ANAEMIA PREDICTS PROLONGED QT INTERVAL IN PREDIALYSIS CHRONIC KIDNEY DISEASE PATIENTS

C Ijoma, I Ulasi, B Anisiuba

Citation

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Abstract

Background. Patients with advanced chronic kidney disease (CKD) have increased cardiovascular mortality of multifactorial aetiology including cardiac arrhythmias. Prolonged QT interval may be responsible for some of the cardiac deaths. This prospective cross sectional study investigated the QTc in predialysis chronic kidney disease patients compared with age and sex matched controls subjects. It also investigated association between QTc and variables that may affect it.Methods. Ninety one patients in CKD stages 3 to 5 and thirty two control subjects matched for age and sex were studied using standard 12-lead electrocardiogram.Results. Fifty four (59.3%) of CKD patients had abnormal QTc defined as QTc ≥0.44. This was observed in all the stages of CKD studied (67% for CKD stage 3, 62% for stage 4 and 58% for stage 5). There was no statistical difference in the frequency of abnormal QTc between the stages of CKD, p = 0.707. All the control subjects had normal QTc with a mean of 0.38±0.02. BMI, SBP, DBP, Hb, and aetiology of CKD correlated with QTc. Only Hb predicted the presence of prolonged QTc in CKD. Conclusion. The QTc interval is significantly prolonged in predialysis CKD patients in this study. This abnormality was present in stages 3 to 5 CKD. This may be a contributing factor to the high cardiovascular mortality in CKD patients. Anaemia was predictive of prolonged QTc in this study. It is reasonable to recommend an ECG as part of the evaluation of all patients with CKD.

INTRODUCTION

Patients with chronic kidney disease are at significantly increased risk for both morbidity and mortality from cardiovascular disease,[1,2.]. Cardiovascular disease accounts for at least 50% of deaths in end stage renal disease [3]. The increase in cardiovascular risk associated with CKD may be due to several mechanisms, including age, haemodynamic overload due to hypertension and anaemia, left ventricular hypertrophy, dyslipidaemia, a high prevalence of diabetes mellitus and impaired glucose tolerance, prothrombin changes, neurohormonal overactivity, and divalent ion abnormalities.[4, 5] More recently other factors known as 'new or non-classic' factors have been identified. These include homocysteine, inflammation, and oxidative stress[6, 7]. This increased risk of cardiovascular mortality may exist in mild renal insufficiency [8-10] and progresses with the severity of renal disease.[11, 12]. Dialysis patients are a high risk group for all cause death. The death rate for all US dialysis patients between 1996 and 1998 was 231/1000 patient years.[13] Cardiac disease is the major cause of death in dialysis patients, accounting for approximately 45% of all-cause mortality.[13] Sudden cardiac death may be implicated in 60% of all cardiac deaths in dialysis patients. In the USRDS database, 'cardiac arrest; cause unknown ' accounted for 47% of all cardiac deaths and another 13% were attributed to arrhythmia.[14] Prolonged QT interval, a measure of heterogeneity of vascular repolarization, has been linked with increased risk of sudden death in dialyzed patients and it may be more prolonged, after haemodialysis.[15-17]

This cross sectional, prospective study was designed to study the QTc in patients with CKD stages 3 to 5 at first presentation before the commencement of renal substitution. The mean QTc of the patients was compared with that of age and sex matched control subjects. The association between the QTc and other factors was studied.

MATERIALS AND METHODS

Chronic kidney disease patients attending the Nephrology Clinic of University of Nigeria Teaching Hospital, Enugu, a tertiary health institution were recruited for the study. The study was conducted between February 2003 and January 2004 after approval by the hospital's Ethics Committee. Informed consent was obtained from each patient and

control subject. Chronic kidney disease was defined as by the National Kidney Foundation Quality Outcome Initiative guidelines (K/DOQI)[18]. Patients were recruited if they were not on dialysis and had calculated glomerular filtration rate (GFR) < 60 ml/min/1.73m^2. No patient received medication known to affect the QT interval. The medical history, medications, height, weight, and blood pressure were documented. Venous blood samples were collected for haemoglobin concentration, serum electrolytes and creatinine assays. The biochemical assays were measured by standardized methods on autoanalyzer. A 12 lead electrocardiogram was recorded for each patient using Cardiette auto ruler electrcardiographic machine. The QT interval was measured manually by one observer using calipers on ECG enlarged on the same photocopier by a factor of 3. The QT interval was measured by first deflection of the QRS complex to the point of T-wave offset, defined by the return of the terminal T-wave to the isoelectric TP baseline. Each QT interval was corrected for patient's heart rate using the Bazette formula: QTc = QT/square root of RR (sec).[19] To measure renal function, estimated glomerular filtration rate (GFR) using the Cockcroft-Gault formula [20] was used. A total of 148 consecutive patients were recruited out of which 91 completed the study. Thirty two control subjects matched for age and sex were also recruited for the study.

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill) version 11.5. For continuous variables, mean values and standard deviations were calculated, and the means were compared using two sample t test. Categorical variables were compared using

the nonparametric test, the chi-square. All tests were two-tailed and P values less than 0.05 were considered significant.

The Pearson's and Spearman rho correlation were used to assess the relationship between QTc the variables: age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), haemoglobin concentration (Hb), serum calcium, phosphate, calcium-phosphate product, aetiology of kidney disease and stage of kidney disease. Linear regression analysis was used to determine the variables that predicted prolonged QTc among the variables that showed association with QTc.

RESULTS

The characteristics of the patients and control subjects are detailed in table 1.

Ninety-one patients (47 males and 44 females) and 32 control subjects (18 males and 14 females) completed the study. There was no difference in the ages (p = 0.176) and the BMI (p = 0.071) of the patients and control subjects.

All the control subjects had normal QTc interval of < 0.44, with a mean of 0.38 ±0.22 (range 0.30 to 0.42). Fifty four (59.3%) of the patients had QTc interval above the normal value of 0.44, (range 0.45 to 0.60). The mean QTc interval of the patients was 0.46±0.05. There was statistically significant difference between the mean QTc interval of the patients and the control subjects, p < 0.001. There was no difference in the mean QTc of the different stages of CKD (0.46±0.05, 0.45±0.06 and 0.46±0.05 respectively for CKD stages 3, 4 and 5), p = 0.707. Pearson and Spearman Rho bivariate correlation analysis of QTc and all the variables tested (age, gender, BMI, aetiology of CKD, SBP, DBP, Hb, CKD stage, serum calcium, serum phosphate, and calcium-phosphate product) showed that SBP, DBP and aetiology of kidney disease positively correlated with QTc while BMI and Hb showed negative correlation with QTc, Table 2. A linear regression analysis of the variables that showed association with QTc using QTc as the dependent variable showed that only haemoglobin predicted the presence of prolonged QTc, Table 3

The causes of chronic kidney disease in this study were chronic glomerulonephritis 26 (28.6%), diabetic nephropathy, 19 (20.9%), hypertensive nephrosclerosis 16 (17.6%), and unknown aetiology 20 (22.0%), Table 4. Of the 91 patients, 3 (3.3%), 21 (23.1%) and 67 (73.6%) were in stages 3, 4 and 5 respectively.

Figure 1

Table 1: Characteristics of the patients and control subjects

Parameter	Patients N = 91	Control subjects N = 32	p-value
Mean age (years)	43.73±13.53	39.84±14.85	0.176
BMI (Kg/m^2)	23.27±3.88	24.71±3.75	0.071
SBP (mmHg)	169.88±36.44	118.41±9.78	<0.001
DBP (mmHg)	103.51±20.81	75.47±6.76	<0.001
Hb (g/dl)	7.80±1.36	13.59±0.95	<0.001
Serum calcium (mmol/L)	2.21±0.24	2.34±0.26	0.010
Serum phosphate (mmol/L)	1.82±0.62	1.39±0.18	<0.001
Serum Calcium x phosphate	3.97±1.34	3.23±0.35	0.003
Serum creatinine (µmol/L)	684.84±269.93	82.95±10.83	<0.001
eGFR (ml/min/1.73m^2)	12.86±7.04	110.17±15.14	<0.001
QTc	0.46±0.05	0.38±0.22	<0.001

Abbreviations: BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, eGFR; estimated glomerular filtration rate, Hb; haemoglobin.

Figure 2

Table 2. Pearson and Spearman Rho bivariate correlation analysis of QTc and variables as appropriate

Variable	Correlation coefficient	p-value
Age	.022	0.810
Gender	.084	0.358
Body mass index	-.229	0.011
Cause of CKD	.494	<0.001
SBP	.329	<0.001
DBP	.335	<0.001
Hb	-.579	<0.001
CKD stage	.047	0.655
Serum calcium	-1.119	0.189
Serum phosphate	.135	0.137
Calcium-phosphate product	.107	0.240

Abbreviations. CKD; chronic kidney disease, SBP; systolic blood pressure, DBP; diastolic blood pressure, Hb; haemoglobin concentration,

Figure 3

Table 3. Linear regression analysis of QTc and variables

Variable	B	Std error	T	p-value
Constant	.537	.039	13.886	0.000
BMI	-.002	.001	-1.675	0.097
SBP	3.673	.000	.182	0.856
DBP	.000	.000	.456	0.654
Hb	-.009	.002	-5.450	<0.001
Aetiology of CKD	.000	.002	.080	0.936

Dependent variable QTc

Abbreviations: BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, Hb; haemoglobin concentration, CKD; chronic kidney disease.

Figure 4

Table 4. Aetiology of kidney disease in the study population

Disease	Number	Percentage
Chronic glomerulonephritis	26	28.6
Diabetes mellitus	19	20.9
Hypertension	16	17.6
HIV	6	6.6
Obstructive uropathy	3	3.3
ADPKD	1	1.1
Unknown	20	22.0
Total	91	100

Abbreviations. HIV; human immunodeficiency virus, ADPKD; autosomal dominant polycystic kidney disease

DISCUSSION

CORRECTED QT INTERVAL IN CHRONIC KIDNEY DISEASE.

In this study, about 60% of predialysis patients with CKD at first evaluation on presentation to the hospital had prolonged QTc intervals. This prolonged QTc was observed in CKD stages 3 to 5 indicating that the abnormality exists long before patients get to ESRD. Earlier studies had demonstrated prolonged QT interval in dialysis patients who already had advanced disease [21-23]. The presence of prolonged QTc has not been well documented in early CKD.

FACTORS RELATED TO THE PRESENCE OF PROLONGED QTC

In this study, of all the variables tested (age, gender, body mass index, systolic blood pressure, diastolic blood pressure, haemoglobin concentration, serum calcium, serum phosphate, calcium-phosphate product, and cause of CKD) only SBP, DBP, BMI, aetiology of CKD and Hb showed any correlation with abnormal QTc. Of significance is that serum calcium, phosphate or calcium-phosphate product did not show and association with QTc. Earlier studies[24, 25] had indicated that the QT interval and QT dispersion correlate with serum calcium and potassium. These studies were on dialysis patients with hypocalcaemia and hyperkalaemia and the correction of these electrolyte abnormalities affected the QT interval and dispersion. The patients in this study were not on dialysis and had relatively normal serum calcium levels with a mean of 2.21±0.14 mmol/L. Similarly the mean potassium levels for patients (4.62±0.85 mmol/L), and control subjects (4.23±0.42 mmol/L) were within normal range.

CONCLUSION

This study has shown a high prevalence of prolonged QTc in predialysis CKD patients compared to normal control subjects in a single centre tertiary hospital in Nigeria. This abnormality was seen as early as CKD stage 3 and persisted through stages 4 and 5 CKD. The QTc abnormality in predialysis CKD in this study correlated with blood pressure, BMI, and haemoglobin concentration. Of all these only haemoglobin concentration predicted the presence of prolonged QT interval.

LIMITATIONS OF THE STUDY

There were small numbers of patients in CKD stages 3 (3%) and 4 (23%) in this study. Majority of the patients were in CKD stage 5. This may have affected the high prevalence of abnormal QTc in these stages of CKD (67% for CKD stage 3 and 62% for CKD stage 4). Still, this shows the presence of abnormal QTc before ESRD.

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Author Information

Chinwuba K Ijoma
Department of Medicine, Renal Unit, University of Nigeria Teaching Hospital

Ifeoma I Ulasi
Department of Medicine, Renal Unit, University of Nigeria Teaching Hospital

Benedict C Anisiuba
Department of Medicine, Cardiology Unit, University of Nigeria Teaching Hospital