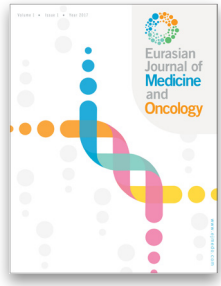
EJMO

DOI: 10.14744/ejmo.2017.55264
EJMO 2017;1(1):19–24



Research Article

The Association Between Corrected QT Dispersion and Iron Parameters in Hemodialysis Diseases

Bulent Erdogan,[1] Zerrin Ozturk Erdogan,[2] Haluk Savli[3]

[1]Deparment of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Turkey
[2]Deparment of Internal Medicine, Edirne State Hospital, Edirne, Turkey
[3]Department of Internal Medicine, Abant Izzet Baysal University Faculty of Medicine, Bolu, Turkey

Abstract

Objectives: Anemia is one of the most common complications to occur in hemodialysis patients. Blood transfusions to correct anemia can result in iron accumulation in the parenchymal tissues. Iron accumulation in the heart leads to fibrosis in the myocardium. The aim of this study was to determine the association between corrected QT dispersion (QTcd) and serum iron parameters in patients with end-stage renal disease.

Methods: A total of 80 subjects (60 patients and 20 healthy) were enrolled in the study. Patients were receiving hemodialysis treatment 3 times a week with regular erythropoietin and iron replacement at least once a year. Patients with cardiac insufficiency; diabetes mellitus; ischemic heart disease diagnosed with effort test or coronary angiography; any acute infectious disease; branch block on electrocardiogram (ECG); arrhythmia, such as atrial fibrillation, bradycardia, or tachycardia; patients using any drug that affects QT interval; and patients with electrolyte disturbances were excluded. Blood sample was taken and ECG recordings were made 1 day after routine hemodialysis to ensure that the patient's laboratory tests and ECG parameters were not affected by acute metabolic effects of dialysis. Patients whose corrected QT (QTc) interval was calculated in at least 9 derivations were included in the study. QTcd was measured by calculating the difference between the longest QTc interval and the shortest QTc interval.

Results: The hematocrit and hemoglobin levels of patients were statistically lower than those of the control group ($p<0.05$ for both). Serum iron level and percent transferrin saturation index were similar between groups. Ferritin level of the patients was statistically higher than the ferritin level of the control group ($p<0.01$). On the other hand, the total iron binding capacity level of the patient group was statistically significantly lower compared with the total iron binding capacity level of the control group ($p<0.01$). The longest QT interval of the patients was statistically significantly longer compared with the control group ($p<0.01$). There was no statistically significant difference between the 2 groups with normal and longer corrected QT dispersion (QTcd) in terms of dialysis duration or age ($p>0.05$). QTcd was not significantly correlated with age, duration of dialysis, calcium, potassium, iron, or ferritin level ($p>0.05$ for all). A statistically significant correlation was only found between QTcd and transferrin saturation index ($r=0.254$; $p<0.05$).

Conclusion: The hemodialysis patients had a longer QTcd compared with individuals with normal renal function in our study. A positive correlation was detected between the transferrin saturation index and QTcd. Iron replacement therapy should be administered more carefully and reduced iron concentration and transferrin saturation index should be targeted in hemodialysis patients with QTcd longer than 50 milliseconds.

Keywords: Corrected QT, ferritin, hemodialysis patient, serum iron, transferrin saturation index

Cite This Article: *Erdogan B, Ozturk Erdogan Z, Savli H. The Association Between Corrected QT Dispersion and Iron Parameters in Hemodialysis Diseases. EJMO. 2017; 1(1): 19-24*

Address for correspondence: Bulent Erdogan, MD. Trakya universitesi Tip Fakultesi, Tibbi Onkoloji Anabilim Dali, Edirne, Turkey
Phone: +90 284 236 49 81 **E-mail:** berdoga@hotmail.com
Submitted Date: June 09, 2017 **Accepted Date:** July 24, 2017 **Available Online Date:** August 03, 2017

Chronic renal failure is defined as the loss of renal function due to progressive and irreversible loss of nephrons arising from various causes. Hemoglobin level below 12 g/dL[1] in patients with renal insufficiency is defined as anemia. Renal anemia is a frequently encountered issue among patients with renal failure who receive hemodialysis, and the main reason underlying this fact is the lack of erythropoietin.[2] Iron deficiency contributes to shortened erythrocyte life span, severe hyperparathyroidism, aluminum toxicity, and anemia due to folate deficiency. Treatment is not recommended if the hemoglobin value does not fall below 10 g/dL in renal patients.[1] Erythropoietin treatment is necessary to treat renal anemia; the patient needs to have sufficient iron stores since the iron requirement of bone marrow will increase with the start of erythropoietin treatment.

Iron deficiency is observed in 25% to 37.5% of patients with renal anemia.[3] Iron replacement is frequently provided to hemodialysis patients. Repeated blood transfusions and uncontrolled iron replacement lead to secondary hemosiderosis. The accumulation of iron in myositis leads to heart damage. Iron loading can lead to restrictive cardiomyopathy. The clinical picture progressing to heart failure can be corrected only with effective chelation therapy. However, iron accumulation in the cardiac conduction system (His bundle and Purkinje system) leads disturbances in signal transduction, thereby causing severe cardiac arrhythmias. Arrhythmia may lead to sudden cardiac death.

The regional disparity in QT distance is associated with the conduction speed of the ventricular conduction system. The difference between the longest QT distance on the ECG and the shortest QT distance is called QT dispersion (QTd), and when corrected QT (QTc) lengths are utilized, it is called the corrected QT dispersion (QTcd). The normal range of this difference is 40 to 50 milliseconds.[4] As the QT dispersion increases, ventricular repolarization homogeneity decreases, and therefore, ventricular instability also increases.[5] An inhomogeneous conduction speed in different parts of the ventricles or repolarization may lead to serious ventricular arrhythmias by means of reentry mechanism or sudden cardiac death.[6]

The aim of this study was to determine the iron parameters of patients with end-stage renal disease (ESRD) and the association between iron and QTcd showing regional heterogeneity in myocardial repolarization.

Methods

Patient Selection

This study was a prospective, matched case-control study. Approval for the research was received from the ethics committee. The Helsinki Declaration principles were observed during the study. Sixty patients aged between 20 and 75 years who had been receiving hemodialysis 3 times a week for at least 1 year due to ESRD and who were regularly given parenteral iron and recombinant human erythropoietin were included.

All patients included in the study were evaluated using anamnesis, physical examination, and ECG. Any patient with cardiac insufficiency; diabetes mellitus; ischemic heart disease diagnosed with effort test or coronary angiography; any acute infectious disease; branch block on ECG; arrhythmia, such as atrial fibrillation, bradycardia, or tachycardia; use of any drug that affects QT interval; or any electrolyte disturbance was excluded.

Blood samples were taken and ECG recordings were made 1 day after routine hemodialysis in order that the patient's laboratory tests and ECG parameters not be affected by acute metabolic effects of dialysis. Fasting blood samples were taken and 12-channel ECG recordings were made in the morning to examine level of hemoglobin, iron, total iron binding capacity, ferritin, creatinine, blood urea nitrogen, sodium, potassium, calcium, phosphorus, albumin, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). The transferrin saturation index was calculated as a percentage using the formula x100.

Twenty healthy subjects with no known systemic disease, using no medication, having received no previous iron replacement therapy, and with similar age and gender characteristics were included in the control group. All of the same laboratory tests and ECG recordings were performed for the patients in the control group.

QT Measurement

Twelve-lead ECG recordings of the patients for QT interval measurement were made 1 day after hemodialysis. ECG recordings were made at 25 mm/second and 10 mm/mV magnitude with a Cardiopet 500 recorder (PETAŞ Profesyonel Elektronik Sanayi ve Ticaret A.Ş., Ankara, Turkey). The distance from the beginning of the Q wave to the last point where the T wave returned to the isoelectrical line was measured in milliseconds as the QT interval. The lowest point between the T and U waves in ECGs with U waves was considered the end of the T wave. When the end of the T wave could not be precisely determined, the reading was not analyzed. The QTc interval was calculated using the Bazzet formula ($QT/\sqrt{RR}$) according to heart rate 26. The average of the QTc interval of 3 consecutive beats in each derivation was taken as the QTc interval of that derivation. Patients whose QTc interval was calculated in at least 9 derivations

Table 1. Laboratory data of hemodialysis patients (n=60)

	Mean	SD
Systolic blood pressure (mmHg)	131.08	21.57
Diastolic blood pressure (mmHg)	76.25	11.59
Heart rate (beats/minute)	79.10	11.52
Glucose (mg/dL)	86.16	20.47
BUN (mg/dL)	54.51	19.84
Creatinine (mg/dL)	6.66	2.07
LDL cholesterol (mg/dL)	99.60	37.96
Triglyceride (mg/dL)	169.55	110.27
HDL cholesterol (mg/dL)	46.97	13.24
Total cholesterol (mg/dL)	177.73	44.61
Albumin (g/dL)	4.17	0.56
Sodium (mEq/L)	138.18	3.20
Potassium (mEq/L)	5.08	0.77
Calcium (mg/dL)	9.26	0.79
Phosphorus (mg/dL)	4.64	1.44
Calcium-phosphorus	43.19	14.88
C-reactive protein (mg/dL)	5.85	11.20
Hematocrit (%)	34.75	4.45
Hemoglobin (g/dL)	11.30	1.48
Serum iron (µg/dL)	67.17	25.94
Total iron binding capacity (µg/dL)	221.27	37.74
Transferin saturation index (%)	30.97	12.68
Ferritin (ng/mL)	726.74	441.05

SD: Standard deviation; BUN: Blood urea nitrogen; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

were included in the study. The QTcd was measured by calculating the difference between the longest QTc interval and the shortest QTc interval. QTcd over 50 milliseconds was considered to be abnormal. All measurements were made manually.

Statistical Analysis

The SPSS for Windows, Version 10.0 (SPSS Inc., Chicago, IL, US) program was utilized for the statistical analyses of the findings. Student's t-test was employed for intergroup comparisons of parameters that showed normal distribution in the comparison of descriptive statistics (mean, SD) as well as quantitative data, while the Mann-Whitney U test was used for intergroup comparisons of parameters that did not show normal distribution. Chi-square test was used to compare qualitative data. Spearman's rho correlation test was used to examine the relationship between parameters. The results were evaluated in a 95% confidence interval and significance was evaluated at the level of $p<0.05$.

Results

Sixty patients, 36 of whom were female and 24 of whom were male, with hemodialysis duration of 40.85±29.56 months were included in the study. The mean age of the patients was 51.40±15.58 years. In addition, a total of 20 healthy individuals, 11 of whom were female and 9 of whom were male, were included in the study as a control group. The mean age of the control group was 47.2±15.49 years. The laboratory data of the hemodialysis group are summarized in Table 1.

Comparison of the iron status of the hemodialysis group and the control group is provided in Table 2. The hematocrit level of the patients was statistically significantly lower compared with the hematocrit and hemoglobin levels of the control group ($p<0.01$). Total iron binding capacity level of the patient group was statistically significantly lower than that of the control group ($p<0.01$). There was no statistically significant difference between groups in the transferrin saturation index ($p>0.05$). The ferritin level of the patients was statistically significantly higher compared with the ferritin level of the control group ($p<0.01$).

A comparison of the QT interval measurements of the hemodialysis and control groups is presented in Table 3. The longest QT interval (QT_{max}) of the patients was statistically significantly longer compared with that of the control group ($p<0.01$). The longest QTc interval (Qtc_{max}) and the shortest QTc interval (Qtc_{min}) of the patients were statistically significantly higher compared with that of the control group ($p<0.01$). The QTd of the patient group was signifi-

Table 2. Comparison of the iron status of hemodialysis patient and control groups

	Patient group (n=60)		Control group (n=20)		Test value; p
	Mean	SD	Mean	SD	
Hematocrit (%)	34.75	4.45	39.97	3.20	t: -4.839; p: 0.001**
Hemoglobin (g/dL)	11.30	1.48	13.56	1.27	Z: -5.086; p: 0.001**
CRP (mg/dL)	5.85	11.20	0.30	0.22	Z: -6.168; p: 0.001**
Serum iron (µg/dl)	67.17	25.94	74.10	18.18	t: -1.106; p: 0.272
TIBC (µg/dL)	221.27	37.74	275.60	43.09	t: -5.381; p: 0.001**
Transferin saturation index (%)	30.97	12.68	27.32	7.54	t: 1.213; p: 0.229
Ferritin (ng/mL)	726.74	441.05	69.25	24.53	t: 6.774; p: 0.001**

SD: Standard deviation; t: Student's t-test; Z: Mann-Whitney U test. Significance level: * p<0.05; ** p<0.01. CRP: C-reactive protein; TIBC: Total iron binding capacity.

Table 3. Comparison of QT interval and dispersion of hemodialysis patient and control groups

	Patient group (n=60)		Control group (n=20)		Test value; p
	Mean	SD	Mean	SD	
Qt_{max} (ms)	390.68	43.13	363.50	16.94	Z: -2.917; p: 0.004**
Qt_{min} (ms)	344.60	37.40	328.50	15.31	Z: -1.745; p: 0.081
Qtc_{max} (ms)	445.38	33.36	407.05	19.75	t: 6.215; p: 0.001**
Qtc_{min} (ms)	389.28	32.57	366.90	17.21	t: 3.927; p: 0.001**
QTd (ms)	46.08	17.40	35.00	6.07	Z: -2.513; p: 0.012*
QTcd (ms)	56.10	20.67	40.15	6.97	Z: -3.357; p: 0.001**

SD: Standard deviation; t: Student's t-test; Z: Mann-Whitney U test. Significance level: * p<0.05; ** p<0.01.

Table 4. Comparison of clinical characteristics of the patients with normal and increased QTcd interval

	Normal QTcd (n=31)		Increased QTcd (n=29)		Test value; p
	Mean	SD	Mean	SD	
Dialysis duration (months)	39.81	30.90	41.97	28.57	t: 0.280; p: 0.780
Age (years)	52.26	13.66	50.48	17.61	t: -0.438; p: 0.663
Creatinine (mg/dL)	8.65	2.07	10.08	3.55	t: 0.352; p: 0.725
LDL cholesterol (mg/dL)	103	39	95	36	t: -0.892; p: 0.375
Total cholesterol (mg/dlL	184	47	170	41	t: -1.187; p: 0.240
Albumin (g/dL)	4.16	0.44	4.18	0.66	t: 0.145; p: 0.884
Potasium (mEq/L)	4.88	0.63	5.29	0.849	t: 2.081; p: 0.051
Calcium (mg/dL)	9.22	0.94	9.31	0.59	t: 0.410; p: 0.682
C-reactive protein (mg/dL)	8.30	15.01	3.24	3.06	t: -1.777; p: 0.081
Hemoglobin (g/dL)	11.31	1.55	13.36	1.45	t: 0.135; p: 0.893
Serum iron (µg/dL)	59.42	22.69	75.45	27.00	t: 2.495; p: 0.015*
Transferin saturation index (%)	27.61	11.58	34.56	13.02	t: 2.187; p: 0.033*
Ferritin (ng/mL)	632.92	385.69	836.62	466.04	t: 1.849; p: 0.070

SD: Standard deviation; LDL: Low-density lipoprotein; QTcd: corrected QT dispersion. t: Student's t-test; Z: Mann-Whitney U test. Significance level: *p<0.05; **p<0.01.

cantly longer compared with that of the control group (p<0.05); the QTcd of the control group of the patients was statistically significantly higher compared with that of the control group (p<0.01).

Table 4 illustrates the comparison of patients with increased QTcd and those with normal QTc dispersion. There was no statistically significant difference between the 2 groups of normal and increased QTcd in terms of dialysis duration or age (p>0.05). There was no statistically significant difference between patients with normal QTcd and increased QTcd in terms of creatinine, LDL, total cholesterol, albumin, potassium, calcium, CRP, hemoglobin and ferritin values (p>0.05). Transferrin saturation index and iron level were higher in patients with increased QTcd compared with those with normal QTcd, and this was statistically significant (p<0.005). The potassium level in the increased QTcd group was determined to be almost significantly high (p=0.051). Though CRP values were different, it was statistically insignificant inasmuch as the SD in patients with normal QTcd was higher.

Table 5. The relationship between QTcd and age, dialysis duration, serum calcium, potasium, iron, ferritin, and transferin saturation index

Hemodialysis group	QTcd	
	r	p
Age (years)	0.149	0.254
Dialysis duration (months)	0.046	0.727
Calcium (mg/dL)	0.008	0.947
Potassium (mEq/L)	0.203	0.119
Serum iron (µg/dL)	0.221	0.088
Transferin saturation index (%)	0.254	0.049*
Ferritin (ng/mL)	0.164	0.210

r: Spearman's rho test; * p<0.05 significance level. QTcd: Corrected QT dispersion.

The relationship between QTcd and calcium, potassium, iron, ferritin, transferrin saturation index, and duration of dialysis treatment of all the patients in the hemodialysis group is examined in Table 5.

No statistically significant relationship was determined in Spearman's rho correlation test between QTcd and age, duration of dialysis, calcium, potassium, iron, and ferritin levels ($p>0.05$); however, a statistically significant relationship was found between QTcd and the transferrin saturation index ($r=0.254$; $p<0.05$).

Discussion

Cardiac complications like heart failure, pericarditis, coronary artery disease, and cardiac arrhythmias are frequently observed in hemodialysis patients. The most frequent cause of death in this group of patients is for cardiovascular reasons.[7] The increase in QTd is related to mortality and morbidity arising from cardiovascular causes.[8] We found that hemodialysis patients had a longer QTcd compared with those with normal renal function.

Anemia is a common complication in hemodialysis patients. Hemodialysis patients were observed to have lower hemoglobin and hematocrit values than the control group in our study. Causes of anemia in patients with chronic renal failure include erythropoietin decrease, iron deficiency, short life span of erythrocyte, inflammation, infection, and aluminum toxicity.[9] Concealed blood loss from the gastrointestinal tract, inadequate iron ingestion in the diet, frequent blood tests, and losses during dialysis are some reasons for the lack of iron often present in this patient group. We observed that 2 of 3 patients included in this study were anemic.

It is advised to have a ferritin level of between 200 and 500 ng/mL and to maintain transferrin saturation above 20%, since resistance to erythropoietin treatment is seen in ESRD patients.[10] Patients were given recombinant human erythropoietin 3 times a week and parenteral iron therapy at least once every 2 weeks in our dialysis group to achieve these values. The transferrin saturation index and ferritin values were found to be higher and the iron levels were found to be lower in the hemodialysis group in this study; however, a difference could not be determined statistically. Only the high ferritin level was determined to be significant statistically ($p<0.001$). Serum ferritin levels may be high as an acute phase reactant due to the increased risk of infection and chronic inflammation in people receiving hemodialysis.[11] The CRP values of the patient group were significantly higher compared with the control group, which made us think of chronic inflammation. As such, the ferritin values in the patient group may not be exactly indicative of iron stores.

Many researchers have drawn attention to the relationship between cardiovascular disease and anemia in dialysis patients. Foley et al. detected that a hemoglobin value lower than 8.8 g/dL is associated with left ventricular dilatation, heart failure, and increased mortality, and that 1 g/dL reduction in hemoglobin value increases mortality independently of other factors.[12] Furthermore, QTd shows local heterogeneity in myocardial repolarization. Slowdown of conduction in the myocardial region or latency in potential action duration due to change in conduction causes local heterogeneity in repolarization. The greater the QTd, the less homogeneity of ventricular repolarization, and therefore, the ventricular instability is greater. Heterogeneous ventricular repolarization may lead to severe ventricular arrhythmia and sudden cardiac death by the reentry mechanism. Hemodialysis patients are known to have a prolonged QT interval, and it is also known that QT interval is associated with premature ventricular complexes.[13] Statistically significant long QT distances were also detected in the hemodialysis group compared with the control group ($p<0.001$) in our study. The normal range of QTcd is between 40 and 50 milliseconds. Individuals with QTcd of longer than 50 milliseconds have an increased risk for severe ventricular arrhythmias and sudden cardiac death.[14] QTcd elongation is present in most dialysis patients and it is known that greater QTd is associated with an increased risk of mortality due to cardiovascular and other causes of death.[15] QTcd was found to be statistically significantly higher in the hemodialysis group in this study ($p<0.001$).

When patients with an upper limit of QTcd longer than 50 milliseconds (29 patients) and shorter than 50 milliseconds (31 patients) in the hemodialysis group were compared with each other, no significant difference was found between the 2 groups in terms of age, duration of dialysis, LDL, total cholesterol, albumin, potassium, calcium, CRP, ferritin, or hemoglobin, though statistically significant difference was found in iron level and transferrin saturation index. On the other hand, while no statistically significant relationship was found between QTcd and age, duration of dialysis, potassium, calcium, iron, or ferritin was seen in the whole patient group ($p>0.05$); there was a statistically significant correlation between QTcd and transferrin saturation index at the level of 25.4% ($p<0.05$). No significant difference was observed in previous studies between QTd and dialysis duration and age.[16] It was also observed in study of Bavbek et al., who examined peritoneal dialysis patients, that increased iron stores were associated with prolonged QTd.[17]

Patients with prolonged QTd have higher levels of iron and transferrin saturation. Numerous studies have revealed the fact that iron overload plays a role in the pathogenesis of atherosclerosis and is associated with deaths related to coronary artery diseases.[18] Iron catalyzes the Haber-Weiss reaction and causes the formation of oxygen radicals. The resulting oxygen radicals lead to the formation of athero-

sclerotic plaque by lipid peroxidation and LDL cholesterol modification.[19] Iron accumulation in the myocardium impairs systolic and diastolic functions and causes an increase in oxidative stress.[20] Iron accumulation in the myocardium has a heterogeneous dispersion. Iron mostly accumulates in the left ventricle of the interventricular septum, as well as in the free wall, and less so in the right ventricle and atrium.[21] Heterogeneous iron deposition and the toxicity caused by iron oxygen radicals in the myocardium is the reason for increased QTd.

Hemodialysis patients in this study had a longer QTcd compared with individuals with normal renal function. No relationship between ferritin level and QTd was detected. It was observed that patients with QTcd longer than 50 milliseconds had a higher iron level and transferrin saturation index. A positive correlation between transferrin saturation index and QTcd was found. Iron replacement therapy should be performed more carefully and reduced iron concentration and transferrin saturation index should be targeted in hemodialysis patients with QTcd longer than 50 milliseconds.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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