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Original research article

Type-2 Diabetes Mellitus Asymptomatic Patients Changes in ECG (Qt - Interval) with or without Microalbuminuria: A Hospital Based Study

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Abstract

Introduction: QT interval abnormalities are the best predictors of cardiovascular deaths .Microalbuminuria is an independent marker for cardiovascular disease in diabetes mellitus. Hence QT interval abnormalities in diabetics with or without microalbuminuria were evaluated in this study.

Material and Methods: This study done in the Dept. of General Medicine at Dr. N. D. Desai Faculty of Medical Science & Research, Nadiad, and NAMO Medical college and research centre from(May 2021 to Dec 2021). Open label controlled study with 214 subjects of either sex. Group A healthy subjects (n=100), group B asymptomatic, type 2 diabetics with no clinical evidence of cardiac disease. Group B subdivided into B1 with microalbuminuria (n=62), B2 without microalbuminuria (n=52). Corrected QT interval (QTC), microalbuminuria, and blood pressure were measured for all subjects. QTC was calculated by using Bazzet's formula .QTC more than 440msec was considered prolonged.

Results: QTC was within normal range in diabetic patients(415+25msec). Highly significant ($p<0.0001$) prolongation was observed in diabetics, compared to healthy subjects. Both B1 ($p<0.0001$) and B2 ($p<0.001$) groups showed a significant increase in QTC than in healthy subjects. Among B1 and B2 groups QTC was not statistically significant.

Conclusion: QTC was more in asymptomatic type 2 diabetics irrespective of microalbuminuria compared to healthy individuals, though values were within normal range.This denotes high risk for future cardiovascular complications in diabetic patients.

Keywords: QT interval prolongation, Diabetes Mellitus, Microalbuminuria, Corrected QT interval, CHD(coronary heart disease),CAD(coronary artery disease)

Introduction

Epidemiological data shows alarming values that predict a worrisome projected future for T2 diabetes mellitus. According to the International Diabetes Federation (IDF), in 2019, diabetes caused 4.2 million deaths; and 463 million adults aged between 20 and 79 years old were living with diabetes, a number that will likely rise up to 700 million by 2045. Diabetes was the underlying cause of at least 720 billion USD in health expenditure in 2019**.** Ninety percent of Diabetic patients have type 2 Diabetes mellitus and it has emerged as one of the 21st' century's

health problems (Stumvoll et at 2005, Leiter. 2005). Additionally, the true disease burden of T2DM is likely an under representation as 1 in 3 diabetic people were under diagnosed, equivalent to 232 million people. The greatest number of people suffering from diabetes are aged between 40 and 59 years old. Incidence and prevalence of T2DM vary according to geographical region, with more than 80% of patients living in low-to-middle-income countries, which poses additional challenges in effective treatment. Patients with T2DM have a 15% increased risk of all-cause mortality compared with people without diabetes with cardiovascular disease (CVD) as the greatest cause of morbidity and mortality associated with T2DM (Unai Galicia-Garcia et,al 2020)- Type -2 DM is a heterogeneous group of disorders characterized by variable degree of insulin resistance, impaired insulin secretion and increased glucose production, as opposed to absolute deficiency of insulin that occurs with type 1 diabetes mellitus (Wagstaff et al. 2002). Diabetes mellitus may lead to complications affecting many organ systems. The microvascular complications are retinopathy, nephropathy and neuropathy. The macrovascular complications are coronary artery disease, peripheral arterial disease and cerebrovascular disease. Nonvascular complications are gastroparesis, infections and skin changes. The main cause of death and morbidity in patients with diabetes is vascular complications (Turner et al. 2005). Diabetes is a known cardiovascular risk factor and there is a necessity to identify the factors that may improve cardiovascular risk in diabetic patients by using non-invasive and low cost approaches (Giunti et al. 2012). One possible way to risk stratification in diabetic patients, is to use QT interval analysis, measured ECGs.QT abnormalities can predict cardiac death in several disease states including chronic heart failure, systemic hypertension and peripheral vascular disease. Two studies have already shown that QT interval abnormalities are particularly best predictors of cardiac death, with regard to Type-2 diabetes mellitus• (Naas et al 19981 Rana et al. 2005). Prevalence of corrected QT interval (QTC) prolongation is 26% in type 2 DM (Sawicki et al 1996). Different factors contribute to the duration of QT Interval,insulin resistance, glucose tolerance, glycemic control and diabetic complications, Thus QTC prolongation in diabetes is of multi-factorial oriqin_(Laitinen et a) 2003).Microalbuminuria is an independent marker of cardiovascular disease .Microalbuminuria alone could not explain the increased morbidity and mortality in diabetic patients. Hence estimation of QT interval and QTC along with microalbuminuria, that reflects total cardiac depolarization and repolarization, could be a better indicator of diabetic cardiac autonomic neuropathy (CAN) (Rutter et al. 2002). Diabetic cardiac autonomic neuropathy (CAN) is a well recognized complication of type 2 DM and its incidence had been reported to be 20-40% (Mate) et al_ 2010).The present study was conducted to determine whether QTC prolongation is linked to microalbuminuria in patients with type 2 diabetes and to investigate their association by comparing with healthy individuals. Our hypothesis was that asymptomatic Type -2 diabetic patients with microalbuminuria had cardiac involvement that might be subclinical, as reflected by more prolonged QTC, as compared to those without microalbuminuria and healthy controls.

Materials and Methods

It was an open label controlled study with a total of 214 subjects of either sex .The present study was conducted in the Dept. of General Medicine at Dr. N. D. Desai Faculty of Medical Science & Research, Nadiad, and NAMO Medical college and research centre from May 2021 to Dec 2021, Inclusion criteria were asymptomatic type 2 diabetic patients with no clinical evidence of cardiac disease, no H/O chest pain or shortness of breath, no H/O cardiac procedures, age between 30-70 years. Exclusion criteria were H/0 coronary heart disease, H/O chest pain or shortness of breath, ECG abnormalities, patients with hepatic and renal abnormalities, type 1 diabetes mellitus, patients taking taking drugs,which affects the QT interval. And patients with abnormal levels of serum Potassium and Calcium were excluded.

The study subjects were divided into 1) Group A — Healthy controls (n=100) 2) Group B — Asymptomatic, type 2 diabetic patients. Group B was again subdivided into 2 groups. Group B 1 diabetic patients with microalbuminuria (n=62), Group B2 diabetic patients without microalbuminuria (n=52). All participants were subjected to detailed history and physical examination, Blood pressure was recorded. Biochemical tests, fasting blood sugar levels (FBS), post-prandial blood sugar (PPBS). Serum potassium, calcium and urine for microalbuminuria were done ECG was taken and QT interval and corrected QT interval (QTC) were calculated. ECG abnormalities were registered according to Minnesota code. QT interval was measured manually in chest leads V3, V4 V5, V6 and limb leads L**II**. Lead with the longest QT interval was taken since QT interval is affected by heart rate. The Interval between two successive R-R waves was calculated and corrected QT (QTC)
interval was calculated using Bazzet's formula (Bazett. 1920)

$$QTC = \frac{QT\ interval}{\sqrt{R - R interval(msec)}}$$

Value of QTC interval exceeding 440 msec was taken as prolonged

For measuring microalbuminuria early morning or spot urine samples were used. Urine was tested using routine dip sticks for RBC, leukocytes and protein. If urine was negative for above, then a sample was sent for microalbuminuria estimation. Specimen was analyzed as soon as possible after the collection, as the storage time and temperature may affect the albumin levels in the urine. Urine albumin levels were measured by immunoturbidimetric method and concentration more than 20 mg/L was taken as positive. The normal microalbuminuria value is less than 20 mg / L. The value greater than 20 mg/L was taken as positive for microalbuminuria (Kleg et al 1997)

Statistical analysis: All values were expressed as mean$\pm$standard deviation (SD).
Analysis of Variance, (ANOVA) was applied to compare the data between the two groups
Unpaired 't' test was used to calculate p value. $P<0.05$ was considered statistically significant.

Results
A total of 214 subjects of either sex were evaluated in the study. Out of which 100 were healthy subjects and 114 were asymptomatic type-2 diabetic patients. In Group A, 60 were males and 40 were females, .Age in Group A was 49$\pm$9.4 years ,in Group B was 53$\pm$10 years. Microalbuminuria in healthy subjects was 8.8$\pm$3.8 mg/ dl and in diabetics, it was 32.4$\pm$54 mg/dI showing highly significant ($p<0.0001$) increase in diabetic patients (Table 1). Microalbuminuria within the diabetic groups, B1 was 49$\pm$69 mg/dl and in Group B was . 12.6$\pm$6.5 mg/dl. There was highly significant ($p<0.0001$) increase in microalbuminuria in Group B1 compared to Group B2 (Table**1**). Both the diabetic groups B1 and B2 showed significant increase in microalbuminuria which was $p<0.0001$ and $p<0.001$ respectively, compared to healthy controls (Table **1)** QTC interval in healthy subjects was 388$\pm$21 msec and in Group B diabetic patients, it was 415$\pm$25 msec which showed highly significant ($p<0.0001$) increase in QTC interval when compared to Group A healthy controls (Table **1**), though they were within the normal range.

In Group B 1, diabetic patients with microalbuminuria, QTC interval was 419±22 rnsec, and in Group B 2, diabetics without microalbuminuria it was 411±28 msec. \Both B1 and B 2 groups showed highly significant increase in QTC interval, which was significant p<0.0001 and p<0.001 respectively, compared to healthy controls (Table **1)** In between B1 and B2, QTC interval was found to be statistically insignificant (Table **I)**. The mean systolic blood pressure (SBP) in healthy subjects was 120±9.0 mm of and in diabetic patients it was 132±18 mm of Hg. There was highly significant (p<0.0001) increase in mean SBP in diabetic patients., compared to healthy controls.Mean diastolic blood pressure (DBP) in healthy subjects was 74±8.0 mm of Hg and in diabetic patient it was 79±11 mm of Hg, showing highly significant increase in diabetics than the healthy subjects. In groups B1 and B2 they did not show any significant difference in both SBP and DBP (Table 1).Fasting blood sugar (FBS) in healthy subjects was 79±9.0 mg/dl whereas in diabetic group it was 126±45 mg/dl. there was highly significant increase in FBS within the diabetic patients compared to the control group. FBS within the diabetic groups B1 and B2 was not statistically significant(Table 1). Postprandial blood sugar (PPBS) in healthy subjects was 132±12 mg/dl whereas in diabetic group B was 187±73 mg/dl showing highly significant increase in PPBS in diabetic patients compared to healthy subjects.Within the diabetic groups B1 and B2 PPBS was not statistically significant. There was no statistically significant difference in serum potassium and serum calcium levels between diabetic patients and healthy controls (Table 1).

Table 1: Characteristics of Study Subjects

Sr. No.	Parameters	Group A [n=100] Mean+SD	Group B [n=114] Mean+SD	P Value	GroupB1 [n=62] Mean+SD	GroupB2 [n=52] Mean+SD	P value
1	SBP (mm of Hg)	120±9.0	132±18	<0.0001	133.5±18.3	130±18.7	NS
2	DBP (mm of Hg)	74± 8.0	79±11	<0.0001	78.2±11.5	80.1±10	NS
3	FBS (mg/dl)	79±9.0	126±45	<0.0001	128±53.1	122.6±32.1	NS
4	PPBS (mg/dl)	132±12	187±73	<0.0001	195±84.4	177.6±58.3	NS
5	Serum K+ mmol/ L	4.4±0.7	4.3±0.7	NS	4.3±0.7	4.2±0.5	NS
6	Serum Ca+2 mg/dl	10.0±0.9	10.1±0.9	NS	10.1±0.9	10.3±0.6	NS
7	Microalbumin in urine(mg/L)	8.8±3.8	32.4±5.4	<0.0001	49±69	12.6±6.5	<0.0001
8	QTC interval (msec)	388±21	415±25	<0.0001	419±22	411±28	NS

Group A-Healty subjects., Group B- Diabetics, Group B1Diabetics with microalbuminuria. Group B2 -Diabetics without microalbuminuria.

SBP-Systolic blood pressure, DBP -Diastolic blood pressure,FBS- Fasting blood sugar PPBS- Post prandial blood sugar,QTC is corrected QT interval**.**

Discussion

In the present study we have observed that microalbuminuria was significantly increased in asymptomatic type 2 diabetes mellitus patients, with no clinical evidence of coronary heart disease,compared to healthy controls. Similar to our findings there are several studies which have demonstrated to have significant microalbuminuria in type 2 diabetic patient (Wirta et al. 1997, Suarez et al. 2005).Presence of microalbuminuria in patients with Type -2 DM was a predictor of clinical proteinuria and increased mortality .It is a strong independent risk factor for cardiovascular disease in diabetic and non-diabetic individuals and may be a useful marker for diffuse endothelial dysfunction (Wirta et al. 1997, Suarez et al.2005.) Microalbuminuria may also be strongly related to confounding factors like hyperglycemia, hypertension, insulin resistance or atherosclerotic disease(Wirta et al. 1997, Groop et al. 1993). Our study showed that QTC prolongation in type 2 diabetes mellitus patients was significantly higher, when compared to healthy controls, though they were within the normal range. Similar to our results Takerbayashi et al observed that type 2 patients had greater QTC prolongation than healthy controls(Takebayashi et al. 2003). With regard to type 2 DM, two studies have shown that QT interval abnormalities are particularly good predictors of cardiac death(Naas et al 1998,Sawick et al 1996). In the previous studies (Porwal et al. 2005,Vegilo et al. 2002) it was observed that QT interval was increased above normal range(>440 msec) in 26% of type 2 diabetes patients with or without microalbuminuria. We observed QTC prolongation > 440 msec in 29% of diabetic patients with or without microalbuminuria in our study. Similar to previous studies we observed QTC was prolonged >440 msec in 18 out of 62 patients with microalbuminuria and 2 out of 52 patients with normoalbuminuria. No subjects had QTC prolongation of >440 msec in the control group..Previous studies demonstrated significant increase of QTC interval in type 2 diabetes mellitus patients with microalbuminuria, when compared to normoalbuminuric diabetic patients (Rutter et al.2002, Yeo et al. 2004). However we found no statistically significant difference in QTC interval within the diabetic patients with or without microalbuminuria. This is because linear regression analysis showed that QT prolongation was not strongly linked to albumin excretion rate but more strongly to factors associated with microalbuminuria such as blood pressure and factor XIIa(Rutter et al. 2002). In our study, diabetic patients had significantly higher microalbuminuria than healthy controls. This might suggest that the microalbuminuria in diabetic patients without overt coronary heart disease could be an early indicator of cardiovascular autonomic neuropathy (Yeo et al 2004).QTC abnormalities can occur independently of autonomic dysfunction or myocardial ischemia and may be related to the process which increases urinary albumin leakage and QT prolongation may contribute to increased mortality observed in microalbuminuria; subjects with type 2 diabetes mellitus (Earle et al 2000, Rutter et al. 2002). QTC interval is an independent marker for coronary heart disease and is a predictor of sudden cardiac death (Naas et al. 1998). In our study we have observed that mean systolic and diastolic blood pressures were significantly higher in diabetic patients, compared to healthy subjects. Our results were consistent with the previous studies (Porwal et al. 2005, Vegilo et al. 2002, Sallas et al. 2006) which reported that diabetic patients tend to have high blood pressure and higher cardiovascular complications which affect QT interval more than healthy individuals. Another study (Spallone et al. 1994) demonstrated that diabetic patients with microalbuminuria had higher mean systolic and diastolic pressures recorded over a 24 hour period, than normoalbuminuric diabetic patients. In

our study, there was no sIgnificant difference in mean systolic and diastolic blood pressures between microalburninuric and normoalbuminuric type 2 diabetic patients, as we have not recorded blood pressure over 24 hour period. However, presence of microalbuminuria that reflects renal involvement in diabetic patients, has been reported as a major determinant of ambulatory blood pressure (Hansen et al. 1992, Hingham et at. 1992). Microalbuminuria has been found independently predictive of mortality in clinical studies in Type-2 diabetic patients (Damsgaard et al.1992). Presence Subclinical autonomic neuropathy is an important determinant of mortality in Type-2 diabetic patients by causing cardiac arrest.(Wirta et al.1997) .Microalbuminuria is an independent risk factor for cardiovascular and renal out- come in a patient with Type 2 diabetes. The evidence that intensive glycemic control reduces the microvascular complications of diabetes is based almost exclusively on prevention of micro- albuminuria. (Peter P.Swoboda et, al 2017). Asymptomatic diabetes mellitus patients with persistent microalbuminuria have markers of diffuse cardiac fibrosis(Peter P.Swoboda et, al 2017) .In recent study there is a significant association between QTc interval prolongation and microalbuminuria as evidenced by a greater number of cases with microalbuminuria having prolonged QTc interval (S,Shakti et ,al 2021)

Conclusion

CAN is a common serious complication seen in Type-2 diabetic patient. It is associated with variety of adverse outcomes including cardiovascular deaths (Xiang Li et al.2012). Hence it is practically difficult to diagnose CAN in the clinics.Screening asymptomatic Type -2 diabetic patients for pronlonged QTC is a simple objective way of diagnosing CAN which can help us to monitor the patients more closely and prevent mortality associated with it. The lifetime risk seems to be invariably high in almost all patients with diabetes.The recent ESC guideline considers that diabetes risk approaches the CHD risk when microalbuminuria is present.(Marcello Casaccia Bertoluci,Viviane Zorzanelli Rocha 2017) Stratification of diabetic patients improves accuracy in prediction of subclinical CAD, silent ischemia and future cardiovascular events.Risk stratification is necessary to individualize treatment,and to reduce morbidity and mortality.

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