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Probing into arrhythmias in type 2 Diabetics

KEYWORDS: QT prolongation, QT dispersion, Hodges formula, spontaneous ventricular tachycardia

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ABSTRACT *Objective: To study arrhythmias in Type 2 Diabetes Mellitus (DM), with special reference to cardiac autonomic neuropathy (CAN).*

Material and methods: A cross-sectional observational study including 50 patients with Type 2 diabetes mellitus and presenting with cardiac arrhythmias (clinically or on ECG), was conducted at a teaching hospital over two years. Bedside tests for CAN were done. Besides routine investigations, echocardiography, stress test and Holter monitoring were done as indicated. The data was compiled and analyzed using Statistical Package for Social Sciences (SPSS v/s 18).

Results:Sinus tachycardia was the commonest arrhythmia (38%) followed by complete heart block (CHB-12 %), and 10% each of sinus bradycardia, ventricular premature complexes (VPCs) & atrial fibrillation (AF). Poorly controlled diabetics showed sinus tachycardia, followed by VPC, AF, CHB and others in that order. Co-morbid illnesses like hypertension and ischemic heart disease correlated with higher incidence of arrhythmias. 54% had prolonged QTc, majority of which (16 patients of 27) showed the presence of CAN. All the patients with arrhythmias responded to conventional pharmacotherapy. Pacemaker implantation- temporary pacing followed subsequently by permanent pacing proved effective in all cases of CHB.

INTRODUCTION

The chronic hyperglycemia of type 1 and type 2 diabetes mellitus (DM) is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. The Framingham Heart Study revealed a marked increase in peripheral arterial disease, congestive heart failure (CHF), coronary artery disease (CAD), myocardial infarction (MI) and sudden death (risk increase from one to five fold) in diabetes. Further, ventricular arrhythmias are frequent in diabetics.1,2 The 'Organization to Assess Strategies for Ischemic Syndromes' (OASIS) Registry states that diabetes significantly increased all case death and the incidence of new MI, stroke and heart failure during a 2 year mean follow up in patients who were hospitalized for unstable angina or non-Q wave MI.3 CAN associated with diabetes probably aggravates CAD. In its incipient form, CAN hardly changes the sinus rhythm. However, in advanced stages, in addition to heart rate variability, changes in ventricular repolarisation also occur.4 Ventricular myocardial depolarization and repolarisation is studied by evaluating the QT interval-heart rate relationship. Its increase contributes to the diagnosis of CAN in diabetics. QTc (corrected QT interval) prolongation, increased QTd (QT dispersion) and increased HbA1c (Glycosylated hemoglobin) is associated with increased mortality, especially in elderly type 2 diabetes.2,5,6,7,8

CASE SERIES

Material and Methods:

Approval from the Ethics committee, for material and methods to be used, was procured before commencing data collection. A cross-sectional observational study of 50 patients was conducted at a teaching hospital over two years. It was aimed at studying occurrence and incidence of various arrhythmias with special reference to glycemic control and CAN. Written informed consent was obtained prior to enrollment.

Detailed history along with physical examination was done of each patient. Tests for CAN were done wherever permissible by the patient's clinical condition. In cases of acute MI, the tests for CAN were done after 1 week and the tests involving Valsalva's manouvre were not done. In cases of severe hypertension, these tests were done once the blood pressure was controlled. Alongwith blood sugar levels; ECG with rhythm strip and calculation of QTc interval, HbA1c level, 2D echo and urine examination were done. Specific tests like thyroid function tests, serum magnesium levels and cardiac enzymes were done as indicated.

(Table 1) Tests for autonomic dysfunction [Resting Heart Rate]

Heart rate in response to deep breathing (E:I ratio) (6 maximum deep breaths in 1 min)
Heart rate in response to Valsalva manoeuvre
Heart rate in response to standing 30:15 ratios.
Blood pressure response to standing (postural systolic drop)
Blood pressure response to sustained handgrip

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The data was compiled and analyzed using Statistical Package for Social Sciences (SPSS v/s 18) and employing descriptive statistics such as frequencies and percentages.

Inclusion Criteria:1) Patients suffering from Type 2 DM. 2) Arrhythmias on ECG on any occasion during presentation or stay in hospital.

Exclusion Criteria: Patients with normal sinus rhythm, and no arrhythmia on ECG on any occasion.

Results:
Fifty patients having DM (above the age of 12 years) with arrhythmias were studied (25 males, 25 females). Sinus tachycardia was the commonest arrhythmia, found in 19 of 50 patients (38%; 12 males and 7 females). This was followed by 6 patients (12%) of CHB (4 males, 2 females), 5 patients (10%) of each sinus bradycardia (1 male, 4 females), VPC (2 males, 3 males) and AF (1 male, 4 female). Our study also showed 3 patients (6%) of paroxysmal supra-ventricular tachycardia (PSVT)- all females, 2 patients (4%) of each atrial premature complexes (APC), sinus Arrhythmia (1 male, 1 female) and finally 2 cases (4%) of 1° Heart Block (2 males). 1 male patient (2%) of ventricular tachycardia (VT) was also present.

We used HbA1c level to classify the glycemic control of diabetes as good (7.5-8.5 gm/dL), fair (8.5-9.5 gm/dL) & poor (above 9.5 gm/dL). 5 patients (10%) showed a good glycemic control, 19 (38%) had a fair glycemic control whereas 26 (52%) had a poor glycemic control. Out of 26 patients with poor glycemic control, 7 patients showed sinus tachycardia, 4 patients showed VPC, 3 patients each had AF and CHB, 2 patients each were of sinus bradycardia, APC, 1o Heart Block, and 1 each of Sinus Arrhythmia, PSVT. Additionally, the only case of ventricular tachycardia (VT) had poor control of diabetes.

Out of 50 patients, 9 had HTN, 5 had IHD, 17 had both HTN and IHD, and 19 had no other co-morbid illnesses. Of the total 5 patients in our study who had AF, 2 patients (4%) had both HTN and IHD, while the remaining 3 had no co-morbid illness. In our study, a total of 29 (58%) patients had prolonged QTc, out of which 18 (36%) were males and 11 (22%) were females. Rest 21 patients (42%) had normal QTc. 31 patients could be tested for CAN. 24 patients (48%) had CAN with prolonged QTc, while 4 patients (8%) had CAN despite normal QTc. Thus, a total of 28 patients (56%) had CAN.

Amongst the 24 patients with prolonged QTc and CAN, 16 patients had sinus tachycardia. This was followed by 3 patients with sinus bradycardia, 2 patients (11.11%) each with sinus arrhythmia and VPC's, and one patient with PSVT. On the other hand, amongst the 4 patients with normal QTc and CAN, 2 patients had sinus tachycardia, 1 patient had VPC and 1 patient had sinus bradycardia.

Hypomagnesemia was present in only 5 subjects (10%, 3 males and 2 females) and was normal in the rest. 1of these 5 had an acute MI, while the rest had only sinus tachycardia. Thyroid function was tested in only 12 patients, as dictated by their clinical presentation. Hypothyroidism was recorded in 4 patients (all female), while the rest had normal thyroid function. 2 patients with hypothyroidism had presence of bradyarrhythmias (1 CHB and 1 First degree AV Block).

All our patients with CHB, AF, PSVT and VT were treated using standard treatment strategies, tailored according to presence or absence of acute coronary syndromes. All of them responded favourably to treatment and zero mortality was recorded.

DISCUSSION
In today's era, complications of DM such as ketoacidosis, infection or electrolyte disturbances rarely result in death. Rather, long term complications due to microangiopathy such as glomeurlopathy and retinopathy, and sequelae of macroangiopathy such as CAD, stroke and gangrene are responsible for majority of the mortality and morbidity. Risk factors for macrovascular disease in diabetics include dyslipidemia with accelerated atherosclerosis, hypertension, obesity, reduced physical activity and cigarette smoking. Risk factors specific to the diabetic population include microalbuminuria, gross proteinuria, elevation of serum creatinine and abnormal platelet function. Vascular diseases account for most of the morbidity and mortality in DM.9,10,11

The Framingham heart study and the OASIS Registry have shown the association of diabetes with increased all case death, new MI, stroke and heart failure.1,3 In the Framingham study conducted in non-diabetic individuals, AF was more common in males than in females.12 Mohammad - Reza, Mazen Jamal M et al in their study showed that AF occurred in 14.9% DM patients vs. 10.3% in the control group and atrial flutter occurred in 4% of DM patients vs. 2.5% of control group.13 J.Merto, L Rustom et al in another study showed that the prevalence of AF was 2 % in patients with only HTN, 6% in patients with both HTN & type 2 DM & 4% in patients with only type 2 DM.14 Both studies suggest an increased incidence of AF in diabetics. This was in concordance with our study. Mohammad-Reza Movahed, M. Mazen Jamal et a115 also performed a multivariate analysis and revealed that CHB was present in 3,240 DM patients (1.1%) Vs 3,367 patients (0.6%) in the control group (Non DM patients). DM remained strongly associated with third- degree AV block (odds ratio, 3.1:95% confidential interval, 3.0 to 3.3; $p < 0.0001$). In our study also, CHB was the second commonest arrhythmia. Christoph Hasslacher, Peter Wahl et a1studied 473 diabetic patients with bradyarrhythmias. 36.1% were males and 45.5 % were females. 2 types of bradyarrhythmias were studied- 1st degree heart block and CHB; in both types there was a female preponderance.16 In our study, these 2 bradyarrhythmias were present in 8 (16%) patients (6 patients with CHB, 2 patients with 1st degree heart block). However, by contrast, we observed a male preponderance.

Carol Chen-Scarabelli, Tizano M. Scarabell et al. in a retrospective study of 336 implantable cardioverter-defibrillator patients (both DM and Non DM) showed that HbA1c levels between 8% and 10% had a significant association with spontaneous VT suggesting that suboptimal glycemic controls, independent of QT or QTc prolongation, increases the risk of spontaneous VT. Optimization of glycemic control may help to reduce the occurrence of ventricular arrhythmias, as well as sudden cardiac death.8 The study by J.Merto, L Rustom et al has highlighted occurrence of AF in DM occurred in relation to HTN and IHD. Another study by C. J. Ostgren, J. Merlo et al 14 of 1739 patients (798 men, 941 women) showed the same results as J.Merto, L Rustom et al. Insulin resistance may be a common underlying mechanism. Incidentally, our only patient of VT had poor glycemic control.

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CAN is a continuation of the progression of a disease process. However, diabetic autonomic neuropathy may even precede development of symptoms of diabetes. Kahn JK et al [17] demonstrated an association of prolonged QTc interval with cardia dysautonomia in DM. CP Mathur, studied 50 cases of DM. He concluded that diabetes with CAN had statistically significant QTc prolongation as compared to diabetics without CAN and control subjects. In his study on diabetic subjects, there were 15 cases with QTc prolongation out of 19 with CAN. None of the diabetics without CAN or control subjects had QTc prolongation.[17] However, we recorded a normal QTc in 4 patients (8%) despite the presence of CAN in our study. Ventricular instability, as manifested in QT abnormalities, contributes to the increased cardiovascular disease affliction. The QT interval reflects the total duration of ventricular myocardial depolarization and re-polarization. The QTc effectively is the QT interval estimated at a rate of 60/minute. A commonly used correction formula is Bazett's formaulal8 where QTc = QT/ √RR interval. The Bazett's formula has been criticized for giving a slight over correction of QT interval at higher heart rates. While the formula of Hodges et al19 (QTc = QT + 1.75 [rate - 60]) has been shown to perform much better. QTc prolongation is a risk factor for sudden death independent of age, and a relative risk of 2-5 has been reported.20,21 QT dispersion is defined as the difference between the maximum and minimum QT interval on the 12 lead ECG (QTd = QT max - QT min).22 Increased QTd indicates non-uniform ventricular re-polarization and provides a substrate for the development of malignant ventricular arrhythmias.23 Increased QTd represents cardiac abnormalities such as fibrosis, hypertrophy, dilatation, ischemia and probably, autonomic dysfunction24,25 and increases cardiovascular risk. Prevalence of prolonged QT interval and increased QTd is higher in people with type 1 and type 2 DM as compared to non-diabetic subjects,5,6,26 especially in the presence of autonomic neuropathy.27 The prevalence of QT prolongation is reported to be 16% in type 1 diabetes (11 % in males and 21 % in female patients)26 and 26% in type 2 diabetes,6 while that of increased QTd has been reported as 7% in type 1 diabetes (8% in men and 5% in women)5 and 33% in type 2 diabetes.6 Compared to microalbuminuria, increased QT dispersion is a better predictor of cardiac death in DM.28 QTd > 78 ms after six years of diabetes predicted cardiac death with 100% sensitivity and 90% specificity i.e. an odds ratio of nine,24 compared with an odds ratio of 1.8 for microalbuminuria (95% Confidence interval, 1.2-2.8) in an overview.29 Patients with QT abnormalities should undergo tests for myocardial ischemia (treadmill test) and left ventricular abnormalities (echocardiogram).25 CAN in diabetes increases risk of sudden death. Hyperglycemia may probably produce ventricular instability by increased sympathetic activity, increased cytosolic calcium content in myocytes or both.30 Insulin stimulates sympathetic activity and diabetes is known to be associated with impaired parasympathetic cardiac control. This is reflected in a reduced ability to regulate heart rate as well as a reduction in heart rate variability.31 The American Diabetic Association and the American Academy of Neurology indicates that testing for prolongation of Bazett's heart rate-QTc is easy and specific for diabetic cardiac autonomic failure.4 In a study of healthy non-diabetic subjects, an independent association between high plasma glucose concentration and increased QTc duration and QTd was reported.32 In another study, mean HbA1c was significantly greater for those with a QTc in the upper tertile compared to the lower tertile among adults with DM (8.0% vs. 7.5%, p<l=0.05) and impaired fasting glucose (5.7% vs. 5.4%, p</=0.05), but there was no difference among adults with normal glucose.33 A United Kingdom Prospective Diabetes Study (UKPDS) cohort analysis revealed that, for every 1% reduction in HbA1c, there was an approximately 14% reduction of all cause mortality and MI.7 Carol Chen-Scarabelli, Tizano M. Scarabell et al. have reported significant association between HbA1c levels and spontaneous VT.8

Timothy M.E. Davis et al studied 5,715 patients with acute MI over 9 years, out of which 12.9% were diabetic. Mortality at 28 days was 12.0% and 28.1% for non-diabetic and diabetic patients, respectively. Ventricular and atrial fibrillation, CHB and pulmonary edema occurred more often in the diabetic group.34 Mohammad-Reza, Mazen Jamal M et al used showed that DM is a strong, independent risk for AF, atrial flutter and CHB in addition to other cardiovascular diseases.13 Mohammad-Reza-Movahed in his article states the increased prevalence of conduction abnormalities, such as right bundle branch block (RBBB), bifascicular block and high degree atrioventricular (AV) block but not left bundle branch block in DM.35

Lindstrom T, Jorfeldt L et al investigated whether hypoglycemia causes electrocardiographic changes and cardiac arrhythmias type 2 diabetics. In conclusion, he supports the hypothesis that hypoglycemia in patients with Type 2 DM may be hazardous by causing cardiac arrhythmias.36 Magnesium deficiency causes or exacerbates insulin resistance in type 2 DM. In diabetics, hypomagnesemia accelerates development and perpetuation of cardiovascular disease. Hypomagnesemia is a significant risk factor for atherogenesis, HTN, IHD, cardiac arrhythmias, coronary vasospasm, MI and sudden cardiac death.37

To conclude, arrhythmias in diabetics could represent an underlying sinister pathology. Each case of arrhythmia in DM warrants adequate evaluation. QTc and QTd are simple, yet invaluable tools to arouse suspicion of CAN. Comorbid illnesses, poor glycemic control, prolonged QTc, QTd and hypomagnesemia correlate with worse prognosis in DM.

Limitations of our study were that the sample was too small to generalize the results of the study; more cardiac investigations including perfusion studies would have added the value for the study. Also, prognosis of the cardiac involvement could not be ascertained as this study was cross sectional.

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REFERENCE

1. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors.The Framingham Study, Circulation 1979;59:8-13. | 2. Macfarlane PW, McLaughlin SC, Rodger JC. Influence of lead selection and population on automated measurement of QT dispersion. Circulation 1998;98:2160-7. | 3. Malmberg K Yusuf S, Gerstein HC et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: Results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry, Circulation 2000;102:1014-1019. | 4. American Diabetes Association, American Academy of Neurology. Consensus statement: Report and Recommendations of the San Antonio Conference on Diabetic Neuropathy. Diabetes Care 1988;11:592-7. | 5. Veglio M, Giunti S, Stevens LK et al. Prevalence of QT Interval Dispersion in Type 1 Diabetes and Its Relation with Cardiac Ischemia: the EURODIAB IDDM Complications Study Group. Diabetes Care 2002;25:702-07. | 6. Veglio M, Bruno G, Borra M et al. Prevalence of increased QT interval duration and dispersion in type 2 diabetic patients and its relationship with coronary heart disease: a population-based cohort. J Inter Med 2002;25:317-24. | 7. Stratton IM, Alder AI, Neil HA et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35) prospective observational study. BMJ 2000;321:405-12. | 8. Carol Chen-Scarabelli, Tiziano M. Scarabell. Suboptimal Glycemic Control, Independently of QT Interval Duration, Is Associated With Increased Risk of Ventricular Arrhythmias in a High-Risk Population. Pacing Clin Electrophysiol. 2006;29(1):9-14. | 9. Rensnick HE, Shorr RI, Kuller L et al. Prevalence and clinical implications of American Diabetes Association-defined and other categories of glucose dysregulation in older adults: The health, aging and body composition study. J Clin Epidemiol 2001;54:869-876. | 10. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology and management. JAMA 2002;287:2570-81. | 11. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: A statement for healthcare professionals from the American Heart Association. Circulation 1999;100: 1134-1146. | 12. William B et al. Epidemiological features of chronic atrial fibrillation. The Framingham study. New Engl J 1982;306 (17):1018 -22. | 13. International Journal of Cardiology 2005;105:315-18. | 14. C. J. Östgren, J. Merlo, L. Råstam, and U. Lindblad. Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community. Diabetes, Obesity and Metabolism 2004;6(5):367–374. | 15. Movahed MR, Hashemzadeh M, Jamal MM. Increased prevalence of third-degree atrioventricular block in patients with type II diabetes mellitus. Chest 2005;128:2611–14. | 16. Christoph Hasslacher, Peter Wahl et al. Diabetes prevalence in patients with bradycardia arrhythmias: Journal Acta Diabetologica 1977;14 (5):229 – 234. | 17. Mathur CP, Gupta D. QTc Prolongation in Diabetes Mellitus – An Indicator of Cardiac Autonomic Neuropathy – JIACM 2006;7(2):130-2. | 18. Bazett HC. An Analysis of the time relations of electrocardiograms. Heart 1920;7:353-70 | 19. Hodges M, Salerno Q, Erlien D. Bazett's QT correction reviewed. Evidence that a linear QT correction for heart rate is better. J Am Coll. Cardiol 1983; 1:694. | 20. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 1991;83:1888-94. | 21. Ahnve S, Gilpin E, Madsen EB et al. Prognostic importance off QTc interval at discharge after acute myocardial infarction: a multicenter study of 865 patients. Am Heart J 1984;108: 395-400. | 22. Dav CP, McComb JM, Camobell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br. Heart J 1990;63:342-4. | 23. Zabel M, Portnoy A, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization; an isolated heart validation study. J Am Coll Cardiol 1995;25:746-52. | 24. Naas AA, Davidson NC, Thompson C, Jung RT, Newton RW, Struthers AD. QT and QTc dispersion are accurate predictors of cardiac death in newly diagnosed non-insulin-dependent diabetes: cohort study. BMJ 1998;316:745-6 | 25. Rana BS, Band MM, Ogston S, Morris AD, Pringle SD, Sjruthers AD. Relation of OT interval dispersion to the number of different cardiac abnormalities in diabetes mellitus. Am Jr Cardiol. 2002;90(5):483-7. | 26. Veglio M, Borra M, Stevens LK et a1. The relationship between QTc interval prolongation and diabetic complications: the EURODIAB IDDM Complication Study Group. Diabetologia 1999;42:68-75. | 27. Sivieri R, Veglio M, Chinglia A et al. Prevalence of QT prolongation in a type 1 diabetic population and its association with autonomic neuropathy. Diabetic Med 1993;10:920-4. | 28. Sawicki PT, Meinhold J, Kiwitt et a1. QT interval dispersion is an important predictor of mortality in NIDDM patients. Diabetes 1996;45(Supple.2),128A. | 29. Dinneen SF, Gerstein HC. The Association of Microalbuminuria and Mortality in Non-Insulin-Dependent Diabetes Mellitus: A Systematic Overview of the Literature. Arch Intern Med 1997;157:1413-18. | 30. Marfella R, Rossi F, Giugliano D. Hyperglycaemia and QT interval: time for re-evaluation. Diabetes Nutri Metab 2001;14:63-5. | 31. Julu P. Vagolytic effect of diabetes mellitus. Brain 1993;116:485-92 | 32. Marfella R, Nappo F, DeAngelis L et a1. The effect of acute hyperglycaemia on QTc duration in a large healthy cohort. Diabetologia 2000;43:571-5. | 33. Brown DW, Giles WH, Greenlund KJ et al. Impaired fasting glucose, diabetes mellitus, and cardiovascular disease risk factors are associated with prolonged QTc duration. Results from the Third National Health and Nutrition Examination Survey. J Cardiovasc Risk 2001;8:227-33. | 34. Timothy M.E. Davis, Richard W. Parsons, Robin J. Broadhurst et al Arrhythmias and Mortality After Myocardial Infarction in Diabetic Patients. American Diabetes Association-Diabetes Care 1998;21(4):637. | 35. Mohammad-Reza-Movahed. Diabetes as a risk factor for cardiac conduction defects: a review. Diabetes, Obesity and Metabolism 2007;9(3): 276-81. | 36. Lindstrom T, Jorfeldt L, Tegler L, Arnqvist HJ. Hypoglycaemia and cardiac arrhythmias in patients with type 2 diabetes mellitus. Diabetes Med 1992;9(6):536-41. | 37. Altura BM, Zhang A, Altura B. Magnesium, hypertensive vascular diseases, atherogenesis, subcellular compartmentation of calcium and magnesium and vascular contractility. Miner Electrolyte Metab 1993;19:323-326. |