

# Evaluation of the Relationship Between Microalbuminuria/Creatinine Ratio and QTc Dispersion in Type 2 Diabetes Mellitus



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## Abstract

**Objective:** The assessment of QTc dispersion (QTd) is of importance in determining the risk of ventricular arrhythmias and cardiac autonomic neuropathy (CAN) in patients with diabetic nephropathy (DN). Our study explored the relationship between the microalbumin/creatinine (MA/crea) ratio and QT(cd) in the context of CAN development in DN.

**Material and Methods:** We selected fifty individuals with a spot urine MA/crea ratio of less than 30 as the control group and fifty individuals with an MA/crea ratio between 30 and 300 as the patient group. QT intervals were calculated using the Bazett formula, taking into account the heart rate.

**Results:** In contrast to the control group, the patient group exhibited a considerably higher median QTc min value (380.63 msn, 361.44–397.30, p: 0.042) and a statistically significant increase in the median QTc max value (439.98 msn, 420.17–460.22, p=0.005). Furthermore, the median MA/crea value (82, 60–300, p<0.0001) was found to be highly significant. However, the median QT(cd) value (61.25 ms, 49.91–81.70, p=0.066) was only marginally significant, with no statistically significant difference between the two groups. It is worth noting that both groups showed a significant difference in terms of QTd (p<0.001). In the control group, where DN had not yet developed, the QT(cd) value could be detected before an increase in the MA/crea value.

**Conclusion:** The findings that both the control group and the patient group exhibited elevated QTcd values suggest that this parameter may be a viable predictor of cardiovascular risk. Furthermore, it is conceivable that QTcd could serve as an early warning sign for cardiovascular risk in diabetic patients who have not yet reached the stage of microalbuminuria.

**Keywords:** QT dispersion; Urine microalbuminuria/creatinine ratio; Diabetes mellitus; International Diabetes Federation; ECG screening

**Abbreviations:** QTd: QTc dispersion; CAN: Cardiac Autonomic Neuropathy; DN: Diabetic Nephropathy; MA/crea: Microalbumin/creatinine; IDF: International Diabetes Federation; ECG: Electrocardiography; MA: Microalbuminuria; BMI: Body Mass Index; FBS: Fasting Blood Sugar; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; TG: Triglycerides; HbA1c: Hemoglobin A1c; TSH: Thyroid-Stimulating Hormone

## Introduction

Per the International Diabetes Federation (IDF), in the year 2007, 246 million people worldwide were diagnosed with diabetes, and an astonishing 46% of them fell within the middle-aged group (40–59 years). If no preventive measures are implemented, it is anticipated that by 2025, the diabetic population will reach 380 million, representing a 55% increase. The lifetime risk of developing diabetes for individuals born in 2000 in the United States is 33% [1]. The primary causes of increased mortality and morbidity in diabetic patients are microvascular and macrovascular complications, with coronary

artery disease and cardiac autonomic neuropathy associated with sudden death and ventricular arrhythmias [2].

Cardiac autonomic neuropathy (CAN) is a condition that can present with various clinical manifestations such as resting tachycardia, orthostatic hypotension, tachycardia-bradycardia episodes, silent myocardial infarction, exercise intolerance, and sudden cardiac death [3]. This condition can go undetected in diabetic patients due to damage to the heart's circulation and nervous system. However, a readily available and inexpensive test, electrocardiography (ECG), can predict the presence of CAN

by calculating the difference between the longest and shortest QT intervals, known as QT dispersion (QTcd) [4]. Studies have shown a high incidence of sudden cardiac death due to malignant ventricular arrhythmias in patients with prolonged QT intervals, either congenital or acquired. The development of CAN is caused by an imbalance in the parasympathetic and sympathetic systems in patients with diabetes, leading to cardiac arrhythmias and cardiac death [5]. The evaluation of the QT interval is a simple and cost-effective method that can predict the risk of cardiovascular complications and sudden death. QT dispersion has been shown to reflect electrical disturbances related to autonomic dysfunction and can serve as a prognostic marker of cardiac mortality in many studies [6].

Microalbuminuria (MA) is detected in approximately 25% of patients with diabetes, and the mortality rate from coronary artery disease is twice as high for those patients who test positive for MA. The prevalence of MA is particularly high among asymptomatic patients with type 2 diabetes and silent myocardial ischemia. The presence of MA is a significant predictor of coronary artery disease in asymptomatic patients with type 2 diabetes [7]. In diabetic patients without known or undetected cardiac disease, MA positivity is associated with impaired myocardial systolic and diastolic functions, and increased QTd, CAN, and left ventricular mass index [8].

There is a growing trend towards the use of non-invasive, convenient, and cost-effective diagnostic tests for diagnosis, monitoring, and mortality detection. In our clinic, we decided to investigate the relationship between the spot urine MA/creatinine ratio of type 2 DM patients that we were monitoring and QTd.

## Materials and Methods

In this study, the archived files of patients who had initially received a diagnosis of type 2 Diabetes at Istanbul Education and Research Hospital Diabetes Clinic were retrospectively examined. The researchers randomly selected 50 patients with a microalbumin/creatinine ratio of less than 30, aged between 36 and 77 years, as the control group. The patient group, which consisted of 50 individuals with a microalbumin/creatinine ratio between 30 and 300, aged between 36 and 79 years, was selected based on the exclusion and inclusion criteria. The study excluded patients with a history of heart failure, heart valve surgery, ischemic heart disease, coronary bypass, ischemic heart disease based on ECG criteria, acute myocardial infarction, bundle branch block, arrhythmia, use of medications that could cause QT prolongation (probuco, amiodarone, erythromycin, clarithromycin), electrolyte disturbances (excluding Na: 125-145meq, K: 3.5-5.5meq, Ca: 8.3-10.6 meq), and serum creatinine value >2. The researchers included the patients' diabetes duration, microalbumin/creatinine ratio, 12-lead ECG recordings, body mass index (BMI), fasting blood sugar (FBS), high-density

lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), total cholesterol, hemoglobin A1c (HbA1c), and thyroid-stimulating hormone (TSH) levels in the study.

## Measurement of QT Dispersion (QTd)

Twelve-lead ECG recordings were collected using the PETAŞ Kardiopet 500 device at a speed of 25 mm/s and a width of 10 mm/mV. The ECG scans were conducted at a high resolution of 300 dpi and saved in JPEG format. The Macromedia Freehand 9 software was utilized for measurements. The QT interval was measured in milliseconds, which is the time from the start of the Q wave to the point where the T wave returns to the isoelectric line. In cases where a U-wave was present, the lowest point between the T- and U-waves was taken as the end of the T-wave. If the end of the T-wave could not be determined accurately, the derivation was not analyzed. The corrected QT interval (QTc) was calculated using the Bazett formula based on the heart rate. The average of the corrected QT (QTc) intervals of three consecutive beats in at least nine derivations was considered as the QTc interval of that derivation. QTc dispersion, which is the difference between the longest and shortest QTc intervals, was measured to assess abnormalities. Those with a QTc dispersion of more than 50 ms were considered abnormal.

## Statistical Analysis

The statistical analysis was carried out using the SPSS 11.5 software. To assess the normality of continuous variables, the Kolmogorov-Smirnov test was employed. Variables exhibiting a Gaussian distribution were reported as mean  $\pm$  SD, while those with a non-Gaussian distribution were presented as medians (25th percentile-75<sup>th</sup> percentile). For comparisons between groups of variables with normal distribution, the Student's t-test was used, while the Mann-Whitney U test was utilized for variables with non-normal distribution. The relationships between variables were investigated using Spearman's correlation coefficient (r). Statistical significance was set at  $p < 0.05$  (two-tailed).

## Results

Our study included a total of 100 type 2 diabetes mellitus patients who were followed up as outpatients at the Istanbul Education and Research Hospital Diabetes Clinic. These patients were divided into two groups based on their microalbumin/creatinine ratios. The control group comprised 50 patients with a microalbumin/creatinine ratio of between 0-30, an average age of 54 years, and a diabetes duration of 8 years. Of these, 26 were female (52%) and 24 were male (48%). The patient group consisted of 50 patients with a microalbumin/creatinine ratio of between 30-300, an average age of 56 years, and a diabetes duration of 10 years. Among them, 28 were female (56%) and 22 were male (44%) (Table 1).

**Table 1:** Statistical Comparisons of Demographic and Clinical Characteristics and Laboratory Data of the Patient and Control Groups.

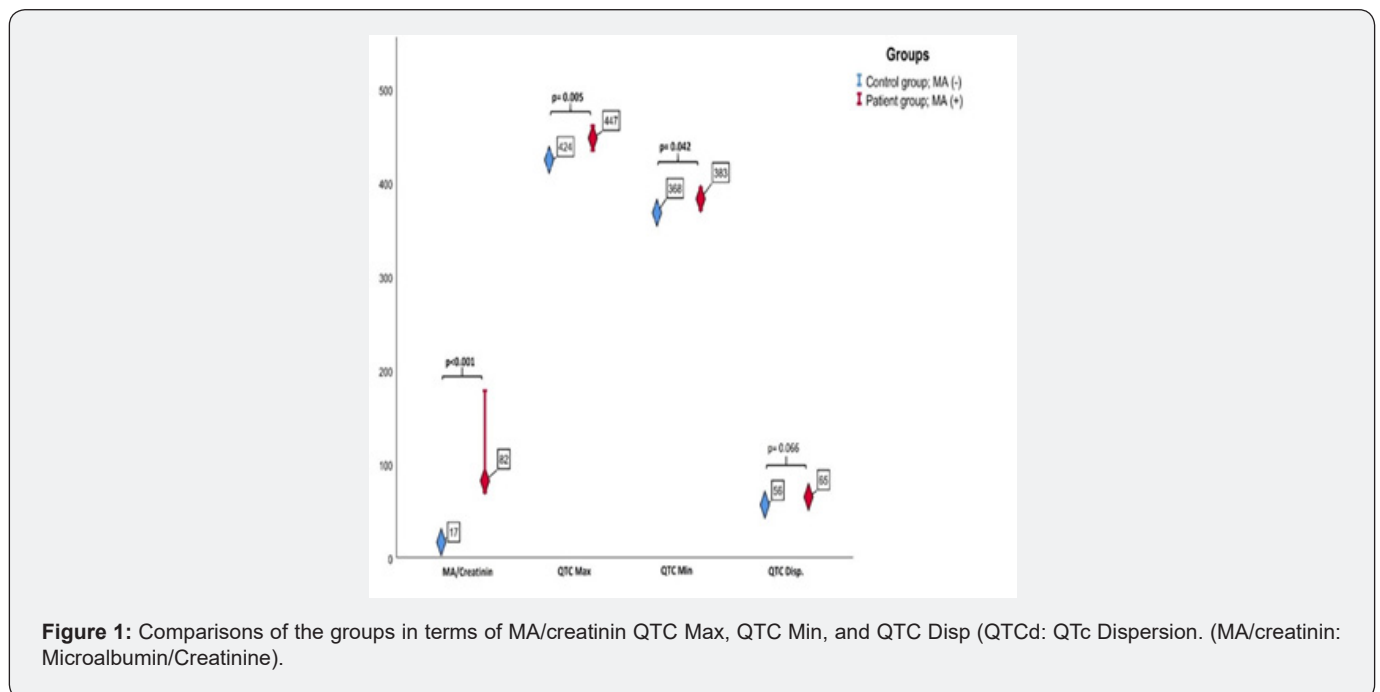
	Control Group (MA -) (n =50)	Patient Group (MA+) (n =50)	P
Age, year	54±9	56±9	=0,186
Sex, female/male	26/24	28/22	=0.841
Diabetes Duration, year	8 (5 - 10)	10(8 -15)	<0,0001
BMI, kg/m 2	29.3±4.8	30,8±6.1	=0, 193
Fasting Blood Sugar, mg/dL	161 (136-210)	210 (176 -302)	<0,001
Total Cholesterol, mg/dL	190 ( 161 -216)	207 (175 -259)	=0,005
Triglycerides, mg/dL	160 (105 206)	185 (124-249)	0,082
HDL-Cholesterol, mg/dL	45±11	44±11	0,727
LDL Cholesterol mg/dL	103 (91 - 130)	123 (103 - 159)	<0,008
TSH, ng/ml,,	1,73 (1,10 - 2,39)	2,01 (1,29 - 3,25)	=0,114
HbA1c, %	9.0±1.6	10,1±1.6	<0,001

TSH value. However, the patient group exhibited significantly higher values for diabetes duration (10 (8-15) years,  $P<0.0001$ ), fasting blood sugar (210 (176-302) mg/dL,  $P<0.001$ ), total cholesterol (207 (175-259),  $P=0.005$ ), median LDL values (123 (103-159) mg/dL,  $P=0.008$ ), and mean HbA1c values (10.1±1.6,  $P<0.001$ ).

The relationship between QT measurement parameters and MA/creatinine in the patient and control groups is shown in Figure 1. Compared to the control group, the patient group displayed a statistically significantly higher median QTCmin value (380.63 msn (361.44 - 397.30,  $p=0.042$ ), a significantly higher median QTC max value (439.98 msn (420.17 - 460.22),  $p=0.005$ ), and a significantly higher median MA/KREA value

(82 (60-300),  $p<0.0001$ ). Although the median QTC disp values (61.25 (49.91 - 81.70),  $p= 0.066$ ) were borderline significant between the two groups, no statistically significant difference was observed. The patient group had a significant and mild positive correlation between MA/crea and QTC Min and the control group had a significant and mild negative correlation between MA/crea and QTC Min ( $p= 0.006$  and  $p<0.006$ , respectively). Both groups revealed a significant and mild positive correlation in terms of QTd and MA/crea ( $p<0.001$ ).

The correlations between MA/crea and QTC parameters in the patient and control groups are depicted in Figures 2-4 and 5-7, respectively.



**Figure 1:** Comparisons of the groups in terms of MA/creatinin QTC Max, QTC Min, and QTC Disp (QTCd: QTc Dispersion). (MA/creatinin: Microalbumin/Creatinine).

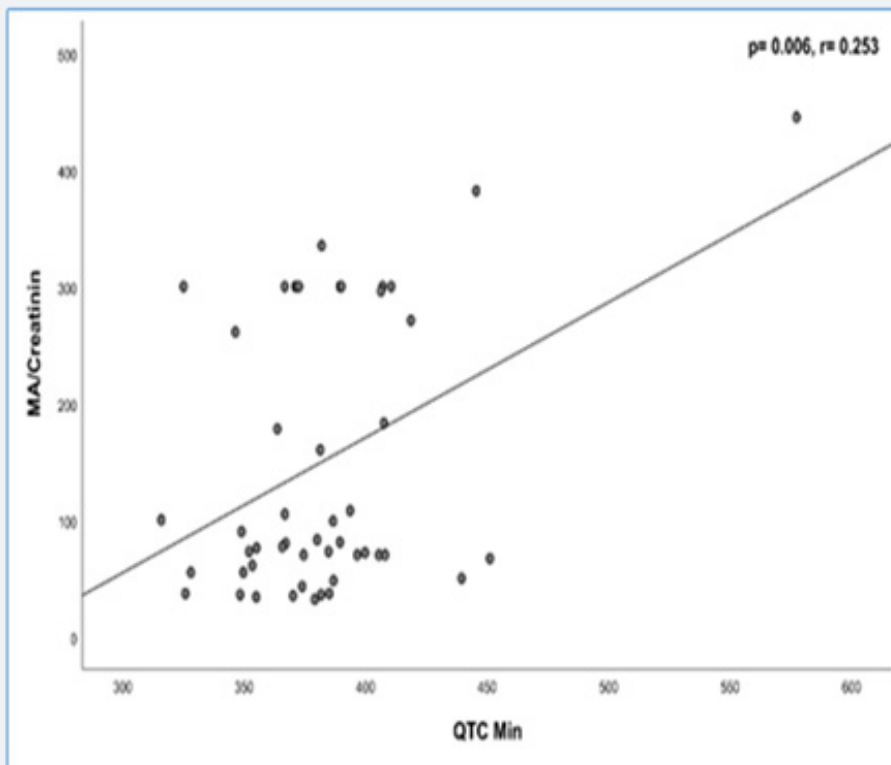


Figure 2: Correlation between MA/crea and QTC Min in the patient group MA/creatinin: Microalbumin/Creatinine.

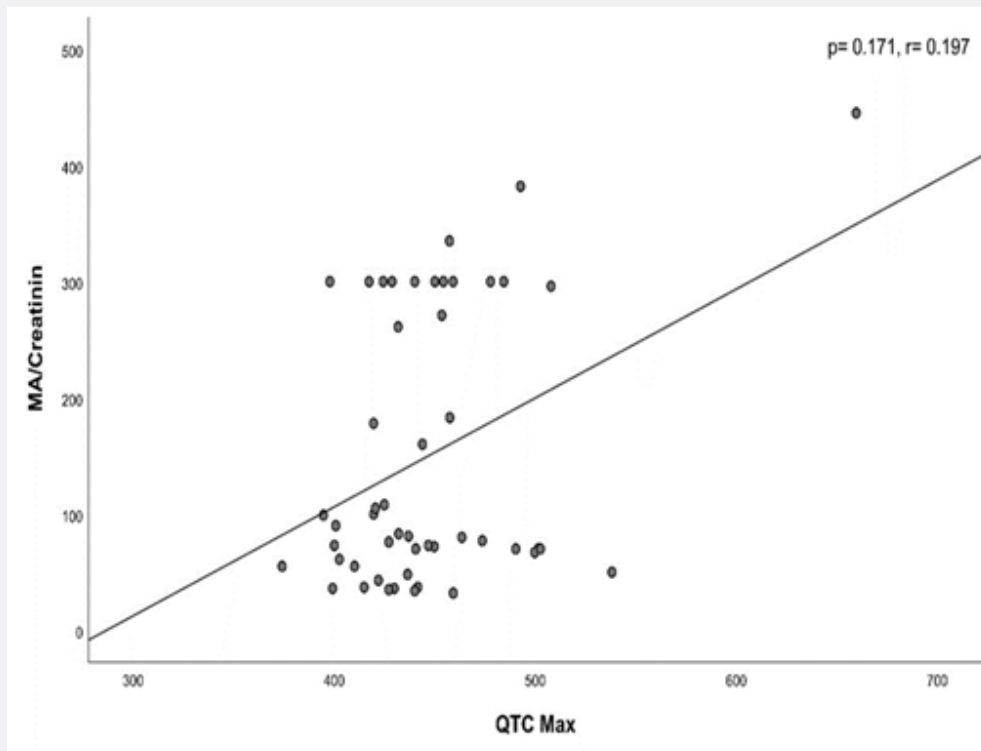


Figure 3: Correlation between MA/crea and QTC Max in the patient group.

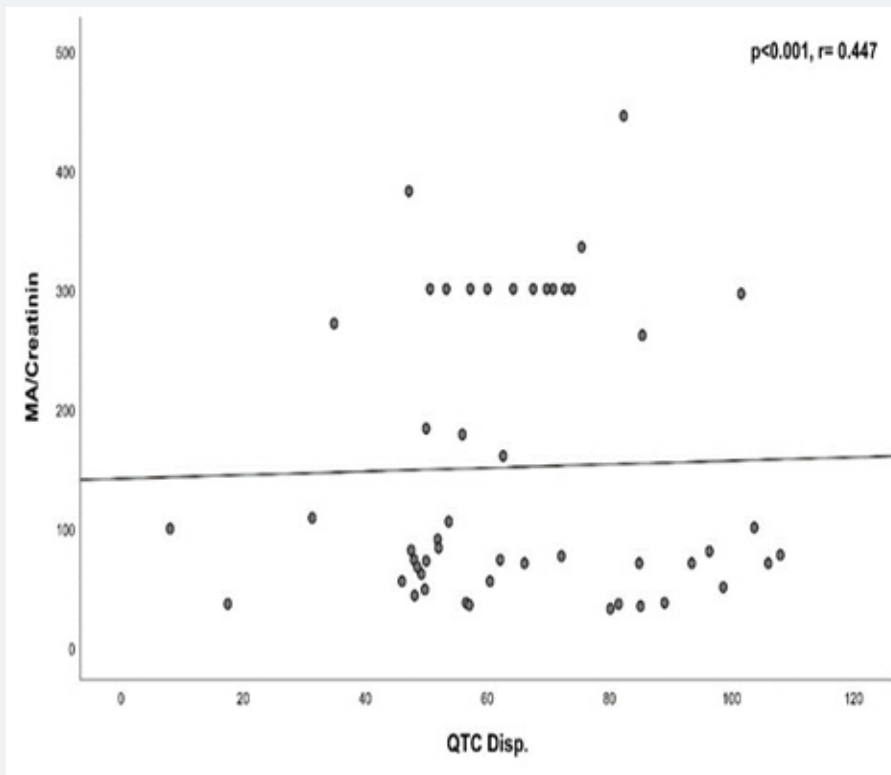


Figure 4: Correlation between MA/crea and QTcd in the patient group QTCd: QTc Dispersion.

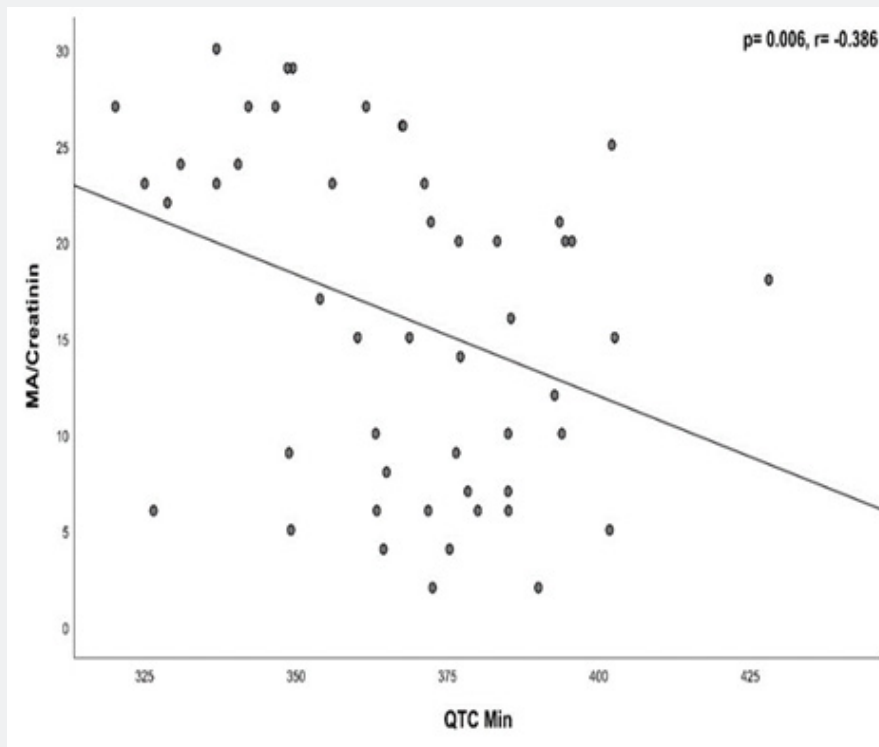


Figure 5: Correlation between MA/crea and QTC Min in the control group.

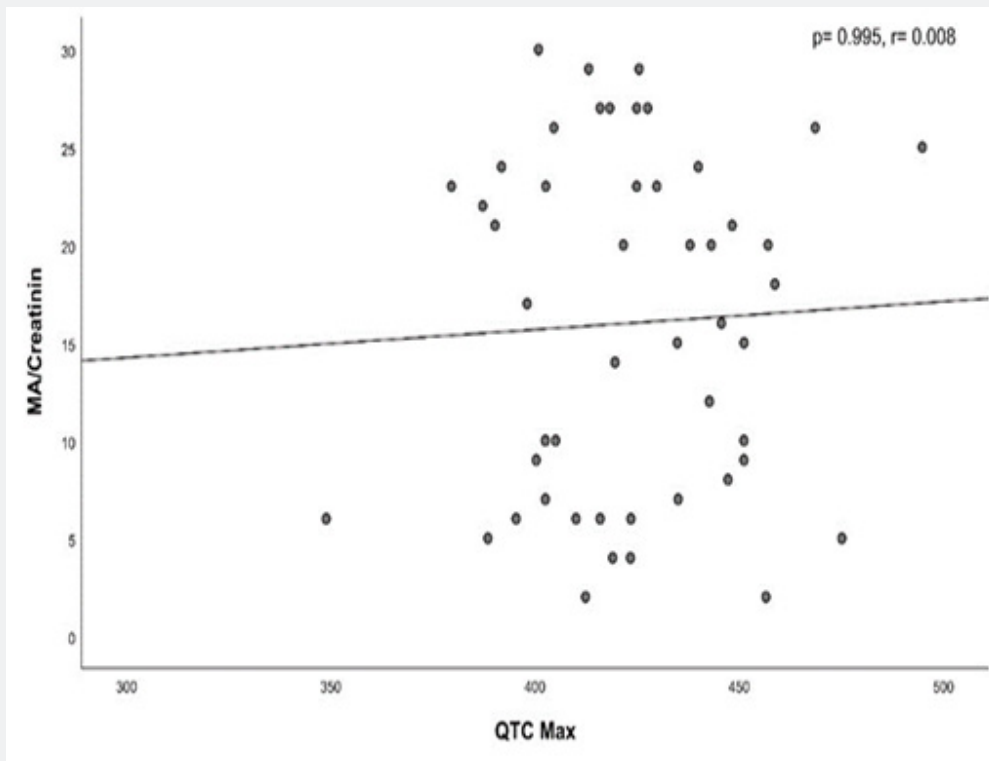


Figure 6: Correlation between MA/crea and QTc Max in the control group.

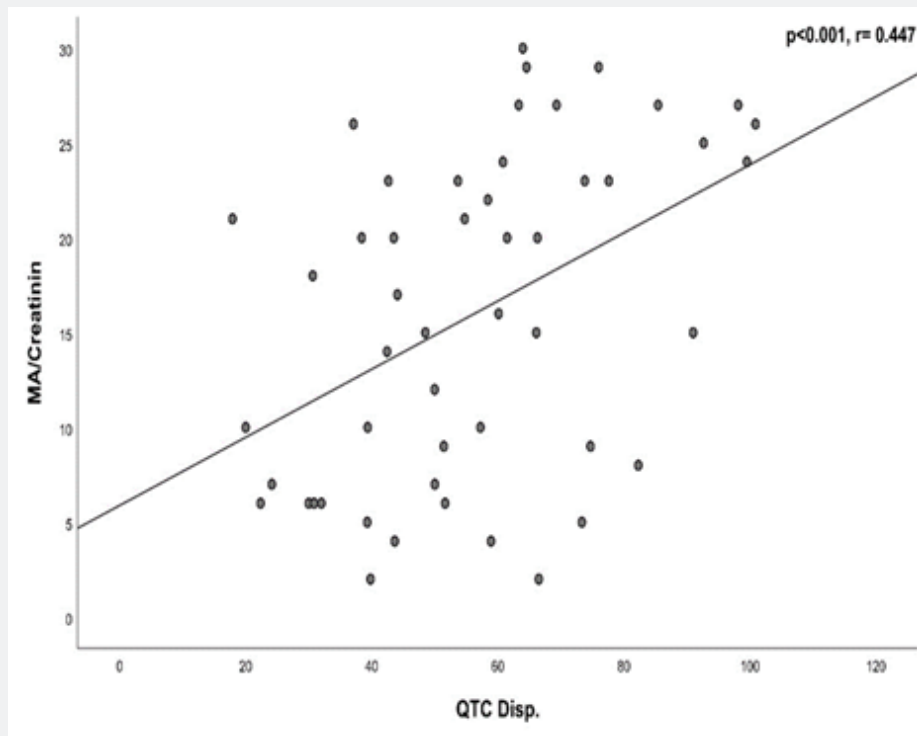


Figure 7: Correlation between MA/creatinin and QTcd in the control group (QTcd: QTc Dispersion).

## Discussion and Conclusion

Patients with either Type 1 or Type 2 diabetes have a significantly higher risk of mortality compared to non-diabetic individuals, with cardiovascular diseases being the primary cause of mortality. Research indicates that diabetes is closely linked to the development of coronary artery disease, CAN, heart failure, arrhythmias, silent cardiac ischemia, and sudden cardiac death [9,10]. Thus, it is essential to develop early diagnostic tests to prevent high mortality rates among patients with diabetes. Several studies have reported the relationship between increased cardiovascular risk and early cardiovascular events, which serve as an early marker of microalbuminuria, a condition used to detect diabetic nephropathy (DN). In one such study conducted by Dinneen and colleagues, it was demonstrated that the presence of microalbuminuria is a reliable predictor of early cardiovascular events, and there is a strong association between the two [11,12].

MA is classically defined as the urinary excretion of albumin above 30 mg/day, but studies have shown that MA levels that indicate an increased cardiovascular risk are much lower than this level [13]. In our study, we used a range of 30-300 for the MA/creatinine ratio, which we determined as the microalbumin level detected by the dipstick method for microalbuminuria detection [14,15].

QT interval reflects the total duration of depolarization and repolarization of the ventricular myocardium. When evaluating the ECG, it is reliable to correct this duration for the heart rate (QTc). Practically, the correction is made according to the Bazett formula [16]. The difference in the duration between QTmax and QTmin is called QTd. It is accepted as a noninvasive indicator reflecting the variability in depolarization-repolarization time in the ventricle due to cardiac ischemia and/or sympathetic stimulation. [17,18]. The objective of our research was to explore the connection between QT parameters, which are indicators of ventricular depolarization and repolarization heterogeneity, and the MA/creatinine ratio, an early marker of DN, which is a complication of diabetes. We aimed to contribute to the development of clinical follow-up and treatment protocols that include easily accessible and inexpensive tests. The increased use of QTcd in patients with CAN highlights its increasing importance, as it reflects the cardiac instability that has developed along with nephropathy [19]. Upon analyzing the outcomes of our research, it was discovered that the longest QTc duration in the patient group differed significantly from that of the control group (as depicted in Figure 1). The QTcd value was found to be borderline statistically significant. Patients with long-standing diabetes and poor blood sugar regulation are more likely to experience complications [20]. This finding is consistent with the results of Rutter et al.'s study, which suggested that the maximum QT interval corrected for heart rate (QT(c) max) was higher in the micro albuminuric group, and QT dispersion (QT(cd)) was similar in both groups. It is proposed that early diabetes-related factors may contribute to QT prolongation. Based on the results of this study, it can be

inferred that QTcd may be a more useful and significant predictor of mortality than other risk factors, in terms of both applicability and accessibility [21].

In this study, risk calculations were conducted for various parameters, with QTcd having the highest risk ratio among them. In numerous studies, QTc dispersion has been found in patients with diabetic autonomic dysfunction, but it was also observed in those without nephropathy [22]. This suggests that monitoring QTcd values may enable early predictions of mortality in patients with CAN before the development of microalbuminuria. The significant association between impaired fasting glucose levels and an increased QTc interval indicates that complications may begin before nephropathy becomes apparent [23]. QT prolongation has been observed in early-stage diabetes, long-duration diabetes, hypoglycemia, hyperglycemia, HbA1c levels, and even during the impaired glucose tolerance test period [24,25]. In particular, HbA1c levels, duration of diabetes, LDL cholesterol levels, and fasting blood glucose levels were found to be significantly different between the two groups and were effective in prolonging QTc duration. The effect of these variables on the statistically significant difference in the QTcd results is inevitable [24,26]. It is suggested that QTcd and QTc max distances, which are more cost-effective and accessible, in addition to having a higher predictive value in terms of earlier predictability, can be used alongside microalbuminuria, particularly before microalbuminuria develops. According to the results of this study, QTcd was the parameter with the highest risk ratio among the factors for which risk calculations were performed. In many studies, QTc dispersion was found in diabetic autonomic dysfunction, but not in patients without nephropathy [22]. This finding suggests that the follow-up QTcd value may predict mortality at an earlier stage in patients with CAN before the development of microalbuminuria. The significant relationship between impaired fasting glucose levels and increased.

The QTc interval may suggest that complications arise before obvious nephropathy becomes apparent [23]. QT prolongation has been observed in the early stages of diabetes, the duration of diabetes, hypoglycemia, HbA1c levels, and even during the impaired glucose tolerance test period [24,25]. We propose that QTcd and QTc max distances, which are more cost-effective and accessible and have a higher predictive value in terms of earlier predictability, can be used alongside microalbuminuria, particularly before microalbuminuria develops. The study under consideration has certain limitations. Firstly, it was conducted retrospectively, and no healthy control group was evaluated. Secondly, the hypertension status was not considered in the differentiation of patients. Lastly, other rare causes that could affect the QT interval could not be detected.

In conclusion, our study revealed that there was no statistically significant correlation between QTcd and MA/creatinine levels in groups with normal and elevated MA/creatinine values. However, notable differences were observed in QTc max duration. The

disparity in QTcd before the diagnosis of diabetic nephropathy in the control group suggests that the incorporation of QTc max and QTcd parameter values, which represent cost-effective, noninvasive, and clinically applicable assessments, into medical practice may be beneficial for the early detection of cardiovascular events. Regular ECG screening for QTc prolongation in patients with type 2 diabetes can help identify individuals at high risk for cardiovascular events and guide appropriate interventions. The use of automated devices that measure QTc parameters can improve the detection and follow-up of patients. Importantly, the evaluation of QTc parameters on ECG should be included in the routine assessment of patients with diabetes mellitus from the time of diagnosis to prevent complications, and this recommendation is supported by the existing medical literature.

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