

QTC PROLONGATION, AN EARLY PREDICTOR OF CARDIOVASCULAR AUTONOMIC NEUROPATHY (CAN) IN POSTMENOPAUSAL DIABETIC WOMEN

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Abstract: To evaluate QTc interval in postmenopausal diabetic women in predicting cardiovascular autonomic neuropathy (CAN). A comparative cross-sectional study was conducted in the Cardiology Department of CMH Lahore and Sir Ganga Ram Hospital, Lahore, from April 2022- April 2023. A total of 80 women were included in the study, which was categorized into 40 pre and 40 postmenopausal women. Both groups were further divided into 20 diabetic and 20 non-diabetic women. A cut-off of 3-5 years was selected for natural menopause and 5-7 years for the available duration of type 2 diabetes. Blood samples were taken to determine serum estradiol levels in all 4 groups. Autonomic neuropathy was assessed by corrected QT interval (QTc), heart rate variability (HRV), Valsalva Ratio (VR), and resting heart rate (RHR). All variables were compared among groups by using SPSS version 20.0. Serum estradiol levels were significantly lowered in postmenopausal as compared to premenopausal women ($p < 0.001$). QTc was significantly different ($p = 0.001$) among all four groups. A statistically significant difference was found between premenopausal diabetic and postmenopausal diabetic groups ($p = 0.001$) and between women of premenopausal non-diabetic and postmenopausal diabetic groups ($p = 0.003$). Differences in RHR ($p = 0.840$), HRV ($p = 0.084$), and VR ($p = 0.129$) were statistically nonsignificant among all four groups. A QTc prolongation is an important tool in investigating cardiac autonomic neuropathy (CAN) predisposition in postmenopausal diabetic women. Therefore, assessment of QTc prolongation could aid in early diagnosis of CAN in postmenopausal diabetic women.

Keywords: Cardiac Autonomic Neuropathy, Postmenopausal Women, Qtc Prolongation, Diabetes

Introduction

Menopause is a biological event in women's life related to aging. It is characterized by permanent cessation of the menstrual cycle due to a decline in estradiol levels from a normal of 70-100 pg/dl to less than 20 pg/dl (Szadowska-Szlachetka et al., 2019). According to WHO, natural menopause is considered when women experience amenorrhea for 12 consecutive months without any obvious pathology (Shankam et al., 2018). The median age for menopause is 51 years (Baker et al., 2018).

Estradiol is the most active and abundant type of estrogen in women. Its physiologic level varies with different phases of the menstrual cycle. The levels are highest immediately before ovulation (110-410 pg/ml), whereas they are lowest in postmenopausal women (below 35 pg/ml) (Verdonk et al., 2019). Estradiol increases vagal and decreases the sympathetic tone of the heart. A decline in estradiol levels shifts the autonomic balance of the heart towards vagal impairment and sympathetic

dominance. This imbalance affects the autonomic modulation of the SA node and is interpreted as cardiovascular autonomic neuropathy (CAN).

CAN is the deterioration of autonomic control of the cardiovascular system. It affects both the sympathetic and parasympathetic divisions of ANS. It is a common form of autonomic dysfunction and is a serious complication of diabetes. It significantly increases cardiovascular mortality and morbidity (Duque et al., 2021). Assessment of CAN can be done by corrected QT interval (QTc), resting heart rate (RHR), heart rate variability (HRV), Valsalva ratio (VR), and orthostatic hypotension (OH).

The QT interval is the period (in seconds) necessary for the total process of depolarization and repolarization of the ventricles. It is rate-dependent and may be altered by numerous pathophysiologic and pharmacologic influences. Corrected QT (QTc) is the QT interval adjusted for heart rate. The area on ECG from the start of the QRS complex to the end of the T wave marks the QT interval. This is then



converted into QTc using the Bazette formula, $QTc = QT/\sqrt{R-R}$ (Ukpabi and Onwubere, 2017). When a balance between right and left-sided sympathetic innervation is disturbed, it results in prolonged QTc. QTc prolongation has been associated with the severity of CAN in DM patients. It is found to be an early predictor of CAN in people with diabetes in most studies. (Vasheghani et al., 2020). Such diabetic patients are at increased risk for arrhythmias. Moreover, QTc prolongation predicts sudden cardiac death in diabetic patients, both type 1 and type 2 (Ninkovic et al., 2016). Testing of QTc is an easy and early predictor of diabetic autonomic neuropathy (Sarvghadi et al., 2020).

The estrogen's role in cardiovascular autonomic control and autonomic dysfunction in pre and postmenopausal women has remained doubtful. The extensive literature study does not reveal the effect of diabetes on the autonomic nervous system in postmenopausal women. This study, by including both pre and postmenopausal women, might help to objectively identify the early stages of CAN, especially in diabetic women with different menstrual statuses. Also, the effect of declining estrogen levels on CAN and its possible aggravation in type 2 diabetic women may be emphasized by this study. The development of autonomic nerve impairment can be reduced by combination therapies directed at various levels of pathogenic pathways. This study evaluated QTc interval in postmenopausal diabetic women in predicting cardiovascular autonomic neuropathy (CAN).

Methodology

A comparative cross-sectional study was conducted in the Cardiology Department of CMH Lahore and Sir Ganga Ram Hospital, Lahore, from April 2022- April 2023. It was carried out according to the Helsinki human rights declaration and was approved by the ethical committee of the Postgraduate Medical Institute (PGMI), Lahore. It was a cross-sectional comparative study involving 80 women, 40 pre and 40 postmenopausal. Both groups were categorized further into diabetic and non-diabetic subgroups. Thorough history taking and physical examination was done for every subject with special attention to defining eligibility for participation in the study. Blood samples were taken to determine fasting blood sugar (FBS) and serum estradiol. Cardiac autonomic functions were assessed by testing both sympathetic and parasympathetic components of ANS. Subjects were abstained from tea, coffee, and cola for 12 hours before tests. All tests were performed in an isolated examination room with a temperature between 25-27 degree Celsius at 10-11 A.M. In premenopausal females, all tests were performed in the menstrual cycle follicular phase to avoid progesterone's effects.

Tests included resting heart rate, blood pressure, and orthostasis. ECG was done using Biopac student lab, a data acquisition system to determine HRV, VR, and QTc.

Cardiovascular autonomic reflex testing:

1. QT interval was calculated from limb lead II by using Biopac student lab data acquisition system. QT interval was then corrected for heart rate using Bazett's $QTc = QT/\sqrt{R-R}$ interval formula.
2. For HRV, the subject was asked to take 6 deep breaths per minute, and lead II ECG was done. HRV was calculated by subtracting maximum and minimum HR and expressed in beats per minute (BPM). Normal HRV was more than 15 BPM, 10-15 BPM was borderline, and <10 BPM was definitive CAN.
3. VR was calculated when subjects performed the Valsalva maneuver in a semi-recumbent position by forcefully expiring into an aneroid manometer connected to a mouthpiece through a rubber tube and maintaining a pressure of 40mmHg for 10-15 sec. Heart rate was measured by Biopac student lab throughout this period of strain and 14sec after the release of strain. VR was calculated by dividing the maximum HR during the period of strain by the minimum heart rate after the strain.
 $VR = \text{Maximum HR} / \text{Minimum HR}$
 $VR > 1.4 \rightarrow \text{normal}$
 $VR = 1.2 \text{ to } 1.4 \rightarrow \text{borderline}$
 $VR < 1.2 \rightarrow \text{autonomic neuropathy}$
4. Orthostasis, a change in blood pressure, was measured as the difference between readings while supine and 2 minutes after assuming an upright posture. $BP > 20\text{-}30$ mm Hg systolic or > 10 mm Hg diastolic BP was significant.
5. Resting Heart rate was calculated by standard technique of palpatory method for full one minute. HR between 60-100 BPM was considered normal, and more than 100 BPM was considered tachycardia.

The data was entered and analyzed using SPSS version 22. Kruskal Wallis test was applied to compare the median IQRs of non-normally distributed data, and one-way ANOVA was applied to compare mean \pm SD of normally distributed data. The Mann-Whitney U test compared the difference in the median (IQR) between the two groups. P-value <0.05 was considered statistically significant.

Results

A total of 80 women participated in the study, 40 pre and 40 postmenopausal. Both groups were further categorized into diabetic and non-diabetic groups. Serum estradiol levels were lowered significantly ($p < 0.001$) in postmenopausal (diabetic and non-diabetic) women compared to premenopausal women, as shown in Table I. Only 5% of the subjects in group

I (premenopausal diabetic) had borderline (QTc = 450-470 msec), and 10% had prolonged QTc (QTc >470 msec). 15% in group II (premenopausal non-diabetic) had borderline QTc values. All others had normal QTc values. In group III (postmenopausal diabetic), 15% had borderline, and 50% had prolonged QTc, and in group IV (postmenopausal non-diabetic), 25% had borderline, and 30% had prolonged QTc, as shown in Table III. As shown in Table IV, QTc was significantly different (p=0.001) between all four groups. The QTc was statistically significantly different (p=0.001) between women of diabetic groups I and III. However, no significant

differences were found between women of premenopausal groups I and II (p=0.279), postmenopausal groups III and IV (p = 0.088), and non-diabetic groups, II and IV (p=0.091) as shown in Table V. There were nonsignificant differences between RHR (p=0.840), HRV (p=0.084) and VR (p=0.129) among all four groups as shown in Table IV. Although postural changes in BP were observed in both SBP and DBP in all four groups, none of the subjects showed orthostatic hypotension (fall in SBP > 20 mmHg or DBP >10 mmHg after changing of posture from supine to standing position).

Table I: Comparison of estradiol between study groups by Kruskal Wallis test

Parameters	Group I	Group II	Group III	Group IV	p-value
Estradiol (pg/ml)	78.50 (59.50-109.75)	83.00 (66.50-123.50)	9.50 (7.25-13.75)	9.00 (7.00-11.00)	<0.0001

Table II: Comparison of Estradiol between 2 Groups by Mann-Whitney U test

Groups	Estradiol (pg/ml)	p-value
Group I	18.93	0.398
Group II	22.08	
Group III	21.73	
Group IV	19.28	
Group I	30.50	<0.001
Group III	10.50	
Group II	30.50	
Group IV	10.50	
Group II	30.50	<0.001
Group III	10.50	

Table III: Frequency distribution of the QTc in the study population

QTc (msec)	Group I (n=20)	Group II (n=20)	Group III (n=20)	Group IV (n=20)
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
Normal <450	17 (85)	17 (85)	7 (35)	9 (45)
Borderline 450- 470	1 (5)	3 (15)	3 (15)	5 (25)
Abnormal >470	2 (10)	0	10 (50)	6 (30)

Table IV: Comparison of Cardiovascular parameters between groups

Parameter	Group I	Group II	Group III	Group IV	p-value
■QTc	415 (398.50-440.75)	428 (407.75-443.50)	468.50 (436.25-595.00)	449.50 (416.25-473.00)	0.001
■HRV	22.50 (16.50-41.75)	39.50 (26-66.75)	21.00 (16.25-69.00)	19.00 (15.25-60.50)	0.084
■VR	1.40 (1.23-1.80)	1.80 (1.40-2.28)	1.35 (1.20-1.57)	1.35 (1.23-1.90)	0.129
▲RHR	81.05±9.12	80.85±8.81	82.75±12.01	83.45±12.72	0.840

Table V: Comparison of QTc (msec) between Groups by Mann-Whitney U test

Groups	QTc(msec)	p-value
Group I	18.50	0.279
Group II	22.50	
Group III	23.65	0.088

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Group IV	17.35	
Group I	14.10	0.001
Group III	26.90	
Group II	17.38	0.091
Group IV	23.63	
Group II	14.93	0.003
Group III	26.08	

Discussion

The study was conducted on 80 women, 40 pre and 40 postmenopausal. Both groups were further divided into diabetic and non-diabetic groups. The study determined the importance of QTc as an early predictor of CAN in postmenopausal type 2 diabetic women. The indicators of CAN, including corrected QT interval QTc, resting heart rate RHR, orthostatic hypotension OH, heart rate variability HRV and Valsalva ratio VR were studied independently in all subjects and then compared between pre and postmenopausal diabetic and non-diabetic women. Serum estradiol levels were also determined and compared in pre and postmenopausal women. The results suggested that diabetes affects cardiac autonomic nerves, further superimposed by autonomic nerve damage due to decreased estradiol levels in postmenopausal women.

It was found that postmenopausal diabetic women had significantly lower serum estradiol levels and more tendency to abnormal (borderline or abnormal) cardiac autonomic function tests compared to other groups.

The current study showed abnormal QTc prolongation in pre-and postmenopausal diabetic women with significant statistical differences ($p=0.001$). The frequency of prolonged QTc was higher in postmenopausal (50% abnormal) than in premenopausal diabetic women (10% abnormal). There was also a statistically significant difference ($p=0.003$) in QTc between premenopausal non-diabetic and postmenopausal diabetic women. This reflected the effect of both diabetes and menopause on autonomic modulation of the heart.

The results align with Ukpabi and Onwubere, who studied the prevalence of QTc prolongation in diabetic patients with and without CAN. A significant association was found between QTc interval prolongation and CAN in type 2 diabetics. It was concluded that QTc prolongation in ECG is a better and early indicator for diagnosing CAN in people with type 2 diabetes (Ukpabi and Onwubere, 2017).

A study on QTc elongation in pregnant women revealed that these levels were critical for diagnosing heart-related diseases (Batmaz et al., 2016). Results by Khoharo also back these findings (Khoharo and Halepoto, 2012).

In contrast, a study conducted by Anuradha et al. 2007 on healthy pre and postmenopausal women found similar QTc intervals in pre and postmenopausal women (Anuradha and Mirza, 2020). The reason could be that they measured estradiol levels in the early part of the follicular phase (2nd / 3rd day of the menstrual cycle) in premenopausal women, which has the minimum levels of this hormone than other phases of the menstrual cycle. In the present study, premenopausal women were selected in the second half of the follicular phase, which has the peak levels of estradiol, so they showed significantly different estradiol levels from postmenopausal women. Another study by Sarvghadi et al. reported no association between QTc elongation and CAN in diabetes patients (Sarvghadi et al., 2020). The study sample was small, besides the study being multi-centered. Since all other factors which could prolong QTc were ruled out in this study group, the prolonged QTc intervals in our group are most likely due to autonomic neuropathy. This study recommends that all postmenopausal diabetic women have routine ECG monitoring for the measurement of QTc. This may detect CAN and patients at risk of lethal arrhythmias and sudden cardiac death.

Conclusion

QTc prolongation is an early predictor of cardiac autonomic neuropathy in postmenopausal diabetic women before symptoms or presence of other markers appear. There is a definite prolongation of QTc in type 2 diabetic women after menopause.

Conflict of interest

The authors declared absence of conflict of interest.

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