electrocardiographic changes, such as QTc prolongation, which were found associated with high risk of SCD, are common in those on HD [20]. In this study, we found high rates of QTc prolongation among hemodialysis patients. QTc prolongation was found to be associated with serum calcium and magnesium change in the first 2 h in our study. Besides, we found high ultrafiltration volume and high initial systolic blood pressure, which reflects the overhydrated state in HD patients, to be associated with QTc prolongation.

In our study, we found a higher intradialytic UF rate in patients with QTc prolongation. In addition, patients with QTc prolongation were with higher SBP levels in the beginning, as well. The higher UF volumes and higher SBP

Table 2 Vital signs and laboratory results during dialysis session

	Group-1 (QT interval normal) ($n=14$)	Group-2 (Prolonged baseline QT interval) ($n=13$)	Group-3 (QT interval prolongation during dialysis) ($n=18$)	p
SBP 0.h (mm/Hg)	118 ± 15	124 ± 28	138 ± 24	**0.04****
DBP 0.h (mm/Hg)	69 ± 13	74 ± 13	76 ± 12	0.28
SBP 2nd h (mm/Hg)	111 ± 15	124 ± 31	125 ± 17	0.14
DBP 2nd h (mm/Hg)	66 ± 10	74 ± 12	72 ± 10	0.20
SBP 4th h (mm/Hg)	109 ± 15	128 ± 29	122 ± 21	0.08
DBP 4th h (mm/Hg)	69 ± 13	75 ± 13	68 ± 11	0.31
QT 0.h (mm)	433 ± 9	476 ± 19	438 ± 20	**< 0.01***, ***
QT 2nd h (mm)	436 ± 15	477 ± 35	460 ± 30	**< 0.01***, **
QT 4th h (mm)	433 ± 20	478 ± 32	471 ± 31	**< 0.01***, **
Ca 0.h (mg/dl)	8.9 ± 0.9	8.8 ± 0.5	8.8 ± 0.8	0.91
Ca 2nd h (mg/dl)	9.8 ± 0.8	9.0 ± 0.6	9.3 ± 0.7	**0.02***
Ca 4th h (mg/dl)	10.1 ± 0.8	9.5 ± 0.8	9.8 ± 0.9	0.22
Delta Calcium.1	0.9 ± 0.6	0.3 ± 0.5	0.5 ± 0.8	**0.046***
Delta Calcium.2	0.4 ± 2.8	0.5 ± 0.4	0.6 ± 0.6	0.251
Delta Calcium.3	0.6 ± 3.1	0.8 ± 0.9	1.03 ± 1.02	0.793
Mg 0.h (mm)	2.3 ± 0.4	2.1 ± 0.3	2.2 ± 0.3	0.35
Mg 2nd h (mm)	2.0 ± 0.3	1.9 ± 0.3	2.0 ± 0.2	0.77
Mg 4th h (mm)	1.9 ± 0.1	1.9 ± 0.09	1.9 ± 0.2	0.75
Delta Magnesium.1	0.1 ± 0.4	0.3 ± 0.4	0.4 ± 0.5	0.483
Delta Magnesium.2	0.09 ± 0.2	0.05 ± 0.3	0.06 ± 0.2	0.933
Delta Magnesium.3	0.2 ± 0.3	0.4 ± 0.3	0.4 ± 0.5	0.551
K 0.h (mmol/L)	4.8 ± 0.2	5.1 ± 0.8	4.8 ± 0.6	0.31
K 4th h (mmol/L)	3.4 ± 0.2	3.5 ± 0.4	3.6 ± 0.3	0.33
Delta Potassium.3	1.4 ± 0.3	1.6 ± 0.6	1.3 ± 0.7	0.290
PTH 0.h (pg/mL)	322 ± 302	431 ± 403	360 ± 263	0.67
PTH 2nd h (pg/mL)	179 ± 213	237 ± 284	318 ± 384	0.45
PTH 4th h (pg/mL)	119 ± 88	281 ± 333	330 ± 485	0.25
Delta PTH.1	144 ± 369	194 ± 226	43 ± 239	0.321
Delta PTH.2	59 ± 210	44 ± 68	12 ± 173	0.249
Delta PTH.3	203 ± 275	250 ± 230	-30 ± 316	0.214
P 0.h (mg/dL)	4.9 ± 1.9	4.5 ± 1.1	4.3 ± 1.1	0.52
P 2nd h (mg/dL)	2.3 ± 1.2	2.2 ± 0.5	2.1 ± 0.3	0.79
P 4th h (mg/dL)	2.1 ± 0.6	2.0 ± 0.5	2.1 ± 0.4	0.95
Delta Phosphorus.1	2.5 ± 1.6	2.3 ± 0.9	2.2 ± 0.9	0.665
Delta Phosphorus.2	0.4 ± 1.05	0.2 ± 0.3	0.07 ± 0.2	0.282
Delta Phosphorus.3	3.0 ± 1.4	2.5 ± 0.8	2.2 ± 1.02	0.182

Bold values indicate statistically significance $p < 0.05$

Notification: The differences of the levels of calcium, magnesium, phosphorus, PTH and potassium between the beginning, 2nd and 4th hours were expressed as delta values. The differences between beginning and 2nd hour were expressed as delta.1; differences between 2nd and 4th hours were expressed as delta.2; differences between the beginning and 4th hour were expressed as delta.3. Statistically significant difference between Group-1 and Group-2 is defined with the marker *; statistically significant difference between Group-1 and Group-3 is defined with the marker **; statistically significant difference between Group-2 and Group-3 is defined with the marker ***

SBP Systolic Blood Pressure; *DBP* Diastolic Blood Pressure; *Ca* Calcium; *Mg* Magnesium; *K* Potassium; *PTH* Parathormone; *P* Phosphorus

levels reflect the overhydrated state of the patients which was shown to be associated with QTc prolongation in the literature [23]. Volume excess contributes to high rates of left ventricular hypertrophy (LVH) that is common among

Table 3 The laboratory parameters of patient groups based on delta QT

	Delta QT-1 (0 h–2nd h)			Delta QT-2 (2nd–4th h)		
	Patients with increased QTc interval ($n=30$)	Patients without increased QTc interval ($n=15$)	p	Patients with increased QTc interval ($n=21$)	Patients without increased QTc interval QT ($n=24$)	p
QTc 0.h (mm)	454 ± 29	444 ± 22	0.18	448 ± 25	446 ± 26	0.81
QTc 2nd h (mm	471 ± 27	432 ± 23	**< 0.01**	467 ± 31	448 ± 30	**0.04**
QTc 4th h (mm)	467 ± 34	449 ± 32	0.10	477 ± 28	447 ± 34	**0.02**
Dialysate Ca (n) 1.25/1.50/1.75 mmol/L	7/23/0	2/12/1	0.23	5/15/1	4/20/0	0.90
Dialysate K (n) 2.0/3.0 mmol/L	15/15	6/9	0.53	11/10	10/14	0.56
Ca 0.h (mg/dl)	8.9 ± 0.8	8.6 ± 0.6	0.16	8.8 ± 0.6	8.9 ± 0.9	0.60
Ca 2nd h (mg/dl)	9.3 ± 0.7	9.5 ± 0.8	0.36	9.3 ± 0.6	9.5 ± 0.9	0.67
Ca 4th h (mg/dl)	9.7 ± 0.8	10.1 ± 1.1	0.14	9.8 ± 0.7	10 ± 1.1	0.42
Delta Calcium.1	0.4 ± 0.6	0.9 ± 0.7	**0.01**	0.6 ± 0.6	0.5 ± 0.8	0.91
Delta Calcium.2	0.4 ± 0.2	0.6 ± 0.7	0.29	0.5 ± 0.6	-0.01 ± 2.1	0.26
Delta Calcium.3	0.8 ± 0.1	1.5 ± 1.1	0.06	1.1 ± 1.2	0.6 ± 2.3	0.35
Mg 0.h (mm)	2.4 ± 0.4	2.02 ± 0.2	**0.003**	2.2 ± 0.4	2.3 ± 0.4	0.15
Mg 2nd h (mm)	2.01 ± 0.2	1.97 ± 0.3	0.68	1.9 ± 0.2	2.0 ± 0.2	0.20
Mg 4th h (mm)	1.90 ± 0.2	1.95 ± 0.1	0.24	1.9 ± 0.1	1.9 ± 0.2	0.50
Delta Magnesium.1	0.4 ± 0.4	0.04 ± 0.3	**0.01**	0.2 ± 0.4	0.2 ± 0.4	0.89
Delta Magnesium.2	0.09 ± 0.2	0.02 ± 0.3	0.34	0.02 ± 0.2	0.1 ± 0.2	0.08
Delta Magnesium.3	0.5 ± 0.4	0.06 ± 0.2	**0.001**	0.3 ± 0.4	0.4 ± 0.4	0.28
K 0.h (mmol/L)	5.0 ± 0.6	4.9 ± 0.8	0.38	5.0 ± 06	4.9 ± 0.7	0.46
K 4th h (mmol/L)	3.6 ± 0.3	3.5 ± 0.4	0.41	3.6 ± 0.4	3.5 ± 0.3	0.49
Delta Potassium.3	1.4 ± 0.6	1.3 ± 0.6	0.68	1.4 ± 0.7	1.5 ± 0.5	0.72
PTH 0.h (pg/mL)	390 ± 307	327 ± 340	0.53	378 ± 305	308 ± 239	0.40
PTH 2nd h (pg/mL)	274 ± 353	206 ± 201	0.49	207 ± 277	283 ± 342	0.42
PTH 4th h (pg/mL)	304 ± 423	144 ± 160	0.16	232 ± 363	250 ± 367	0.86
Delta Parathormone.1	− 116 ± 265	− 121 ± 328	0.96	− 25 ± 266	− 171 ± 250	0.06
Delta Parathormone.2	30 ± 153	− 61 ± 178	0.08	− 33 ± 176	25 ± 158	0.26
Delta Parathormone.3	− 87 ± 311	− 182 ± 217	0.29	− 58 ± 249	− 147 ± 289	0.28
P 0.h (mg/dL)	4.6 ± 1.7	4.5 ± 0.8	0.80	4.7 ± 1.6	4.5 ± 1.4	0.55
P 2nd h (mg/dL	2.4 ± 0.9	2.06 ± 0.4	0.24	2.3 ± 1.0	2.3 ± 0.5	0.96
P 4th h (mg/dL)	2.1 ± 0.5	1.9 ± 0.3	0.19	2.2 ± 0.5	2.1 ± 0.4	0.33
Delta Phosphorus.1	2.4 ± 0.8	2.2 ± 1.3	0.64	2.5 ± 1.2	2.2 ± 1.2	0.49
Delta Phosphorus.2	0.1 ± 0.3	0.2 ± 0.7	0.39	0.1 ± 0.3	0.3 ± 0.8	0.27
Delta Phosphorus.3	2.5 ± 0.8	2.6 ± 1.2	0.98	2.6 ± 1.2	2.5 ± 1.1	0.92

Bold values indicate statistically significance $p < 0.05$

Notification: The differences in the levels of calcium, magnesium, phosphorus, PTH and potassium between the beginning, 2nd and 4th hours were expressed as delta values. The differences between beginning and 2nd hour were expressed as delta.1; differences between 2nd and 4th hours were expressed as delta.2; differences between the beginning and 4th hour were expressed as delta.3. Delta QT-1 was calculated by the following formula: (QTc at 2nd hour-QTc at the beginning). Delta QT-2 was calculated by the following formula: (QTc at 4nd hour-QTc at 2nd hour). In terms of delta QTc-1 and delta QTc-2, patients were also grouped as 'patients with increased QTc interval' and 'patients without increased QTc interval'

SBP Systolic Blood Pressure; *DBP* Diastolic Blood Pressure; *Ca* Calcium; *Mg* Magnesium; *K* Potassium; *PTH* Parathormone; *P* Phosphorus

patients with ESRD with a reported prevalence of 75 percent [24]. LVH is a major risk factor for cardiovascular morbidity and mortality in patients with ESRD [25]. LVH is also associated with QTc prolongation and increased mortality rates [26]. Change in the plasma volume and electrolytes during hemodialysis may have a triggering effect on arrhythmias which has an influence on cardiovascular stress. The beneficial effect of tight blood pressure and volume control on

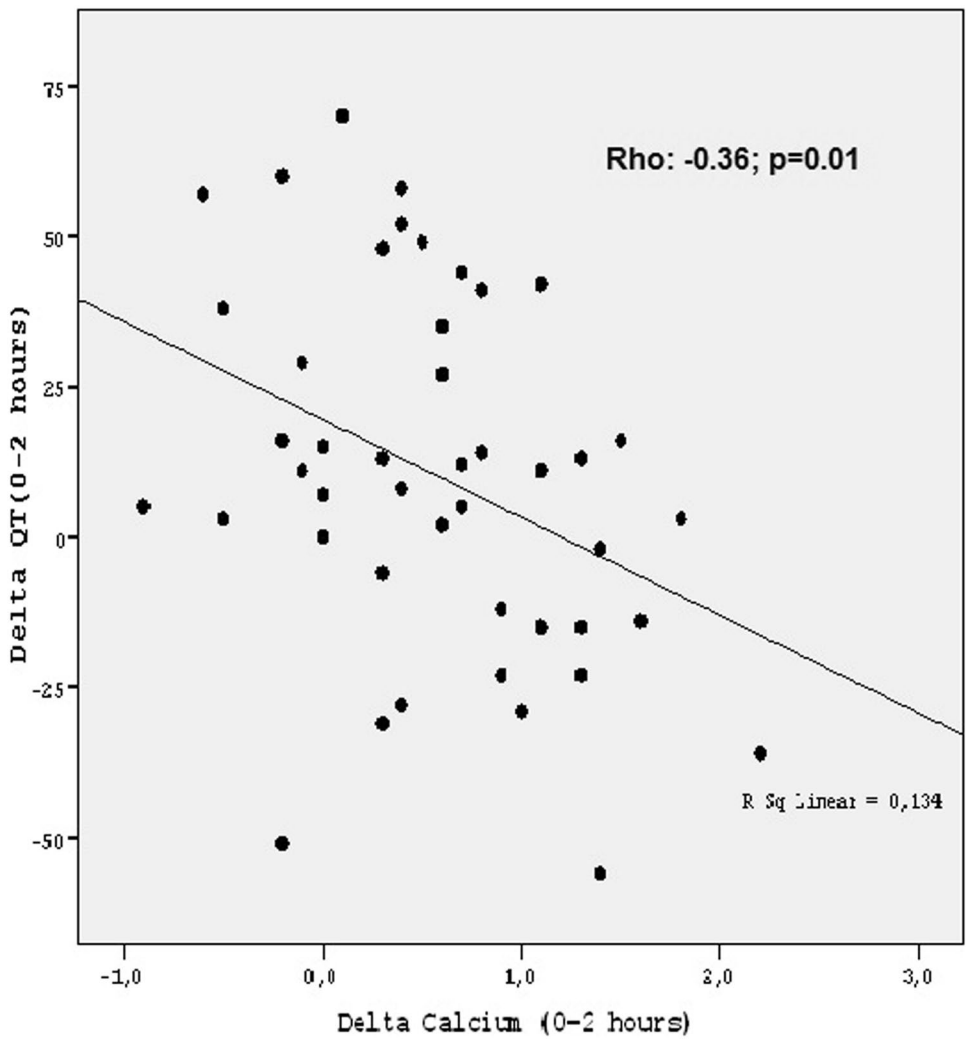

Fig. 1 Correlation between QTc interval change and calcium change in the first two hours

mortality rates in HD patients can be attributed to the effect on QTc prolongation.

In the literature, there are conflicting results about the association of calcium and potassium concentrations with the risk of arrhythmias and arrhythmic events including SCD. Low dialysate calcium concentration was found associated with longer corrected QTc interval (> 440 ms) in a study [27]. On the other hand, results from the EVOLVE trial reported no association between baseline dialysate calcium or serum-dialysate calcium gradient with sudden cardiac death [28]. Although the dialysates of the patients were not constant, the vast majority of the patients received the same dialysate and we found no statistically significant difference between patient groups in terms of dialysate calcium and dialysate potassium. Studies such as the HEMO and DOPPS, which include predominantly prevalent dialysis patients have reported an increased risk of mortality in calcium levels less than 8.5–9 mg/dl [29, 30]. Besides, prolonged QT interval was found associated with rapid decrease in serum calcium or potassium [7, 11, 12]. In a study, conducted by Nie Y et al., electrocardiographic abnormalities and QTc interval were assessed in patients undergoing HD. Lower serum calcium, potassium and higher brain natriuretic peptide (BNP) were found in patients with QTc prolongation [8]. In our study, there was no decrease in calcium levels during the HD session. This might be the result of a small number of patients using dialysate with low calcium due to well-controlled calcium, phosphorus and PTH levels. Even in these cases, a low increase in calcium levels during dialysis resulted in an increase in QTc interval. Therefore, using low calcium dialysate should be avoided in high-risk patients in terms of QTc prolongation. Besides, an increase in calcium levels in the first 2 h was lower in patients with increased QTc interval, which might be the consequence of a relatively hypo-calcemic state in those patients. These results support the idea that higher the increase in calcium levels during dialysis the lower the risk for QTc prolongation which is consisted with the findings of the study conducted by Kim et al. [20, 31].

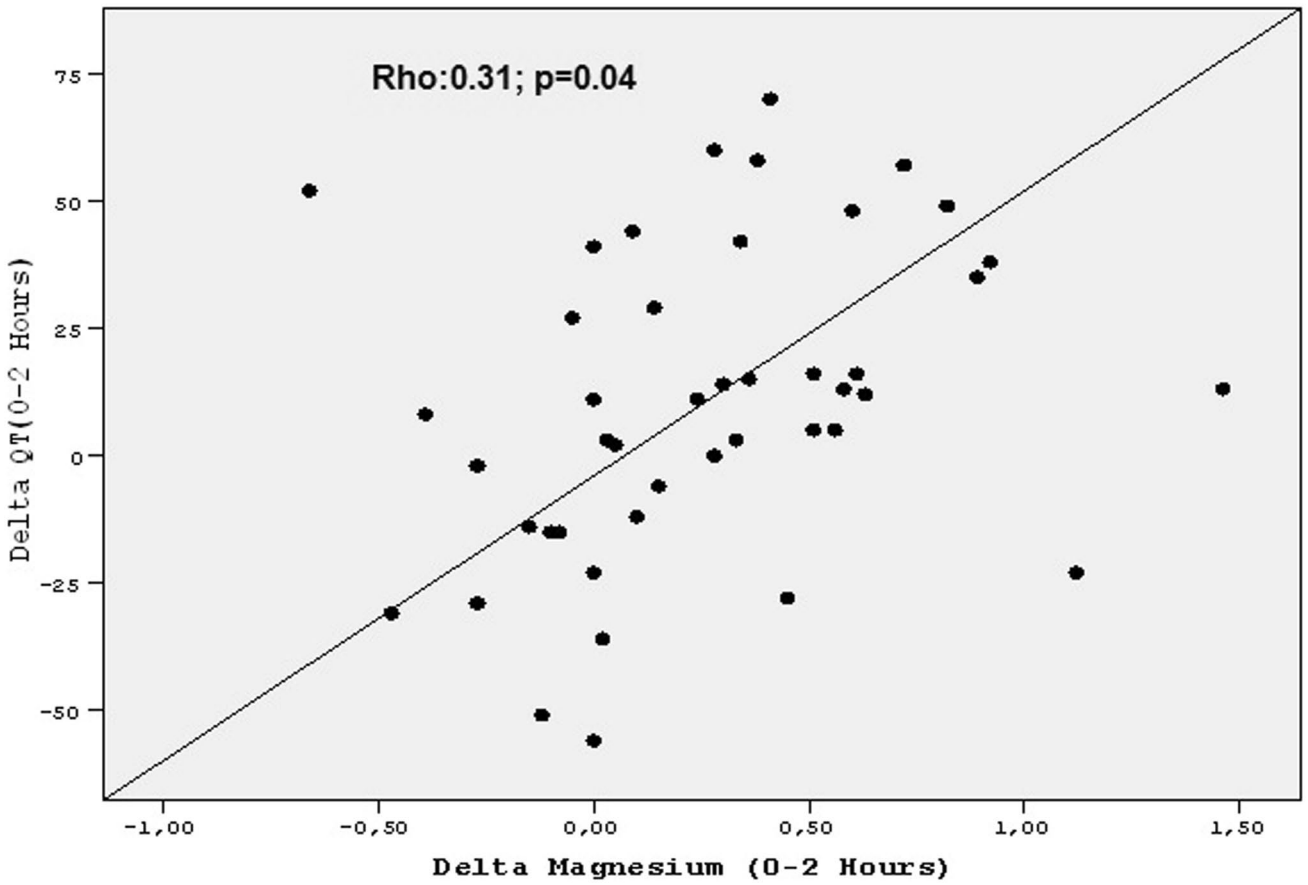

Fig. 2 Correlation between QTc interval change and magnesium change in the first two hours

Serum potassium has been shown to increase the risk of sudden cardiac arrest and all-cause mortality in dialysis patients with serum potassium levels less than ≤ 4.0 mmol/L [32]. The initial potassium levels of the patient groups were more than 4.0 mmol/L in our study.

Although baseline magnesium levels were found higher in patients with increased QTc interval, the decrease in magnesium levels in terms of magnesium change was found higher in those patients. There are no sufficient studies in the literature about the effect of magnesium on QTc interval. In a case report, it was shown that a rapid decrease in magnesium levels result in QTc prolongation [18]. Similarly to the changes in calcium increased QTc interval might be the consequence of that relatively hypomagnesemic state as well. Although no association was found between changing dialysate magnesium concenctration and QTc interval in a randomized controlled trial in the literature, we found a positive correlation between magnesium change in the first 2 h and QTc interval in our study [33]. On the other hand, serum magnesium levels and magnesium changes were not found independently associated with QTc prolongation. Large-scale studies are needed on this subject.

Although we found no significant difference between patient groups in terms of age, patients with QTc prolongation were relatively older than patients with normal QTc. In the literature, there are many studies revealing the association between age and QTc prolongation including the study of Rabkin et al. [21]. They revealed a positive correlation between age and QTc prolongation rates. Our findings were in accordance with the findings in the literature. In a study, Leotta G et al. investigated the relationship between QTc interval and cardiovascular risk factors. They found QTc prolongation to be associated with an increased risk of coronary heart disease, arrhytmias and SCD [22]. Although a statistically significant difference between groups was not found in our study, the rates of CVD history were higher in patients with QTc prolongation compared to patients with normal QTc. The reason for the insiginificance of our results may be that the CVD rates in our patients and the average age of our patients are lower than the studies in the literature.

Limitations of our study were as follows: the number of patients in this study was relatively small; the impact of QTc prolongation on our cases, mortality or morbidity was not evaluated. The potassium change in the first 2 h of hemodialysis could not be evaluated. Besides, data on albumin levels at 2nd

and 4th hour, pH and dialysate bicarbonate that could affect the ionized calcium levels were not available. The correlation with QTc prolongation could be driven by abnormal cardiac geometry. The use of cardiac ultrasound to correlate with SBP and UF, might have provided more objective results.

Conclusion

QTc prolongation is common among dialysis patients. The change in serum magnesium and calcium levels in the first 2 h are associated with QTc prolongation. At the same time, high systolic blood pressure and high ultrafiltration rates, which are both indicators of hypervolemia, are related to QTc prolongation. Although QTc prolongation was found independently associated wtih UF volume and calcium change in the first 2 h, attention to calcium and magnesium levels and struggle for hypervolemia in the management of dialysis patients might be helpful to reduce QTc prolongation and related possible adverse cardiac outcomes. Large-scale studies are needed on this subject.

Funding The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declarations

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval All the procedures were implemented after the approval of the University of Health Sciences Izmir Bozyaka Training and Research Hospital Ethics Committee. This study was carried out in accordance with the Helsinki Declaration standards.

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

References

1. Samanta R, Chan C, Chauhan VS (2019) Arrhythmias and sudden cardiac death in end stage renal disease: epidemiology, risk factors, and management. Can J Cardiol 35(9):1228–1240
2. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A (2018) Cardiovascular disease in dialysis patients. Nephrol Dial Transplant 33(3):28–34
3. Pilmore HL, Xiong F, Chobi Y, Poppe K, Lee M, Legget M et al (2020) Impact of chronic kidney disease on mortality and cardiovascular outcomes after acute coronary syndrome: a nationwide data linkage study (ANZACS-QI44). Nephrology (Carlton) 25(7):535–543
4. Shatri S, Tangri N, Tighiouart H et al (2012) Predictors of sudden cardiac death: a competing risk approach in the hemodialysis study. Clin J Am Soc Nephrol 7:123
5. Rantanen JM, Riahi S, Schmidt EB, Johansen MB, Sogaard P, Christensen JH (2020) Arrhythmias in patients on maintenance dialysis: a cross-sectional study. Am J Kidney Dis 75(2):214–224
6. Jebali H, Ghabi H, Mami I, Fatma LB, Smaoui W, Kaab BB et al (2020) Evaluation of electrocardiographic findings before and after hemodialysis session. Saudi J Kidney Dis Transpl 31(3):639–646
7. Tumlin JA, Roy-Chaudhury P, Koplan BA, Costea AI, Kher V, Williamson D et al (2019) Relationship between dialytic parameters and reviewer confirmed arrhythmias in hemodialysis patients in the monitoring in dialysis study. BMC Nephrol 20(1):80
8. Nie Y, Zou J, Liang Y, Shen B, Liu Z, Cao X, Chen X, Ding X (2016) Electrocardiographic abnormalities and QTc ınterval in patients undergoing hemodialysis. PLoS One 11(5):e0155445
9. Liu P, Wang L, Han D, Sun C, Xue X, Li G (2020) Acquired long QT syndrome in chronic kidney disease patients. Ren Fail 42(1):54–65
10. Khaledifar A, Momeni A, Hasanzadeh K, Amiri M, Sedehi M (2014) Association of corrected QT and QT dispersion with echocardiographic and laboratory findings in uremic patients under chronic hemodialysis. J Cardiovasc Echogr 24(3):78–82
11. Chorin E, Rosso R, Viskin S (2016) Electrocardiographic manifestations of calcium abnormalities. Ann Noninvasive Electrocardiol 21(1):7–9
12. Chua CE, Choi E, Khoo EYH (2018) ECG changes of severe hypokalemia. QJM 111(8):581–582
13. Jadoul M, Thumma J, Fuller DS et al (2012) Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Clin J Am Soc Nephrol 7:765
14. Pun PH, Lehrich RW, Honeycutt EF et al (2011) Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. Kidney Int 79:218
15. Herzog CA, Mangrum JM, Passman R (2008) Sudden cardiac death and dialysis patients. Semin Dial 21:300
16. Pun PH, Middleton JP (2017) Dialysate potassium, dialysate magnesium, and hemodialysis risk. J Am Soc Nephrol 28(12):3441–3451
17. Kanbay M, Yilmaz MI, Apetrii M, Saglam M, Yaman H, Unal HU et al (2012) Relationship between serum magnesium levels and cardiovascular events in chronic kidney disease patients. Am J Nephrol 36:228–237
18. Umapathi KK, Lee S, Jacobson J, Jandeska S, Nguyen HH (2020) Magnesium supplementation shortens hemodialysis-associated prolonged QT. Cureus 12:e9132
19. Neira V, Enriquez A, Simpson C, Baranchuk A (2019) Update on long QT syndrome. J Cardiovasc Electrophysiol 30(12):3068–3078
20. Kim ED, Watt J, Tereshchenko LG, Jaar BG, Sozio SM, Kao WHL et al (2019) Associations of serum and dialysate electrolytes with QT interval and prolongation in incident hemodialysis: the predictors of arrhythmic and cardiovascular risk in End-Stage renal disease (PACE) Study. BMC Nephrol 20(1):133
21. Rabkin SW, Cheng XJ, Thompson DJ (2016) Detailed analysis of the impact of age on the QT interval. J Geriatr Cardiol 13:740–748
22. Leotta G, Maule S, Rabbia F, Del Colle S, Tredici M, Canadè A et al (2005) Relationship between QT interval and cardiovascular risk factors in healthy young subjects. J Hum Hypertens 19:623–627
23. Sun GZ, Zhou Y, Ye N, Wu SJ, Sun YX (2019) Independent influence of blood pressure on QTc Interval: results from a General Chinese population. BioMed Res Int 2019:1656123

24. Matsushita K, Kwak L, Sang Y, Ballew SH, Skali H, Shah AM et al (2017) Kidney disease measures and left ventricular structure and function: the atherosclerosis risk in communities study. J Am Heart Assoc 6(9):e006259
25. Nitta K, Iimuro S, Imai E, Matsuo S, Makino H, Akizawa T et al (2019) Correction to: Risk factors for increased left ventricular hypertrophy in patients with chronic kidney disease: findings from the CKD-JAC study. Clin Exp Nephrol 23(1):99
26. Stewart GA, Gansevoort RT, Mark PB et al (2005) Electrocardiographic abnormalities and uremic cardiomyopathy. Kidney Int 67:217
27. Genovesi S, Dossi C, Vigano MR et al (2008) Electrolyte concentration during hemodialysis and QT interval prolongation in uraemic patients. Europace 10(6):771–777
28. Pun PH, Abdalla S, Block GA et al (2016) Cinacalcet, dialysate calcium concentration, and cardiovascular events in the EVOLVE trial. Hemodial Int 20(3):421–431
29. Tentori F, Blayney MJ, Albert JM et al (2008) Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis outcomes and practice patterns study (DOPPS). Am J Kidney Dis 52(3):519–530
30. Wald R, Sarnak MJ, Tighiouart H et al (2008) Disordered mineral metabolism in hemodialysis patients: an analysis of cumulative effects in the hemodialysis (HEMO) study. Am J Kidney Dis 52(3):531–540
31. Matsumoto Y, Miro Y, Kageyama S, Arihara K, Sato H, Nagat K et al (2019) Changes in QTc interval in long-term hemodialysis patients. PLoS One 14(1):e0209297
32. Karaboyas A, Zee J, Brunelli SM, Usvyat LA, Weiner DE, Maddux FW et al (2017) Dialysate potassium, serum potassium, mortality and arrhythmia events in hemodialysis: resuts from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 69(2):266–277
33. Afshinnia F, Doshi H, Rao PS (2012) The effect of different magnesium concentrations on QTc dispersion in hemodialysis patients. Ren Fail 34:408–412