

# Relationship between Corrected QT Interval (QTc) Prolongation and Insulin Resistance in Obese Adult Male Subjects

Zarchi Theint Theint Hlaing, Soe Minn Htway, Mya Thanda Sein

## ABSTRACT

QT Interval prolongation is common in insulin resistance state obesity. Insulin-induced hyperpolarization might be involved in ventricular repolarization leading to QTc lengthening. Therefore, this study is designated to investigate the relationship between corrected QT interval (QTc) prolongation and insulin resistance in obese adult male subjects. Apparently healthy adult male subjects (n=100) aged between 18-35 years residing in Magway Township were recruited by simple random sampling method. Then all the eligible subjects were categorized into 2 groups: non-obese [body mass index (BMI) 18.5 to 24.9 kg/m<sup>2</sup>, n= 40] and obese group [BMI ≥ 30.0 kg/m<sup>2</sup>, n=60] by their anthropometric parameters. Serum fasting glucose was measured by glucose oxidase method. Serum insulin level was determined by Enzyme-Linked Immunosorbent Assay (ELISA). Insulin sensitivity was calculated by Homeostatic Model Assessment (HOMA-IR). The QT interval was measured by routine 12-lead ECG and corrected QT interval (QTc) was calculated according to Bazett's formula. In the present study, insulin sensitivity (HOMA-IR) was higher in obese subjects (4.64±2.3) than that of non-obese subjects (2.5±0.89) (p< 0.001). There was significant positive correlation between QTc and HOMA-IR (r = 0.41, p< 0.001, n = 100) in this study. HOMA-IR >3.8 was considered as insulin resistance (IR) and QTc > 440ms was regarded as QTc interval prolongation. Insulin resistance was significantly associated with prolonged QTc interval in the study population (X<sup>2</sup>=7.3, p< 0.05, n=100). Risk of QTc interval prolongation was 3.4 times higher in subjects with IR (Odd ratio = 3.4; 95% confidence interval = 1.37 to 8.45). It was concluded that prolonged QTc interval is associated with insulin resistance state.

**Keywords:** Body Mass Index; Insulin resistance; Obesity; QTc prolongation.

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## I. INTRODUCTION

QT interval is the time from the start of the Q wave to the end of the T wave. It represents both ventricular depolarization and repolarization. It can be measured by routine 12-lead ECG with lead II rhythm strip for 10 seconds [1]. QTc is the corrected QT interval with heart rate of 60 beats/min. It was calculated by Bazett's formula [2].

$$QTc(ms) = \frac{QT(ms)}{\sqrt{R-R(s)}}$$

QTc value between 350–420 ms is regarded as normal QT interval and its value more than 420 ms indicates prolonged QT interval [3]. Prolonged QTc interval is the representation of delayed ventricular repolarization, and it can be the risk factor for the development of ventricular tachyarrhythmias, syncope and sudden cardiac death [4]-[6]. Some studies reported an association between QT interval and cardiac risk factors and mortality [7], [8].

There are some evidence demonstrating the relationship between insulin sensitivity and QTc in type 2 diabetes [9], [10]. Insulin resistance means the inability of insulin to produce its usual biological actions at circulating concentrations which are effective in normal subject. Hyperinsulinemia is usually a condition to compensate the insulin resistance [11]. One of physiological action of insulin is increased permeability of many cells to potassium. Insulin increased resting membrane potential of excised rat muscle [12]. Insulin hyperpolarizes plasma membranes and affects ventricular repolarization [13]. There is little information about the relationship between QTc and insulin resistance in obesity since obesity is hyperglycemic and hyperinsulinemic state. Therefore, this study was designated to investigate the relationship between QTc prolongation and insulin resistance in obese adult male subjects.

## II. MATERIAL AND METHODS

Apparently healthy adult male subjects (n=100) aged between 18-35 years residing in Magway Township were recruited according to inclusion and exclusion criteria. Subjects with history of heart disease, diabetes mellitus, current smoker and current alcoholic were excluded. Apparently healthy adult male subjects were selected by simple random sampling method. The procedure was explained and written informed consent was obtained. Anthropometric measurement was done at Ward Administrator Office. Then all the eligible subjects were categorized into 2 groups: non-obese [body mass index (BMI) 18.5 to 24.9 kg/m<sup>2</sup>, n= 40] and obese group [BMI ≥ 30.0 kg/m<sup>2</sup>, n=60] by their anthropometric parameters. Fasting blood sample (5 ml) was taken from antecubital vein under aseptic condition by using a disposable syringe and needle for each subject. Blood will be collected in two separate blood collecting tubes: one ml of blood will be collected in tube containing 10 mg of sodium fluoride for determination of blood sugar and 4 ml of blood in another tube for serum separation. The blood sample was allowed to clot for 30 minutes at room temperature and centrifuged for 15 minutes at 3000 rpm. Serum will be separated and collected in sample tubes and stored at (-20 °C) until the blood sample analysis. Serum glucose level was determined on the same day of blood collection. Serum fasting glucose was measured by glucose oxidase method and serum insulin level was measured by enzyme linked immunoassay (ELISA) kit method. Insulin sensitivity was calculated by following formula (HOMA: Homeostatic Model Assessment) [14].

$$HOMA-IR = \frac{Insulin (\mu IU / mL) \times glucose (mmol / L)}{22.5}$$

HOMA-IR >3.8 is considered as insulin resistance state.

After 15 minute rest, routine 12-lead ECG was also performed. Lead II rhythm strip for 10 seconds was taken. The R-R intervals and QT intervals were measured. Corrected QT interval (QTc) was calculated using Bazett's formula [2]. Data were analyzed by using SPSS software for Window. All data were expressed as mean ± SD. Statistical analysis of the two sets of data (non-obese group and obese group) was carried out by independent student t Test. Correlation studies were computed by Pearson's correlation. Differences were considered significant when P < 0.05.

## III. RESULTS

Table 1 showed the general characteristics of the subjects. Fig. 1 indicated the comparison of HOMA-IR values between non-obese and obese subjects. Fig. 2 point out the comparison of QTc interval in non-obese and obese subjects. There was significant positive correlation between insulin sensitivity and QTc (Fig. 3). Table 2 specified Odd ratio of QTc prolonged in normal and insulin resistance subjects.

TABLE 1: Characteristics of the subjects (Mean ± SD)

|                          | Non-obese<br>(n = 40)<br>(Mean ± SD) | Obese<br>(n = 60)<br>(Mean ± SD) |
|--------------------------|--------------------------------------|----------------------------------|
| Age (years)              | 22.30 ± 1.77                         | 23.50 ± 2.24                     |
| Weight (kg)              | 59.70 ± 4.21                         | 85.53 ± 8.37                     |
| Height (m)               | 1.62 ± 0.49                          | 1.65 ± 0.06                      |
| BMI (kg/m <sup>2</sup> ) | 22.91 ± 1.11                         | 31.68 ± 1.76                     |

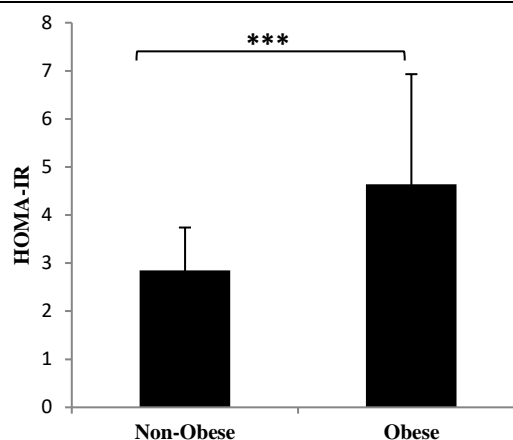


Fig. 1. Comparison of HOMA-IR values between non-obese and obese subjects.

\*\*\* indicates significant difference at p<0.001.

NB: Comparison was done by independent student t test.

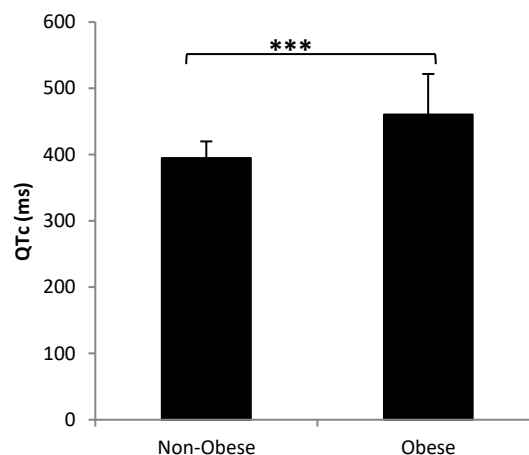


Fig. 2. QTc of non-obese and obese subjects.

\*\*\* indicates significant difference at p<0.001.

NB: Comparison was done by independent student t test.

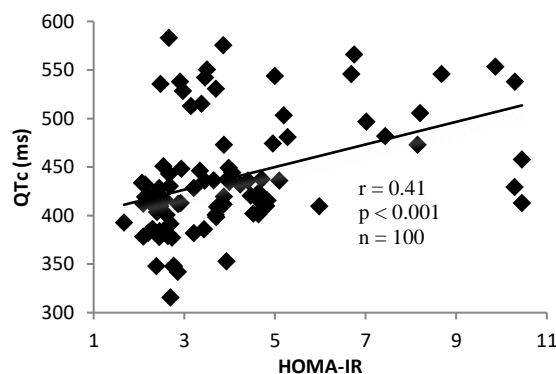


Figure 3. Correlation between insulin sensitivity and QTc.

QTc = corrected QT interval.

HOMA-IR = insulin sensitivity.

r = Pearson's correlation coefficient.

n = total number of subjects

TABLE 2: ODD RATIO OF QTc PROLONGED IN NORMAL AND INSULIN RESISTANCE SUBJECTS

| Groups                            | Normal QTc (QTc<440ms) | QTc prolonged (QTc>440ms) | Odd ratio | 95% CI       |
|-----------------------------------|------------------------|---------------------------|-----------|--------------|
| Normal (HOMA-IR <3.8)             | 54                     | 14                        |           |              |
| Insulin Resistance (HOMA-IR >3.8) | 17                     | 15                        | 3.4       | 1.37 to 8.45 |

#### IV. DISCUSSION

In the present study, the fasting blood glucose level of obese subjects was  $5.01 \pm 0.43$  mmol/L and that of non-obese subjects was  $4.68 \pm 0.34$  mmol/L ( $p < 0.05$ ). Serum insulin level of obese subjects ( $21.96 \pm 2.76$   $\mu$ LU/mL) was significantly higher than that of non-obese subjects ( $13.7 \pm 4.16$   $\mu$ LU/mL) ( $p < 0.05$ ). Although fasting blood glucose of all non-obese and obese subjects who participated in this study had within normal range (fasting plasma glucose: 3.5 to 6.1 mmol/L), the mean HOMA-IR value was higher in obese subjects ( $4.64 \pm 2.3$ ) than that of non-obese subjects ( $2.5 \pm 0.89$ ) ( $p < 0.001$ ). HOMA-IR  $> 3.8$  was considered as insulin resistance [15]. In addition, 4 out of 40 non-obese subjects had insulin resistant state and 28 out of 60 obese subjects had insulin resistant (Odd ratio = 7.88; 95% confidence interval = 2.49 to 24.89). The risk of insulin resistance was 7.88 times in obese subjects than non-obese subjects. This study was coincided with other previous studies which had shown that there is a significant strong epidemiological association between obesity and the development of insulin resistance [16-19]. In the present study, the observed increase in fasting serum insulin in the obese subjects compared with that of the non-obese subjects might be due to a compensatory increase in insulin secretion and thus maintaining the plasma glucose level within the normal range.

In the present study, the QTc of non-obese subjects was  $393.7 \pm 22.34$  ms and that of obese subjects was  $461.71 \pm 61.85$  ms ( $p < 0.001$ ). It was consistent with the studies of Corbi et al., Guven et al., Arslan et al., Ozkan et al., Hlaing et al. They reported that the obese group had more prolonged QTc than the non-obese group [1], [3], [20]-[22]. These studies stated that the possible mechanism of the prolonged QTc interval might be due to autonomic dysfunction and increased serum insulin level in obesity. Aleksandra et al. [23] found that the QTc interval was significantly longer in metabolic syndrome patients than in the control group ( $411.1 \pm 35.72$  vs.  $390.95 \pm 26.31$  ms,  $p < 0.05$ ) and there was a statistically significant positive correlation between the length of the QTc interval and HOMA-IR ( $r = 0.38$ ,  $p < 0.01$ ) [23]. There was also significant positive correlation between QTc and HOMA-IR ( $r = 0.41$ ,  $p < 0.001$ ,  $n = 100$ ) in this study. Moreover, insulin resistance was significantly associated with prolonged QTc interval in the study population ( $X^2 = 7.3$ ,  $p < 0.05$ ,  $n = 100$ ). Additionally, 15 out of 32 insulin resistant subjects had prolonged QTc intervals although 14 out of 68 normal subjects had prolonged QTc intervals (Odd ratio = 3.4; 95% confidence interval = 1.37 to 8.45). Therefore, the risk of QTc interval prolongation was 3.4 times higher in subjects with insulin resistance. It was reported that there was the

direct effect of exogenous insulin on QTc [13]. In adults, compensatory hyperinsulinemia may lead to persistent QTc lengthening in insulin-resistant patients with obesity, even in the absence of autonomic neuropathy. Insulin causes QTc prolongation directly or through sympathetic activation [24].

These findings support the findings of previous studies. Thus, it can be assumed that the prolonged QTc of obese subjects in the present study might be due to obesity induced hyperinsulinaemia and insulin resistance state. It could be due to the physiological action of insulin by increasing the membrane permeability of the cells and hyperpolarized the plasma membrane that results in prolonged QTc interval.

#### V. CONCLUSION

The risk of the QTc interval prolongation was 3.4 times higher in subjects with insulin resistance. There was a significant positive correlation between QTc and HOMA-IR. It can be concluded that compensatory hyperinsulinemia may lead to QTc lengthening in insulin-resistant state obesity.

#### VI. LIMITATION OF THE STUDY

As a cross sectional analytical study, it cannot clearly establish the causative effect of insulin resistance on QTc interval. The present study does not explore the autonomic neuropathy which can affect insulin sensitivity.

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