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Research Article

Serum Testosterone Level and Corrected QT Interval (QTc) in Non-obese and Obese Adult Male Subjects

Zarchi Theint Theint Hlaing[1], Soe Minn Htway[2], Nwe Nwe Yee[3] and Mya Thanda Sein[4]*

[1]*Assistant Lecturer, Department of Physiology, University of Medicine, Magway, Myanmar*

[2]*Associate Professor, Department of Physiology, University of Medicine, Magway, Myanmar*

[3]*Professor and Head, Department of Physiology, University of Medicine, Mandalay, Myanmar*

[4]*Professor and Head, Department of Physiology, University of Medicine, Magway, Myanmar*

***Corresponding Author**: Mya Thanda Sein, Professor and Head, Department of Physiology, University of Medicine, Magway, Myanmar.

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Abstract

Objective: To study serum testosterone level and corrected QT interval (QTc) in non-obese and obese adult male subjects.

Material and Methods: Multistage sampling method was done. Non-obese group [body mass index (BMI) 18.5 to 24.9 kg/m^2, n = 30) and obese group [BMI ≥ 30.0 kg/m^2, n = 60] were recruited. According to waist circumference (WC), obese group was subdivided into generally obese group (WC < 90 cm; n = 30) and centrally obese group (WC ≥ 90 cm; n = 30). Serum testosterone level was determined by enzyme-linked immunosorbent assay (ELISA). The QT interval was measured by routine 12-lead ECG with Lead II rhythm strip for 10 seconds and corrected QT interval (QTc) was calculated.

Results: Serum testosterone level of obese subjects was significantly lower than that of non-obese subjects (Mean ± SD: 3.98 ± 2.35 vs 5.81 ± 2.35 ng/mL; p < 0.001). QTc of obese subjects (462.75 ± 63.44 ms) was significantly higher than that of non-obese subjects (395.87 ± 25.43 ms) (p< 0.001). Serum testosterone level of centrally obese subjects (3.41 ± 1.31 ng/mL) was significantly lower than that of generally obese subjects (4.55 ± 1.24 ng/mL; p < 0.05) whereas QTc of centrally obese subjects (488.28 ± 63.18 ms) was significantly higher than that of generally obese subjects (437.22 ± 53.38 ms) (p < 0.001). Only 1 out of 30 non-obese subjects (3.33%) and 16 out of 60 (26.67%) obese subjects from the present study had testosterone deficiency (< 3 ng/mL). Risk of developing testosterone deficiency among centrally obese subjects was 4.3 times greater than that of generally obese subjects (Odd ratio = 4.33; 95% confidence interval = 1.2 to 15.61). Similarly, only 1 out of 30 non-obese subjects (3.33%) and 30 out of 60 (50%) obese subjects had prolonged QT interval (> 440 ms). The risk for prolonged QT interval was 4.0 times more likely in centrally obese subjects than generally obese subjects (Odd ratio = 4.0; 95% confidence interval = 1.37 to 11.70). Nine out of 17 (53%) testosterone deficient subjects had prolonged QTc and 35 out of 73 (48%) subjects with normal testosterone level had prolonged QTc (Odd ratio = 1.1; 95% confidence interval = 0.4 to 2.7) and there was weak correlation between serum testosterone level and QTc (r = - 0.246, p< 0. 05, n = 90). It can be assumed that testosterone may play some role in prolonged QT interval.

Conclusion: Obesity increases the risks for testosterone deficiency and prolonged QT interval. These risks are more increased in centrally obese than generally obese male subjects. Testosterone deficiency might be attributed to cardiovascular risk.

Keywords: *Body Mass Index; Obesity; QT; Testosterone; Waist Circumference*

Introduction

Obesity is associated with high incidence of cardiovascular risk [1]. Increased cardiac mortality among obese subjects is associated with sudden death and fatal arrhythmias. Fatal arrhythmia is known to be linked to prolonged cardiac ventricular repolarization. QTc means the corrected QT interval with heart rate. The corrected QT interval estimates the QT interval at a heart rate 60 beats/min. This allows comparison of QT values over time at different heart rates. QT interval is defined as the time from the start of Q wave to the end of T wave. It represents both ventricular depolarization and repolarization. It was measured by routine 12-lead electrocardiogram (ECG) after 15 minute-rest (lying quietly on the bed) with limb electrodes attached. Paper speed was set at 25 mm/s and manual calibration 1 mV = 10 mm was carefully adjusted before recording. Lead II rhythm strip for 10 seconds was also taken [2]. QT durations were corrected by using Bazett's formula ($QTc = QT/\sqrt{RR}$) where RR = 60/HR. Bazett's formula is one of the most commonly and widely used QT correctional formulae in the clinical literature [3].

Since QT interval prolongation is a risk factor for cardiovascular morbidity and mortality, several studies used large databases of individuals undergoing medical screening to define the normal QT [4-7]. The values of QTc were defined as follows; QTc between 350- 420 ms as normal; less than 350 ms of QTc is considered as shorten QTc, whereas more than 440 ms in men and 460 ms in women are considered as long QTc; long QT syndrome [7]. Prolonged QTc interval is a hallmark of delayed ventricular repolarization and a marker for the potential of ventricular tachyarrhythmias, syncope and sudden cardiac death [8-10].

According to previous evidences, serum testosterone level might play a crucial role in incidence of cardiovascular diseases (CVD). Some studies have shown that relatively low androgen level was observed in men with chronic heart failure and stated that low testosterone predicted the increased risk of the cardiovascular diseases [11-15]. These studies also reported that all causes of mortality and mortality rate of cardiovascular diseases were increased in testosterone deficient men compared with those with normal testosterone level. However, other studies point to increased cardiovascular risk associated with a high circulating androgen level [16-18]. It was found that more cardiovascular events occurred in men with testosterone therapy compared with those who received placebo [16]. It is still controversial whether high or low serum testosterone level is attributed to risk of CVD.

Indeed, testosterone is a regulator of the action potential duration and ventricular repolarization [19]. Pham., *et al*. studied the action potential of isolated right ventricular myocardium of rabbit [20]. It was shown that action potential duration was significantly shorter in male than female and testosterone level was negatively correlated with the duration of action potential. Another study done by Liu., *et al*. also reported that dihydrotestosterone administration in castrated male rabbits shortened QT interval [21]. Moreover, testosterone increases the density of repolarizing potassium currents, which is due to changes in both gating kinetics of the delayed rectifier potassium currents (Ikr) and shortening the duration of the QT interval [15,21].

In an observational study, standard ECG recordings were performed in 26 men (mean age 39.2 ± 2.17 years) with pituitary or testicular hypogonadism and QTc intervals were measured according to Bazzett's formula. It has been reported that prolonged QTc interval (i.e. > 440 ms) was found in four of 26 hypogonadal patients [22].

Another confirming study was done in 2011 and showed that the prevalence of prolonged QT interval (i.e. > 440 ms) was considerably higher in hypogonadal obese men compared with eugonadal obese men. In that study, 163 obese subjects were classified as eugonadal or hypogonadal according to serum testosterone levels (that is greater or less than 9.9 nmol/L). In this study, QTc were longer in hypogo-

nadal compared with eugonadal obese men (419 ± 3.2 vs 408 ± 3.4 ms) ($p < 0.05$). Prolonged QTc interval (i.e. > 440 ms) was also more frequent among hypogonadal compared with eugonadal obese man ($p < 0.05$) and the relative risk factor for abnormal QTc was 2.34 times higher in persons with lower testosterone level (95% CI 1.09 to 5.34). However, serum testosterone level was not correlated with QTc [9].

The effects of testosterone on the cardiovascular system remain incompletely understood. Thus, further confirmatory study is needed to explore the relationship between serum testosterone level and cardiovascular risk in obese subjects. Moreover, it was not clear whether central obesity has more decrease serum testosterone level and prolonged QT intervals than general obesity.

Therefore, this study is designated to determine serum testosterone level, and QT interval in non-obese, generally obese and centrally obese male subjects and the correlation between serum testosterone level and QT interval. This study would support the needed information about the effect of testosterone on cardiovascular risk in male subjects.

Material and Methods

Selection of participants

At the first stage, five quarters were chosen from total 15 quarters in Magway Township by using simple random sampling method. All the male subjects aged between 18 - 35 years residing in selected five quarters without family history of diabetes mellitus and heart disease, chronic smoking and alcohol drinking were selected. After that, anthropometric measurement was done and BMI was calculated. At the second stage, they were categorized into two groups; non-obese group (BMI 18.5 to 24.9 kg/m2) and obese group (BMI ≥ 30 kg/m2) from each quarter. This resulted in 5 non-obese groups and 5 obese groups. At the third stage, six subjects from non-obese group and 12 subjects from obese groups were recruited to this study by simple random sampling method. Therefore, 30 subjects for non-obese group and 60 subjects for obese group were recruited. According to WC, obese group was subdivided into generally obese group (WC < 90 cm; n = 30) and centrally obese group (WC ≥ 90 cm; n = 30).

Data collection and blood sample analysis

All subjects were instructed to arrive "Ward Administrator Office" at 7 am the next day. 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 [4].

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

About 3 ml of venous blood was withdrawn from antecubital vein under aseptic condition by using a disposable syringe and needle for each subject. The blood sample was allowed to clot for 30 minutes at room temperature and centrifuged for 15 minutes at 3000 rpm. Serum sample was kept in screw-tight bottle which were stored at -20°C until analysis in Common Research Laboratory, University of Medicine, Magway. Serum testosterone level was determined by Enzyme-Linked Immunosorbent Assay (ELISA).

Statistical analysis of data

Data were analyzed by using SPSS software for Window (version 23, SPSS Inc., Chicago, IL, USA). All data were expressed as mean ± SD. Statistical analysis of the two sets of data (non-obese group and obese group) and the three sets of data (non-obese group, generally obese group and centrally obese group) for each analysis were carried out by independent student t Test, the ANOVA and post-hoc test. Correlation studies were computed by Pearson's correlation. Chi-squared test was used to determine whether there are significant associations between obesity, testosterone deficiency and prolonged QT interval. Differences were considered significant when $P < 0.05$.

Results

Table 1 and 2 showed the anthropometric characteristics of subjects participated in this study (Mean ± SD). Table 2 indicated characteristics of generally obese and centrally obese subjects (Mean ± SD). Table 3 revealed Odd ratio of testosterone deficiency in generally obese and centrally obese subjects. Table 4 specified Odd ratio of prolonged QTc in generally obese and centrally obese subjects. Table 5 point out Odd ratio of prolonged QTc in normal and testosterone deficient subjects. Comparisons of serum testosterone level and QTc between three groups were shown in figure 1 and 2 respectively. Serum testosterone level was significantly and negatively correlated with QTc as shown in figure 3. There were negative correlations between serum testosterone level and BMI as well as WC (Figure 4). The correlations between QTc and BMI as well as WC were shown in figure 5.

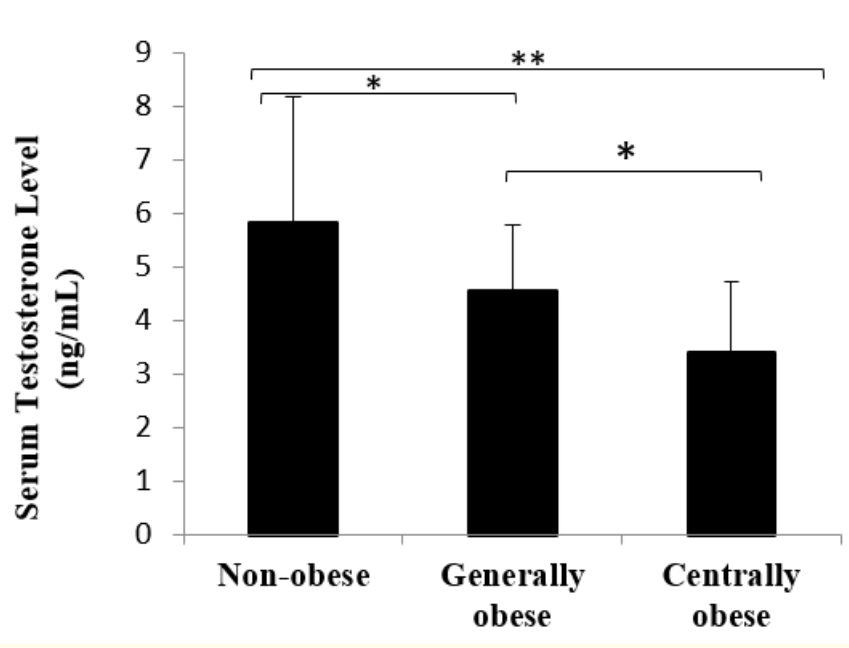


Figure 1: *Indicated serum testosterone level of non-obese, generally obese and centrally obese subjects.*

**: Indicates significant difference at p < 0.05.*

***: Indicates significant difference at p < 0.001.*

NB: Comparison was done by ANOVA and post-hoc test.

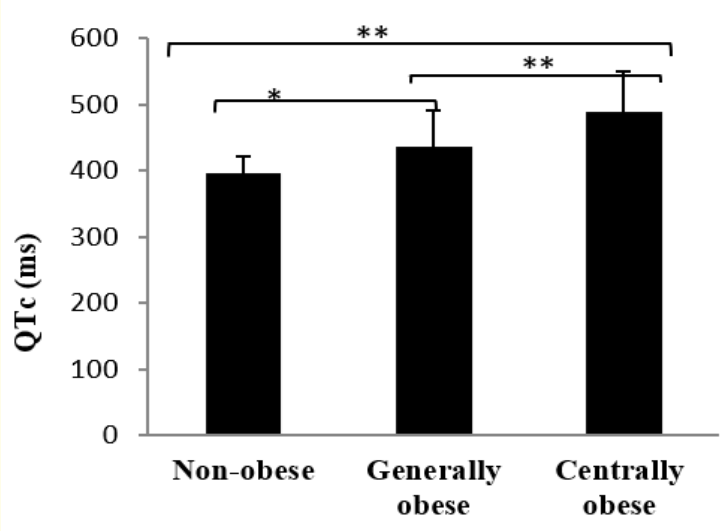


Figure 2: *Showed QTc of non-obese, generally obese and centrally obese subjects.*

**: Indicates significant difference at p < 0.01.*

***: Indicates significant difference at p < 0.001.*

NB: Comparison was done by ANOVA and post-hoc test.

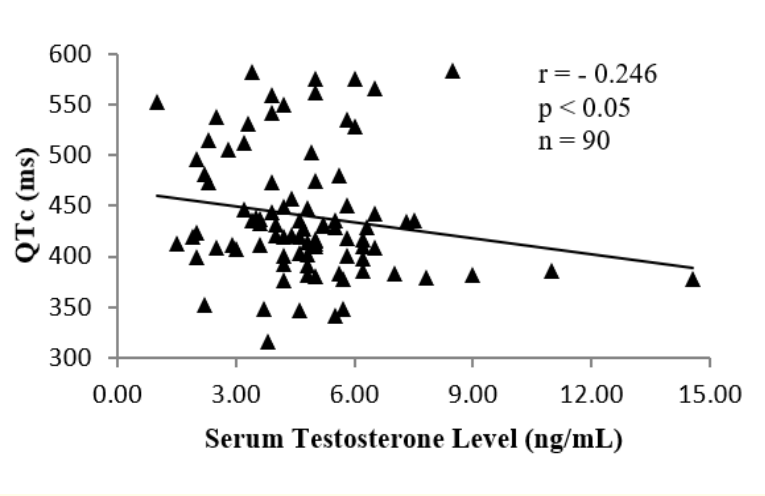


Figure 3: *Presented correlation between serum testosterone level and QTc.*

QTc: Corrected QT Interval; r: Pearson's Correlation Coefficient; n: Total Number of Subjects.

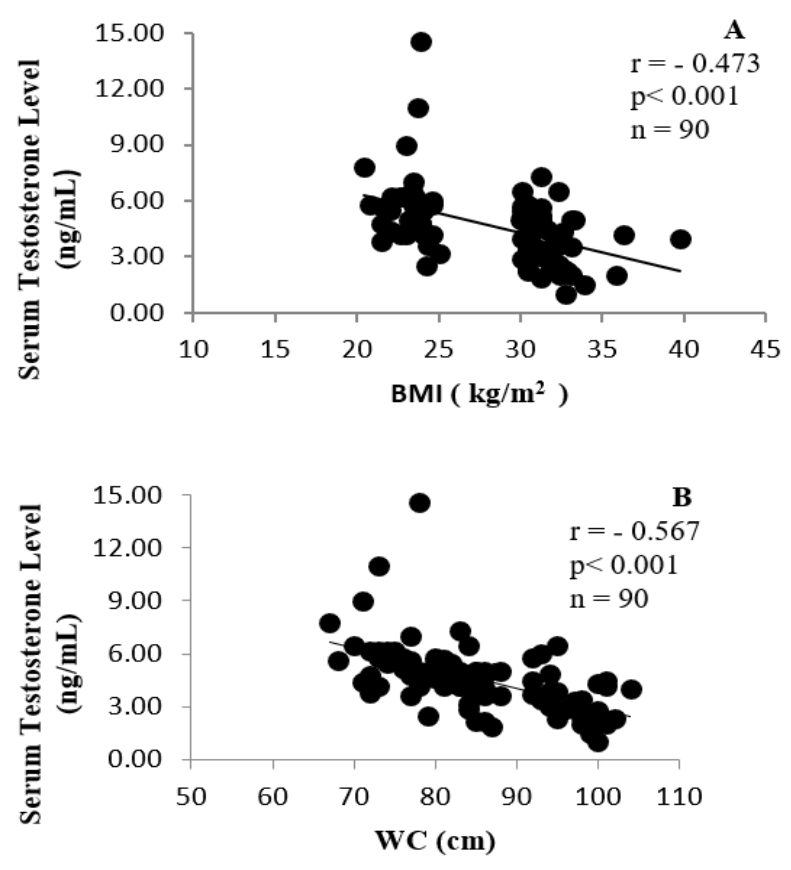
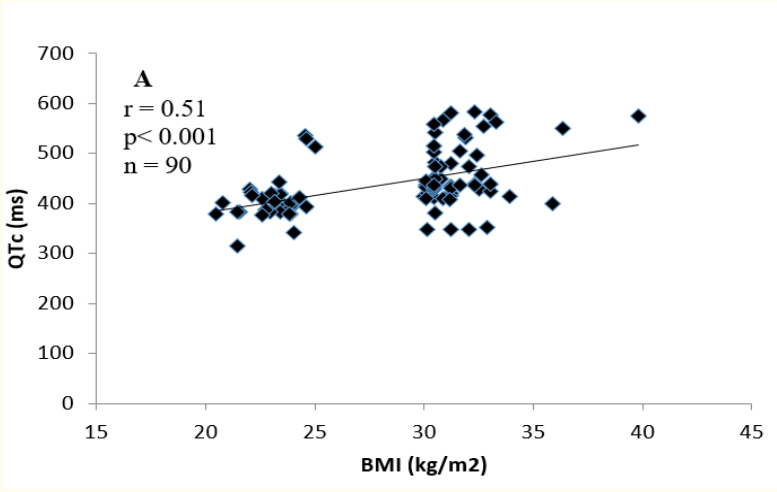


Figure 4: *Revealed correlation between serum testosterone level and BMI (Panel A) and WC (Panel B). BMI: Body Mass Index; WC: Waist Circumference; r: Pearson's Correlation Coefficient; n: Total Number of Subjects.*



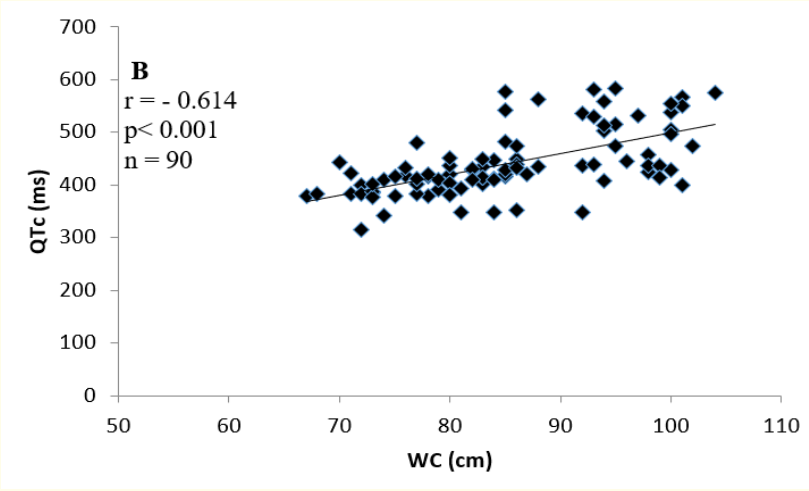


Figure 5: *Revealed correlation between QTc and BMI (Panel A) and WC (Panel B).*

BMI: Body Mass Index; WC: Waist Circumference; r: Pearson's Correlation Coefficient; n: Total Number of Subjects.

	Non-Obese (n = 30) (Mean ± SD)	**Obese (n = 60) (Mean ± SD)**
Age (years)	22.23 ± 1.76	23.62 ± 2.37
Weight (kg)	60.33 ± 4.15	85.55 ± 8.37
Height (m)	1.62 ± 0.05	1.65 ± 0.05
BMI (kg/m^2)	22.99 ± 1.08	31.36 ± 1.94
WC (cm)	75.27 ± 4.09	90.32 ± 7.45

Table 1: *Characteristics of the subjects (Mean ± SD).*

BMI: Body Mass Index; WC: Waist Circumference.

	Generally obese (n = 30) (Mean ± SD)	**Centrally obese (n = 30) (Mean ± SD)**
Age (years)	23.77 ± 2.93	23.47 ± 1.66
Weight (kg)	83.37 ± 5.30	87.73 ± 10.24
Height (m)	1.64 ± 0.57	1.66 ± 0.57
BMI (kg/m^2)	30.92 ± 0.89	31.81 ± 2.54
WC (cm)	83.63 ± 2.91	97.00 ± 3.47

Table 2: *Characteristics of generally obese and centrally obese subjects (Mean ± SD).*

BMI: Body Mass Index; WC: Waist Circumference

Groups	Normal Testosterone	Testosterone deficiency	Odd ratio	95% CI
Generally obese	26	4		
Centrally obese	18	12	4.3	1.2 to 15.61

Table 3: *Odd ratio of testosterone deficiency in generally obese and centrally obese subjects.*

Group	QTc normal	QTc prolong	Odd ratio	95% CI
Generally obese	20	10		
Centrally obese	10	20	4.0	1.37 to 11.70

Table 4: *Odd ratio of prolonged QTc in generally obese and centrally obese subjects.*

Group	QTc normal	QTc prolong	Odd ratio	95% CI
Normal subject	38	35		
Testosterone deficient subject	8	9	1.1	0.47 to 2.72

Table 5: *Odd ratio of prolonged QTc in normal and testosterone deficient subjects.*

Discussion

Testosterone has 19 carbon atoms, is produced from cholesterol, and mainly by Leydig cells in the testes. There was diurnal variation of serum testosterone level, which peak around 08:00 A.M. and lowest in the late afternoon. Prior to puberty, testosterone level is usually low in males. However, after puberty, testosterone level increases and reaches its peak around the age of 20-25 in men. As aging occurs, testosterone levels decline [23]. In the present study mean age of non-obese, generally obese and centrally obese groups were 22.23 ± 1.76, 23.77 ± 2.93 and 23.47 ± 1.66 years, respectively and there was no significant difference in age between all three groups of the subjects. Normal adult testosterone level is 10.4 - 34.7 nmol/L or 300 - 1000 ng/dL or 3-10 ng/mL [24]. In the present study, mean serum testosterone level of non-obese subjects (BMI = 22.99 ± 1.08; n = 30) was 5.81 ± 2.35 ng/mL, which was within the normal range. It was relatively comparable with that of non-obese subjects (BMI = 24.5 ± 0.47; n = 10) in previous study done by Isidori., *et al* [24]. Mean serum testosterone level of obese subjects (3.98 ± 1.39 ng/mL, n = 60) was significantly lower than that of non-obese group ($p < 0.001$). This finding of the present study agreed with the previous studies [24-26].

In the present study, central obesity is determined by WC, indirect measurements of visceral fat distribution and the decrease in testosterone levels appears to be more pronounced in centrally obese subjects than generally obese ($p < 0.05$). In addition, 1 out of 30 (3.33%) non-obese subjects, 4 out of 30 (13.33%) generally obese subjects and 12 out of 30 (40%) centrally obese subjects from the present study had testosterone deficiency. Therefore, risk of lower testosterone level was 4.3 times increased in centrally obese subjects than generally obese subjects (Odd ratio = 4.33; 95% confidence interval = 1.2 to 15.61). In addition, there were significant negative correlations between serum testosterone level and BMI ($r = - 0.473$, $p < 0.001$, $n = 90$) as well as WC ($r = - 0.567$, $p< 0.001$, $n = 90$). It was agreed with the studies of Osuna., *et al.* [27], Allan., *et al*. [28], Khan., *et al*. [29] and Shoujun., *et al*. [30]. It was also noted that WC has stronger correlation with serum testosterone compared with BMI. This finding was consistent with the studies done by Allan., *et al*. [28] and Khan., *et al.* [29]. Thus, the findings in the present study can conclude that central obesity has greater risk for testosterone deficiency.

According to normal physiology, testosterone is synthesized from cholesterol mainly in the leydig cells and is also formed from androstenedione secreted from the adrenal cortex. Cholesterol is converted to pregnenolone which is hydroxylated in the 17 position and then subjected to side chain cleavage to form dehydroepiandrosterone. Androstenedione is also formed via progesterone and 17-hydroxyprogesterone. Dehydroepiandrosterone and androstenedione are then converted to testosterone [23]. Testosterone can be converted into estrogen via aromatase enzymes which is secreted by adipose tissue [31-33]. Excessive visceral fat causes increased conversion of androgens into estrogens lead to increase in circulating estradiol levels. This increase in circulating estradiol levels may in turn lead to an inhibition of the hypothalamic GnRH secretion and LH pulsatility which results in a reduction of gonadal testosterone production [34,35].

Additionally, estrogen excess may also directly inhibit gonadal 17-α hydroxylase and thus inhibiting Leydig cell steroidogenesis [37].

Inflammatory mediators, such as the adipokines, IL-6 and TNF-α have been already shown to negatively influence on HCG-induced testosterone secretion directly from Leydig cells [37-39]. Furthermore, adipose tissue is known to secrete pro-inflammatory adipokines in case of obesity [40,41]. An explanation of low serum testosterone levels in obese subjects could be a proinflammatory status in testes.

Additionally, visceral adiposity is closely associated with insulin resistance and compensatory hyperinsulinemia [2]. It was found that hyperinsulinemia may directly exert a suppressive effect on testicular Leydig cell steroidogenesis [38,39,43,44]. All these studies taken together suggest the possibility that central obesity causes reduced serum testosterone level.

In the present study, mean QTc of non-obese subjects (n = 30) was 395.87 ± 25.43 ms which is within the normal range [6]. This value is relatively comparable with the previous studies [2,5,25,26]. In addition, mean QTc of obese subjects [462.75 ± 63.44 (ms), (n = 60)] was significantly longer than that of non-obese subjects ($p < 0.001$). It was agreed with the studies of Corbi., *et al.* [3], Arslan., *et al*. [8], Guven., *et al*. [46] and Ozkan., *et al*. [47] reporting more prolong QTc in obese group than non-obese group. In their studies, possible mechanism of the prolonged QTc interval might be due to autonomic dysfunction and increased serum insulin level in obesity [3,46]. Even in the absence of autonomic neuropathy, insulin resistance state and obesity induced compensatory hyperinsulinaemia may lead to prolonged QTc. Although present study did not measure serum insulin concentration, obesity is well established feature of hyperinsulinaemia. Thus, it can be assumed that prolonged QTc of obese subjects in the present study might be due to obesity induced hyperinsulinaemia.

According to previous studies obesity causes dyslipidaemia, abnormal cardiomyocyte lipid deposits and lipotoxicity of the myocardium [47,48]. Lalani., *et al.* has reported that fatty infiltration of the myocardium impaired ventricular activation and repolarization [47]. Moreover, adipocytokines from epicardial fat can prolong action potential duration by decreasing delayed rectifier outward currents [33]. Additionally, obesity causes structural changes to the heart including myocyte hypertrophy and fibrosis [49]. All these changes in obesity may lead to conducting abnormality and prolonged QTc interval.

Another possible mechanism of prolonged QTc in obese male subjects is testosterone deficiency. It has been established that testosterone increases the expression of adrenergic receptors, L-type calcium channel and sodium-calcium exchanger in isolated cardiomyocytes. Moreover, testosterone is a regulator of the action potential duration, ventricular repolarization and tendency to ventricular arrhythmia [10]. It has also been shown that testosterone stimulates nitric oxide synthase and increases the secretion of nitric oxide. The releasing nitric oxide induces shortening in the duration of the action potential by activating the slow component of delayed rectifier potassium current and inhibiting L-type calcium currents [50].

In the present study, there was significant negative correlation between serum testosterone level and QTc ($r = -0.246$, $p < 0.05$, $n = 90$). Contrary to this study, Giraldi., *et al*. reported that QTc was not correlated with serum testosterone level ($r = 0.12$) [10]. In the present study, 9 out of 17 (53%) testosterone deficient subjects had prolonged QTc and 35 out of 73 (48%) subjects with normal testosterone level had prolonged QTc. According to the odd ratio (Odd ratio = 1.1; 95% confidence interval = 0.4 to 2.7) and weak correlation between serum testosterone level and QTc, it can be assumed that testosterone may play some role in QT interval prolongation.

In accordance with findings of previous studies, central or visceral adipose tissue is a major risk factor for QTc prolongation. In support of this concept, present study found out that QTc of centrally obese ($n = 30$) was significantly higher than that of generally obese group ($n = 30$) ($p < 0.001$). In the present study, only 1 out of 30 (3.33%) non-obese subjects had prolonged QTc although 10 out of 30 (33.33%) generally obese subjects and 20 out of 30 (66.66%) centrally obese subjects had prolonged QT interval. The risk for prolonged QT interval was 4.0 times more likely (Odd ratio = 4.0; 95% confidence interval = 1.37 to 11.70) in centrally obese subjects than generally obese subjects. Thus, centrally obese subjects had more risk for cardiovascular diseases compared with generally obese subjects.

In addition, there was strong correlation between QTc and BMI ($r = 0.51$, $p < 0.001$, $n = 90$) as well as WC ($r = 0.614$, $p < 0.001$, $n = 90$). The correlation between QTc and WC was stronger than the one between QTc and BMI, indicating that central obesity is a more important predictor of prolonged QTc than general obesity. Accordingly, prolonged QTc in obese subjects from the present study might be partly attributable to lower serum testosterone level.

Conclusion

Based on findings of the present study, it can be concluded that central obesity is a major risk factor for testosterone deficiency and cardiovascular disease. Obesity itself might play a crucial role in the pathogenesis of cardiovascular diseases and testosterone has some role in the development of prolonged QTc. Other mechanisms might also participate in the development of cardiovascular diseases.

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Conflicting Interest

Nil.

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