Serum Cotinine, Serum F2-isoprostane and Risk of Metabolic Syndrome in Adult Male Tobacco Users

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ABSTRACT

Data on risk of metabolic syndrome among various forms of tobacco consumption in Myanmar tobacco users are currently limited. The present study aimed to determine and compare nicotine metabolites serum cotinine, oxidative stress marker serum F2-isoprostane in adult male tobacco users, and to find out relationships between these parameters and risk of metabolic syndrome. This cross-sectional study was done in 30 to 45 years old males: 84 cigarette smokers, 84 cheroot smokers and 84 betel quid with tobacco chewers. Metabolic syndrome was defined by National Cholesterol Education Program Adult Treatment Panel III definition. Serum cotinine concentration of cigarette smokers was significantly higher than that of cheroot smokers (p=0.026), however, no significant difference was seen between cigarette smokers and betel quid with tobacco chewers (p=1.000), and between cheroot smokers and betel quid with tobacco chewers (p=0.248). Serum F2-isoprostane concentration was significantly higher (p=0.001) in cigarette smokers than cheroot smokers and betel quid with tobacco chewers (p=1.000). Compared with betel quid with tobacco chewers, cigarette smokers had 5.2 times (95% CI, 2.3-11.4) (p<0.001) and cheroot smokers had 1.4 times (95% CI, 0.62-3.3) (p=0.402) higher risk of having metabolic syndrome. There was a significant association between the presence of metabolic syndrome and high serum cotinine as well as high serum F2-isoprostane. A significant correlation between serum cotinine and serum F2-isoprostane was found in betel quid with tobacco chewers, but not in cigarette smokers and cheroot smokers. The present study showed that both nicotine and oxidative stress take part in the pathogenesis of metabolic syndrome. Cigarette smoking has the highest risk of having metabolic syndrome, however, cheroot smoking as well as betel quid with tobacco chewing is related to metabolic syndrome as well.

Keywords: Cotinine, F2-isoprostane, Metabolic syndrome, Tobacco.

I. INTRODUCTION

Tobacco is regarded as the most addictive substance in the world [1]. About 79.8% of Myanmar males are tobacco users [2]. This is the highest percentage among South-East Asia countries [3]. There are two main forms of tobacco use: smoking and smokeless tobacco use. Cigarette smoking is the most common form of smoked tobacco use but some people prefer cheroot, a kind of smoked tobacco made traditionally by hands. Among various forms of smokeless tobacco use in Myanmar, betel quid chewing is the most popular one, and is very common in people who want to give up smoking.

Multiple biomarkers of tobacco exposure have been reported among which cotinine appears to be the most specific and sensitive biomarker [4]. Cotinine, the major metabolite of nicotine, is formed in the liver by the cytochrome P450 2A6 enzyme [5]. In comparing serum cotinine levels between smokers and betel quid with tobacco chewers, the results are still controversial [6], [7]. It has been noted that composition of betel quid varies from country to country. In fact, Myanmar betel quid contains tobacco according to individual preference. Moreover, Myanmar cheroot is prepared by adding varying amounts of tobacco. Yet, there is no data regarding cotinine level in Myanmar.

Metabolic syndrome includes the constellation of various metabolic abnormalities including obesity, hyperglycemia, dyslipidemia and elevated blood pressure. It has been reported that smoking [8] and betel quid chewing [9] are associated with risk of metabolic syndrome. In Myanmar, only a few studies reported derangement of some of metabolic markers in smokers, and only one study had determined the risk of metabolic syndrome in betel quid chewers. Thus, there is limited evidence regarding risk of metabolic syndrome in Myanmar tobacco users. Moreover, though tobacco use has been proven to have risk of metabolic syndrome, mechanisms leading to occurrence and
progression of the disease are multiple and still under investigation.

Oxidative stress plays an important role in development of metabolic syndrome [10]. Evidence suggests that smoking can cause oxidative modification in vivo [11], [12]. Tobacco contains not only nicotine as a pro-oxidant [13] but also many other pro-oxidants compounds such as phenolic compounds [14], nitrate and metals [15]. It was suggested that potential mechanism of increased oxidative stress associated with smoking is either due to nicotine [13] or the direct actions of various pro-oxidants present in tobacco [16].

F2-isoprostane which is an isomer of prostaglandin F2α (PGF2α), has been regarded as the most reliable marker for assessing oxidative stress [17], [18]. Although increased level of F2-isoprostane in smokers has been reported by some studies [11], [12], the relationship between serum cotinine and F2-isoprostane was still contentious in smokers [19], [20]. Thus, the relationship between nicotine and F2-isoprostane in smokers is needed to be elaborated.

Therefore, the present study aimed to determine and compare serum cotinine, serum F2-isoprostane levels and the risk of metabolic syndrome among cigarette smokers (CS), cheroot smokers (CH) and betel quid with tobacco chewers (BQTC), and to explore the role of nicotine and oxidative stress in pathogenesis of metabolic syndrome in tobacco users by determining the association between serum cotinine, serum F2-isoprostane and risk of metabolic syndrome. It is hoped that information on risk of metabolic syndrome in different tobacco users can be useful in raising public awareness of deleterious effects and danger of tobacco use.

II. PROCEDURE

This study was done after the approval of the Research and Ethics Committee of University of Medicine 1, Yangon (Approved number – 115/UM1, REC.2017). A total of 252 adult male tobacco users residing in Yangon, age between 30–45 years, participated in the present study: cigarette smokers (CS) (n=84), cheroot smokers (CH) (n=84), betel quid with tobacco chewers (BQTC) (n=84). Current cigarette smokers who smoke at least 7 cigarettes per day for a year without betel quid chewing and cheroot smoking were regarded as CS, current cheroot smokers who smoke at least 5 cheroots per day for a year without betel quid chewing and cigarette smoking as CH, and current betel quid with tobacco chewers who chew at least 10 betel quids per day for a year without smoking as BQTC.

Written informed consent was taken. Body weight and standing height were measured by weight-height scale. Waist circumference was measured by measuring tape. Blood pressure was measured by auscultatory method with mercury sphygmomanometer after 15 minute-sitting rest.

The subjects were requested to avoid smoking or betel quid chewing the whole morning before blood sample collection. After 8-hour overnight fasting, about 5 mL was withdrawn. Within two hours of sample collection, the samples were transported in ice box (+2 °C to +8 °C) to Postgraduate Research Laboratory, Department of Physiology, University of Medicine 1, Yangon. The plasma glucose was determined by Glucose oxidase, phenol, 4-amino phenazone method on the day of blood collection. After centrifugation of blood samples, serum samples were kept in four separate screw-tight bottles and stored at -20°C until analysis for determination of cotinine, F2-isoprostane, triglyceride and high-density lipoprotein cholesterol (HDLc). Cotinine and F2-isoprostane were determined by ELISA kits (Cloud-Clone, USA). Serum triglycerides level was determined by glycerol phosphate oxidase/phenol aminophenazone method. Serum HDLc level was determined by precipitation method.

According to the criteria of National Cholesterol Education Program Adult Treatment Panel III [21], metabolic syndrome is diagnosed if three of the following metabolic markers are fulfilled, i.e., elevated waist circumference (>90 cm in men), increased fasting plasma glucose (≥110 mg/dL), elevated blood pressure (if systolic blood pressure >135 mmHg and diastolic blood pressure >85 mm Hg), raised triglyceride level (≥150 mg/dL), low high-density lipoprotein cholesterol (<40 mg/dL in men).

Data was analyzed by using the Statistical Package for Social Science (SPSS) software version 22. Numerical variables were expressed as mean±SD. One way ANOVA was used for comparison of serum cotinine concentrations among three groups and post-hoc analysis was done by Bonferroni test. For comparison of serum F2-isoprostane concentrations, Kruskal Wallis test was used. The p value <0.05 was considered statistically significant. For determination of risk of metabolic syndrome, crude odds ratio was analyzed by simple logistic regression and adjusted odds ratio was done by multiple logistic regression. The results were expressed as times increasing in odds of having metabolic syndrome. For determination of association between serum levels of cotinine, F2-isoprostane and risk of metabolic syndrome, Chi-square was used.

III. RESULTS

General characteristics are relatively comparable among the study groups (Table I). Serum cotinine concentrations of CS, CH and BQTC were 1494.66±632.51, 1262.68±460.21 and 1415.63±599.61 pg/mL respectively. Serum cotinine concentration of CS was significantly higher than that of CH (p=0.026). However, no significant difference was seen between CS and BQTC (p=1.000), as well as between CH and BQTC (p=0.248) (Fig. 1).

Serum F2-isoprostane concentrations (median, IQR) of CS, CH and BQTC were 168.26 (116.85–847.54), 109.92 (26.97–291.68) and 91.82 (59.22–179.82) pg/mL respectively. Serum F2-isoprostane concentration was significantly higher (p=0.001) in CS than CH and BQTC, but no significant difference was observed between CH and BQTC (p=1.000) (Fig. 2).

Prevalence of metabolic syndrome were 50% in CS, 25% in CH and 14.3% in BQTC. Risk of metabolic syndrome among the study groups is shown in table II. Relationship between risk of metabolic syndrome and serum cotinine as well as serum F2-isoprostane in tobacco users was shown in table III. No significant correlation was seen between serum cotinine and serum F2-isoprostane concentrations in tobacco users (r=0.12, p=0.07, n=252). There was also no correlation...
between serum cotinine and serum F2-isoprostane concentrations in CS \((r=-0.08, \ p=0.46, n=84)\), and in CH \((r=0.17, \ p=0.11, n=84)\). However, a significant moderately strong positive correlation was seen in BQTC \((r=0.58, \ p<0.001, n=84)\).

**TABLE I: THE ARRANGEMENT OF CHANNELS**

| TABLE I. GENERAL CHARACTERISTICS OF THE STUDY GROUPS | CS \((n=84)\) | CH \((n=84)\) | BQTC \((n=84)\) |
|---|---|---|---|
| Age (years) | 36.6±5.3 | 38.2±5.1 | 36.2±4.6 |
| Height (m) | 1.66±0.07 | 1.64±0.06 | 1.62±0.07 |
| Weight (kg) | 65.29±9.39 | 61.13±10.02 | 59.03±8.87 |
| BMI (kg/m²) | 23.72±3.06 | 22.82±3.63 | 22.37±3.19 |
| Resting SBP (mmHg) | 133.21±10.6 | 134.95±10.4 | 129.05±11.41 |
| Resting DBP (mmHg) | 94.69±8.52 | 95.5±9.81 | 93.43±11.92 |

Data are presented as mean±SD.

One-way ANOVA and post hoc Bonferroni test.

1 indicates significant difference between CS and BQTC \((p<0.05)\).

2 indicates significant difference between CH and BQTC \((p<0.05)\).

3 indicates significant difference between CS and CH \((p<0.05)\).

**TABLE II. RISK OF METABOLIC SYNDROME AMONG THE STUDY GROUPS**

| Tobacco users | OR\(^a\) (95% CI) | p value | OR\(^b\) (95% CI) | p value |
|---|---|---|---|---|
| BQTC (ref) | 1 | 1 | 1 | 1 |
| CS | 6 (2.9-12.7) | <0.001 | 5.2 (2.3-11.4) | <0.001 |
| CH | 2 (0.9-4.4) | 0.084 | 1.4 (0.6-3.3) | <0.402 |

* Simple logistic regression.

* Multiple logistic regression adjusted for age, BMI and physical activity.

**TABLE III. RELATIONSHIP BETWEEN SERUM COTININE, SERUM F2-ISOPROSTANE AND METABOLIC SYNDROME IN TOBACCO USERS**

| Tobacco users \((n=252)\) | Metabolic syndrome (+) | Metabolic syndrome (-) | Total | \(\chi^2\) | p value |
|---|---|---|---|---|---|
| Low serum cotinine | 0 | 46 (100%) | 46 | 23.84 | <0.001 |
| High serum cotinine | 75 (36.4%) | 131 (63.6%) | 206 |  |  |
| Low serum F2-isoprostane | 0 (0%) | 63 (100%) | 63 | 35.59 | <0.001 |
| High serum F2-isoprostane | 75 (39.7%) | 114 (60.3%) | 189 |  |  |

Pearson Chi-square test.

**FIGURES**

**Fig. 1.** Fasting serum cotinine concentrations among CS, CH and BQTC.

NS = Non-significant \((p>0.05)\), S = Significant \((p<0.05)\).

One-way ANOVA and post hoc Bonferroni test.

**Fig. 2.** Fasting serum F2-isoprostane concentrations among CS, CH and BQTC.

NS = Non-significant \((p>0.05)\), S = Significant \((p<0.001)\).

Kruskal Wallis test.

**IV. DISCUSSION**

Cotinine measurement from human body fluids can provide an assessment of exposure to tobacco [22]. Cotinine concentration 1000 pg/mL in serum [23] and in saliva [24] is used as a cut-off value for the status of tobacco exposure; high tobacco exposure vs low tobacco exposure. In the present study, 84 out of 84 (100%) of CS, 59 out of 84 (70.2%) of CH, and 63 out of 84 (75%) of BQTC had serum cotinine concentration above this cut-off value, indicating that majority of the subjects from three study groups had high nicotine exposure. In addition, a significant positive correlation between serum cotinine concentration and daily amount of consumption \((r=0.282, \ p<0.001, n=252)\) was seen, suggesting that like cigarette smoking, cheroot smoking as well as betel quid with tobacco chewing might cause high tobacco exposure if daily amount of consumption is high.

Mean serum cotinine concentration of non-tobacco-users \((n=19)\) was also determined and was 729.39±302.08 pg/mL. Therefore, all three study groups (i.e., tobacco users) had significantly higher serum cotinine levels than the non-tobacco-users, regardless of the type of tobacco usage.

There was a significant difference in serum cotinine concentrations among the three study groups with the highest level in the CS group. Nicotine contents of cigarettes, cheroots and betel quids were not determined in the present study. However, Thein, et al. [25] reported that a cigarette contains 24.5±0.05 mg nicotine and a cheroot contains 14.3±0.02 mg nicotine. A relatively low nicotine contents was detected in betel quids \((0.6-1.6 \text{ mg/g wet weight of the quid}) [26]\). Thus, it could be assumed that difference in serum cotinine concentrations between the study groups might be due to difference in nicotine contents in cigarettes, cheroots and betel quids. The highest serum cotinine level in CS might be due to high nicotine contents of cigarettes although there were variations among individual brands.

In the present study, mean serum cotinine concentration of BQTC was higher than that of CH and was as high as CS. Chewed tobacco augments nicotine absorption through oral mucosa [27] and alkalinizing agents (e.g., lime) and catechu bark added to the quid could enhance the release of nicotine when mixed with tobacco leaves [7].
Concerning serum cotinine concentration between CS and CH of the present study, mean serum cotinine concentration of CS was significantly higher than that of CH. Moreover, daily consumption number for CH was ≥5 cheroots per day whereas that for CS was ≥7 cigarettes per day in the present study. Higher tobacco exposure in CS than CH might be due to higher number of daily consumption and higher content of nicotine in cigarettes [25].

Relatively lower serum cotinine concentration was seen in the present study compared with previous studies [6], [7]. This might be due to differences in the nicotine content of tobacco products, sampling methods, different methods of cotinine measurement, way of smoking and type of cigarette.

Cigarette contains not only nicotine as a source of oxidative stress [13] but also many other varieties of pro-oxidants [15]. For cheroots, major ingredient is crashed tobacco [28] and for betel quid, major constituents are betel leaves, areca nut, lime and additive tobacco. Both areca nuts [29] and nicotine of tobacco [13] can cause oxidative stress. Therefore, all forms of tobacco consumption can cause increased reactive oxygen species (ROS) formation, resulting in oxidative stress. F2-isoprostane is an eicosanoid of non-enzymatic origin, produced by the random oxidation of phospholipids by oxygen radicals [11]. Blood and urinary F2-isoprostane levels were found to be elevated in oxidative stress [11]. High serum F2-isoprostane concentration is defined as serum F2-isoprostane concentration equal or more than 50 pg/mL [18]. In the present study, 68 out of 84 (81%) of CS had high serum F2-isoprostane concentration. Although CH and BQTC had significantly lower serum F2-isoprostane concentration than CS in the present study, 57 out of 84 (67.9%) of CH and 64 out of 84 (76.2%) of BQTC had serum F2-isoprostane concentration equal or above 50 pg/mL. Therefore, it was evidenced that oxidative stress occurs in all forms of tobacco consumption, irrespective of the types of tobacco use.

Nicotine directly or indirectly involves in the pathophysiology of metabolic syndrome and its individual components [30], [31]. Arecoline of betel quid also contributes to pathophysiology of metabolic syndrome [32]. Moreover, some investigators reported that oxidative stress is one of the risk factors in the development of metabolic syndrome [19], [33].

In the present study, 42 out of 84 (50%) of CS, 21 out of 84 (25%) of CH and 12 out of 84 (14.3%) of BQTC had metabolic syndrome according to NCEP/ATP III definition. The percentage of metabolic syndrome in CS in the present study (50%) was consistent with that of 57.3% prevalence rate in a China study [34]. However, it was much higher compared to 27.4% prevalence of an Oslo study [35] and 20.1% prevalence of a Japan study [36]. Difference in cut-off value of waist circumference could be the reason of inconsistent prevalence of metabolic syndrome among these studies. The prevalence of metabolic syndrome in the BQTC of the present study (14.3%) was comparable to 10.1% prevalence of Taiwan study [37].

It has been documented that elevated serum cotinine and serum F2-isoprostane levels might be reflective of the risk of metabolic syndrome in tobacco users [38], [39]. In the present study, serum cotinine and serum F2-isoprostane levels of the CS were higher than those of CH and BQTC. Therefore, it is recognizable that CS had the highest nicotine exposure and oxidative stress, and thus risk of metabolic syndrome would be more apparent in them.

According to the results, BQTC had the lowest risk of having metabolic syndrome among the study groups. When BQTC group was regarded as reference, CS had 5.2 times (95% CI, 2.3-11.4) (p<0.001) higher risk and CH had 1.4 times (95% CI, 0.62-3.3) (p=0.402) higher risk of having metabolic syndrome, after adjusting for age, BMI, and physical activity.

Apparantly healthy non-tobacco-users were not included in the present study. However, one previous study from our department determined risk of metabolic syndrome in normal healthy non-tobacco-users and in betel quid chewers, using same methodology and same inclusion criteria as the present study [9]. When age-matched non-tobacco-users of this previous study (n=22) were regarded as reference for the analysis of risk of metabolic syndrome in the study groups of the present study, it was found that CS had 17.1 times (95% CI, 3.4-86.5) (p<0.005), CH had 4.8 times (95% CI, 0.9-24.4) (p=0.060), and BQTC had 3.3 times (95% CI, 0.6-17.8) (p=0.163) higher risk of having metabolic syndrome than the non-tobacco-users, with adjustment for age, BMI and physical activity. Therefore, the present results revealed that regarding risk of metabolic syndrome, betel quid with tobacco chewing is as much dangerous and harmful as cigarette smoking. Likewise, cheroot smoking is also related to metabolic syndrome and derangement of metabolic parameters.

In the present study, a significant association was observed between high serum cotinine concentration and metabolic syndrome among tobacco users approving that high tobacco exposure can significantly increase the risk of metabolic syndrome, regardless of the route of consumption: smoking or chewing. Moreover, a significant association was noted also between high serum F2-isoprostane and metabolic syndrome in tobacco users. Since F2-isoprostane is regarded as the best available representative of oxidative lipid damage in the body [11], the present finding also confirmed that oxidative stress in tobacco users is related to metabolic syndrome despite of variations in nicotine contents, pro-oxidant contents, types of pro-oxidants and number of daily consumptions among them.

Nicotine produces oxidative stress while metabolizing into cotinine [13] whereas pro-oxidant compounds of tobacco produces oxidative stress while combusting from burning end [15]. In the present study, no significant correlation between serum cotinine and F2-isoprostane was observed among tobacco users; in both CS and CH. Therefore, it could be implied that F2-isoprostane signifies the oxidative stress caused by other pro-oxidant compounds in tobacco rather than nicotine and nicotine could not be the main contributor of oxidative stress in both CS and CH.

However, in case of BQTC, nicotine might be the main contributor of oxidative stress. This suggestion is supported by finding of a significant positive correlation between serum cotinine and F2-isoprostane in BQTC of the present study (r=0.581, p<0.001, n=84), indicating nicotine-related oxidative stress. In fact, nicotine [15] as well as areca nuts [33] produces oxidative stress but betel quid with tobacco...
chewers usually add less areca nut whereas as betel quid without tobacco chewers add much areca nuts [9].

V. CONCLUSION

In conclusion, serum cotinine and F2-isoprostane levels of the CS were highest among the study groups, and thus risk of having metabolic syndrome was utmost in them. Furthermore, it was found that both nicotine and oxidative stress have a role in the pathophysiology of metabolic syndrome. Some Myanmar people believed that betel quid chewing is less dangerous than cigarette smoking, and therefore use this habit to quit smoking. Moreover, some rural Myanmar people still concern cheroots as a cultural and traditional mark in their ceremonies, considering cheroots are made of natural ingredients and have no potential health hazards. However, the present study indicated that cheroot smoking and betel quid with tobacco chewing also had the risk of having metabolic syndrome, and thus, tobacco is related to metabolic syndrome regardless of the type of consumption.

A. Limitation of study

One of the limitations of the present study was that apparently healthy non-tobacco-users were not included. So as to conclude the evidence about the risk of metabolic syndrome among the tobacco users, non-tobacco-users group should be involved. Moreover, in order to determine the relationship between the contents and tobacco exposure in different tobacco users, chemical analysis on the constituents of different brands of cigarettes, cheroots and betel quids with tobacco is recommended. Furthermore, individuals with metabolic syndrome have a chance to develop diabetes mellitus and cardiovascular diseases such as myocardial infarction and stroke. In order to study any risk of developing such complications in tobacco users, a longitudinal study is recommended.

B. Conflicts of interest

The authors declare that they have no competing interests.

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