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ARTICLE

Comparison of formulae for calculating the corrected QT (QTc) interval in an adult population attending a diabetes clinic at a rural hospital in South Africa.

BN Mkhwanazi[a]*, L Govender[a] and S Pillay[b]

[a]*Discipline of Dietetics and Nutrition, University of KwaZulu-Natal, Durban, South Africa*
[b]*School of Clinical Medicine, University of KwaZulu-Natal, Durban, South Africa*
**Correspondence: mkhwanazib@ukzn.ac.za*

Background: A prolonged corrected QT (QTc) interval on the electrocardiograph is an important marker of cardiac autonomic neuropathy and increased risk of developing arrhythmias. Various formulae exist for the calculation of QTc, the most common being Bazett's, which is also the default formula utilised by the Edan SE® ECG machine to automatically calculate QTc. Little or no literature exists on the comparisons of the various formulae in patients living with diabetes, more especially in those diabetes patients with HIV infection.
Methods: Retrospective ($n = 631$) electrocardiographs were collected and analysed. QT and RR were measured for QTc calculation. QTc was calculated using three formulae, namely Bazett (QTcB), Fridericia (QTcFri) and Framingham (QTcFram). Additionally, the automated QTc (QTcM), which used Bazett's formula, was recorded for comparison purposes. To determine the optimal formula for QTc calculation, slopes and r^2 using a QTc/RR regression analysis were calculated. The formula with the r^2 closest to zero was deemed superior when compared with its counterparts.
Results: The QTc Bazett was the worst-performing formula for QTc calculation, with the QTcFri performing best across both type 2 and type 1 diabetes patients with or without HIV infection. To validate which formula was employed in the automated QTc result, a mean difference comparison was performed, which indicated a non-significant difference between the machine-calculated QTcM and QTcB ($p = 0.572$, 0.384, 0.980) in all groups except for the type 1 diabetic group without HIV ($p = 0.009$). These findings indicated that the automated QTc employed Bazett's formula.
Conclusion: Evidence from this study has shown that the best formula to calculate QTc in patients with DM, with and without HIV infection, is the Fridericia formula. The authors advise that careful consideration should be taken when selecting a formula for QTc calculation. This will improve precision diagnosis and patient care.

Keywords: antiretroviral therapy, corrected QT (QTc) calculation, type 2 diabetes mellitus, human immunodeficiency virus, type 1 diabetes mellitus

Introduction

Poorly controlled diabetes mellitus (DM) leads to complications such as diabetic autonomic neuropathy (DAN).[1] DAN is an often neglected and not well-understood complication due to its asymptomatic nature, which has the possibility of resulting in sudden cardiac death. A well-researched manifestation of DAN is cardiovascular autonomic neuropathy (CAN), which is characterised by devastating complications in the form of arrhythmias, silent myocardial ischaemia and sudden cardiac death.[2] A recent study indicates that CAN is associated with prolonged QTc, which could be attributed to cases of sudden death.[3]

As part of a complete evaluation of an electrocardiogram (ECG), the QT interval needs to be assessed. The QT interval generally measures the duration of ventricular repolarisation and is measured from the onset of the QRS complex to the end of the T-wave. However, for accurate comparison purposes, QT should be corrected for the heart rate (QTc).[4]

The corrected QT (QTc) is, therefore, the gold standard in pharmaceuticals and clinical studies. There are, however, numerous ways in which QTc can be calculated; these include Bazett's, Fridericia's and Sagie's formula.[5] Bazett's formula remains the most often used, although there is not much consensus in the available literature. In 1920, Bazett derived the QT correction formula by dividing the observed QT interval by the square root of the RR interval. Using Bazett's formula, the corrected QT interval (Qtc) is calculated as QT/RR. A limitation of Bazett's method is possible over-correction at higher heart rates and under-correction at lower heart rates.[6] Consequently, other formulae have been proposed to better describe the QT–heart rate relationship.[7] Nonetheless, Bazett's formula remains recommended for the clinical data of infants and young children.[8]

Fridericia proposed an alternative correction formula to cater for over- and under-correction of Bazett's formula with fast and slow heart rates, respectively.[9,10] Fridericia's modifications are thought to work well in adults who have an average heart rate that ranges between 60 and 90 bpm.[8] Fridericia's formula is not without limitations, as some authors have indicated that it may be unsuitable for paediatric patients and may lead to significant under-correction of QTc.[8,11] On the other hand, two studies have demonstrated that, among the QT methods, the Fridericia formula performed accurately for the measurement of QT intervals in a middle-aged population.[12,13] In an effort to improve the QT correction, Sagie *et al.*[7] proposed a new linear correlation formula for adjusting the QT interval for heart rate based on the ECG study of 5 018 subjects from the Framingham Heart Study.[7]

A recent study by Vandenberk *et al.* 2016 demonstrated that the Framingham and Fridericia formulae provide the best QT

Table 1: Demographics and clinical parameters

Factor	All patients	Male	Female	*p*-value
N (%)	631	205 (33)	426 (67)	**< 0.0001**
Type 1 DM	101	53 (53)	46 (47)	0.395
Type 2 DM	529	145 (27)	376 (73)	**< 0.0001**
HIV positive	104	38 (37)	65 (63)	**0.0002**
HIV negative	526	161 (31)	356 (69)	**< 0.0001**
Mean ± SD:				
Age (years)	52.9 ± 16.0	48.2 ± 16.6	55.17 ± 15.3	**< 0.001**
Systolic BP (mmHg)	135.3 ± 26.6	128.6 ± 26.1	138.6 ± 26.2	**< 0.001**
Diastolic BP (mmHg)	78.0 ± 14.0	79.8 ± 13.70	77.2 ± 14.2	**0.03**
HR (bpm)	78.8 ± 15.5	73.8 ± 15.4	81.3 ± 15.00	**< 0.001**
Duration of DM (years)	10.16 ± 8.7	8.41 ± 7.8	11.0 ± 8.9	**< 0.0001**
Duration of HIV (years)	1.25 ± 3.4	1.46 ± 3.7	1.14 ± 3.3	0.06
QTc (ms):				
QT interval	344.1 ± 126.7	394.69 ± 215.9	379.1 ± 41.5	0.152
QTcB	429.9 ± 40.4	416.0 ± 31.0	436.5 ± 42.7	**< 0.001**
QTcFram	379.3 ± 39.4	379.7 ± 34.40	379.1 ± 41.5	0.867
QTcFri	411.8 ± 35.1	403 ± 25. 4	415.9 ± 38.3	**< 0.001**
QTcM	430.34 ± 28.3	416.7 ± 25.1	436.8 ± 27.5	**< 0.001**
Prolonged QTc, *n* (%):				
QTcB	166 (26)	30 (5)	56(9)	0.507
QTcFram	20 (3)	5 (0.8)	12 (2)	0.864
QTcFri	55 (9)	7 (1)	20 (3)	0.773
QTcM	144 (23)	19 (3)	44 (7)	0.536

N: number of participants; DM: diabetes mellitus; HIV: human immunodeficiency virus; QTc: corrected QT
Values in bold denote $p < 0.05$.

correction as compared with Bazett's formula for a healthy adult population.[5] These results suggest that, with enough available data, either the Fridericia or the Framingham formula should be considered the 'standard' formula for QTc calculation clinically in an adult population. It remains unclear in the literature which formula is useful for QTc generation in patients living with either HIV or DM or both. This study aimed to evaluate which formula performs best in these populations. Additionally, this study also evaluated the influence of heart rate on QTc.

Methodology

A retrospective study was undertaken, and data were obtained from the Harry Gwala Regional Hospital (formerly Edendale Hospital) diabetes clinic to evaluate which formula was superior for QTc calculation. Edendale Hospital is situated in a rural part of Pietermaritzburg. The diabetic clinic at this regional hospital was established to ensure proper patient care for individuals living with DM. A purposive sampling technique was used to conduct this study. The sample comprised record files of all patients who visited the diabetes clinic from January 1, 2018–December 31, 2019. All ECG recordings were performed using the Edan SE 1200® (San Diego, CA, USA) by a trained ECG technician. A manual calliper was used to calculate the QT interval.

Lead II was used for calculating the QTc interval as this was the lead used for the rhythm strip and, as such, was the longest lead for measurement. The beginning of the QT interval was captured as the earliest onset of the QRS complex in lead II. The maximum slope intercept method was used to define the end of the T-wave. The end of the QT interval was taken as the last point of the T-wave over lead II, where the down-sloping limb joined the baseline.[14,15]

QTc values were manually calculated using all three formulae (Bazett, Framingham and Fridericia). The QTc result was also captured from the ECG report, which the ECG machine automatically generated using the Bazett formula. The reference values used were based on the fact that the normal QTc range for males is from 350 to 450 ms and for females 360–460 ms. These values were used as cut-offs when calculating the prolonged QTc for male and female participants in this study.

QTc calculation

1. $QTcB = QT/RR^{1/2}$ [14]
2. $QtcFri = QT/RR^{1/3}$ [10]
3. $QtcFra = QT + 0.154\ (1\text{-}RR)$[16]
4. QTcM refers to the automated QTc calculated by the machine using Bazett's formula.

Using a population-based approach, the relation between QTc (ms) and RR (ms) was determined using regression analysis for QTc/RR per subject. The template QTcxRR + intercept was used to calculate linear regression. Because the ideal QTc correction should not depend on the RR interval, the slope of the regression (B) and R^2 should, therefore, be close to zero, indicating less influence of the RR interval. Based on this premise, a formula showing QTc/RR analysis with an R^2 closest to zero was deemed ideal for QTc calculation.[5,13,17]

Experimental design

The data were stratified into the following groups to determine which formula was most suitable for calculation within each group.

Group 1: Patients with type 2 diabetes without HIV ($n =$ 438)

Group 2: Patients with type 2 patients living with HIV ($n =$ 90)

Group 3: Patients with type 1 diabetes without HIV ($n =$ 87)

Group 4: Patients with type 1 living with HIV ($n = 14$)

Statistical analysis

QTc values were compared using repeated measures of one-way ANOVA followed by pair-wise comparison with Tukey correction. A QTc/RR linear regression was performed to calculate the slope (B value) and the intercept with their 95% CIs. Slopes were compared using repeated-measures ANOVA followed by pairwise comparison with Bonferroni correction. Bland–Altman plots with the calculation of bias and limits of agreement were performed to illustrate differences between correction formulae.

Results

Data from 631 patients were used for this analysis in this study. The majority of the study population were females 67% ($n =$ 426) and patients living with type 2 diabetes mellitus (84%, $n =$ 529). The age of the study participants was 52.9 ± 16.0 years, with females being significantly older than the male participants ($p < .001$). Females had significantly higher systolic blood pressure and heart rate than male patients ($p < 0.001$). The QTc values were also significantly higher in females when compared with males using all formulae except when using QTcFram. On average, the patients had had diabetes for > 10 years and those that had HIV infection and DM had had HIV infection for at least one year. QTcB and QTcM indicated that there were 166 (26) and 144 (23) participants with prolonged QTc (> 450 ms), respectively. This is contrary to QTcFri, which indicated that 55 (9) participants had prolonged QTc while QTcFram showed 20 (3) participants to have extended QTc. There was a higher number of female participants with prolonged QTc than male participants across all formulae, although the difference was not statistically significant ($p > 0.05$) (Table 1).

Table 2 indicates that there were significant differences in QTc values ($p < 0.001$) for all formulae except for the QTcM vs. QTcB comparisons in patients with T2DM with and without HIV infection ($p = 0.572$ and 0.384, respectively). The smaller QTc mean difference between QTcM and QTcB validates that the machine used Bazett's formula for the QTc calculation.

Similarly, in patients with T1DM there were significant differences noted in QTc calculations. Table 3 demonstrates that patients with T1DM without HIV showed a similar significant ($p < 0.001$) trend to those patients with T2DM with respect to the QTc values. Patients with T1DM with HIV had statistically significant QTc values for all comparisons except for the QTcM vs. QTcB comparison ($p = 0.980$).

QTc/RR analysis for patients with T2DM

The QTc/RR analysis (Table 4) indicates that QTcFr is the best QT correction formula for patients living with T2DM while Framingham and Bazett's correction formulae performed the worst, having the highest coefficients and R^2 values.

QTc/RR analysis for patients with T1DM

Here again, the QTc/RR analysis indicated that the QTcFr was the best QT correction formula for patients living with T1DM.

Table 2: Comparison of QTc values between correction formulae for patients with Type 2 DM living without or with HIV

Comparison	Mean difference	95% confidence interval		p-value
		Lower	Upper	
Group 1: T2DM without HIV ($n = 438$):				
QTcM vs. QTcFram	51.766	48.267	55.266	**< 0.001**
QTcM vs. QTcFr	18.094	16.224	19.963	**< 0.001**
QTcM vs. QTcB	−0.546	−2.442	1.351	0.572
QTcFram vs. QTcFr	−33.673	−36.071	−31.274	**< 0.001**
QTcFram vs. QTcB	−52.312	−56.049	−48.576	**< 0.001**
QTcFr vs. QTcB	−18.639*	−19.979	−17.300	**< 0.001**
Group 2: T2DM with HIV ($n = 90$):				
QTcM vs. QTcFram	54.426	47.080	61.772	**< 0.001**
QTcM vs. QTcFr	20.563	16.317	24.809	**< 0.001**
QTcM vs. QTcB	1.905	−2.419	6.228	0.384
QTcFram vs. QTcFr	−33.864	−38.736	−28.991	**< 0.001**
QTcFram vs. QTcB	−52.522	−60.147	−44.896	**< 0.001**
QTcFr vs. QTcB	−18.658	−21.414	−15.902	**< 0.001**

T2DM: Type 2 diabetes mellitus, HIV: human immunodeficiency virus, QTcM indicates QT correction with the machine, QTcFr indicates QT correction with Fredericia, QTcFram indicates QT correction with Framingham, QTcB indicates QT correction with QTc Bazett. Values in bold denote $p < 0.05$.

Table 3: Comparison of QTc values between correction formulae for type 1 diabetic patients living with and without HIV

Comparison	Mean difference	95% confidence interval		p-value
		Lower	Upper	
Group 3 T1DM without HIV ($n = 87$):				
QTcM vs. QTcFram	38.429	29.721	47.137	**< 0.001**
QTcM vs. QTcFr	9.082	3.831	14.333	**0.001**
QTcM vs. QTcB	−7.242	−12.599	−1.886	**0.009**
QTcFram vs. QTcFr	−29.347	−35.041	−23.653	**< 0.001**
QTcFram vs. QTcB	−45.672	−54.645	−36.698	**< 0.001**
QTcFr vs. QTcB	−16.325	−19.612	−13.038	**< 0.001**
Group 4 T1DM with HIV ($n = 14$):				
QTcM vs. QTcFram	53.348	32.359	74.338	**< 0.001**
QTcM vs. QTcFr	18.923	9.687	28.159	**0.001**
QTcM vs. QTcB	.068	−5.607	5.742	0.980
QTcFram vs. QTcFr	−34.425	−47.329	−21.522	**< 0.001**
QTcFram vs. QTcB	−53.281	−73.417	−33.144	**< 0.001**
QTcFr vs. QTcB	−18.855	−26.096	−11.615	**< 0.001**

Key: T1DM: Type 1 diabetes mellitus, HIV: human immunodeficiency virus, QTcM indicates QT correction with the machine, QTcFr indicates QT correction with Fredericia, QTcFram indicates QT correction with Framingham, QTcB indicates QT correction with QTc Bazett. Values in bold denote $p < 0.05$.

Table 4: Results from QTc (ms) / RR (ms) Analysis for patients with T2DM with and without HIV

	Slope			Constant			
		95% CI			95% CI		
Formula	Coefficient	Lower	Upper	Coefficient	Lower	Upper	R^2
Group 1: T2DM without HIV:							
QTcM	−57.847	−73.162	−42.531	479.174	466.875	491.472	0.114
QTcFram	144.084	128.128	160.040	268.470	255.657	281.283	0.425
QTcFr	−12.853	−29.874	4.167	425.666	411.998	439.334	0.005
QTcB	−99.814	−117.513	−82.115	512.751	498.539	526.964	0.223
Group 2: T2DM with HIV:							
QTcM	−46.521	−86.439	−6.603	468.365	436.674	500.056	0.057
QTcFram	159.968	121.591	198.344	252.449	221.971	282.926	0.441
QTcFr	.000	−41.713	41.712	411.303	378.176	444.430	< 0.001
QTcB	−89.850	−133.655	−46.046	500.165	465.377	534.953	0.160

T2DM: Type 2 diabetes mellitus, HIV: human immunodeficiency virus, QTcM indicates QT correction with the machine, QTcFr indicates QT correction with Fredericia, QTcFram indicates QT correction with Framingham, QTcB indicates QT correction with QTc Bazett.

Table 5 presents the QTc/RR analysis and indicates that Fridericia is the best QT correction formula for T1DM living with and without HIV. Fridericia's formula demonstrated the smallest coefficient of −20.71 and R^2 of 0.15 and −2.335 and R^2, which is less than 0.001 for T1DM without and with HIV, respectively.

Comparison of slopes between correction formulae for patients with T2DM

It is worth noting that the mean difference between QTcM and QTcB was 41.967 and reflected the smallest mean difference compared with all the other formulae for T2DM without HIV, while the difference between QTcFri and QTcB was 86.961 for the type 2 diabetes group without HIV. A similar trend was observed in type 2 diabetes patients living with HIV, where the difference between QTcM and QTcB was the smallest at 43.329 as compared with 89.850 for the comparison between QTcFri and QTcB (Table 6).

Comparison of slopes between correction formulae for patients with T1DM

Table 7 indicates that the mean difference in slopes was significantly ($p < 0.001$) different for the type 1 diabetic group living without HIV. The smallest numerical difference was noted for the QTcM and QTcB comparison. A similar trend was observed for type 1 diabetic patients living with HIV, except for QTcM versus QTcB, which was not statistically significant.

Bland–Altman calculations

Tables 8 and 9 show the Bland–Altman calculations of bias and limits of agreements between the QTc formulae for T2DM and T1DM. The analysis demonstrated good agreement between the Bazett and the machine-calculated QTc across T1DM and T2DM groups. However, there was poor agreement between Bazett and the other three formulae. A similar trend was observed in patients with T1DM living with or without HIV.

Discussion

This study explored the most suitable formula for QTc calculation in patients living with DM with or without HIV infection. It was conducted in a low-resource setting in South Africa and reports for the first time which formula is best suitable for QTc. A comparison was made between three formulae, Bazett, Fridericia's and Framingham's, and a machine-calculated QTc, which used Bazett's formula. The use of Bazett's formula is very common in clinical studies, perhaps due to the fact it was discovered earliest as compared with the other formula. Despite its popularity, researchers have questioned its continued use, especially in the adult population, as there is evidence of significant variability and inconsistencies.[5,8,18] Our study

Table 5: Results from QTc (ms) / RR (ms) Analysis for patients with T1DM with and without HIV

	Slope			Constant			
		95% CI			95% CI		
Formula	Coefficient	Lower	Upper	Coefficient	Lower	Upper	R^2
Group 3: T1DM without HIV:							
QTcM	−65.085	−99.923	−30.247	466.100	437.292	494.907	0.143
QTcFram	134.179	99.249	169.109	266.290	237.406	295.173	0.413
QTcFr	−20.705	−57.725	16.314	421.075	390.463	451.686	0.015
QTcB	−108.787	−147.266	−70.308	508.735	476.917	540.553	0.276
Group 4: T1DM with HIV"							
QTcM	−92.054	−194.992	10.883	499.845	419.048	580.643	0.260
QTcFram	158.332	97.775	218.889	252.544	205.011	300.076	0.751
QTcFr	−2.335	−72.268	67.597	411.424	356.533	466.316	< 0.001
QTcB	−91.849	−168.769	−14.929	499.619	439.243	559.995	0.386

T1DM: Type 1 diabetes mellitus, HIV: human immunodeficiency virus, QTcM indicates QT correction with the machine, QTcFr indicates QT correction with Fredericia, QTcFram indicates QT correction with Framingham, QTcB indicates QT correction with QTc Bazett.

Table 6: Comparison of slopes between correction formulae for patients with T2DM

		95% confidence interval		
Comparison	**Mean difference**	**Lower**	**Upper**	***p*-value**
Group 1: T2DM without HIV:				
QTcM vs. QTcFram	−201.931	−204.717	−198.606	**< 0.001**
QTcM vs. QTcFr	−44.993	−48.064	−41.655	**< 0.001**
QTcM vs. QTcB	41.967	38.625	45.318	**< 0.001**
QTcFram vs. QTcFr	156.937	156.119	157.485	**< 0.001**
QTcFram vs. QTcB	243.898	242.477	244.789	**< 0.001**
QTcFr vs. QTcB	86.961	86.346	87.316	**< 0.001**
Group 2: T2DM with HIV:				
QTcM vs. QTcFram	−206.489	−213.456	−199.568	**< 0.001**
QTcM vs. QTcFr	−46.520	−53.966	−39.35	**< 0.001**
QTcM vs. QTcB	43.329	35.423	50.748	**< 0.001**
QTcFram vs. QTcFr	159.968	158.389	161.321	**< 0.001**
QTcFram vs. QTcB	249.818	247.118	252.078	**< 0.001**
QTcFr vs. QTcB	89.850	88.708	90.778	**< 0.001**

T2DM: Type 2 diabetes mellitus, HIV: human immunodeficiency virus, QTcM indicates QT correction with the machine, QTcFr indicates QT correction with Fredericia, QTcFram indicates QT correction with Framingham, QTcB indicates QT correction with QTc Bazett. Values in bold indicate $p < 0.05$.

aimed to resolve which formula may be better for QTc calculation.

To validate which formula was employed in the automated QTc result, a mean difference comparison was performed, indicating the non-significant difference between the machine-calculated QTcM and QTcB. These results were further corroborated by mean differences between the slopes for QTcM and QTcB, which were smallest by comparison with other formulae regardless of the HIV status. Additionally, the Bland–Altman analysis indicated agreement between the QTcM and QTcB by comparison with the other formulae. These findings indicated that the automated QTc employed Bazett's formula.

It was, however, interesting to note that QTc Bazett was the worst-performing formula for QTc calculation, with QTcFri performing best across both type 2 and type 1 diabetes patients with or without HIV infection. These results are consistent with the literature, which suggests that Bazett's formula over-corrects in QTc in faster heart rates while under-correcting in slower heart rates.[5,8,17,18] Whilst it must be noted that these studies are population-based, there exists a commonality amongst them, which is the inferiority of Bazett's formula. The superiority of QTcFri over QTcB has been reported in several studies where Fridericia's formula had a slope closest to zero following a QTc/RR analysis, indicating minimal influence over the corrected value.[5] The general consensus in the literature is that the Bazett formula should be discontinued as this can result in diagnostic errors.[5,18,19] Additionally, since QTc is used in clinical trials to determine the cardiotoxicity of new drugs in clinical trials, it is advisable that an improved correction like Fridericia's be used. A recent study done on 539 healthy participants indicated that the Bazett correction was more variable as compared with all other formulae investigated.[18] Indeed, the same phenomenon was observed in our study where QTcB showed that 26% of patients had prolonged

Table 7: Comparison of slopes between correction formulae for patients with T1DM

		95% confidence interval		
Comparison	**Mean difference**	**Lower**	**Upper**	***p*-value**
Group 3: T1DM without HIV:				
QTcM vs. QTcFram	−199.264	−209.463	−187.328	**< 0.001**
QTcM vs. QTcFr	−44.380	−54.749	−32.953	**< 0.001**
QTcM vs. QTcB	43.702	33.061	54.749	**< 0.001**
QTcFram vs. QTcFr	154.884	152.194	156.897	**< 0.001**
QTcFram vs. QTcB	242.966	238.007	246.595	**< 0.001**
QTcFr vs. QTcB	88.082	85.785	89.726	**< 0.001**
Group 4: T1DM with HIV:				
QTcM vs. QTcFram	−250.386	−262.493	−238.02	**< 0.001**
QTcM vs. QTcFr	−89.719	−100.734	−78.628	**< 0.001**
QTcM vs. QTcB	−0.205	−11.07	10.579	1
QTcFram vs. QTcFr	160.667	157.613	163.538	**< 0.001**
QTcFram vs. QTcB	250.181	244.775	255.247	**< 0.001**
QTcFr vs. QTcB	89.514	87.132	91.739	**< 0.001**

T1DM: Type 1 diabetes mellitus, HIV: human immunodeficiency virus, QTcM indicates QT correction with the machine, QTcFr indicates QT correction with Fredericia, QTcFram indicates QT correction with Framingham, QTcB indicates QT correction with QTc Bazett. Values in bold indicate $p < 0.05$.

Table 8: Bland–Altman analysis between QT correction formulae in patients with T2DM

Comparison	Bias	SD of Bias	95% confidence interval	
			Lower	Upper
Group 1: T2DM without HIV:				
QTcM vs. QTcFram	51.77	−36.87	−20.50	124.04
QTcM vs. QTcFr	18.09	−19.70	−20.51	56.70
QTcM vs. QTcB	−0.55	−19.99	−39.72	38.63
QTcFram vs. QTcFr	−33.67	−25.28	−83.22	15.87
QTcFram vs. QTcB	−52.31	−39.37	−129.49	24.86
QTcFr vs. QTcB	−18.64	−14.12	−46.30	9.03
Group 2: T2DM with HIV:				
QTcM vs. QTcFram	54.43	−34.87	−13.92	122.78
QTcM vs. QTcFr	20.56	−20.16	−18.94	60.07
QTcM vs. QTcB	1.90	−20.52	−38.32	42.13
QTcFram vs. QTcFr	−33.86	−23.13	−79.20	11.47
QTcFram vs. QTcB	−52.52	−36.20	−123.47	18.43
QTcFr vs. QTcB	−18.66	−13.08	−44.30	6.99

T2DM: Type 2 diabetes mellitus, HIV: human immunodeficiency virus, QTcM indicates QT correction with the machine, QTcFr indicates QT correction with Fredericia, QTcFram indicates QT correction with Framingham, QTcB indicates QT correction with QTc Bazett.

QTc compared with QTcFri, demonstrating that only 9% of patients had QTc prolongation.

The data indicate that more female participants had prolonged QTc than male participants; while these data had no statistical significance, they may be of biological importance. A similar trend was observed in several studies where females were more susceptible to prolonged QTc.[20,21] The difference in QTc values is thought to be, in part, influenced by hormonal differences between males and females, although full mechanisms warrant investigation.[22] It is interesting, however, that studies involving children under two years of age reported fewer inconsistencies with Bazett's correction results. Phan *et al.* showed that Bazett had the smallest slope when compared with the Fridericia, Hodges and Framingham formulae, thus indicating the suitability of Bazett's formula for a young population.[8] This led them to the conclusion, in agreement with our study, that Fridericia may be better suited for an adult population as compared with Bazett's formula.[8]

Table 9: Bland–Altman analysis between QT correction formulae in patients with T1DM

Comparison	Bias	SD of bias	95% confidence interval	
			Lower	Upper
Group 3: T1DM without HIV:				
QTcM vs. QTcFram	38.43	−40.37	−40.70	117.56
QTcM vs. QTcFr	9.08	−24.34	−38.63	56.80
QTcM vs. QTcB	−7.24	−24.83	−55.92	41.43
QTcFram vs. QTcFr	−29.35	−26.40	−81.09	22.40
QTcFram vs. QTcB	−45.67	−41.61	−127.21	35.87
QTcFr vs. QTcB	−16.32	−15.24	−46.19	13.54
Group 4: T1DM with HIV:				
QTcM vs. QTcFram	53.35	−34.73	−14.73	121.43
QTcM vs. QTcFr	18.92	−15.28	−11.03	48.88
QTcM vs. QTcB	0.07	−9.39	−18.34	18.47
QTcFram vs. QTcFr	−34.43	−21.35	−76.27	7.42
QTcFram vs. QTcB	−53.28	−33.32	−118.60	12.03
QTcFr vs. QTcB	−18.86	−11.98	−42.35	4.63

T1DM: Type 1 diabetes mellitus, HIV: human immunodeficiency virus, QTcM indicates QT correction with the machine, QTcFr indicates QT correction with Fredericia, QTcFram indicates QT correction with Framingham, QTcB indicates QT correction with QTc Bazett. Values in bold indicate $p < 0.05$.

Conclusion

Prolonged QTc interval on the electrocardiograph is an important marker of cardiac autonomic neuropathy and an increased risk of developing arrhythmias. Various formulae exist for calculating QTc, the most common being Bazett's, which is also the default formula utilised by the Edan SE® ECG machine to automatically calculate QTc. Little or no literature exists on the comparisons among the various formulae in patients living with diabetes, more especially in those diabetes patients with HIV infection. Evidence from this study has shown that the best formula to calculate QTc in patients with DM, with and without HIV infection, is the Fridericia formula. The authors advise that careful consideration should be taken when selecting a formula for QTc calculation. While clinicians and technicians may not have the time to manually calculate QTc in a busy hospital setting, modern ECG machines allow for manual adjustment of the QTc formula. This will improve precision diagnosis and patient care.

Limitations of study

As this was a retrospective study, no causal relationships could be established; rather, associations were determined. QRS was not collected as a parameter in this study; medication or diabetes and/or HIV infection might have influenced the QTc.

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ORCID

BN Mkhwanazi http://orcid.org/0000-0003-1181-3587

References

1. Freeman R. Diabetic autonomic neuropathy. Handb Clin Neurol. 2014;126:63–79.
2. Verrotti A, Prezioso G, Scattoni R, et al. Autonomic neuropathy in diabetes mellitus. Front Endocrinol. 2014;5:205.
3. Vasheghani M, Sarvghadi F, Beyranvand MR, et al. The relationship between QT interval indices with cardiac autonomic neuropathy in diabetic patients: a case control study. Diabetol Metab Syndr. 2020;12(1):102.
4. Postema PG, Wilde AAM. The measurement of the QT interval. Curr Cardiol Rev. 2014;10(3):287–294.
5. Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to Use for QT monitoring? J Am Heart Assoc. 2018;7(16): e004252.
6. Brouwer J, Van Den Berg MP, Grobbee DE, et al. Diagnostic performance of various QTc interval formulas in a large family with long QT syndrome type 3: Bazett's formula not so bad after all. Ann Non Electr Off J Int Soc Holter Non Electr. 2003;8(4):269–274.
7. Sagie A, Larson MG, Goldberg RJ, et al. An improved method for adjusting the QT interval for heart rate (the framingham heart study). Am J Cardiol. 1992;70(7):797–801.
8. Phan DQ, Silka MJ, Lan YT, et al. Comparison of formulas for calculation of the corrected QT interval in infants and young children. J Pediatr. 2015;166(4):960-4.e1-2.

9. Hazeki D, Yoshinaga M, Takahashi H, et al. Cut-offs for screening prolonged QT intervals from fridericia's formula in children and adolescents. Circ J Off J Japanese Circ Soc. 2010;74(8):1663–1669.
10. Fridericia L. Die systolendauer im elektrokardiogramm bei normalen menschen und bei herzkranken. Acta Med Scand. 1920;53:469–486.
11. Benatar A, Decraene T. Comparison of formulae for heart rate correction of QT interval in exercise ECGs from healthy children. Heart (British Cardiac Society). 2001;86(2):199–202.
12. Puddu PE, Jouve R, Mariotti S, et al. Evaluation of 10 QT prediction formulas in 881 middle-aged men from the seven countries study: emphasis on the cubic root fridericia's equation. J Electrocardiol. 1988;21(3):219–229.
13. Strohmer B, Schernthanere C, Paulweber B, et al. Gender-specific comparison of five QT correction formulae in middle-aged participants in an atherosclerosis prevention program. Med Sci Monitor Int Med J Exp Clin Res. 2007;13(4):Cr165-71.
14. Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. Circulation. 1952;6(3):378–388.
15. Postema PG, Wilde AA. The measurement of the QT interval. Curr Cardiol Rev. 2014;10(3):287–294.
16. Sagie A, Larson M, Goldberg R, et al. An improved method for adjusting the QT interval for heart rate (the framingham heart study). Am J Cardiol. 1992;70:797–801.
17. Dogan A, Tunc E, Varol E, et al. Comparison of the four formulas of adjusting QT interval for the heart rate in the middle-aged healthy turkish men. Ann Non Electr Off J Int Soc Holter Non Electr. 2005;10(2):134–141.
18. Andršová I, Hnatkova K, Šišáková M, et al. Influence of heart rate correction formulas on QTc interval stability. Sci Rep. 2021;11(1):14269.
19. Andric T, Winckel K, Tanzer T, et al. Bazett's correction formula overestimates the corrected QT among patients with antipsychotic induced tachycardia. Schizophr Res. 2021;231:22–23.
20. Stramba-Badiale M, Locati EH, Martinelli A, et al. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h holter recordings. Eur Heart J. 1997;18(6):1000–1006.
21. Rabkin SW. Impact of Age and Sex on QT prolongation in patients receiving psychotropics. Can J Psychiatry. 2015;60(5):206–214.
22. Kannankeril P, Roden DM, Darbar D. Drug-induced long QT syndrome. Pharmacol Rev. 2010;62(4):760–781.

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