Abstract

Objective. This study determined the relationship between plasma adiponectin level and corrected QT interval (QTc) in smokers and non-smokers.

Methodology. This cross-sectional analytical study was undertaken in 30 smokers and 30 non-smokers. Plasma adiponectin level was determined by enzyme-linked immunosorbent assay (ELISA). The QT interval was measured by routine 12-lead ECG with Lead II rhythm and QTc was calculated.

Results. Mean plasma adiponectin level was significantly lower in smokers (27.89±15 µg/ml) than that of non-smokers (52.13±21.57 µg/ml) (p<0.001). Mean QTc interval was significantly longer in smokers than that of non-smokers (415.37±29.9 versus 395.63±26.13 ms, p<0.01). Moreover, low plasma adiponectin level was significantly associated with prolonged QTc interval in the study population (n=60, r=-0.407, p=0.001). There was weak negative significant correlation between plasma adiponectin level and QTc interval in the study population (n=60, r=-0.407, p=0.001). There was weak negative significant correlation between plasma adiponectin level and QTc interval (n=60, r=-0.407, p=0.001). Moreover, low plasma adiponectin level was significantly associated with prolonged QTc interval in the study population (n=60, Fisher's exact p value<0.05). Risk of QTc interval prolongation was 4.3 times higher in subjects with low plasma adiponectin level (OR,4.27; 95% CI,1.05-17.46).

Conclusion. Smokers have greater risk for low plasma adiponectin level and prolonged QTc interval. There is a relationship between plasma adiponectin level and QTc interval.

Key words: smoker, adiponectin, QTc

INTRODUCTION

Adiponectin is a 247 amino-acid protein secreted from adipocytes and exerts beneficial effects on the cardiovascular system by directly acting on vascular smooth muscle cells, endothelial cells and cardiac myocytes. It can mediate anti-atherosclerotic, anti-fibrotic, anti-apoptotic and anti-inflammatory effects. Thus, low plasma adiponectin level is associated with increased prevalence of cardiovascular diseases (CVD).

Animal study reported that adiponectin plays a role in expression of transient outward potassium channel (Iₒ) and duration of action potential in rat ventricular muscles. A loss of Iₒ channel protein expression and function was associated with action potential prolongation which was reflected by QT prolongation. The QT interval represents the time from onset of ventricular depolarization to completion of repolarization. When QT interval is prolonged, repolarization is irregular with increased incidence of ventricular arrhythmias and sudden death.

QTc means corrected QT interval with heart rate because normal QT interval decreases as heart rate increases. QTc interval was calculated using Bazett’s formula as follows: QTc=QT/√RR. A QTc interval of more than 440ms in men and 460ms in women is considered prolonged. So, it can be assumed that adiponectin might be associated with QT interval. Only a few studies are available focusing on the role of adiponectin in QTc interval in humans. In a study done in Japan, it was shown that QTc interval had inverse correlation with adiponectin in healthy male subjects. Further studies are needed to explore the association between adiponectin and QTc interval.

According to previous studies, the circulating adiponectin level was significantly decreased in smokers compared to non-smokers. Present study selected the smokers as participants to determine the association between plasma adiponectin level and QTc interval. Thus, present study investigated the relationship between plasma adiponectin level and corrected QT interval in male adult smokers and non-smokers.
METHODOLOGY

This cross-sectional analytical study was undertaken in apparently healthy male subjects 18-40 years old, residing in Hlaingthaya Township, Yangon, Myanmar from April 2018 to December 2018. The present study used the non-probability convenience sampling method. No (8) Quarter was selected from 22 Quarters in Hlaingthaya Township since that quarter has high population density. We asked for approval from the local administrator for recruitment of apparently healthy male subjects between 18-40 years old. Voluntary written informed consent was obtained after thorough explanation of research purpose and procedures.

All participants underwent history taking and physical examination. Subjects with no acute illness and no known history of hypertension, diabetes, ischemic heart disease, cerebrovascular accident, arrhythmia, peripheral arterial disease, renal disease and bronchial asthma were regarded as apparently healthy subjects. Individuals with the following characteristics were excluded from the study: those who consumed heavy alcohol (more than 3 units of alcohol per day) that decreased adiponectin levels as a result of increased tumor necrosis factor-α; individuals who chewed betel quid with tobacco containing nicotine that affects both adiponectin and QT interval; individuals who are currently taking drugs that altered adiponectin concentration like omega 3 fish oil, niacin and statin; individuals who are currently using antimicrobial agents such as fluoroquinolones, erythromycin, antidepressant agents such as amitriptyline that prolonged QT interval.

Each participant was interviewed by using a questionnaire to collect history of cigarette smoking including average number of cigarettes smoked per day and duration of cigarette smoking. Those who currently smoke a minimum of 10 cigarettes per day for at least 5 years were selected as smokers and those who have never smoked any form of tobacco in their life and with no history of smoking in their family members were defined as non-smokers.

Subjects with normal body mass index (BMI) (18.5-24.9 kg/m²) were selected. Resting arterial blood pressure was measured in lying position using a mercury sphygmomanometer and a stethoscope by an indirect method. The average of three measurements taken over a one-minute interval was used. Subjects having systolic blood pressure (SBP) >120 mmHg and diastolic blood pressure (DBP) >80 mmHg were excluded according to American Health Association guideline 2017.

Sample size was calculated by using Rosner’s formula:$n = \frac{(\sigma_1^2 + \sigma_2^2)Z_{\alpha/2}^2 + Z_{\beta}^2}{\delta^2}$

\(n\) = number of subjects for each group
\(\delta\) = \(X_2 - X_1\)
\(\sigma_1^2\) = variance of \(X_1\)
\(\sigma_2^2\) = variance of \(X_2\)
\(Z_{\alpha}\) = the Z value from normal distribution associated with a probability of 1-\(\alpha\)
\(Z_{\beta}\) = the Z value from normal distribution associated with a probability of 1-\(\beta\)

If \(\alpha = 0.05\), \(Z_{0.025} = 1.96\)
If \(\beta = 0.01\), \(Z_{0.01} = 2.326\)

According to the adiponectin level derived from Fan et al.\(^\text{17}\)

\(X_1\) = mean plasma adiponectin level of smoker = 2.49 µg/ml
\(X_2\) = mean plasma adiponectin level of non-smoker = 3.23 µg/ml
\(\sigma_1\) = standard deviation of smoker = 0.35
\(\sigma_2\) = standard deviation of non-smoker = 0.37
sample size \(n = 9\)

According to the QTc value derived from Sharma et al.\(^\text{18}\)

\(X_1\) = mean QTc interval of smoker = 413.9 ms
\(X_2\) = mean QTc interval of non-smoker = 377.9 ms
\(\sigma_1\) = standard deviation of smoker = 34.17
\(\sigma_2\) = standard deviation of non-smoker = 20.88
sample size \(n = 23\)

A total of 60 male adult subjects (30 smokers and 30 non-smokers) were recruited in the present study.

The study was conducted in the morning between 7 to 9 am in the fasting state. At the beginning, fasting blood sugar level was determined by pricking the fingertip using a glucose meter. Subjects having fasting blood sugar (FBS) levels >110 mg/dl were excluded from the study. Routine 12 lead ECG was performed using ECG machine (CM 100, Shenzhen Comen Medical Instruments Co., Ltd., China) after the subjects were allowed to lie down comfortably on the bed with attachment of limb electrodes for 15 minutes. Paper speed was 25 mm/s and manual calibration was carefully adjusted at 10 mm/mV before recording. Lead II rhythm strip was also taken for 10 seconds. QT interval was measured from the start of Q-wave to the end of T-wave in a normal beat. Heart rate was calculated from average R-R intervals of the beat within 10 seconds. QT intervals and R-R intervals were measured using vernier caliper. Then, QTc interval was calculated by using Bazett’s formula (QTc=QT/RR).\(^\text{9}\) Then, 3 milliliters of fasting venous blood was drawn from the antecubital vein under aseptic condition using a disposable syringe and needle for each subject. Blood samples were collected into a tube containing EDTA disodium anticoagulant and carried to the common research laboratory of the University of Medicine 2. On arrival, plasma separation was done by centrifuging at 2000 rpm at 4°C for 10 minutes and stored at -20°C until sample analysis. Plasma adiponectin level was determined by Adiponectin ELISA Kit (ab99968, Abcam, UK).

Data entry and analysis were done by SPSS software (version 22, SPSS Inc., Chicago, IL, USA). Data were described by mean ± SD. Independent "t" test was used to compare the plasma adiponectin level and QTc interval between smokers and non-smokers. Correlation studies were computed by Pearson’s correlation. Chi-square test was used to determine whether there are significant associations between smoking, plasma adiponectin level and QTc interval. Values of \(p<0.05\) were accepted as statistically significant. This study was approved by Ethics Review Committee, University of Medicine 2, Yangon.

RESULTS

The general characteristics of the study population are shown in Table 1. Mean age, BMI, SBP, DBP and FBS of two

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groups showed no significant differences indicating that both groups were comparable to each other. Heart rate of the two groups showed significant difference.

**Table 1. Baseline characteristics of the subjects**

| Parameters | Non-smokers (Mean±SD) | Smokers (Mean±SD) | p value |
|------------|------------------------|-------------------|---------|
| Age (years) | 25.43±3.52             | 26.47±4.1         | 0.29    |
| BMI (kg/m²) | 20.95±2.1              | 21.67±1.66        | 0.15    |
| SBP (mmHg)  | 112±7.14               | 113.3±7.58        | 0.49    |
| DBP (mmHg)  | 70.3±7.18              | 72.7±14           | 0.37    |
| FBS (mg/dl) | 103±10.8               | 107.2±3.98        | 0.06    |
| HR          | 72.13±9.45             | 81.5±11.89        | 0.001   |

Table 1 shows the comparison of plasma adiponectin level between smokers and non-smokers. There was a significantly lower mean plasma adiponectin level in smokers compared with non-smokers (27.89±15 versus 52.13±21.57 µg/ml) (p=0.001). Mean QTc intervals were 415.37±29.9 and 395.63±26.13 ms for smoker and non-smoker groups respectively. Mean QTc interval of smokers was significantly higher than that of non-smokers (p<0.01) (Figure 2).

Correlation between plasma adiponectin level and QTc interval in the study population is illustrated in Figure 3. There was a weak negative correlation between plasma adiponectin level and QTc interval in the whole study population (r=-0.407, p=0.001, n=60) (Figure 3A). This was statistically significant. When the study population was subdivided into smokers and non-smokers, significant weak negative correlation was only observed in smokers (n=30) (r=-0.434, p=0.017) (Figure 3B) but not in non-smokers (n=30) (r = - 0.175, p=0.35) (Figure 3C). According to Fumeron et al., plasma adiponectin level of healthy individuals presented in a wide range from 20 to 45 µg/ml. Thus, adiponectin value under 20 µg/ml was considered as low adiponectin level in the present study and it was observed in 11 out of 30 (36.7%) smokers and 2 out of 30 (6.7%) non-smokers. Therefore, risk of lower plasma adiponectin level was 8.1 times higher in smokers than non-smokers (odds ratio (OR), 8.1; 95% confidence interval (CI), 1.61-40.77). Also, smokers had higher proportion of low adiponectin level compared to non-smokers (z value=2.84, p=0.005).

In the present study, 9 out of 30 (30%) smokers and 2 out of 30 (6.7%) non-smokers had prolonged QTc interval (>440 ms). Therefore, risk of prolonged QTc interval was 6 times higher in smokers than non-smokers (OR, 6.0; 95% CI=1.17-30.73). Smokers also had a higher proportion of prolonged QTc interval compared to non-smokers (z value=2.33, p=0.02).

It was also noted that 5 out of 13 (38.5%) subjects with low plasma adiponectin level had prolonged QTc interval and 6 out of 47 (12.8%) subjects with normal plasma adiponectin level had prolonged QTc interval (>440 ms). Therefore, risk of prolonged QTc interval was 4.3 times higher in subjects with low plasma adiponectin level than subjects with normal plasma adiponectin level (OR, 4.27; 95% CI=1.05-17.46). Table 2 showed that there is a significant association between low plasma adiponectin level and prolonged QTc interval in the whole population (n=60, Fisher’s exact p value <0.05).

**Table 2. The association between low plasma adiponectin level and prolonged QTc interval in total population (n=60)**

| Variable       | Prolonged       | Normal       | * p value |
|----------------|-----------------|--------------|-----------|
| Subjects with  |                 |              | <0.05     |
| Low adiponectin| 5(38.5%)        | 8 (61.5%)    |           |
| Normal adiponectin | 6(12.8%)      | 41 (87.2%)   |           |

*Indicates significant difference (p<0.05) Comparison was done by independent "t" test

Figure 1 shows the comparison of plasma adiponectin level between smokers and non-smokers. There was a significantly lower mean plasma adiponectin level in smokers compared with non-smokers (27.89±15 versus 52.13±21.57 µg/ml) (p<0.001). Mean QTc intervals were 415.37±29.9 and 395.63±26.13 ms for smoker and non-smoker groups respectively. Mean QTc interval of smokers was significantly higher than that of non-smokers (p<0.01) (Figure 2).

Comparison was done by independent “t” test

Figure 1. Plasma adiponectin level in smokers and non-smokers.

Figure 2. QTc interval in smokers and non-smokers.
by determining carotid intima media thickness, lipid profiles and ECG and have shown that CVD risk is increased in smokers. Constituents of cigarette smoke are mainly nicotine, carbon monoxide, and free radical mediated oxidant gases which not only potentially contribute to cardiovascular diseases but also inhibit the adiponectin gene expression. Thus, the present study recruited smokers to investigate the role of adiponectin on QTc interval.

In the present study, among the smokers, the mean number of cigarettes smoked per day was 12.5±4.8 and mean cigarette smoking duration was 7.8±2.9 years. The present study showed that significant decrease of mean plasma adiponectin level was observed in smokers compared with non-smokers. The findings agree with the reports of previous studies. In addition, risk of lower plasma adiponectin level was 8.1 times greater in smokers than non-smokers (OR,8.1; 95% CI, 1.61-40.77). Thus, the present study can conclude that smokers have greater risk for low plasma adiponectin level.

Several explanations have been proposed for the mechanisms by which smoking reduces adiponectin concentration. In previous in vitro and in vivo studies, nicotine itself induces lipolysis through local nicotinic cholinergic (nAchR) and catecholaminergic receptors in adipose tissue and inhibits the expression of the adiponectin gene in cultured mouse 3T3-L1 adipocytes. Moreover, nicotine also has direct actions on the differentiation of adipocytes by increasing peroxisome proliferator-activated receptor-γ (PPAR-γ), which is essential for inducing differentiation from preadipocytes to mature adipocytes. Supraphysiological activation of PPARγ caused adipogenesis disturbances which may cause enhanced lipolysis and dysfunction of adipokine secretion. Smoking provokes oxidative stress and inflammatory cytokines that reduce adiponectin concentration. Oxidative stress disrupts activation of a key molecule, phosphatidylinositol 3-kinase (PI3K) for the secretion of adiponectin in adipocytes.

**DISCUSSION**

An animal study has shown that adiponectin affects channel proteins (I_v) in rat ventricular myocyte and hypoadiponectinaemia may be involved in prolongation of QT interval. Komatsu et al. reported that there was inverse relationship between adiponectin and QTc interval in healthy men. Contrary to this study, Wu et al. recently reported that there was positive association between adiponectin level and QTc in patients with stable angina. As there is limited information regarding the association between adiponectin and QT interval, further studies are needed to clarify the role of adiponectin on QT interval.

Cigarette smoking is a major cause of cardiovascular diseases. Many studies investigated CVD risk in smokers...
cytokines such as TNF and IL-6 had been found to have negative interaction with adiponectin secretion in in-vivo and in-vitro studies. Another reason for low adiponectin concentration in smokers might be due to impaired vessel wall. Adiponectin accumulates in the injured vascular walls increasing consumption of circulating adiponectin. Mean QTc interval of smokers was 415.37±29.9 ms and significantly longer than non-smokers (395.63±26.13 ms) (p<0.01) in the present study. The finding of the present study agreed with previous studies. Contrary to the present study, Devi et al. showed that there was no significant difference in QT interval between smokers and non-smokers. In the present study, 9 out of 30 (30%) smokers and 2 out of 30 (6.7%) non-smokers had prolonged QTc interval (>440 ms). Therefore, risk of prolonged QTc interval was 6 times greater in smokers than non-smokers (OR, 6; 95% CI, 1.17-30.73). Based on the findings in the present study, we can conclude that smokers have greater risk of QTc interval prolongation. Possible mechanism of prolonged QTc interval might be due to constituents of cigarette smoke such as nicotine, carbon monoxide and oxidant gas. These constituents induce fibrosis at different cardiac sites which in turn lead to altered cardiac conduction and repolarization abnormalities. Additionally, nicotine interacts directly with channel protein in ventricular myocytes and blocks cardiac K+ currents (including delayed rectifier current and inward rectifier current) with preferential inhibition of Ios. Thus, it decreased repolarizing current and prolonged action potential, which is reflected as prolongation of the QT interval. Moreover, smoking induced inflammatory marker, TNF-α decreases Ios which prolongs action potential duration in rat ventricular myocytes. In the present study, 5 out of 13 (38.5%) subjects with low plasma adiponectin level had prolonged QTc interval and 6 out of 47 (12.8%) subjects with normal adiponectin level had prolonged QTc interval (>440 ms). Therefore, risk of prolonged QTc interval was 4.3 times greater in subjects with low plasma adiponectin level than subjects with normal plasma adiponectin level (OR, 4.27; 95% CI, 1.05-17.46). It indicated that occurrence of prolonged QTc interval was increased with low plasma adiponectin level. Moreover, significant weak negative correlation was found between plasma adiponectin level and QTc interval in this study population (r=-0.407, p=0.001, n=60). This finding was similar to previous study done by Komatsu et al., reporting that QTc had negative correlation with adiponectin in Japanese healthy men (β=-0.272, p=0.0048). The study also noted that significant weak negative correlation was observed in smokers only (smokers: r=-0.434, p=0.017, n=30; non-smokers: r=-0.175, p=0.35, n=30).

Furthermore, Wang et al., also reported that adiponectin supplementation restored the duration of action potential and the QT interval on the ECG back to normal by increasing Ios channel protein level in ventricular myocytes. Their findings supported our study since 1µg/ml decrease in plasma adiponectin level was associated with a 0.544 ms prolongation in QTc interval on observed value of the present study.

CONCLUSION

We found that mean plasma adiponectin concentration of smokers was significantly lower than that of non-smokers. Corrected QT interval was significantly prolonged in smokers compared to non-smokers. Thus, 8.1 times greater risk of low plasma adiponectin and 6 times greater risk of QTc interval prolongation were observed in smokers compared with non-smokers.

In addition, risk of prolonged QTc interval was 4.3 times higher in subjects with low plasma adiponectin level than subjects with normal plasma adiponectin level. A significant weak negative correlation as well as a significant association between plasma adiponectin level and QTc interval was observed in the whole study population. Thus, it can be concluded that relationship exists between plasma adiponectin level and QTc interval.

Limitation of the study

As a cross sectional analytical study, it cannot clearly establish the causative effect of adiponectin level on QTc interval. This study is not powered as an interventional study which provides specific conclusions to clarify the link between adiponectin and QTc interval. Moreover, due to relatively small sample size, the confidence intervals of the odds ratios are very wide e.g., smoking and QTc: OR 6 (1.17–30.73). The possibility of second hand smoke was not accounted for in both groups, especially for the non-smokers in the present study.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declared no conflicts of interest.

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