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Association between nephropathy and QT dispersion in type 2 diabetic patients

Tip 2 diabetes hastalarında proteinüri ve QT dispersiyonu arasındaki ilişki

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Abstract

Aim: Due to increased diabetes and diabetes-related mortality all over the world, the importance of appropriate and readily available screening tests for diabetic patients is increasing. In this study, we investigated the relationship between urine protein/creatinine ratio and QT dispersion. We aimed to determine the association between nephropathy and autonomic neuropathy, the two significant complications of diabetes, through simple and achievable tests.

Methods: We retrospectively evaluated the medical records of 45 male and 50 female patients, who were attended at diabetes outpatient clinic with a diagnosis of type 2 diabetes in one month period. A 12-lead electrocardiogram (ECG), HbA1 and glucose levels were evaluated. Urinary protein/creatinine ratios (P/K) were measured at spot intervals. ECGs were transferred to the computer environment, and QT intervals were calculated and corrected for the patient's heart rate using Bazett's formula. QT-max (longest QT interval), QT-min (shortest QT interval) and QT-dispersion analyzes were performed in two groups, in all patients by excluding those with ischemic heart disease. The threshold value for proteinuria detection was 91 mg/g. Spot urine protein/creatinine ratio of less than 91mg/g was accepted as normal, and those with over 91mg/g were classified as proteinuric.

Results: The mean QT-min (388.50 ± 27.28 ms), QT-max (441.25 ± 29.76 ms) and QT dispersion (52,74 ± 16,80 ms) were significantly higher than the reference values in both groups-in all patients by excluding those with ischemic heart disease. When all cases and those with ischemic heart disease were excluded, QT dispersion value was higher in patients with proteinuria (those with urine P/K levels 91 mg/g and above). This difference was not statistically significant. (p> 0.05) In this study, we found that QT durations were long independent of cardiovascular disease in diabetic patients, but not associated with protein/creatinine ratio

Conclusion: As a result, in this study, we examined the relationship between spot urine protein/creatinine ratio and QT intervals in diabetic patients, and we did not find a significant association between the two parameters. Although there have been studies in the literature showing that there is a relationship between albumin/creatinine ratio and QT intervals, we could not find an association with P/K ratio.

Keywords: Proteinuria, QT dispersion, Urine protein creatinine ratio

Öz

Amaç: Tüm dünyada artan diyabet ve diyabete bağlı mortalite nedeniyle diyabet hastalarında uygun ve kolay ulaşılabilir tarama testlerinin önemi artmaktadır. Idrar protein/kreatinin oranı ve QT dispersiyonu arasındaki ilişkiyi araştırdığımız bu çalışmada amacımız diyabetin iki önemli komplikasyonundan nefropati ve otonom nöropati arasındaki ilişkiyi basit ve ulaşılabilir testler ile saptayabilmekti.

Yöntemler: Bir aylık süre içinde, tip 2 diyabet tanısı ile diyabet polikliniğine başvuran, 45 erkek, 50 kadın hastanın tıbbi kayıtları retrospektif olarak tarandı. Hastalara 12 derivasyonlu elektrokardiyogram (EKG), HbA1c, glukoz değerleri bakıldı. İdrar protein kreatinin oranı(P/K), spot idrar örneklerinden ölçüldü. EKG'ler bilgisayar ortamına aktarılarak QT süreleri hesaplandı ve kalp hızına göre Bazett formülü ile düzeltildi. QT-max (en uzun QT süresi), QT-min (en kısa QT süresi) ve QT-dispersiyonu analizleri tüm hastalar ve iskemik kalp hastalığı olanlar hariç tutularak iki grup olarak çalışıldı. Proteinüri için eşik değer 91mg/g olarak lındı. 91mg/g ve üzeri proteinüri , 91mg/g altında olanlar normal olarak gruplandırıldı.

Bulgular: Hastaların QT-min (388,50±27,28 msn), QT-max (441,25±29,76 msn) ve QT-dispersiyonu (52,74±16,80 msn) değerleri ortalaması iskemik kalp hastalığı olanlar çıkarılsa da referans değerlerden uzun bulundu. Hem tüm olgularda, hem de iskemik kalp hastalığı olan olgular hariç tutulduğunda idrar protein/kreatinin oranına göre, proteinürisi olanlarda (idrar P/K 91mg/g ve üzerinde olanlar), QT dispersiyon değerleri normal olanlara göre (idrar P/K 91 mg/g'dan az olanlar) daha yüksek bulundu. Bu fark istatistiksel olarak anlamlı saptanmamıştır (p>0,05). Çalışmamızda, QT sürelerinin diyabet hastalarında kardiyovasküler hastalıklardan bağımsız olarak uzun olduğunu ancak protein/kreatinin oranı ile anlamlı ilişkisi olmadığını tespit ettik.

Sonuç: Sonuç olarak, diyabetik hastalarda spot idrar protein/kreatinin oranı ile QT intervalleri arasındaki ilişkiyi incelediğimiz bu çalışmada iki parametre arasında anlamlı ilişki saptanamamıştır. Literatürde A/K oranı ile QT intervalleri arasında ilişki olduğunu gösteren çalışmalar bulunsa da P/K oranı ile ilişki saptayamadık.

Anahtar kelimeler: Proteinüri, QT dispersiyonu, İdrar protein kreatinin oranı

Introduction

Diabetes Mellitus (DM) is the fastest growing mortality and morbidity cause throughout the world over the last 20 years. Especially in developed and developing countries, the prevalence is increasing due to changing eating habits, industrialization, and a sedentary lifestyle. Diabetes is known to cause many serious complications such as coronary heart disease, chronic renal failure, and retinopathy. A multinational study by the World Health Organization (WHO) has shown that coronary heart disease, in patients with type 2 diabetes, was the most important cause of death [1]. The cause of 34% of deaths resulting from DM worldwide is coronary artery disease.

Cardiac autonomic neuropathy is a common complication, associated with increased mortality of diabetes. Increased cardiovascular death and neuropathy are associated with many systemic symptoms and functional decline [2,3]. Assessment of QT interval is an inexpensive method of determining the risk of high cardiovascular complications and sudden death. The prolonged QT and QT dispersion in the general population reflect the abnormality of ventricular myocardial repolarization. Diabetes itself a well-known cardiovascular risk factor continues to threat health even after normalization with other classical risk factors such as hypertension, dyslipidemia, smoking, homocysteinemia and lack of exercise. The QT interval adjusted for heart rate was reported to be significantly and independently associated with the presence and severity of cardiac autonomic neuropathy in diabetic patients [4]. QT interval and QT dispersion may be found to be prolonged in both hypoglycemia and hyperglycemia [5,6].

Proteinuria is considered both to be an independent risk factor for cardiovascular and renal diseases and to demonstrate the target organ damage [7]. In particular, the detection of elevated protein excretion in the urine is known to have diagnostic value in the detection of the onset of renal diseases, and the amount of protein elicited is used to assess the disease process and the efficacy of the treatment [8,9]. The National Kidney Foundation recommends regular screening of protein excretion in urine in patients at risk of developing the renal disease [10]. In practice, as a screening test, detection of proteinuria in strips is often used in spot urine, and protein determination in 24-hour urine samples is used as the gold standard for quantitative evaluation because of changes in urinary protein excretion during the day [11]. It was reported that there was a strong correlation between spot urine protein/creatinine ratio (P/K) and proteinuria at 24 h in the studies performed, and protein ablation could be used as a reliable indicator [11-14].

The aim of this study was to investigate the relationship between proteinuria and QT dispersion, indicated with nephropathy and autonomic neuropathy in diabetic patients, through achievable tests.

Materials and methods

The study was conducted between November and December 2013, in the Haseki Education Research Hospital Diabetes outpatient clinic. Among 200 patients followed up with a diagnosis of type 2 diabetes, those who were receiving medications that affect QT duration, with complete bundle branch block, atrial fibrillation and second or third-degree atrioventricular block were excluded. 50 females (52.6%) and 45 males (47.4%) eligible for the study protocol were included. The 12-lead ECG and biochemical examination including fasting blood glucose, HbA1c, creatinine, LDL, triglyceride, and spot urine protein/creatinine ratio were performed. The hospital records were reviewed for the presence of neuropathy, and retinopathy, and for the medications. The ECGs were scanned at high resolution and transferred to the computer as a jpeg file. Using the Adobe Photoshop CC (Adobe Inc., USA) program measurements were performed. From the beginning of the Q wave to the end of the T wave range was measured as QT interval. QT intervals corrected with Bazzet formula for heart rate. ($Qtc = QT / \sqrt{RR}$) Measured at least three QT intervals from each successive corridor. The difference between the longest QT (QTmax) and the shortest QT (QT min) was calculated as QT dispersion (Qtd). The measurements were checked by two different investigators. P/K were measured at spot intervals. The threshold value for proteinuria detection was 91 mg/g [15]. Spot urine protein/creatinine ratio of less than 91mg/g was accepted as normal, and those with over 91mg/g were classified as proteinuric.

Statistical analysis

The IBM SPSS Statistics 23 (IBM Ltd, USA) program was used for descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum). Student's t-test was used for two group comparisons of the parameters that showed a normal distribution. Mann Whitney U test was used for two group comparisons of the parameters that showed abnormal distribution. Pearson correlation analysis and Spearman correlation analysis were used to evaluate the inter-parameter relationships. The significance level was set at $p < 0.01$ and $p < 0.05$.

Results

Of the 95 patients included in the study, 52.6% (n = 50) were female, 47.4% (n = 45) were male. The ages of the patients ranged from 33 to 81 years with an average of 57.52 ± 10.47 years. Patients' diabetes duration ranged from 1 to 35 years with an average of 12.34 ± 7.11 years. Ischemic heart disease (coronary artery bypass grafts, coronary stent tissue) was present in 23.1% (n = 22) of all patients. QT-max, QT-min and QT-dispersion analyzes were performed in two groups, in all patients by excluding those with ischemic heart disease. Demographic characteristics are summarized in Table 1.

The mean QT-min (mean 388.50 ± 27.28 ms), QT-max (mean 441.25 ± 29.76 ms) and QT dispersion (mean 52.74 ± 16.80 ms) were significantly higher than the reference values in both groups. Corrected QT (QTc) was above 440 milliseconds (ms) in the majority of patients with untreated, genetically determined hereditary long QT syndrome. QTc in healthy controls was at 440-465 ms. These values were taken as the basic levels, and QTc values below 420 ms were strictly normal, values between 420-440 ms were at the limit, and QTc values above 440 ms were considered high [16,17].

Table 1: Demographic characteristics of patients

		All patients (n=95)		Excluding those with ischemic heart disease (n=73)	
		n	%	n	%
Gender	Female	50	52.6	42	57.5
	Male	45	47.4	31	42.5
Hypertension		58	61.1	36	49.3
Retinopathy		36	37.9	25	34.2
Neuropathy		49	51.6	33	45.2
		Min-Max	Mean±SD	Min-Max	Mean±SD
Age		33-81	57.52±10.47	33-80	56.04±10.73
DM duration		1-35	12.34±7.11	1-35	11.66±6.98
Plasma glucose		90-368	177.09±69.77	94-368	183.01±73.12
HbA1c		5.9-14.0	8.05±1.53	5.9-14.0	8.17±1.63
Urine P/K		0.0-2.5	0.32±0.47	0.0-2.5	0.35±0.53
LDL		35-225	114.56±36.93	35-225	114.29±35.38
Total cholesterol		91-309	189.84±43.48	91-309	189.90±43.38
Triglycerides		51-752	151.65±92.36	51-752	157.30±99.40
QT-max		391-533	441.25±29.76	391-529	440.57±29.99
QT-min		341-463	388.50±27.28	341-463	390.29±26.88
QT-dispersion		18-95	52.74±16.80	18-95	50.08±16.60

DM= Diabetes Mellitus,P/K= Urine protein/creatinine ratio, QT-max= longest QT, QT-min= shortest QT

There was no statistically significant correlation between QT dispersion value and DM duration, Hb1Ac, BUN, triglyceride and P /K ratio (p> 0.05 for all). A statistically significant negative correlation was found between QT dispersion value and LDL level at the level of 21.0% (R: - 0,215, p: 0,037, p <0.05).

In gender comparison, QT-max (447.36±33.98 msn in females, 434.47±23.28 msn in males) and QT-min (397.04±26.92 msn in females, 379.02±20.91 msn in males) values in women were significantly longer than those in men. QT dispersion was found to be longer in males than in females (50.33 ± 17.19 ms in females, 55.44 ± 16.22 ms in males), but this difference was not statistically significant. (P> 0.05)

When all cases and those with ischemic heart disease were excluded, QT dispersion value was higher in patients with proteinuria (those with urine P/K levels 91 mg/g and above). This difference was not statistically significant. (P> 0.05) (Table 2, 3). There was no significant relationship between QT values and neuropathy and retinopathy.

Table 2: QT-max, QT-min and QT-dispersion analyzes in all patients

(n=95)	Urine P/K		p
	Normal (n=25)	Proteinuric (n=70)	
QT-max	432.08±22.28	444.53±31.76	0.074
QT-min	382.48±20.07	390.66±27.33	0.175
QT dispersion	49.60±13.77	53.87±17.77	0.279

Student's t test

Table 3: QT-max, QT-min and QT-dispersion analyzes in those with ischemic heart disease were excluded

(n=73)	Urine P/K		p
	Normal (n=18)	Proteinuric (n=55)	
QT-max	434.00±20.16	442.35±31.79	0.312
QT-min	385.59±17.27	391.75±27.06	0.381
QT dispersion	48.41±11.28	50.60±17.58	0.631

Student's t test

Discussion

QT dispersion has been used frequently in recent years as a noninvasive and inexpensive method that reflects the repolarization heterogeneity of ventricular myocardium. The repolarization of the ventricles occurs in integrity. However, under normal conditions, repolarization does not start at the same moment throughout the entire ventricle and not at the same time. This is named as repolarization dispersion. In pathological conditions, homogeneity in repolarization deteriorates further and is detected as prolonged QT dispersion. QT interval abnormalities were associated with coronary artery disease, left ventricular hypertrophy, blood pressure, autonomic dysfunction and metabolic syndrome. There are also studies showing the relationship between microalbuminuria and QT interventions in patients with type 1 and type 2 diabetes [14,18]. In a study comparing healthy individuals with impaired fasting glucose, no difference was found in QT dispersion, but QT changes between heart rates were found to be higher in the group with impaired glucose tolerance [19].

In this study, all patients were selected from diabetic individuals and the mean QT values of the patients were found to be longer than the reference interval. However, due to the absence of a control group, the contribution of other parameters is not known. Twenty-two (23.1%) of our patients had ischemic heart disease (coronary artery bypass graft or coronary angiography stenosis and stent). Since it is known that ischemic heart diseases affect QT intervals, statistical analyzes were performed for both all patients and excluding those with ischemic heart disease. QT periods were also found to be longer when patients with ischemic heart disease were excluded. This is consistent with the literature that diabetes affects the QT interval independently of cardiovascular complications [20,21].

In our study, we aimed to investigate the relationship between QT intervals and urinary protein creatinine ratio in type 2 diabetic patients. Despite studies done with the ratio of albumin/creatinine in the literature, there is no study with more commonly used protein/creatinine ratio. In recent years, the use of spot urine P/K ratio has become widespread as it is more advantageous than the measurement of albumin/creatinine ratio due to cost and availability. Some researchers have found that there is a strong correlation between spot urine P/K ratio and 24-hour urinary protein levels, but these two tests cannot be used interchangeably [22]. However, in many studies, different threshold values of P/K ratio have been determined. This is why researchers should try to set different thresholds for different clinical situations. In a study conducted by Yamamoto et al., The P/K ratio and the albumin/creatinine ratio were compared to find that the 91 mg/g threshold value for the total P/K ratio measured in the spotting of microalbuminuria in diabetic patients was 90.8% sensitive and 91.9% specific [15]. In this study, 91 mg/mg value was accepted as the threshold value for microalbuminuria. There was no statistically significant difference in the proteinuria between the normal (n = 25) and proteinuric (n = 70) groups while QT intervals were longer in the proteinuria group. Previous studies suggest a relationship between microalbuminuria and QT dispersion in studies using albumin/creatinine ratio. Psallas et al., in their research of QT dispersion and microalbuminuria in patients with type 1 and type 2 diabetes, found that patients with type 2 diabetes had significantly higher QT dispersion of microalbuminuria as an independent indicator. In a study comparing 63 type 1 diabetes, 121 type 2 diabetes and healthy control groups, QT dispersion was found to be significantly longer in those with microalbuminuria in the type 2 diabetes group. It is argued that microalbuminuria is the most reliable predictor of QT dispersion in patients with type 2 diabetes [18]. Rutter et al. [23] compared microalbuminuric and normoalbuminuric groups regarding QT dispersion, and QTmax

was found to be longer in the microalbuminuric group and QT dispersion was found to be similar. As a result of this study, it was commented that the QT intervals were changed by microalbuminuria-related blood pressure and Factor XIIa rather than albumin excretion. In these two studies, Albumin/creatinine ratio was used as the microalbuminuria test.

In our study, significant differences were found between QT intervals between male and female groups. QTmin and QTmax values were found to be longer in female patients than in males. QT dispersion was longer in men, but the difference was not statistically significant. In all studies on gender, it was shown that QT interval is longer in females. In women, accordingly, long QT syndrome and associated clinical situations such as QT prolongation induced by drug have been found to be higher risk than men [24,25].

In our study, patients' QT-max and QT-min values were positively correlated with HbA1c, a statistically significant relationship was determined. In a study conducted on 27 healthy volunteers and examining the effect of acute hyperglycemia on the QT interval, acute hyperglycemia was found to increase both QT max duration and QT dispersion [6]. The authors suggested that in addition to the mechanisms that cause QT interval prolongation in diabetic patients, hyperglycemia may also be a contributing mechanism. In another study, QT distances were measured in patients admitted to the hospital with the new diagnosis of diabetes and hyperglycemia, pre-treatment and after normoglycemia with insulin treatment. The QTmax and QTdispersion distances before treatment were significantly high. There was no significant change in QTmax and QTdispersion durations after treatment, but QTdispersion durations after treatment were significantly longer compared to the healthy control group [26]. In a study from Turkey to investigate the relationship between QT and blood glucose changes, hypoglycemia and hyperglycemia were associated with prolonged QT and QT dispersion [27]. These results demonstrate the importance of optimal glycemic control regarding cardiovascular mortality.

The limitation of this study is that, the study was conducted retrospectively and we did not have a control group. Due to the absence of a control group, the contribution of parameters that could affect QT duration is not known.

As a result, in this study, we examined the relationship between spot urine protein/creatinine ratio and QT intervals in diabetic patients, and we did not find a significant association between the two parameters. Although there have been studies in the literature showing that there is a relationship between albumin/creatinine ratio and QT intervals, we could not find an association with P/K ratio. Because the P/K ratio is inexpensive, readily applicable and achievable test for determining microalbuminuria, we believe that comprehensive studies can be performed.

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