Incidence of QTc Prolongation in Type 2 Diabetes Mellitus and it´s Relation to Cardiac Autonomic Neuropathy

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Abstract

Recently there has been growing interest in the relationship between diabetes and QTc. Prevalence of prolonged QTc interval is higher in people with type 2 diabetes as compared to non-diabetic subjects, especially in the presence of autonomic neuropathy. QTc prolongation in diabetic autonomic impairment has been reported by numerous authors and also has been reported to lead to sudden death.

Objective: The main aim of this study is to estimate the incidence of QTc prolongation in type 2 diabetes mellitus and its relationship to cardiac autonomic neuropathy.

Methods: From January 2009 to September 2009, we enrolled 150 type 2 diabetic patients attending the Sulaimani diabetic centre. We also enrolled 100 non diabetic control groups.

Both group underwent measurement of QT interval, subsequently QTc estimated according to Bazett equation. We also performed 5 cardiovascular autonomic tests including resting heart rate measurement, heart rate variation with inspiration and expiration, valsalva maneuver, blood pressure response to handgrip and standing.

Results: Among the 150 cases 13 were found to have prolonged QTc (8.7%), 11 were females 2 were males (p value 0.041). No one in the control group showed prolonged QTc. Regarding cardiac autonomic neuropathy (CAN), 106 cases had CAN 35, 40 and 31 for early, definite and severe cases, respectively. There was significant correlation between QTc & CAN (p value 0.000) QTc prolongation was significantly related with increasing age (p value 0.010) and female gender (p value 0.041) but no relationship was found with duration of DM (p value 0.520).

Sensitivity of prolonged QTc for detection of CAN was 20%, with specificity and positive predictive value of 98.7% and 92.3%, respectively.

Conclusions: We realized that QTc prolongation occur in cardiac autonomic neuropathy due to DM and it´s highly specific for CAN but insensitive. It is significantly correlated with age & gender but no relation found with duration of DM.

Keywords: QTc Prolongation, Cardiac Autonomic Neuropathy, Diabetes Mellitus.

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Introduction

Diabetes mellitus (DM) is an important metabolic disorder that can affect almost every organ system in the body. Cardiovascular disease is one of its most common complications that increase morbidity and

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mortality in these patients. Diabetes is reaching epidemic proportions in many parts of the world with the number of subjects with diabetes expected to double during the next 30 years[1]. The cardiovascular complications of diabetes mellitus can be classified into three groups: 1. Atherosclerotic coronary artery disease 2. Diabetic cardiomyopathy 3. Cardiac autonomic neuropathy (CAN). Cardiac autonomic neuropathy is a common but frequently overlooked complication of diabetes, which can lead to a diverse spectrum of clinical manifestations ranging from impairment of exercise tolerance to sudden cardiac death[2]. New scintigraphic imaging techniques have demonstrated that cardiac dysinnervation can occur early in the course of diabetes and is often asymptomatic, but can rapidly progress with poor metabolic control and result in a complex array of clinical outcomes[3]. Although the impact of cardiac dysinnervation on myocardial stability and function remains unclear and somewhat controversial, recent data have highlighted its role in the development of altered myocardial blood flow regulation, impaired left ventricular (LV) function, and potentially in the development of diabetic cardiomyopathy[4].

QT Interval and DM:

QT intervals in the electrocardiogram reflect depolarization and repolarization of ventricular muscle, or duration of the intracellular action potential. Since QT intervals are influenced by heart rate, corrected QT intervals (QTc) was defined by Bazett in 1920[5].

The main problem with QT interval assessment is that there is no universally recognized standard method of analysis or of lead selection. It may not be possible to measure QT interval in every lead, and measurement may be less than precise. QT intervals vary significantly among leads [6]. Most normal reference ranges are based upon measurements from lead II [7]. However, some suggest using whichever limb lead best shows the end of the T wave[8]; or leads V2 or V3, in which QT measurements are typically the longest[6]; or leads V5 or V6, because of the clarity of the Q-wave onset and T-wave termination.

QT interval can be measured erroneously by misinterpreting either the beginning of the QRS complex or the end of the T wave. The reasons for QT abnormalities in diabetes are not completely understood. It has been proposed that hyperglycemia may produce ventricular instability by increased sympathetic activity, increased intracellular calcium content in myocytes or both[9] .There is a wealth of data to link QT abnormalities with cardiac ischemia, but these abnormalities have been found even in newly diagnosed diabetic patients with no apparent cardiac disease.

Congenitally long QTc intervals can cause sudden death due torsades de pointes type of polymorphic ventricular tachycardia and ventricular fibrillation. [10]. QTc prolongation in diabetic autonomic impairment has been reported by numerous authors & also has been reported to lead to sudden death. [11]

Prolonged QTc in diabetes has been interpreted as a consequence of imbalance between right and left sympathetic activity and as a marker of electrical instability Consensus statements released by the American Diabetic Association and the American Academy of Neurology indicate that testing for prolongation of Bazett's QTc is easy and specific for diabetic cardiac autonomic failure. However, is seldom used to evaluate alteration in cardiac sympathetic innervation in the clinical setting because of its insensitivity for

autonomic failure. A meta-analysis recently concluded that measurement of QTc is a more accurate test for autonomic failure in young men with diabetes and that normal QTc rules out autonomic failure best among diabetic patients in whom it is most sensitive.[12] Under normal circumstances, the duration of repolarization depends upon the heart rate. The QT interval is longer at slower rates and shorter at faster rates. For this reason, formulas have been developed to "correct" the QT interval for heart rate. The most commonly used rate correction formula was developed by Bazett.

QTc= QT/ √R-R (sec)

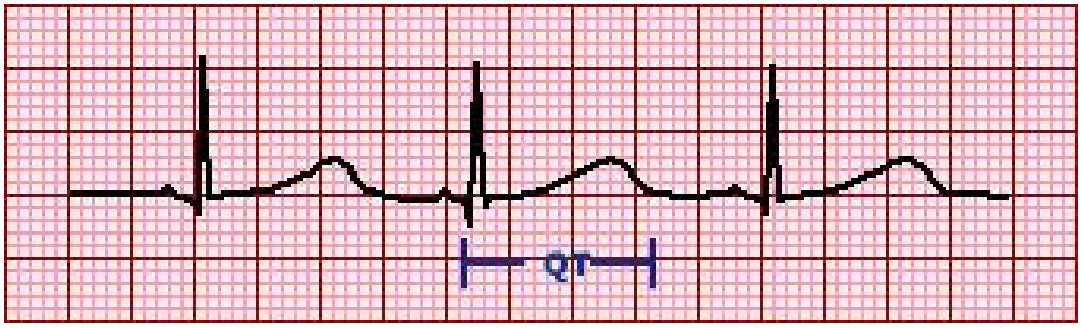

Figure 1. QT Interval

Table 1. The five autonomic function tests to detect cardiac autonomic neuropathy and the scores obtained for each in the patients expressed as points

Autonomic function	categories	test Points
1. Resting heart rate		
<100 beats/min	normal	0
100–110 beats/min	borderline	0.5
>110 beats/min	abnormal	1
2. Heart rate variability on deep breathing		
>15 beats/min	normal	0
15–10 beats/min	borderline	0.5
<10 beats/min	abnormal	1
3. Valsalva ratio (longest RR interval: shortest RR interval)		
>1.2	normal	0
1.2–1.10	borderline	0.5
<1.10	abnormal	1
4. Increase in diastolic blood pressure during sustained handgrip		
>15 mm Hg	normal	0
15–10 mm Hg	borderline	0.5
<10 mm Hg	abnormal	1
5. Postural hypotension (fall in systolic blood pressure)		
<20 mm Hg	normal	0
20–30 mm Hg	borderline	0.5
>30 mm Hg	abnormal	1

Table 2. Incidence of prolonged QTc

Variables	Frequency	Percent
QTc interval		
Normal	137	91.3
Prolonged	13	8.7

Epidemiology of CAN:

CAN is usually detected using widely available indirect standardized cardiovascular reflex tests, which evaluate the integrity of the complex reflex arcs. These assessments in general, identify abnormalities of cardiovascular innervation in 16–20% of subjects with diabetes [13].

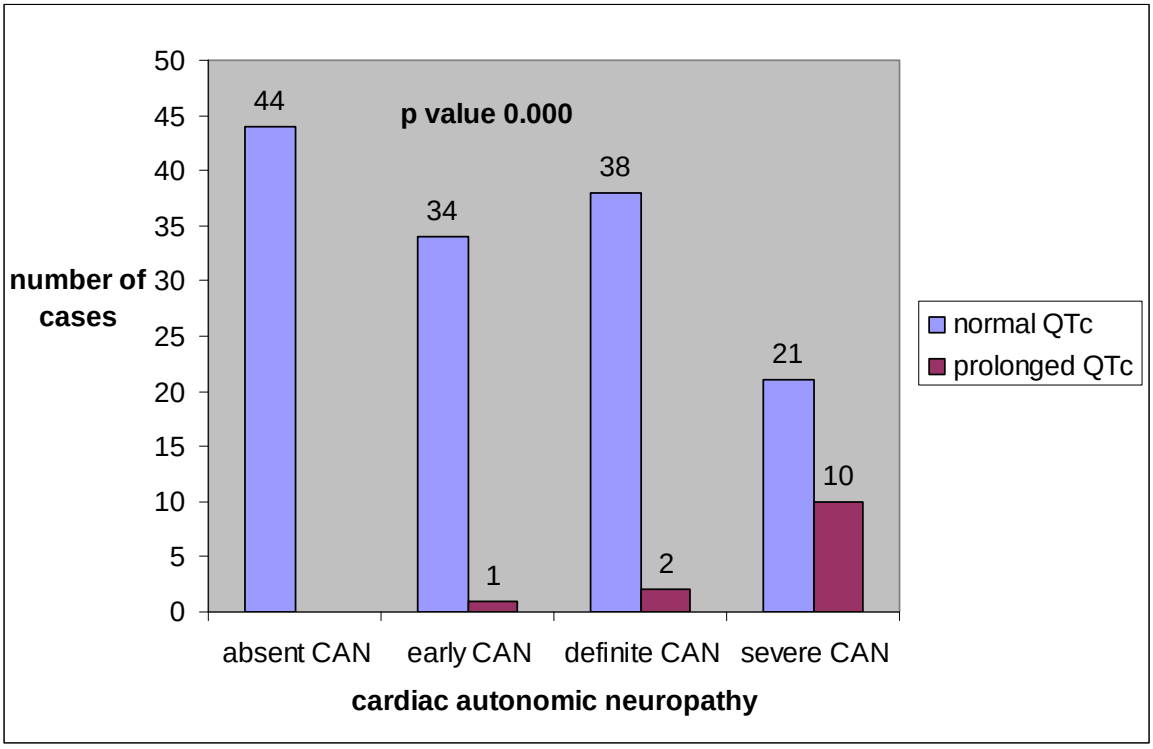

Figure 2. QTc and CAN

CAN is correlated with diabetes duration and retinopathy and is independently associated with obesity in type 2 diabetes [14]. The frequency of parasympathetic CAN has been reported to be 20% at 5 years and 65% at 10 years[15] and sympathetic CAN 7% at 5 years and 24% at 10 years.

Recently, CAN has also been extensively evaluated using more direct, but expensive techniques involving radiolabeled analogs of norepinephrine, which are actively taken up by cardiac sympathetic nerve terminals[16-17]. These techniques have identified a specific cardiac sympathetic dysinnervation complicating diabetes, and proven to be useful in not only determining the prevalence of cardiac sympathetic dysinnervation, but have also been utilized to follow its progression and its response to therapeutic intervention. Both [I^{23}] *meta*iodobenzylguanidine (MIBG) and [C^{11}] *meta*hydroxyephedrine (HED) have been extensively utilized to assess the integrity of

cardiac sympathetic innervation.Clinical manifestations of CAN includes: resting tachycardia[18]exercise intolerance{Autonomic dysfunction impairs exercise tolerance [19].reduces response in heart rate and blood pressure (BP) [20] and blunts increases in cardiac output in response to exercise[21], diabetic patients who are likely to have CAN should be tested for cardiac stress before undertaking an exercise program.[22]}, other manifestations of CAN includes intraoperative and perioperative car diovascular instability [23-24] orthostatic hypotension [25], orthostatic tachycardia and bradycardia syndromes[26], silent myocardial Ischemia/cardiac denervation syndrome [27].

Table 3. Cardiac autonomic function tests in type2 DM

Variables	Frequency	percent
Resting tachycardia		
Normal	138	92.0
Borderline	9	6.0
Abnormal	3	2.0
Heart rate variation in insp. & exp.		
Normal	49	32.7
Borderline	26	17.3
Abnormal	75	50.0
Valsalva ratio		
Normal	85	56.7
Borderline	25	16.7
Abnormal	40	26.7
BP response to hand grip		
Normal	77	51.3
Borderline	45	30.0
Abnormal	28	18.7
Postural hypotension		
Normal	122	81.3
Borderline	3	2.0
Abnormal	25	16.7

Patients and Methods:

From Jan 2009 to September 2009, we enrolled 150 type 2 diabetic patients attending the Sulaimani diabetic centre in Kurdistan region of Iraq. They were 88 females & 62 males and we also enrolled 100 non diabetic control group**,** 61 females and 39 males. Both groups underwent measurement of QT interval and QTc estimated according to Bazzet's equation:

$$QTc = QT/\sqrt{R\text{-}R}\ (sec)$$

QT interval measured from lead II in all cases to avoid difference in QT interval between different leads called QT dispersion. QT interval measured in seconds. The R-R interval measured in Small Square then multiplied by 0.04 to be changed to seconds. Then QT interval divided by square root of R-R interval in seconds. Normal value is ≤ 440 milliseconds in male and ≤ 460 milliseconds in female[28]. We also performed 5 cardiovascular autonomic tests including resting heart rate measurement, heart rate variation with

inspiration and expiration, valsalva maneuver, blood pressure response to handgrip and standing. Cases who were excluded are the following: Hypertensives, clinically evident cerebrovascular disease, Ischemic heart disease, Electrolyte disturbances such as (hypokalemia, hypocalcaemia and hypomagnesaemia), drugs causing QT prolongation, fever, anemia, thyrotoxicosis. Autonomic tests:[29]

Table 4. QTc relation with age, gender, duration of DM

Variables	QTc Interval		P value
	Normal N (%)	Prolonged N (%)	
Ages group			
< 50 years	40(97.56)	1(2.43)	0.010
50-60 years	65(94.2)	4(5.7)	
> 60 years	32(80)	8(20)	
Gender			
Female	77(87.5)	11(12.5)	0.041
Male	60(96.8)	2(3.2)	
Duration of DM			
< 5 years	93(93.0)	7(7.0)	0.520
5-10 years	33(89.2)	4(10.8)	
> 10 years	11(84.6)	2(28.4)	

Table 5.CAN relation with age, gender, duration of DM

Variables	Cardiac autonomic neuropathy				P value
	Absent N (%)	Early CAN N (%)	Definite CAN N (%)	Severe CAN N (%)	
Age groups					
< 50 years	13(31.7)	17(41.46)	8(19.5)	3(7.31)	< 0.001
50-60 years	21(30.4)	15(21.7)	22(31.88)	11(15.94)	
> 60 years	10(25)	3(7.5)	10(25)	17(42.5)	
Gender					
Female					0.989
Male	25(28.4)	21(23.9)	24(27.3)	18(20.5)	
	19(30.6)	14(22.6)	16(25.8)	13(21.0)	
Duration of DM					
<5 years	32(32.0)	29(29.0)	26(26.0)	13(13.0)	0.006
5-10 years	11(29.7)	4(10.8)	11(29.7)	11(29.7)	
>10 years	1(7.7)	2(15.4)	3(23.1)	7(53.8)	

1. Resting heart rate: After a 15 minutes of rest ECG taken for the patients and heart rate measured. Normal value is less than 100 beat/min, 100-110 b/min is borderline and 110 b/min and more is abnormal.
2. Heart rate variation with inspiration and

expiration: the patient was put in supine position and asked to breath deeply & slowly at a rate of 6 breath per minute (5 sec in, 5 sec out) by counting in 2,3,4,5 out 2,3,4,5. We measured greatest heart rate difference between inspiration & expiration. Normally it is ≥15 b/min, values of 10-15 b/ min is border line and less than10 b/min is abnormal.

3. Valsalva maneuver: ECG done while the patient is sitting and breathing into a tube attached to a sphygmomanometer to keep pressure at 40 mmHg (one third of systolic BP) for 15 seconds then pressure is released and ECG recorded for 30 sec after the maneuver. The ratio of longest R-R interval after the maneuver to shortest R-R interval during the maneuver was obtained. Normal value is ≥1.2, 1.1-1.2 is borderline and less than 1.1 is abnormal.
4. Blood pressure response to handgrip: Take resting diastolic pressure. Maintain handgrip in other arm at 30% of maximum voluntary pressure for up to 5 minutes record rise to just before handgrip release at 5 minutes.

Normal value is >15 mmHg, 10-15 mmHg is borderline and less than 10 mmHg is abnormal.

5. Blood pressure response to standing: blood pressure measured at rest then rechecked after 2 min of standing .Systolic blood pressure fall >30 mmHg is abnormal ,20-30 mmHg is borderline and less than 20 mmHg is normal.[29]

The patients are classified into 4 groups according to CAN score: the score calculated from the sum of the scores of the 5 tests [29]

CAN score 0: absent CAN
CAN score 0.5–1.5: early CAN
CAN score 2–3: definite CAN
CAN score >3.5: severe CAN

Statistical analysis done using ANOVA test or Chi square test whenever indicated, and P value was regarded as statistically significant if its <0.05

Results:

One hundred fifty type 2 DM patients & 100 non diabetic patients were enrolled. In the case group 58.7% were female & 41.3% were males compared with 61% & 39% for the control group, respectively. Minimum duration of DM was 1year & maximum was 30 years. The cases divided into 2 groups depending on the duration of DM .100 cases had duration of DM of less than 5 years and 37 cases have duration of DM between 5-10 years , 13 cases had duration of more than 10 years.

Of the 150 cases 13 were found to have prolonged QTc (8.7%) (Table -2-), 11 were females 2 were males (p value 0.041). No one in the control group showed prolonged QTc. Regarding cardiac autonomic neuropathy 106 cases had CAN (70.5%) 35 cases had early ,40 cases had definite and 31 cases had severe CAN (23.3%, 26.6% & 20.6% for early, definite & severe cases, respectively). In the control group 51 cases had CAN (51%) 32 cases had early and 19 cases had definite CAN(32% and 19% respectively).There was significant correlation between QTc & CAN (p value 0.000) as showed in Figure 2.

Table 3 showed different cardiac autonomic function tests in type 2 diabetic patients in the study and the least abnormality among the tests was for resting tachycardia. QTc prolongation was significantly related with increasing age > 60 years (p value 0.010) & gender (p value 0.041) but no relation was found with duration of DM (p value 0.520) Table -4-.While CAN was significantly related to increasing age (p value less than 0.001)& duration of DM (p value 0.006) no relation

was found with gender (p value 0.989).Table-5-.Sensitivity of QTc for detecting CAN is 20%, specifity 98.7% and positive predictive value of 92.3% as had shown in Table 6.

Table 6. Sensitivity, specificity, positive predicted value of QTc for detecting CAN

Prolonged QTc interval for detecting CAN	Type 2 diabetes mellitus (%)
Sensitivity	20
Specificity	98.7
Positive predictive value	92.3

Discussion

In this study we tried to assess the relation between CAN & QTc in type 2 DM patients .Incidence of QTc prolongation was 8.7% among cases & 0% among control group. Value of 8% versus 2% was observed by Ali Pourmoghaddas and Ali Hekmatnia[30] While it was 78.94% when observed by CP Mathur and Deepak Gupta[31] this variation may be because they had included cases of type 1 DM patients also and QTc and CAN more prevalent and more severe in type 1 diabetics as observed by Otto-Buczkowska E et al.[32]

There was significant relationship between QTc and CAN (p value 0.000) same was observed by J M Pappachan, J Sebastian, B C Bino, et al.[33] (p value 0.001).

There was significant correlation between QTc & age (p value 0.010) same was observed by J M Pappachan, J Sebastian, B C Bino, et al[33]. While in our study we found QTc prolongation is more among female 11% versus 2% in male (p value 0.041). Same was observed by Gary T. C. Ko et al.[34]. While K. TAKEBAYASHI, et al.[35] concluded that there is no significant gender difference in QTc prolongation among type 2 DM with CAN, The reason may be due to smaller sample which was taken by TAKEBAYASHI, et al.[35] (58 cases versus 150 cases included in our study) and Ali Pourmoghaddas and Ali Hekmatnia[30] did not mention anything regarding gender difference. Another reason is larger number of females included in our study compared with males and longer QT interval in females. Regarding CAN incidence of 70.5% in this study compared with 34.2% by Odusan O, Familoni OB, Raimi TH[36], The reason of this variation probably is due to difference in glycemic control of cases between the two studies .Regarding CAN incidence in the control group which was 51% may be attributed to decline in autonomic function with age as showed by Masari Amano, Eiichi Oida, Toshio Moritani[37].

Regarding abnormality of different autonomic function tests in the case group, resting tachycardia in 2%, abnormal heart rate variation with breathing in 50%, abnormal valsalva ratio in 26.7%, BP response to handgrip abnormality in 18.7%, postural hypotension in 16.7% compared with 30%, 33%, 45%, 33% ,38% respectively observed by J M Pappachan, J Sebastian, B C Bino, et al[33] .The reason is that their study included both type 1 and type 2 DM and CAN is more severe in type 1 diabetics.

There was no significant correlation between QTc & duration of DM (p value 0.520) in contrast to that observed by J M Pappachan, J Sebastian, B C Bino, et al[33] .The explanation may be because most of our cases had duration of DM less than 10 year (91.3%) and that exact duration of the disease

in type 2 DM is difficult to estimate and we estimated the duration from the time of diagnosis as stated by the cases which may be not accurate. Furthermore a multivariate analysis eliminated effect of duration of diabetes on QTc prolongation observed by Tentolouris N et al.[38].

There was significant relationship between CAN with age (p value less than 0.001) and duration (p value 0.006) but not with gender (p value 0.989) same was observed by J M Pappachan, J Sebastian, B C Bino, et al[33] (p value 0.001 , 0.013 and 0.397 respectively).

Sensitivity of QTc was 20% low for detecting CAN same was observed by Whitsel EA, et al.[12]. While it has high specificity and positive predicted value 98.7% and 92.3% respectively compared to sensitivity of 82.6%, and specificity of 100% observed by CP Mathur and Deepak Gupta[31]. However, the majority of studies with larger sample sizes reported sensitivities as low as 26–29% as observed also by Tentolouris N et al.[38].

Conclusion

We realized that QTc prolongation occur in cardiac autonomic neuropathy due to DM & it´s highly specific for CAN but insensitive. It is significantly correlated with age & female gender but no relation found with duration of DM.

Recommendation

Annual assessment of cardiac autonomic function for diabetic patient attending our diabetic centre in Sulaimani with estimation of QTc.

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شيوع إطالة مقطع QTc لدى المصابين بداء السكر من النوع الثاني وعلاقتها باعتلال الجهاز العصبي التلقائي

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الملخص

تمت دراسة العلاقة بين المصابين بداء السكر من نوع الثاني, مع احتمالية إطالة مقطع QTc للتخطيط الكهربائي للقلب. وتم ذلك بالمقارنة مع عينة قياسية من غير المصابين بداء السكر، وقد حصلنا على الإطالة في مقطع QTc لدى مرضى السكر من النوع الثاني، والمصابين باعتلال الجهاز العصبي التلقائي القلبي، وإنّ هذه العلاقة تم بحثها من باحثين آخرين، وحيث وجدوا أنّ هنالك فئة أصيبت بالموت المفاجئ من المصابين باعتلال الجهاز العصبي التلقائي.

الهدف: إن الهدف الرئيس لهذه الدراسة، هو إيجاد العلاقة بين إطالة QTc في التخطيط الكهربائي للقلب والمصابين باعتلال الجهاز العصبي التلقائي لدى المرضى المصابين بداء السكر من النوع الثاني.

الطريقة: لقد تم تسجيل (150) مريضاً مصاباً بداء السكر من النوع الثاني بين المراجعين في مركز رعاية مرضى السكر في السليمانية للفترة من كانون الثاني 2009 إلى أيلول 2009، وللمقارنة تم اختيار عينة من (100) شخص غير مصاب بداء السكر (كعينة قياسية)، وتم حساب QTc في كلتا العينتين، بعد إجراء التخطيط الكهربائي للقلب مع أداء خمسة اختبارات خاصة بالجهاز العصبي التلقائي الخاص بفسلجة (القلب الوعائي) من ضمنها قياس معدل نبضات القلب عند الاستراحة، اختلاف معدل نبضات القلب عند الشهيق والزفير، عملية الفالزالفا، وحساب ضغط الدم عند قبض اليد وعند الوقوف. وتم تشخيص اعتلال الجهاز العصبي التلقائي, حسب النتائج المستحصلة من الاختبارات.

النتائج: بعد الحصول على النتائج تبيّن أن (13) مريضاً كانوا يعانون إطالة QTc، من مجموع المرضى في الدراسة الذي يساوي (150) مريضاً أي (8.7%)، والعدد أعلاه كان يشمل (11) مريضة (إناث)، ومريضين اثنين (من الذكور)، وقيمة P (0.041) الإحصائية معتمدة لهذه النتائج. ولم نحصل على إطالة QTc في المجموعة القياسية. وتم الحصول على (106) حالات مصابة باعتلال الجهاز العصبي التلقائي، وبالترتيب التالي 35, 40, 31 كحالات مبكرة، أكيدة، شديدة على التوالي.

وتم الحصول على نتائج معتمدة للعلاقة بين إطالة QTc واعتلال الجهاز العصبي التلقائي القلبي وبقيمة P (0.000)، وكانت النتائج معتمدة بالنسبة للعمر والجنس وبقيمة P(0.010)، P(0.041) على التوالي، ولكنها لم تكن معتمدة بالنسبة لفترة المرض بالسكري بقيمة P(0.520).

إن حساسية إطالة QTc لتشخيص اعتلال الجهاز العصبي التلقائي القلبي كان 20%، ولكن قيم درجة النوعية والتنبؤ الإيجابي كانت 98.7%، و92.3% على التوالي.

الاستنتاجات: لقد تم استنتاج أن إطالة QTc تدل على اعتلال الجهاز العصبي التلقائي القلبي بسبب داء السكر، وإنّ هذه العلاقة ذات قيمة نوعية عالية مع حساسية قليلة. وتم الحصول على علاقة رابطة قوية بالنسبة للعمر والجنس، ولكن هذه العلاقة كانت معدومة بالنسبة لفترة المرض بالسكري.

الكلمات الدالة: QTc، المصابين بداء السكري، اعتلال الجهاز العصبي.