Evaluation of Cardiac Repolarization and Serum Electrolytes in Pre-Dialytic Stages of Chronic Kidney Disease

Kronik Böbrek Hastalığının Diyaliz Öncesi Evrelerinde Kalp Repolarizasyonu ve Serum Elektrolitlerinin Değerlendirilmesi

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ABSTRACT

OBJECTIVE: Patients with chronic kidney disease (CKD) have increased risk for cardiac arrhythmias. Other than comorbidities like diabetes mellitus and cardiovascular disease, factors like acidosis, uremia and electrolyte imbalance may contribute to this risk. The aim of this study was to evaluate electrocardiography (ECG) measurements of ventricular repolarization and search for related clinical features like serum electrolytes that may indicate a risk for arrhythmias in patients with pre-dialytic CKD.

MATERIAL and METHODS: The study included 107 patients with stage 3-5 CKD and 49 healthy individuals. ECG parameters; QT, QTc, Tp-e, Tp-e/QT and Tp-e/QTc were measured on ECG recordings from all participants. Clinical features and serum electrolyte values were recorded.

RESULTS: Mean QTc of patients were higher than healthy controls (p=0.008). We found positive correlations with QTc measurements and serum magnesium and phosphorus levels. We demonstrated that Tp-e, Tp-e/QT and Tp-e/QTc were negatively correlated with potassium levels (p=0.023, 0.042, 0.013). Regression for clinical features revealed no other relation for these correlations.

CONCLUSION: Measuring ECG parameters may help to identify additional risk factors for arrhythmogenesis. We found increased QTc measurements in pre-dialytic CKD patients who were younger than in previous studies. Tp-e, Tp-e/QT and Tp-e/QTc were negatively correlated with serum potassium. Electrolyte imbalances like hypokalemia might unravel the susceptibility for arrhythmias in CKD patients.

KEY WORDS: Cardiac repolarization, Chronic kidney disease, Tp-e interval, QTc, Potassium

ÖZ

AMAÇ: Kronik böbrek hastalığında (KBH) kardiyak aritmi riski artmıştır. Diyabet ve kardiyovasküler hastalık gibi komorbiditeler dışında, asidoz üremi ve elektrolit bozukluğu gibi faktörler de bu riske katkıda bulunur. Çalışmanın amacı, diyaliz öncesi KBH evrelerinde elekrokardiyografik (EKG) ventriküler repolarizasyon ölçütlerini değerlendirmek ve elektrolit bozukluğu gibi bunlara etki edebilecek klinik özellikleri saptamaktır.

GEREÇ ve YÖNTEMLER: Çalışmaya evre 3-5 KBH tanılı 107 hasta ve 49 sağlıklı kontrol dahil edildi. Tüm katılımcılardan EKG parametreleri; QT, QTc, Tp-e, Tp-e/QT ve Tp-e/QTc ölçümü yapıldı. Klinik özellikler ve serum elektrolitleri kaydedildi.

BULGULAR: Hastaların ortalama QTc değeri kontrollerden daha yüksekti (p=0.008). QTc ölçümleri ile serum magnezyum ve fosfor seviyeleri arasında pozitif korelasyonlar bulduk. Tp-e, Tp-e/QT and Tp-e/QTc ölçümlerinin serum potasyum seviyeleri ile negatif korele olduğu görüldü (p=0.023, 0.042, 0.013). Klinik özelliklerle yapılan regresyon analizlerinde, bu korelasyona etki eden ilave faktör saptanmadı.

SONUÇ: EKG parametrelerinin ölçümü aritmogenez için ilave risk faktörlerinin tanımlanmasına yardımcı olabilir. Diyaliz öncesi KBH hastalarında, geçmişteki çalışmalardan daha genç bir hasta popülasyonu ile artmış QTc ölçümleri saptadık. Tp-e, Tp-e/QT ve Tp-e/QTc ölçümleri serum potasyum seviyeleri ile negatif korele idi. Hipokalemi gibi elekrolit denge bozukluklarının, KBH hastalarındaki kardiyak aritmilere olan duyarlılığı açığa çıkarabilmesi mümkündür.

ANAHTAR SÖZCÜKLER: Kardiyak repolarizasyon, Kronik böbrek hastalığı, Tp-e intervali, QTc, Potasyum

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INTRODUCTION

Cardiovascular disease (CVD) is the main cause of death in patients with chronic kidney disease (CKD). The outcomes of CVD and cardiac failure worsen as CKD patients progress to end stage renal disease (ESRD). Cardiac arrhythmias are among these vex outcomes which may lead to sudden cardiac death (SCD) (1,2). While making the effort for diagnosis and treatment of CVD in CKD, preventive approaches against other complications like cardiac dysrhythmias should not be put on the back burner. Measuring intervals of repolarization on the electrocardiogram (ECG) may be helpful to determine a potential risk for cardiac arrhythmias (3,4). In this manner, we may be able to detect patients with CKD who are more prone to fatal arrhythmias and SCD with a quite simple methodology.

Prolongation of repolarization parameters on ECG can be associated with cardiac arrhythmias and SCD. These parameters are measurements of QT, QTc (corrected QT) and Tp-e intervals, Tp-e/QT and Tp-e/QTc ratios, all of which were shown to be associated with increased risk for ventricular arrhythmias (3,5,6).

Other than ischemic cardiomyopathy and myocardial fibrosis, factors like electrolyte imbalance, metabolic acidosis, uremic toxins, use of proarrhythmic drugs and elevated blood pressure may also induce cardiac arrhythmias in patients with CKD (2,3). Therefore, the aim of this study was to evaluate the ECG measurements of ventricular repolarization and search for related clinical features like serum electrolyte levels that may indicate a potential risk for fatal arrhythmias or SCD in patients with pre-dialytic CKD.

MATERIAL and METHODS

Study Group Selection

The study groups were 107 patients with stage 3 to 5 CKD (55 male, 52 female; mean age: 56.8±14.3 years) diagnosed by Department of Nephrology at Sutcu Imam University Faculty of Medicine in Kahramanmaras, Turkey; and, 49 age- and gender-matched healthy volunteers (23 male, 26 female; mean age: 49.1±14.4 years). Patients on maintenance hemodialysis and chronic peritoneal dialysis programs, patients with abnormal thyroid function tests, heart failure, valvular disease, atrial fibrillation, bradycardia (<60 bpm), tachycardia (>100 bpm) and those who had undergone cardiac revascularisation procedures within a year were excluded from the study. Patients who had widened QRS or volrage criteria for left ventricular hypertrophy on ECG and those taking antiarrhythmic (procainamide, flecainide, amiodarone, digoxin, etc.), antipsychotic and antidepressant medication were also excluded. The leading etiology for CKD in the patient group was diabetes mellitus (DM) (39.2%), followed by hypertension (HT) (33.6%), glomerulonephritis (11.2%) and polycystic kidney disease (7.4%). The study was conducted between August 2016 and April 2017. With the informed consent of all participants, the study was approved by the local ethics review board.

ECG Measurements

A 12-lead ECG recording with a speed of 50 mm/s was obtained from all participants. Intervals of RR, QT, and Tp-e were measured in precordial lead V_6. When an artifact was present on ECG, the alternative lead V_5 was used. The Bazett formula ($QT/\sqrt{RR}$) was used to calculate the QTc for adjusting QT to heart rate. Any QTc > 450 ms was considered as prolonged QTc (6,7). Tp-e was measured on the isoelectric line as the distance between the projection of the peak of the T wave and the intersection point of the tangent of the descending limb. Tp-e/QT and Tp-e/QTc ratios were also recorded along with these measurements.

Clinical Data Collection

Any CKD patient with acute kidney injury was either excluded from the study or included after the decrease of serum creatinine to baseline levels. Comorbid conditions of CKD patients like DM, HT and CVD were noted. Blood pressures were recorded and serum and urine samples for laboratory values were obtained at the time of ECG. Estimated GFR (glomerular filtration rate) was calculated based on the MDRD (Modification of Diet in Renal Disease) formula {GFR = 186.3 X (serum creatinine$^{-1.154}$) X (age$^{-0.203}$) X (0.742 for females)} for each patient with CKD (8). Stage of CKD (3 to 5) and use of medication (antihypertensives, calcium containing phosphate binders, sodium bicarbonate) were also recorded.

Statistical Analysis

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS inc., an IBM Co., Somers, NY). Values were expressed as mean ± standard deviation (SD) or percentages. Student's t test or chi-square test was used to analyze results for categorical variables. The Mann-Whitney U test was used to analyze results for non-categorical variables. Pearson and Spearman correlation tests were used for correlation analysis. Linear regression analysis was performed with enter method. The distribution of the dependent variables used in linear regression was normal. A p value that was <0.05 was accepted as statistically significant.

RESULTS

ECG Parameters

The mean QT, QTc and Tp-e intervals of 107 patients with stage 3-5 CKD were 369.5±35.7, 409.3±30.3 and 72.2±11.9 ms respectively. The mean Tp-e/QT and Tp-e/QTc ratios of the patient group were 0.19±0.03 and 0.17±0.03 ms. Meanwhile, the mean QT, QTc and Tp-e intervals of the 49 healthy individuals were 371.8±32.6, 397.3±22.9 and 70.7±10.6 ms respectively. The mean Tp-e/QT and Tp-e/QTc ratios of the control group were 0.20±0.09 and 0.17±0.02 ms. When the patient and control groups were compared for these ECG parameters, the mean QTc

of the patient group was significantly higher than the control group (p = 0.008). The differences in all other parameters were not significant. Minimum and maximum values measured for Tpe, QT and QTc were 44/98, 260/480 and 346/483 ms respectively. The comparison of CKD patients and healthy controls in terms of demographic features and mean ECG parameters are presented in Table I.

Clinical Data

Forty-two (39.3%) of the total 107 CKD patients had a diagnosis of DM, 63 (58.8%) were diagnosed as HT and 21 (19.6%) had proven CVD. Forty-nine (45.7%) of the patients were using calcium channel blockers and 43 (25.2%) were on renin-angiotensin system blockers. The mean systolic and diastolic blood pressure readings at the time of the ECG recording were 140±25.6 and 81.1±10.2 mmHg respectively. Mean GFR of the patient group was 24.5 mL/min according to the MDRD formulation. Clinical features and laboratory findings of the patient group including serum levels for electrolytes are shown in Table II.

Comparison of ECG Parameters and Clinical Data

ECG measurements of CKD patients (QT, QTc and Tp-e intervals, Tp-e/QT and Tpe/QTc ratios) were not different

Table I: Demographics and ECG parameters of CKD patients and healthy controls.

Variable	Patients (n=107)	Controls (n=49)	p
Age (years)	56.8±14.3	49.1±14.4	0.84
Gender (male/female)	55/52	23/26	0.68
Body mass index (kg/m^2)	26.5±4.7	27.6±5.2	0.67
QT (ms)	369.5±35.7	371.8±32.6	0.25
QTc (ms)	409.3±30.3	397.3±22.9	**0.008**
TP-e (ms)	72.2±11.9	70.7±10.6	0.22
TP-e/QT	0.19±0.03	0.20±0.09	0.19
TP-e/QTc	0.17±0.03	0.17±0.02	0.59

Table II: Clinical features and laboratory values of the patient group (n=107).

Variable	n (%)
DM	42 (39.3)
HT	63 (58.8)
CVD	21 (19.6)
CKD Stage 3/4/5	34 (31.7) /48 (44.8) /24 (22.4)
CCB	49 (45.7)
RASB	43 (25.2)
Diuretic	35 (32.7)
BB	31 (29)
Phosphate binder	19 (17.8)
$NaHCO_3$ capsules	64 (59.8)

Variable	Mean±SD
SBP (mm Hg)	140±25.6
DBP (mm Hg)	81.1±10.2
Creatinine (mg/dL)	2.7±1.4
Hemoglobin (g/dL)	11.9±2
Potassium (meq/L)	4.6±0.7
Calcium (mg/dL)	8.9±0.7
Phosphorus (mg/dL)	3.7±1
Magnesium (mg/dL)	1.9±0.4
Uric acid (mg/dL)	7.1±1.8
Bicarbonate (meq/L)	21.4±3.6
UPCR (mcg/mg)	73.5±35.5
eGFR (mL/min)	24.5±11.1

DM: Diabetes mellitus, **HT:** Hypertension, **CVD:** Cardiovascular disease, **CKD:** Chronic kidney disease, **CCB:** Calcium channel blockers, **RASB:** Renin-angiotensin system blockers, **BB:** Beta blockers, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **UPCR:** Urine protein-creatinine ratio, **eGFR:** Estimated glomerular filtration rate.

in terms of age, gender, CKD, blood pressure and use of antihypertensives or phosphate binders. The mean QT, QTc and, Tp-e measurements and, Tp-e/QT and Tp-e/QTc ratios of the diabetic subgroup were not different from the non-diabetics. When we compared the mean data of ECG measurements for patients with or without proven CVD, the length of QTc interval showed significant difference only. The mean QTc of CKD patients with proven CVD was higher than those without CVD (423.6±27.5 > 405.7±30.0, p = 0.015). Fourteen (13%) CKD patients had prolonged QTc and this result did not reveal any significance compared to any of the variables.

Serum levels of creatinine, haemoglobin, potassium, calcium, phosphorus, magnesium, uric acid, bicarbonate and, level of proteinuria and estimated GFR of the CKD patients were analyzed along with their ECG measurements. No relationship was found between the ECG parameters and any of the variables; creatinine, haemoglobin, calcium (corrected to albumin), uric acid, bicarbonate, urine protein/creatinine ratio and estimated GFR. The mean QT and QTc of patients that were taking diuretics were higher than those who were not (379.9±36.8 > 362.8±33.5, p = 0.015 and 421.5±30.6 > 401.3±27.4, p = 0.001).

Twenty (18.7%) of the patients had hypermagnesemia (serum magnesium > 2.3 mg/dL). The length of QT and QTc intervals on ECG were positively correlated with serum magnesium levels (p = 0.012 and 0.019 respectively). Linear regression analysis with different variables revealed that 23.4 and 21.8% of the length of the QT and QTc intervals could be explained by the increase in serum magnesium levels and, 19.8% and 17.8% of the length of QT and QTc intervals could be explained by the presence of proven CVD. There was a significant positive correlation between the serum phosphorus level and QTc interval (p = 0.007). Multiple regression analysis for this result revealed that 16.1% of the correlation between QTc interval and serum phosphorus level could be explained with the presence of proven CVD.

The length of Tp-e interval and Tp-e/QT and Tp-e/QTc ratios in the patient group were negatively correlated with serum potassium levels (p= 0.023, 0.042 and 0.013 respectively). Multiple linear regression analysis revealed no significant association for different independent variables. Univariate associates of ECG parameters in CKD patients are presented in Table III.

DISCUSSION

Since CKD and heart disease usually coexist and contribute to the pathophysiology of one and other, striving against cardiorenal syndrome and CVD in patients with CKD requires an elaborative and multidisciplinary approach. Evaluation of measurements of repolarization on ECG to identify the potential risks for fatal arrhythmias could provide clinically useful information for the CKD population.

The QT interval is a measurement between the start of the Q wave and the end of the T wave on ECG. It is the electrical activity that reflects ventricular depolarization and repolarization. The QT interval shortens at faster heart rates and it can be adjusted to the heart rate using formulations (i.e. Bazett's, Fredericia's

Table III: Univariate associates of ECG parameters in CKD patients.

	QT		QTc		TP-e		TP-e/QT		TP-e/QTc	
Variable	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Age	-0.002	0.982	0.144	0.139	-0.057	0.561	-0.60	0.537	0.003	0.972
Creatinine	0.107	0.272	0.186	0.056	0.018	0.853	-0.141	0.674	-0.112	0.253
Hemoglobin	-0.019	0.846	-0.158	0.103	-0.062	0.526	-0.58	0.556	-0.005	0.959
Potassium	-0.081	0.404	-0.35	0.72	**-0.220**	**0.023**	**-0.197**	**0.042**	**-0.239**	**0.013**
Calcium	-0.75	0.441	-0.188	0.053	-0.58	0.553	-0.004	0.966	0.029	0.770
Phosphorus	0.189	0.052	**0.259**	**0.007**	-0.018	0.856	-0.137	0.160	-0.137	0.176
Magnesium	**0.243**	**0.012**	**0.228**	**0.019**	0.075	0.446	-0.073	0.459	0.072	0.466
Uric acid	0.000	0.993	-0.154	0.114	0.131	0.177	0.142	0.145	0.169	0.081
Bicarbonate	0.060	0.543	0.153	0.119	0.096	0.327	0.070	0.479	-0.032	0.746
Albumin	0.024	0.809	-0.84	0.389	-0.047	0.634	-0.061	0.535	0.036	0.713
UPCR	0.126	0.206	0.091	0.36	-0.003	0.975	-0.082	0.410	-0.071	0.474
eGFR	0.012	0.898	-0.132	0.174	-0.022	0.823	-0.039	0.692	0.131	0.179

UPCR: Urine protein-creatinine ratio, **eGFR:** Estimated glomerular filtration rate.

or Framingham) to form the QTc. The length of a normal QTc interval measures 350 to 440 ms in men and 350 to 460 ms in women on a standard ECG which is less than half the of RR. Prolongation of QT (or QTc) interval indicates a potential risk of ventricular arrhythmias and SCD (6,7,9).

While the QT interval reflects the dispersion of ventricular depolarization and repolarization, the Tp-e interval on ECG indicates the distribution of the repolarization process only. The peak of T-wave on ECG represents the point when epicardial repolarization ends and the end of T-wave which points to midmyocardium represents total myocardial repolarization. So, the Tp-e interval reflects transmural dispersion of repolarization (5,10,11). Some studies refer to Tp-e as a measure that represents a global, rather than the transmural dispersion of repolarization. If so, Tp-e interval on ECG could only be a surrogate parameter providing trifle information over that of QT interval in terms of identifying a risk for arrhythmias like ventricular tachycardia (10,12,13). Nevertheless, prolongation of Tp-e interval (amplified dispersion of repolarization) on a standard ECG was set out to be an indicator for cardiac arrhythmias in many studies (3,5,14,15).

The possible advantage of measuring the Tp-e interval is that the increases in Tp-e and QT intervals are not always proportional. When the measurements are accurate, this parameter could be more useful in terms of determining repolarization abnormalities. Since the Tp-e and QT intervals are increasing with larger body sizes and decreasing with faster heart rates, another ECG parameter, the Tp-e/QT ratio which is downsized to a more narrow range of values was asserted to be a more sensitive index for arrhythmogenesis (16-18).

In the current study, we evaluated the measurements of ECG intervals that are related to dispersion of cardiac repolarization (QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc) in 107 patients with stage 3-5 CKD and 49 healthy individuals. The mean QTc was significantly higher in the patient group compared to healthy controls (p=0.008). Prolongation of QTc on ECG measures is a predictor for cardiovascular mortality and SCD among patients with CKD and in the general population as well (4,9,19). Previous studies already demonstrated that the length of QT and QTc intervals are more prolonged in CKD patients compared to the general population. Yet, we have a younger patient population than many of these studies which included elderly patients with CKD (20-22). Therefore, our result could be interpreted as another indicator of the increased risk for arrhythmias in the CKD population with a younger age distribution.

Electrolyte imbalances may easily induce cardiac arrhythmias in CKD patients who are already prone to CVD (3,22). QT prolongation and ventricular arrhythmias may frequently be in association with low magnesium levels (7,9,23). Oddly enough, we found a positive correlation between serum magnesium levels and the length of QT and QTc intervals in patients with CKD (p= 0.012 and 0.019 respectively). Together with multiple regression analysis, we observed that the QT values of our patients with a history of CVD might be interfering with this correlation. Accordingly, we think that coinciding hypermagnesemia and CVD in the study population is the reason for this result. Recent studies suggest that high serum magnesium levels may even be protective against vascular calcification (23,24). After all, hypermagnesemia is a common condition among patients with CDK and the ECG manifestations of hypermagnesemia could be just like those we observe in hyperkalemia (i.e. prolonged PR, increased QT and peaked T wave) (25). Therefore, hypermagnesemia may not be an innocent bystander in terms of arrhythmogenesis in patients with CKD but such an assumption sure needs to be validated. We did not find any relation between ECG parameters and serum levels of calcium, uric acid or bicarbonate in patients with CKD. Again the QTc interval was positively correlated with serum phosphorus levels (p=0.007). This relation could be conceived as a reflection of hyperphosphatemia on CVD and vascular calcification (4,26).

It is not easy to state whether CKD itself is associated with cardiac repolarization abnormalities or is due to the accompanying comorbid conditions. Sherif et al. demonstrated a significant increase in measurements of QTc in stage 2 to 5 CKD patients along with the progression of the disease, but the increase in Tp-e measurements was not significant. They attended to exclude the CKD patients with structural heart disease and electrolyte imbalance. However, their study was retrospective and also included the patients on maintenance hemodialysis (27).

The effect of serum electrolyte levels on alteration of cardiac repolarization can ideally be revealed by comparing ECG measurements after rapid transmembrane electrolyte changes. A study by Scherr et al. revealed an association with increased QT and Tp-e intervals and hypokalemia and hypomagnesemia after excessive exercise consisting of participating in a marathon (28). Patients on maintenance hemodialysis may be prone to fatal arrhythmias just after hemodialysis as well. Rapid electrolyte shifts from tubuloinerstitium during hemodialysis treatment may quite likely change the length of Tp-e and QT intervals and increase the risk for ventricular arrhythmias. These patients also have increased risk of arrhythmias before the session of a routine hemodialysis due to volume overload, metabolic acidosis and increased serum potassium (4,29,30). Therefore, we did not include patients on chronic hemodialysis program in this study. It would be more reasonable to evaluate chronic hemodialysis patients in a separate study for measurements of impaired repolarization on ECG.

There are not many studies that evaluated the Tp-e interval and Tp-e/QT and Tp-e/QTc ratios in the CKD population. Although their results were hardly significant, Kalantzi et al. demonstrated increased Tp-e interval and Tp-e/QT ratio in patients with end stage renal disease (ESRD) after a session of hemodialysis (31). On the contrary, another study by Monfared

et al. revealed a decrease in Tp-e/QT ratio (not in Tp-e) after a haemodialysis session. It is noteworthy that both ECG parameters were significantly decreased in the same patient group after renal transplantation (5). The mean Tp-e interval values of ESRD patients or healthy controls in different studies were not consistent with each other (5,27,31,32). The reasons for this heterogeneity of the results could be the retrospective nature of the studies, small sample size, variation of heart rate and also measurement bias. Since Tp-e is a very short interval on ECG, it requires an attentive measurement.

Even though the mean Tp-e value of our patient group was higher than that of the healthy control group (72.2±11.9 > 70.7±10.6 ms), the difference did not reach significance. Measuring Tp-e intervals in a larger group of pre-dialytic CKD patients might reveal a significant difference over healthy individuals. Our results showed a negative correlation between serum potassium levels with the Tp-e interval and Tpe/QT and Tpe/QTc ratios ($p = 0.023$, 0.042 and 0.013 respectively). Adjusting for many variables including other laboratory values, DM, HT and CVD showed that none of them were confounding to this correlation.

Depolarization of the myocytes is initiated by cardiac sodium channels (action potential upstroke due to sodium influx), which leads to voltage-gated calcium channel activation and muscle contraction. Besides, the repolarization process occurs following the outward current generated by the voltage-gated potassium channels (33,34). Hyperkalemia turns out to be the most important electrolyte imbalance that could cause SDC in patients with ESRD but it is generally well tolerated during the pre-dialytic stages of CKD (2,19). On the other hand hypokalemia, usually accompanied by hypomagnesemia, may also pose a threat by altering ventricular repolarization and increasing action potential duration in patients who are susceptible to arrhythmias (4,35). Luckily, mildly increased serum potassium and magnesium levels could be protective against this impaired repolarization in pre-dialytic CKD (3,33).

We must keep in mind that a hypokalemic state may also become evident in patients with CKD due to renal tubular acidosis, post-obstructive diuresis and administration of diuretics, insulin or drugs that could damage the renal tubular epithelium. The negative correlation we found between Tp-e interval and serum potassium levels manifests a relation between cardiac repolarization abnormalities and electrolyte imbalance. The higher mean QT and QTc values we found in the patients taking diuretics is another result supporting our hypothesis. We infer that hypokalemia might facilitate arrhythmogenesis in patients with CKD.

A limitation to our study could be the sample size. A larger group of CKD patients might have revealed increased Tp-e interval and Tp-e/QT and Tp-e/QTc ratios compared to healthy controls along with the significantly increased QTc measurements. Another limitation could be the effect of other comorbid conditions on cardiac repolarization that we were not able to detect in patients with pre-dialytic CKD.

CONCLUSIONS

Patients with CKD have increased risk for arrhythmias and SCD. In this study we showed that QTc measurements were increased in stage 3-5 CKD patients who were younger than many of the previous studies. We found that Tp-e interval and Tp-e/QT and Tp-e/QTc ratios, which are promising ECG parameters to indicate cardiac repolarization abnormalities, were negatively correlated with serum potassium levels and these correlations did not reveal any associations with other variables after regression analysis.

There is no doubt that the risk factors for fatal arrhythmias and SCD in the general population will coincide with risk factors for CVD. However, identifying these risk factors in the CKD population could be more complex. This is because of the additional factors such as electrolyte imbalance or acid-base disorders which may also contribute to arrhythmogenesis. Hypokalemia must not be overlooked in patients with CKD because it might unravel the susceptibility for ventricular arrhythmias.

Conflict of Interest Statement

The authors declare that they have no competing interests.

REFERENCES

1. Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG, Eckardt KU, Kasiske BL, McCullough PA, Passman RS, DeLoach SS, Pun PH, Ritz E: Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80(6):572-586
2. Alsheikh-Ali AA, Trikalinos TA, Ruthazer R, Terrin N, Wong JB, Sarnak MJ, Estes NA 3rd, Kent DM: Risk of arrhythmic and nonarrhythmic death in patients with heart failure and chronic kidney disease. Am Heart J 2011;161(1): 204-209
3. Di Lullo L, Rivera R, Barbera V, Bellasi A, Cozzolino M, Russo D, De Pascalis A, Banerjee D, Floccari F, Ronco C: Sudden cardiac death and chronic kidney disease: From pathophysiology to treatment strategies. Int J Cardiol 2016;217:16-27
4. Di Iorio B, Bellasi A: QT interval in CKD and haemodialysis patients. Clin Kidney J 2013;6(2):137-143
5. Monfared A, Assadian Rad M, Feizkhah M, Kazemnezhad E, Esmaeili S, Rastjou Herfeh N, Hedayatsafa R: Comparison of tpe changing on ECG, in pre and post dialysis and post transplantation. Nephrourol Mon 2016;8(3):e35864
6. Hansen S, Rasmussen V, Torp-Pedersen C, et al: QT intervals and QT dispersion determined from a 12-lead 24-hour Holter recording in patients with coronary artery disease and patients with heart failure. Ann Noninvasive Electrocardiol 2008;13:22-30

7. Topilski I, Rogowski O, Rosso R, Justo D, Copperman Y, Glikson M: The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. J Am Coll Cardiol 2007;49:320-328
8. Levey AS, Coresh J, Greene T, et al: Chronic kidney disease epidemiology collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145:247-254
9. Montanez A, Ruskin JN, Hebert PR, et al: Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: A review and qualitative overview of the prospective cohort studies. Arch Intern Med 2004;164: 943-948
10. Kors JA, Ritsema van Eck HJ, van Herpen G: The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol 2008; 41:575-580
11. Watanabe N, Kobayashi Y, Tanno K, et al: Transmural dispersion of repolarization and ventricular tachyarrhythmias. J Electrocardiol 2004;37:191-200
12. Opthof T, Coronel R, Wilms-Schopman FJ, Plotnikov AN, Shlapakova IN, Danilo P Jr, Rosen MR, Janse MJ: Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion. Heart Rhythm 2007;4(3):341-348
13. Opthof T, Janse MJ, Meijborg VM, Cinca J, Rosen MR, Coronel R: Dispersion in ventricular repolarization in the human, canine and porcine heart. Prog Biophys Mol Biol 2016;120(1-3):222-235
14. Haarmark C, Hansen PR, Vedel-Larsen E, Pedersen SH, Graff C, Andersen MP, et al: The prognostic value of the Tpeak-Tend interval in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. J Electrocardiol 2009;42:555-560
15. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, et al: Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol 2011;4:441-447
16. Tokatli A, Kiliçaslan F, Alis M, Yiginer O, Uzun M: Prolonged Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in patients with type 2 diabetes mellitus. Endocrinol Metab (Seoul) 2016;31(1):105-112
17. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, Yan GX: T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008;41(6):567-574
18. Castro-Torres Y, Carmona-Puerta R, Katholi RE: Ventricular repolarization markers for predicting malignant arrhythmias in clinical practice. World J Clin Cases 2015;3(8):705-720
19. Deo R, Shou H, Soliman EZ, Yang W, Arkin JM, Zhang X, Townsend RR, Go AS, Shlipak MG, Feldman HI: Electrocardiographic measures and prediction of cardiovascular and noncardiovascular death in CKD. J Am Soc Nephrol 2016; 27(2):559-569
20. Kestenbaum B, Rudser KD, Shlipak MG, Fried LF, Newman AB, Katz R, Sarnak MJ, Seliger S, Stehman-Breen C, Prineas R, Siscovick DS: Kidney function, electrocardiographic findings, and cardiovascular events among older adults. Clin J Am Soc Nephrol 2007;2(3):501-508
21. Dobre M, Brateanu A, Rashidi A, Rahman M: Electrocardiogram abnormalities and cardiovascular mortality in elderly patients with CKD. Clin J Am Soc Nephrol 2012;7(6):949-956
22. Hage FG, de Mattos AM, Khamash H, Mehta S, Warnock D, Iskandrian AE: QT prolongation is an independent predictor of mortality in end-stage renal disease. Clin Cardiol 2010;33:361-366
23. Musso CG: Magnesium metabolism in health and disease. Int Urol Nephrol 2009;41(2):357-362
24. Sakaguchi Y, Hamano T, Nakano C, Obi Y, Matsui I, Kusunoki Y, Mori D, Oka T, Hashimoto N, Takabatake Y, Takahashi A, Kaimori JY, Moriyama T, Yamamoto R, Horio M, Sugimoto K, Yamamoto K, Rakugi H, Isaka Y: Association between density of coronary artery calcification and serum magnesium levels among patients with chronic kidney disease. PLoS One 2016;11(9):e0163673
25. Jhang WK, MD, Lee YJ, Kim YA, MD, Park SJ, Park YS: Severe hypermagnesemia presenting with abnormal electrocardiographic findings similar to those of hyperkalemia in a child undergoing peritoneal dialysis. Korean J Pediatr 2013;56(7):308-311
26. Claes KJ, Heye S, Nuyens D, Bammens B, Kuypers DR, Vanrenterghem Y, Evenepoel P: Impact of vascular calcification on corrected QT interval at the time of renal transplantation. Am J Nephrol 2012;35: 24-30
27. Sherif KA, Abo-Salem E, Panikkath R, Nusrat M, Tuncel M: Cardiac repolarization abnormalities among patients with various stages of chronic kidney disease. Clin Cardiol 2014; 37:417-421
28. Scherr J, Schuster T, Pressler A, Roeh A, Christle J, Wolfarth B, Halle M: Repolarization perturbation and hypomagnesemia after extreme exercise. Med Sci Sports Exerc 2012; 44(9):1637-1643
29. Severi S, Grandi E, Pes C, Badiali F, Grandi F, Santoro A: Calcium and potassium changes during haemodialysis alter ventricular repolarization duration: In vivo and in silico analysis. Nephrol Dial Transplant 2008; 23:1378-1386
30. Di Iorio B, Torraca S, Piscopo C, Sirico ML, Di Micco L, Pota A, Tartaglia D, Berardino L, Morrone LF, Russo D: Dialysate bath and QTc interval in patients on chronic maintenance hemodialysis: Pilot study of single dialysis effects. J Nephrol 2012;25:653-660
31. Kalantzi K, Gouva C, Letsas KP, Vlachopanou A, Foulidis V, Bechlioulis A, Katopodis KP, Goudevenos CA, Korantzopoulos P: The impact of hemodialysis on the dispersion of ventricular repolarization. Pace 2013;36:3:322-327
32. Guclu A, Sipahioglu MH, Icli A, Alpay MF, Narman S: Tp-e/QT and Tp-e/QTc ratio in hemodialysis and peritoneal dialysis patients. Turk Neph Dial Transpl 2016;25(3):273-278
33. Mozos I: Laboratory markers of ventricular arrhythmia risk in renal failure. Biomed Res Int 2014;2014:509204
34. Priest BT, McDermott JS: Cardiac ion channels. Channels (Austin). 2015;9(6):352-359
35. Foglia PE, Bettinelli A, Tosetto C, Cortesi C, Crosazzo L, Edefonti A, Bianchetti MG: Cardiac work up in primary renal hypokalaemia-hypomagnesemia (Gitelman syndrome). Nephrol Dial Transplant 2004;19(6):1398-1402