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A Study on QTc Prolongation as An Indicator of Cardiac Autonomic Neuropathy in Diabetic Patients at Bir Hospital, Nepal

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ABSTRACT

Background: Diabetes mellitus frequently leads to cardiac autonomic neuropathy (CAN), a complication that disrupts heart rate control and vascular function, increasing the risk of silent myocardial ischemia and sudden cardiac death. Prolonged QTc interval on ECG has emerged as a reliable marker for detecting CAN.

Method: A cross-sectional study was conducted on 100 diabetic patients at NAMS, Bir Hospital, Nepal, from September 2021 to June 2022. Data on QTc intervals and other clinical parameters were analyzed using STATA 13.0 software.

Result: Among the 100 patients, 60% were diagnosed with CAN. Of these, 20% had severe CAN and 40% had early-stage CAN. Patients with severe CAN had a longer duration of diabetes and higher blood sugar levels compared to those without CAN. QTc interval was significantly prolonged in 58% of patients with CAN, indicating a strong correlation between QTc prolongation and CAN severity.

Conclusion: QTc interval prolongation is closely associated with the severity of CAN, making it a practical and efficient tool for early detection in diabetic patients. Recognizing prolonged QTc can help identify patients at higher risk of sudden cardiac death, emphasizing the need for further large-scale studies.

Key words: diabetes mellitus; cardiac autonomic neuropathy; QTc Interval.

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INTRODUCTION

Diabetes mellitus (DM) refers to a group of metabolic disorders marked by elevated blood glucose levels. It occurs due to either insufficient insulin production by the pancreas or the inability of the body's cells to respond effectively to insulin.[1] As of 2019, an estimated 463 million adults aged between 20 and 79 years were living with diabetes worldwide, with projections suggesting this number could rise to 700 million by 2045.[2] Approximately two-thirds of these individuals are believed to reside in low and middle-income countries (LMICs). However, the precise burden of diabetes and related mortality in these regions remains unclear due to limited data.[2,3] In Nepal, the prevalence of diabetes is notably high, affecting 8.5% of the population.[4] In 2017, diabetes was responsible for approximately 10,145 deaths, ranking as the 11th leading cause of disability-adjusted life years (DALYs), with a rate of 1226 DALYs per 10,000 population.[5] The cardiovascular complications associated with diabetes mellitus encompass atherosclerotic coronary artery disease, diabetic cardiomyopathy, and cardiac autonomic neuropathy (CAN).[6] Insulin resistance is a key factor in the development and progression of these cardiovascular conditions.[7] Among the microvascular complications, CAN is particularly prevalent, with risk factors including the duration of diabetes, advanced age, and the severity of nephropathy.[8] Achieving effective glycemic control in the early stages of diabetes is crucial for preventing CAN.[8] Studies indicate that the prevalence of asymptomatic CAN is approximately 3.7 times higher than symptomatic cases.[9] Symptoms of CAN may include weakness, dizziness, frequent urination, nocturia, and upper body sweating.[6] These symptoms require attention, as CAN is associated with an increased risk of silent myocardial ischemia and sudden cardiac death.[10] The presence of CAN is strongly linked to higher morbidity and mortality, including complications such as coronary artery disease, stroke, and silent myocardial ischemia.[11] To ensure early diagnosis and timely management,

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it is recommended that patients with type 2 diabetes undergo neuropathy screening from the time of diagnosis.[12] Management of CAN focuses on symptom control and slowing disease progression. Key strategies include lifestyle modifications, intensive glycemic control, antioxidants, and managing orthostatic hypotension.[6] Despite the significance of cardiac autonomic neuropathy, there is currently no research from Nepal investigating QTc prolongation as an indicator of CAN in individuals with diabetes. Several non-invasive diagnostic tests are available, including the Ewing methodology for autonomic function, baroreflex sensitivity testing, and assessments of beat-to-beat blood pressure and heart rate variability.[13] Additional approaches, such as 24-hour Holter monitoring for heart rate turbulence parameters and tests measuring sweat production from dermal foot perspiration, have also been used.[6] However, while these methods are sensitive and reliable, they are labor-intensive and not practical for large-scale screening of diabetic populations. Prolongation of the corrected QT interval (QTc) on electrocardiograms (ECGs) has emerged as a specific, rapid, and objective tool for detecting CAN.[14] This study aims to explore the relationship between QTc prolongation and diabetic cardiac autonomic neuropathy, with the goal of improving early detection. Early diagnosis and timely treatment of CAN could help reduce complications and enhance the quality of life for patients with diabetes.

METHODS

An analytical Cross-sectional observational study was conducted in the department of Internal Medicine, National Academy of Medical Sciences, Bir-Hospital, Kathmandu, Nepal. Ethical approval was taken from institutional review commitee of National Academy of Medical Sciences, Bir-Hospital, Kathmandu, Nepal. This study was conducted among Diabetes mellitus patient attending to both outpatient and in-patient department of Bir Hospital were included in the study. This study was conducted from Sept 2021 to Jun 2022 AD. Non-probability technique was used to select the sample. While sample sized was calculated by taking prevalence from previous study, which is 65.2% = 0.652 [7]. By taking maximum tolerable error of 10 % and using the following statistical sample size calculation formula

For infinite population: $n= z^2pq/d^2$ [17].

Where, n is the sample size, z is the confidence level set at 95%, which is 1.96, q is the proportion of the sample elements that do not have the particular attribute,

q = 100-p% or (1-p) =100-65.2%(1-0.652) = 34.8% (0.348)

d is the permissible error 10% (0.1)

$$n= z^2pq/d^2$$
$$= \{(1.96)^2 \times 0.652 \times 0.348\}/ (0.1)^2$$
$$= 87.16$$
$$\cong 88$$

To reduce the non-response error, 10% sample was added.

n = 88+ 10% of 88
= 88+ 8.8
= 96.8 ≅ 97

The required sample size for study was 100.

Inclusion criteria:

All Diabetic patients who had cardiac sinus rhythm, stable vital sign and aged 18-75 years.

Exclusion criteria

Pregnant and breastfeeding women, as well as individuals with known or newly diagnosed cases of congenital heart disease and rheumatic valvular heart disease, require special consideration in clinical and medical settings. Additionally, the presence of symptoms such as anemia, hypoxia, hypovolemia, sepsis, renal failure, or other conditions that impact heart rhythm and orthostatic hypotension necessitates careful monitoring and management. Patients taking medications that influence cardiac rhythm, QT intervals, or blood pressure, including calcium channel blockers and beta blockers, are of particular concern. Exceptions may apply to those using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, but medications like antiarrhythmic drugs, tricyclic antipsychotics, and phenothiazines are noteworthy for their potential effects on cardiac function and overall health.

Intervention Details

Patients visiting OPD/Emergency department and admitted cases in Bir Hospital of diabetes mellitus were evaluated and enrolled after taking the informed consent. The patients fulfilling the inclusion criteria were clinically evaluated and various investigations including blood and ECG studies as mentioned in data collection section noted in proforma.

A comprehensive medical history and clinical examination were conducted following a structured proforma.[15] To assess cardiac autonomic neuropathy (CAN), the following five diagnostic tests were administered to each participant: (1) measurement of resting heart rate, (2) evaluation of blood pressure for postural or orthostatic hypotension, (3) heart rate response to the Valsalva maneuver, (4) heart rate variability during deep breathing, and (5) changes in diastolic blood pressure during isometric exercise. Each test outcome was classified into distinct categories based on the degree of abnormality detected, with specific points assigned accordingly.[18] The cumulative CAN score was used to categorize participants as having no CAN (score of 0), early CAN (score of 1), definite CAN (score of 2), or severe CAN (score of 3). Additionally, the QT interval was measured through an electrocardiogram (ECG), and the corrected QT interval (QTc) was calculated using Bazett's formula: $QTc = QT / \sqrt{RR}$.[19] A QTc value exceeding 440 milliseconds was considered indicative of a prolonged interval. The results were analysed by appropriate statistical methods. The result was expressed as mean +/- standard deviation, frequency, percentage, student t-test was used to compare mean of two different groups and simple linear regression was used see association. P value <0.05 was considered significant.

Data was collected using a structured proforma covering the identification, personal history, history, and blood investigations. Patients fulfilling the inclusion criteria were explained about the nature of the study and informed written consent was obtained from those willing to get enrolled.

All the cases were recruited from all diabetes mellitus patients belonging to the age group of 18 to 75 years fulfilling the inclusion criteria, presenting at OPD and emergency department and from admitted cases of diabetes mellitus.

Data was entered in EpiData 3.1 version and the statistical package for social sciences (SPSS) version 16 was used for data analysis. Results was presented in tables. Descriptive and inferential data was presented in frequency, percentage, mean ± standard deviation, student t-test was used to compare Mean of two different groups, simple linear regression was used to see association and statistical significance of the results was assessed. For this study a 95% confidence interval was accepted and a p-value <0.05 was taken as significant.

RESULTS

Table 1 indicates that out of 100 respondents, majority of the respondents (29%) belonged to age group 58-67 years and majority of the respondents were male (54%). Table 2 indicates that majority of the male respondents (13) belonged to age group 48-57 years and 58-67 years. And majority of female respondents (16) belonged to age group 58-67 years.

Table 3 shows that a minority (20%) of the respondents had severe cardiac autonomic neuropathy,40% of the respondents had early cardiac autonomic neuropath whereas 40% had no cardiac autonomic neuropathy. And 65 (65%) of the respondents had normal QTc interval and 35(35%) of the respondents had prolonged QTc interval.

Table 1. Socio-demographic variables of the study respondents. (n=100)

Variables	Frequency (%)
Age Group (years)	
18-27	2 (2)
28-37	10 (10)
38-47	18 (18)
48-57	23 (23)
58-67	29 (29)
≥ 68	18 (18)
Sex	
Male	54 (54)
Female	46 (46)

Table 4 shows that there was no significant difference between cardiac autonomic neuropathy between male

Table 2. Respondent's sex based on age category (n=100)		
Age group (year)	**Male (n)**	**Female (n)**
18-27	0	2
28-37	8	2
38-47	9	9
48-57	13	10
58-67	13	16
>68	11	7
Total	54	46

and female (p-value: 0.69).

Table 5 shows that there was no significant difference between QTc between male and female (p-value: 0.47).

Table 6 shows that there was a significant relation between cardiac autonomic neuropathy and duration of diabetes mellitus (P-value: 0.001). With one unit increase in duration of diabetes mellitus, cardiac autonomic neuropathy was higher by 0.023 unit (95% CI: -0.012-0.058). Duration of DM 8.90 ± 5.45 (without CAN) and 13.23 ± 7.10 (with CAN). And there was significant relation between cardiac autonomic neuropathy and QTc interval (P-value: <0.001). The value of cardiac autonomic neuropathy differs by 0.007 units while the value of QTc differs by one unit (95% CI: 0.003-0.011).

Table 3. CAN Score and QTc Interval distribution of the study respondents. (n=100)	
Variables	**Frequency (%)**
CAN Score	
No CAN (0-0.5)	40 (40)
Early CAN (1-2)	40 (40)
Severe CAN (≥ 2.5)	20 (20)
QTc	
Normal QTc (≤ 440 m sec)	65 (65)
Prolong QTc (> 440 m sec)	35 (35)

Table 4. Student's t-test for the significant difference between the mean of CAN and sex. (n=100)						
Sex	**Frequency**	**Mean**	**SD**	**95% CI**		**p-value**
Male	54	1.2	1.11	0.89	1.5	0.69
Female	46	1.29	1.13	0.95	1.63	
Combined	100	1.245	1.118			
Diff.		0.089				

Table 5. Students t-test for the significant difference between the mean of QTc and sex. (n=100)						
Sex	**Frequency**	**Mean**	**SD**	**95% CI**		**p-value**
Male	54	402.9	54.5	388.08	417.83	0.47
Female	46	410.6	52.25	395.13	426.17	
Combined	100	406.5	53.34			
Diff.		7.68				

Table 6. Association of CAN with duration of diabetes mellitus and QTc interval. (n=100)				
CAN	**Coefficient**	**95% CI**		**p-value**
Duration of DM	0.023	-0.012	0.058	0.001
QTc interval	0.007	0.003	0.011	0

DISCUSSION

Diabetes mellitus (DM) represents a significant global health concern, with its prevalence projected to increase from 4% in 1995 to 5.4% by 2025. The World Health Organization (WHO) anticipates that this rise will disproportionately affect developing nations, exacerbating the burden of diabetes-related complications. Among these complications, cardiac autonomic neuropathy (CAN) emerges as a critical consequence of prolonged diabetes duration. Determining the exact prevalence of CAN poses challenges, primarily because of its asymptomatic nature or nonspecific symptoms. Advances in diagnostic methods have led to cardiovascular reflex tests that can detect minimal autonomic dysfunctions[22]. Ewing et al.[23] developed a classification system for autonomic abnormalities using three heart rate response tests-the Valsalva ratio, heart rate variability during deep breathing, and resting heart rate-alongside two blood pressure tests: postural drop in systolic blood pressure and the rise in diastolic blood pressure during sustained handgrip. Based on these assessments, patients are classified into normal, early, or severe stages of CAN. Our study adhered to this classification framework. In our study, 60 out of 100 patients were diagnosed with CAN, resulting in a prevalence rate of 60%. This aligns with findings from other studies. Research by Nijhawan et al.[24], Barthwal et al.[25], and Kumar et al.[26] reported prevalence rates of 36.2%, 60%, and 60%, respectively, for diabetic CAN. Our analysis found a correlation between the duration of diabetes and the severity of CAN. For example, Kumar et al.[26] reported that a diabetes duration of 3.19 ± 2.81 years was not associated with CAN, whereas a longer duration of 8.52 ± 6.26 years was linked to its presence. Similarly, Barthwal et al.[25] observed that a diabetes duration of 3.51 ± 2.81 years did not correlate with CAN, but a

duration of 7.11 ± 3.49 years was associated with the condition. In our study, a duration of 8.90 ± 5.45 years was not linked with CAN, but a duration of 13.23 ± 7.10 years was correlated with its presence. These findings reinforce the conclusion that longer diabetes duration is a significant risk factor for CAN. Abnormalities in autonomic function are well-established contributors to QTc prolongation. Bellavere et al.[27] emphasized that diabetic CAN should be considered among the long QT syndromes. Our study demonstrated that QTc intervals were significantly prolonged in diabetic patients with severe CAN, averaging 467.14 ± 45.44 ms ($p < 0.001$), compared to early CAN (420.47 ± 55.33 ms, $p < 0.2$, not significant) and patients without CAN (378.18 ± 38.86 ms, $p < 0.2$, not significant). These findings align with prior studies: Barthwal et al.[25] (426 ± 24.4 ms), Veglio et al.[28] (421 ± 26 ms), Kumar et al.[26] (423 ± 22 ms), Shimbakuro et al.[29] (449 ± 13 ms), Mathur et al.[30] (449.31 ± 21.9 ms), and Pappachan et al.[3], further supporting the association between QTc prolongation and CAN in diabetic patients. The study evaluated cardiovascular autonomic neuropathy (CAN) among 100 individuals with diabetes. Participants' ages ranged from 27 to 74 years, with a large proportion belonging to the 51–60-year age group. The average age was 45.76 ± 14.17 years. The cohort included 54 males (54%) and 46 females (46%). The duration of diabetes varied from 2 to 26 years, with a mean duration of 11.2 ± 6.75 years. A longer disease duration was observed in patients with severe CAN compared to those with early or no signs of CAN. Out of the total participants, 60 (60%) were found to have CAN, of which 20 (20%) exhibited severe CAN, while 40 (40%) had early-stage CAN. Patients with severe CAN also demonstrated significantly higher blood glucose levels than those without CAN. Additionally, 35 participants (58%) with CAN showed a significantly prolonged QTc interval on electrocardiogram analysis.

CONCLUSIONS

In conclusion, our study highlights the significant prevalence of CAN in patients with diabetes, particularly with increased disease duration. The correlation between CAN and QTc prolongation underscores the importance of monitoring cardiac autonomic function to prevent severe cardiovascular complications. Future research should focus on refining diagnostic approaches and exploring effective interventions to mitigate these risks.

Limitation

Our study also has some limitations. First, we could not establish the temporality in the relationship among diabetes patients attending a tertiary care hospital located in Kathmandu, Nepal due to cross sectional design of the study. Second, our study was conducted among diabetes patients attending a tertiary care hospital located in Kathmandu, Nepal. Therefore, it may not necessarily represent the entire Nepalese diabetes population. A potential limitation of our study was its small sample size and subjects from 18 to 75 years were only included in the study.

Conflict of Interest: None

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