

Evaluation of the Frequency of QTc Dispersion and Its Relationship with Clinical and Laboratory Parameters in Dialysis Patients

Diyaliz Hastalarında QTc Dispersiyonun Sıklığının ve Klinik ve Laboratuvar Parametrelerle İlişkisinin Değerlendirilmesi

ABSTRACT

OBJECTIVE: QTc dispersion is defined as the difference between the maximal and minimal correct QT interval on standard 12-lead ECG. Increased QTc dispersion has been reported in ESRD patients. In our study, we aimed to evaluate the frequency of QTc dispersion and its relationship between clinical and laboratory parameters in patients on regular dialysis programme.

MATERIAL and METHODS: Sixty patients underwent dialysis (30 HD, 30 CAPD) and another 30 healthy subjects were enrolled into the study. The standard 12 lead ECGs were performed and QTcd was measured from all dialysis patients and control subjects. Blood samples were collected for the measurement of laboratory parameters.

RESULTS: Dialysis patients showed significantly higher QTcd than control subjects (55.75±36.48 versus 28.73±28.27; p=0.001). Patients with QTcd >50 ms had significantly higher SBP, urea and ferritin levels, but significantly lower iron binding capacity and calcium levels compared those with QTcd ≤ 50 ms (p<0.05). Positive correlations were found between QTcd and urea, ferritin and SBP levels, and inverse correlations with iron binding capacity level (p<0.05).

CONCLUSION: The frequency of QTc dispersion was 40% among the dialysis patients. Although serum calcium was significantly lower in patients who had QTcd >50 ms than QTcd ≤ 50 ms (p<0.05), there was no significant correlation between QTcd and calcium.

KEY WORDS: QTcd, Dialysis patients, Arrhythmia, Electrocardiography, Calcium

ÖZ

AMAÇ: 12 derivasyonlu standart EKG’de en uzun QTc mesafesi ile en kısa QTc mesafesi arasındaki fark QTc dispersiyonu olarak tanımlanır. SDBY hastalarında artmış QTc dispersiyonu bildirilmiştir. Biz çalışmamızda, diyaliz hastalarında QTc dispersiyonunun sıklığını ve klinik ve laboratuvar parametrelerle ilişkisinin değerlendirilmesini amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya 60 diyaliz hastası (30 HD, 30 PD) ve 30 sağlıklı birey dahil edildi. Tüm diyaliz hastalarının ve katılımcıların 12 derivasyonlu elektrokardiyografileri çekildi ve QTcd ölçüldü. Laboratuvar parametreleri için kan örnekleri toplandı.

BULGULAR: Diyaliz hastaları kontrol grubundan daha yüksek QTcd’ye sahipti (55,75±36,48 ve 28,73±28,27; p=0.001). QTcd >50 ms olan hastalar QTcd ≤ 50 ms olanlarla karşılaştırıldığında, SKB, üre ve ferritin anlamlı olarak daha yüksek, Ca ve demir bağlama kapasitesi anlamlı olarak daha düşüktü (p<0,05). QTcd ile üre, ferritin, SKB arasında pozitif, demir bağlama kapasitesi arasında ters korelasyon saptandı (p<0,05).

SONUÇ: Diyaliz hastaları arasında QTc dispersiyonunun sıklığı %40’tı. QTcd >50 ms olan hastalarda, QTcd ≤ 50 ms olanlardan göre daha düşük serum kalsiyumu olmasına karşın, QTcd ve Ca arasında anlamlı bir korelasyon mevcut değildi.

ANAHTAR SÖZCÜKLER: QTcd, Diyaliz hastaları, Aritmi, Elektrokardiyografi, Kalsiyum

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INTRODUCTION

The life span of patients with chronic kidney disease (CKD) is reduced, especially those with end stage renal disease (ESRD). Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with CKD. According to a number of recent reports, it is known that half of the patients receiving chronic hemodialysis therapy die of cardiovascular disease (1). There is a high prevalence of cardiac arrhythmias in patients with end-stage renal disease (ESRD) (2) and a large proportion of cardiovascular mortality in dialysis patients is caused by sudden death (3). Early diagnosis of CVD is therefore so important.

QT dispersion (QTd), defined as the difference between the maximal and minimal QT interval on standard 12-lead ECG. QT dispersion (QTd) is a measure of the heterogeneity of ventricular repolarization obtained via standard surface electrocardiogram (ECG) (4) and is reported to be increased in various 'high-risk' groups, such as diabetic patients (5), patients with cardiac failure (6), patients with essential hypertension (7) and patients with ESRD (8,9).

Increase in correct QT dispersion [QTcd (correct QTmax–correct QTmin)] may reflect an increase in regional inhomogeneity of myocardial repolarisation and predispose to arrhythmias (10).

It has been reported that QTc dispersion is an independent predictor of cardiovascular death and associated with arrhythmia related death in ESRD patients (11). QT and QTc dispersion is an easily obtainable, noninvasive, simple, inexpensive, and widely available method of risk stratification in patients receiving renal replacement therapy (1).

The present study was designed to evaluate the frequency of QTc dispersion and its relationship between clinical and laboratory parameters in patients on regular dialysis programme.

MATERIALS and METHODS

A total 60 patients underwent dialysis (30 patients underwent regular haemodialysis (HD) and 30 patients underwent continuous ambulatory peritoneal dialysis (CAPD)) and another 30 healthy subjects as a matched controlled subjects were enrolled into the study. The haemodialysis were carried out in a standard setting (Fresenius 1998 device; Fresenius Medical Care, Germany) with F6 and F8 polysulfone capillaries (Fresenius) for 5 hours per session, 3 times per week and bicarbonate dialysate containing (in mM) 135 Na⁺, 2.0 K⁺, 1.25 Ca⁺², and 1.0 Mg⁺² was used. CAPD patients dialyzed with lactate-buffered glucose and 1,25mmol/lit Ca⁺⁺ dialysate and were given four treatments of two-liter exchanges per day were enrolled into the study. The data of patients were classified into two groups: Group 1 (60 dialysis patients) and group 2 (30 healthy subjects).

The study protocol was approved by the Local Human Research Ethics Committee and informed consent was obtained from all patients at the time of study enrollment.

Exclusion criteria were, 1) diabetes mellitus, 2) patients with LV systolic ejection fraction <60%, 3) patients taking class 1 and class 2 antiarrhythmic drugs 4) patients who did not have good dialysis adequacy (URR <65%), 5) ECG-detected signs of cardiac arrhythmias and unmeasurable T waves, 6) patients who have ischaemic heart disease.

All patients of systolic and diastolic blood pressures were measured from the right arm after at least 5 minutes resting. Patients' demographic characteristics were taken from patient files and themselves.

Blood samples were collected for the measurement of biochemical (urea, Na, K, calcium, phosphorus, albumin, iron, iron binding capacity, ferritin), hematological (hemoglobin) and serological analysis (CRP) after 12 hour fasting from patients before dialysis session and from healthy subjects in the morning.

Electrocardiography

The standard 12 lead ECGs were performed (NIHON KOHDEN, JAPAN with a 25 mm/s paper speed, gain 10 mm/mV) from all dialysis patients (before dialysis session) and control subjects. Cornell product and Sokolow-Lyon Voltage for LVH and QTcd were measured manually from ECG records.

Cornell product (RaVL + SV3 X QRS duration ≥ 2440 mm.ms, add 6 mm for women) (12); and Sokolow-Lyon voltage (SV1 + RV5 or V6 ≥ 35 mm) (13) were used to identify LVH.

The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined by the return of the terminal T wave to the isoelectric TP baseline. If the end of the T wave was not clear in a particular lead then it was excluded from analysis. Each QT interval was corrected for heart rate with using Bazett's formula: QT / √R-R. The QTc dispersion was determined as the difference between the maximum and the minimum of the QTc in different leads on the same recording.

Data for matched controls in most studies suggest that QT dispersion in normal subjects is usually between 40 and 50 msec (14). In a population-based study involving 3285 adults and children by Macfarlane et al. suggested that QT dispersion ≤50 ms indicated normality (15).

QTc dispersion > 50 ms was considered abnormal in the present study.

Statistical analysis

The data were analyzed using SPSS software version 11.5. Data were expressed as mean ± standard deviation (SD). Student t test was performed to compare the dependent and independent variables. Chi-square test was used for the evaluation of the dependent variables, Pearson's correlation test was used for the analysis of the relationship between the parameters. *P* values <0.05 were considered statistically significant.

RESULTS

Demographic, clinical, laboratory and electrocardiographic characteristics of the groups are shown in Table I. There were 28 men and 32 women with a mean age of 39.45±15.18 years in group 1 compared with 16 men and 14 women with a mean age of 44.43±16.70 years in group 2 (p=0.551 and p=0.159, respectively).

Serum levels of urea, K, phosphorus and ferritin in group 1 were significantly higher than in group 2 (p<0.05), while serum levels of iron, iron binding capacity, albumin and hemoglobin were significantly lower (p<0.05). Cornell product, Sokolow-Lyon Voltage and QTcd values were significantly higher in group 1 than group 2 (p<0.05).

The frequencies of abnormally prolonged QTcd was significantly higher in dialysis group than control group (p<0,05) and is shown in Table II.

The dialysis patients were divided into 2 groups according to whether their measurements of corrected QT (QTc) dispersion were longer than 50 ms. Patients with QTcd >50 ms had significantly higher SBP, urea and ferritin levels, but significantly

lower iron binding capacity and calcium levels compared those with QTcd ≤ 50 ms. Comparison between patients with abnormally prolonged QTcd >50 ms and patients with normal QTcd≤50 ms are shown in Table III.

Significantly positive correlations were found between QTcd and urea, ferritin and SBP levels (p<0.05), and inverse correlations with iron binding capacity level (p<0.05).The correlations between QTcd and study parameters are shown in Table IV.

DISCUSSION

Despite a decline in cardiovascular death has been seemed in the general population, cardiovascular disease is the leading cause of mortality in patients with CKD. Several studies have reported that the ventricular arrhythmia, sudden and cardiac deaths are relatively frequent in HD patients (16). QTc dispersion (QTcd) were defined as the differences between the minimal and maximal QTc values in each of the 12 leads studied and reflects differences in ventricular recovery times (17).

Kirvelä et al. reported that QTc dispersion was significantly greater in ESRD patients (18). Another study by Morris

Table I: Demographic, clinical, laboratory and electrocardiographic characteristics of the groups.

Parameters	Group 1 (n=60)	Group 2 (n=30)	p
Gender (M/F)	28/32	16/14	0.551
Age (years)	39.45±15.18	44.43±16.70	0.159
Urea (mg/dl)	131.35±38.72	29.66±8.90	<0.001
Na (mg/dl)	135.90±8.20	137.90±1.91	0.192
K (mg/dl)	4.44±0.92	4.01±0.35	0.016
Calcium (mg/dl))	8.65±0.94	8.93±0.45	0.133
Phosphorus (mg/dl)	5.19±1.48	3.55±0.54	<0.001
Albumin (gr/dl)	3.32±0.45	3.94±0.57	<0.001
Hemoglobin (gr/dl)	11.46±1.85	13.51±2.60	<0.001
Iron (µg/dl)	59.85±28.81	88.83±57.02	0.002
Iron binding capacity (µg/dl)	116.06±49.05	220.60±88.48	<0.001
Ferritin (ng/ml)	575.03±479.13	73.43±72.61	<0.001
CRP (mg/dl)	6.07±3.13	5.57±4.01	0.554
SBP (mm Hg)	131.33±21.89	123.66±16.13	0.093
DBP (mm Hg)	85.08±12.60	80.66±9.89	0.097
QTcd (ms)	55.75±36.48	28.73±28.27	0.001
Cornell product (mm/ms)	1.53±0.73	1.13±0.62	0.013
Sokolow-Lyon Voltage (mm)	24.75±10.14	19.13±5.55	0.006

CRP, C-reactive protein; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure;

Table II: The frequency of QTc dispersion between two groups.

Parameters	Group 1 (n=60)	Group 2 (n=30)	p
QTcd (1>50 ms, 2≤50 ms) ½	24/36	4/26	0.010

Table III: Comparison between patients with abnormally prolonged QTcd >50 ms and patients with normal QTcd ≤50 ms.

Parameters	QTcd >50 ms (n= 24)	QTcd ≤50 ms (n= 36)	p
Gender (M/F)	9/13	19/19	0.496
Age (years)	39.27±13.28	39.55±16.36	0.946
Dialysis duration (month)	72.05±5.20	68.10±4.43	0.620
SBP(mm Hg)	141.36±18.59	129.73±22.23	0.043
DBP (mm Hg)	89.09±11.50	84.34±12.31	0.146
Urea (mg/dl)	159.72±30.25	124.44±39.43	0.001
Na (mg/dl)	137.09±2.11	135.21±10.16	0.397
K (mg/dl)	4.68±1.06	4.31±0.82	0.137
Calcium (mg/dl)	8.18±1.02	8.80±0.90	0.017
Phosphorus (mg/dl)	5.25±1.23	5.15±1.62	0.796
Albumin (gr/dl)	3.30±0.51	3.37±0.33	0.574
Hemoglobin (gr/dl)	11.29±1.25	11.56±2.13	0.585
Iron (µg/dl)	68.31±36.05	54.94±22.77	0.083
Iron binding capacity (µg/dl)	93.31±42.37	129.23±48.28	0.005
Ferritin (ng/ml)	757.40±450.05	501.55±459.72	0.041
CRP (mg/dl)	6.32±4.07	5.48±3.57	0.328

et al. showed that QT dispersion was significantly higher in hemodialysis patients compared with control subjects (19). Wu et al. (20) evaluated QTc dispersion in 102 nondiabetic patients undergoing peritoneal dialysis and another 102 control subjects and found that QTc dispersion of PD patients was significantly longer than the control subjects (69.8±40.0 versus 55.2 ± 33.6 ms; P<0.01). Our results confirmed previous studies that dialysis patients showed a higher QTcd compared with control subjects (55.75±36.48 versus 28.73±28.27; p=0.001). An abnormally prolonged QTcd>50 ms was found in 40% of dialysis patients.

Increased QTc dispersion measurements on a surface electrocardiogram (ECG) have shown to be a useful and reliable means for predicting susceptibility to life threatening ventricular arrhythmias (20). HD appears to cause diverse ECG abnormalities (21). Arrhythmias may be caused by the rapid changes in intracellular and extracellular electrolytes during the dialysis session, in hearts that are susceptible due to

both myocardial ischaemia and intramyocardiocytic fibrosis. Nakamura et al. suggested that higher incidence of ventricular arrhythmia might reflect the greater likelihood that uraemic conditions associated with a triggering event may initiate a sustained ventricular arrhythmia (22).

Most patients with CKD have cardiac abnormalities including left ventricular hypertrophy (LVH), left ventricular dilatation (LVD) or systolic dysfunction (23). Clinical and echocardiographic cardiovascular disease were highly prevalent at the start of ESRD therapy, on echocardiography 15% had systolic dysfunction, 32% left ventricular dilatation and 74% left ventricular hypertrophy (24). Despite presenting lower sensitivity than echocardiography, ECG is a low-cost, highly reproducible test and the usefulness of ECG is stressed by its ability to detect electrophysiological changes such as QTc and QTc dispersion, which can be correlated with the high frequency of sudden death among this population (25).

Table IV: Correlations between QTcd with study parameters.

Parameters	r	P
QTcd & Urea	0.281	0.007
QTcd & Iron binding capacity	-0.219	0.038
QTcd & Ferritin	0.226	0.032
QTcd & SBP	0.233	0.027
QTcd & DBP	0.092	0.390
QTcd & Cornell product	0.103	0.336
QTcd & Sokolow-Lyon Voltage	0.059	0.578
QTcd & Age	-0.017	0.877
QTcd & Na	0.012	0.909
QTcd & K	0.082	0.445
QTcd & Calcium	0.106	0.323
QTcd & Phosphorus	0.123	0.247
QTcd & Albumin	-0.032	0.762
QTcd & Hemoglobin	-0.012	0.907
QTcd & Iron	-0.098	0.360
QTcd & CRP	0.048	0.652

In a study of 162 men with systemic hypertension Perkiömäki et al, QTc dispersion were significantly longer in the patients with left ventricular hypertrophy than in those without hypertrophy (26). In another study by Yildiz et al. found that there was a correlation between the prolongation of QT dispersion with the left ventricular mass index in HD patients, but not in PD patients (8). In the present study; as compared with controls, Cornell product (1.53±0.73 mm/ms versus 1.13±0.62 mm/ms; p=0.013) and Sokolow-Lyon Voltage (24.75±10.14 mm versus 19.13±5.55 mm; p=0.006) which reflects LVH were significantly higher in dialysis patients. But, there was no correlation found between QTcd with Cornell product and Sokolow-Lyon Voltage (p>0.05).

In a study by Mangoni et al., 191 consecutive healthy subjects were examined (101 males and 90 females, age range 19–89 years) and reported that age did not have any impact on QTd (27). In another large study by Macfarlane et al. (15) also found no significant age differences (QT dispersion of 24±8 ms, 25±8 ms, 25±8 ms, and 24±10 ms in the age groups <30, 30–40, 40–50, and >50 years, respectively). Compatible with the findings of previous studies, there was no significant correlations found between QTcd and age (p=0.877). In addition, when we compared between patients with abnormally prolonged QTcd >50 ms and patients with normal QTcd≤50 ms, age was not significantly different between the groups (39.27±13.28 versus 39.55±16.36, p=0.946).

To the best of our knowledge, few studies have been published regarding the association of iron status with QTc dispersion in ESRD patients. Wu et al, in a study including 102 PD patients and 102 control subjects, observed that patients with QTc dispersion longer than 74 ms had higher transferrin saturation (TSAT; P = 0.022) than the other patients and a strong association of QTc dispersion with transferrin saturation (20). In another study by Dervişoğlu et al.(28) examined the relationship with iron stores and corrected QT dispersion in patients undergoing haemodialysis and reported that serum iron levels were significantly associated with greater QTc dispersion (r=0.324, p=0.042), but other electrolyte levels, duration of dialysis, TSAT and serum ferritin levels were not. In contrast to the findings by Dervişoğlu et al, we found a significantly positive correlation between QTcd and ferritin levels which reflects iron stores in the present study. In addition, patients with QTcd >50 ms had significantly higher ferritin levels, but significantly lower iron binding capacity levels compared those with QTcd ≤ 50 ms.

In vitro and in vivo studies have suggested that a large iron load might change electrical conduction of the cardiomyocytes (24,25). It is suggested that in the heart, iron deposition is not homogeneous, greatest amount of iron collects in the left side of the ventricular septum and free wall and may contribute to the arrhythmogenicity (29,30). Iron overload in dialysis patients induces arrhythmias, which may be measured by the surrogate marker of QTc dispersion (31)

A study in which different dialysate calcium (1.25, 1.5 and 1.75 mmol/l) was examined by Nappi et al. to evaluate the effect of dialysate calcium concentration on cardiac electrical stability during HD treatment in 23 ESRD patients (17). They reported that HD treatments with dialysate Ca⁺⁺ concentrations of 1.25 mmol/L was the only procedure that induced a significant increase in QTc dispersion (from 38± 19 to 49± 18 ms, p< 0.05). Wu et al. (16) founded that PD patients with QTc dispersion longer than 74 ms had higher levels of serum calcium (P = 0.038). In contrast to the findings by Wu et al, in the present study calcium levels were significantly lower in patients who had QTcd (>50 ms) than QTcd (≤ 50 ms) (p<0.05). However, there was no significant correlations between QTcd and calcium. It is suggested that the dialysate calcium content affects both the relaxation properties and the electrical stability of the myocardium and low-calcium dialysate increases the QT interval and dispersion (17) .

In conclusion; the frequency of QTc dispersion was 40% among the dialysis patients and QTcd had positive correlation between urea, ferritin, and SBP but had negative correlation between iron binding capacity. Although serum calcium was significantly lower in patients who had QTcd >50 ms than QTcd ≤ 50 ms (p<0.05), there was no significant correlation between QTcd and calcium.

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