Smoking Associates With Visceral Fat Accumulation Especially in Women

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Background: Smoking and metabolic syndrome (MetS) are major public health problems in modern society and are important risk factors of cardiovascular disease (CVD). The association of smoking, MetS, and CVD is widely reported, but reports targeted to women are few. In the present study, we evaluated risk factors, including visceral fat area (VFA), for CVD and development of subclinical atherosclerosis in female smokers especially.

Methods and Results: Subjects consisted of 162 apparent healthy female and male smokers, and 315 age-matched never-smokers who underwent a health examination in the Osaka University Health Care Center. For female smokers, lifestyle and carotid intima-media thickness (IMT) were evaluated. Triglycerides were significantly higher and high-density lipoprotein-cholesterol significantly lower in smokers than in never-smokers for both men and women. However, VFA was significantly high only in smoking women when compared with never-smokers. Multivariate analysis revealed that age, body mass index, and smoking were the independent predictors of high VFA in women. In addition, annual IMT increase was significantly higher in smokers than never-smokers in women.

Conclusions: VFA was notably high in female smokers, but the difference was not observed in men. Smoking habit is an important risk factor of visceral fat accumulation and progression of subclinical atherosclerosis in women. (Circ J 2014; 78: 1259–1263)

Key Words: Intima-media thickness; Metabolic syndrome; Smoking; Visceral fat; Women

Smoking is a risk factor of various diseases, such as cancer, pulmonary disease, and cardiovascular disease (CVD).1–4 The World Health Organization (WHO) reports that nearly 6 million people are killed by smoking each year. In the early 1990s, WHO estimated that there were 1.1 billion smokers, including 900 million men and 200 million women. Among these populations, 700 million men and 100 million women are in developing countries, whereas 200 million men and 100 million women are in developed countries.5 In the recent 5 decades, the population of smoking men has declining slowly, but among women, especially in developing countries, it appears to be rising.6 The increasing number of smoking women is not only a problem for developing countries, but also a major problem in Japan.

Numerous risk factors for CVD have been reported, such as hypertension, diabetes, and dyslipidemia, which are the components of metabolic syndrome (MetS).7,8 Visceral fat accumulation is considered as the major cause of clustering of these risk factors.9–13 Smoking is the number 1 risk factor for the onset of acute myocardial infarction in women, whereas hypertension is the number 1 risk in men.14 In addition, the risk of CVD increases in female smokers with early menopause and use of oral contraceptives.8 In modern society, smoking habit and MetS are major public health problems, and both are important risk factors of CVD.2,15,16

To date, there have been many studies reporting the association of smoking habit, MetS, and CVD,17–19 but only a small number of reports have been targeted to female smokers. In the present study, we assessed and compared the risk factors, including visceral fat accumulation, for CVD, development of subclinical atherosclerosis, and inflammatory response between smokers and never-smokers especially in women.

Study Subjects
Subjects were smokers (55 female, 107 male) and randomly selected age-matched never-smokers (107 female, 208 male) who underwent health examinations in the Osaka University Health Care Center during 2004–2012. All subjects were apparently healthy Japanese, 45–61 years of age, did not take any
Table 1. Characteristics of the Study Subjects

| All       | Smokers | Never-smokers | P value | Smokers | Never-smokers | P value |
|-----------|---------|---------------|---------|---------|---------------|---------|
| n         | 477     | 55            | 107     | 107     | 208           |         |
| Age (years) | 51.7±4.8 | 51.7±4.8 | 51.7±4.8 | 51.7±4.8 | 51.7±4.8 |         |
| BMI (kg/m²) | 22.9±3.0 | 21.8±3.8 | 21.0±2.3 | 0.16    | 23.9±3.0 | 23.6±2.6 | 0.65    |
| WC (cm)   | 80.6±8.7 | 74.8±10.2 | 73.6±6.4 | 0.42    | 84.7±7.3 | 83.4±7.0 | 0.13    |
| SBP (mmHg) | 120±16  | 117±16       | 112±14  | 0.15    | 126±13  | 122±16   | 0.028   |
| DBP (mmHg) | 77±13   | 72±13       | 69±12   | 0.10    | 82±10   | 81±12    | 0.27    |
| VFA (cm²) | 84.5±39.9 | 60.1±37.8 | 47.5±19.1 | 0.040 | 105.6±35.8 | 97.1±34.8 | 0.05 |
| UA (mg/dl) | 5.5±1.3 | 4.4±1.2       | 4.4±0.8  | 0.83    | 6.1±1.2 | 5.9±1.2  | 0.16    |
| TG (mg/dl) | 109±88  | 94±59        | 70±29   | 0.027   | 151±127 | 111±80   | 0.001   |
| HDL-C (mg/dl) | 60±15  | 63±15        | 70±14   | 0.005   | 53±14   | 57±13    | 0.004   |
| LDL-C (mg/dl) | 126±29 | 123±27       | 126±27  | 0.53    | 124±30  | 128±30   | 0.13    |
| FPG (mg/dl) | 90±12   | 86±10        | 84±6    | 0.47    | 93±10   | 94±13    | 0.58    |
| HbA1c, %   | 5.1±0.4 | 5.2±0.4       | 5.1±0.3  | 0.049   | 5.2±0.5 | 5.1±0.4  | 0.24    |

Data are mean±SD. Values in bold, P<0.05.

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; TG, triglycerides; UA, uric acid; VFA, visceral fat area; WC, waist circumference.

Table 2. Correlation Between Visceral Fat Area and Level of Smoking in Women

| Smoking Habit | τ  | P value |
|---------------|----|---------|
| Cigarettes per day | 0.261 | 0.03 |
| Brinkman index | 0.223 | 0.042 |

Evaluation of Carotid Atherosclerosis

Carotid atherosclerosis in the women was evaluated by performing ultrasound examination of the carotid artery as described previously. Changes in the IMT (delta [D] maximum IMT and D mean IMT) during 1 year were measured for 69 women who visited annually for medical checkup (31 smokers, 38 never-smokers). Statistical Analysis

Data were analyzed using SPSS 19 (IBM Corp, Armonk, NY, USA). Kendall’s rank correlation coefficient and stepwise multiple regression analysis were used to analyze variables. Student’s t-test or Mann-Whitney U test was used to assess the difference between 2 groups. Statistical significance was set at P<0.05.

Results

Characteristics of Subjects

Characteristics of the study subjects are summarized in Table 1. The mean age of total subjects was 51.7±4.8 years. Triglycerides (TG) were significantly higher and high-density lipoprotein-cholesterol (HDL-C) significantly lower in smokers than never-smokers in both women and men. Systolic blood pressure (SBP) was significantly higher only in male smokers than never-smokers. On the other hand, HbA1c was significantly higher only in female smokers than never-smokers. VFA was also significantly high in female smokers comparing with never-smokers. Male smokers showed higher VFA than male never-smokers, but it was not significant. Moreover, the number of cigarettes smoked per day and Brinkman index significantly correlated with VFA in female smokers (Table 2). In spite of the significant accumulation of visceral fat, WC did not show any significant enlargement in female smokers. In addition, other anthropometric measures of obesity, such as BMI and WC did not show any significant differences between smokers and never-smokers for either women or men.

Determinants of VFA in Women

To elucidate the determinants of visceral fat accumulation in female smokers, the relationship between VFA and possibly af-
factors was analyzed in women. As shown in Table 3, age, BMI, WC, and smoking significantly correlated with VFA. For further analysis, stepwise regression analysis was performed (Table 4), in which WC was excluded as a variable because of high collinearity with BMI. From the stepwise regression analysis, age, BMI, and smoking significantly correlated with VFA, suggesting that these were the independent determinants of visceral fat accumulation.

Table 3. Correlation Between Visceral Fat Area and Its Risk Factors in Women

| Factor        | \( \tau \) | P value |
|---------------|------------|---------|
| Age           | 0.136      | 0.006   |
| BMI           | 0.580      | <0.0001 |
| WC            | 0.708      | <0.0001 |
| Smoking       | 0.120      | 0.040   |
| Alcohol intake| 0.022      | 0.690   |
| Psychological stress | -0.019 | 0.730 |
| Sleep shortage| 0.019      | 0.746   |

Values in bold, P<0.05. Abbreviations as in Table 1.

Effect of Smoking on IL-6 and hs-CRP Concentrations in Women

Serum IL-6 and hs-CRP concentration were measured to confirm the mechanism of atherosclerosis in smokers. IL-6 was significantly higher in smokers than in never-smokers, and hs-CRP was also higher in smokers than in never-smokers, but was not significantly different (Figure 2). From the measurement of IL-6 and hs-CRP, inflammatory response was suggested as one of the mechanisms for the progression of subclinical atherosclerosis in female smokers.

Table 4. Independent Variables for Visceral Fat Area Increase

| Factor | \( \beta \) | P value |
|--------|------------|---------|
| Age    | 0.104      | 0.011   |
| BMI    | 0.777      | <0.0001 |
| Smoking| 0.122      | 0.003   |

R=0.822, Adjusted R²=0.670. Abbreviation as in Table 1.

Evaluation of VFA Measurement by Impedance Method

As shown in Table 5, VFA estimated by impedance method in women also correlated with MetS-related factors as did BMI and WC.

Discussion

In this study, the notable result is that the VFA of female smokers was much higher than in never-smokers, whereas BMI and WC showed no significant differences. Generally, women have higher percent body fat than men and the fat distributes peripherally, such as the hips and thighs. Abdominal subcutaneous fat is also rich in women. Therefore, VFA in women is markedly less than that in men when WC is the same. In premenopausal women, body fat is mainly located in peripheral subcutaneous depots, whereas men tend to accumulate more fat in central visceral depots, independent of age. After women enter menopause, body fat distribution changes and it tends to accumulate in visceral depots. Menopause induces estrogen deficiency and results in visceral fat accumulation. Our questionnaires did not include information about menopause, so we divided the subjects into 2 groups at age 50, the average age of menopause, and compared VFA in both groups (data not shown). The VFA of female smokers was significantly higher than in never-smokers in the younger group. On the other hand, in the older group, VFA in smokers was also high compared with that in never-smokers but without significant difference. Further examination is necessary to clarify the underlying mechanism of the difference between the younger and older groups.

Although VFA presented a significant difference by smoking habit in women, no difference in WC was observed. Previous studies have reported that WC correlates with VFA and that measurement of the waist is recommended for VFA evaluation. However measurement of WC has a limitation in women, because their fat distribution differs from that of men, especially in the premenopausal state. WC includes both visceral and subcutaneous fat, and there is high variability by factors such as sex, race and age. Therefore, WC does not always have the same significance as VFA. Generally, WC measurement is adopted to evaluate VFA in a health examination; however from the present study’s results, measurement of VFA seems to be more valuable than WC especially in women.

It is reported that VFA examined by CT well predicts the clustering of metabolic risk factors compared with other anthropometric indexes, such as BMI and WC. In the present study, VFA measured by impedance method showed a significant correlation with MetS-related factors as did BMI and WC (Table 5). Therefore, the evaluation of VFA by impedance method seems to be as useful as BMI and WC. Ryo et al reported that the impedance method is reliable for measuring VFA as compared with CT, and that it is simple, safe and transportable. Dual x-ray absorptiometry provides a roughly accurate measurement of VFA, but it is as costly and complex as CT. It might be useful to adopt the impedance method for evaluating visceral fat in annual health examinations.

The present study showed that age, BMI, and smoking are independent predictors of visceral fat accumulation in women. Although this has been previously reported, it is interesting that smoking presents a stronger correlation with VFA increase than does age in women, as shown in this study. Smoking is a major risk factor for visceral fat accumulation and the development of MetS in women.

Previously, we reported that smoking promoted the progression of IMT in men. Now, we found prominent progression of subclinical atherosclerosis also in female smokers, according to carotid IMT evaluation. Other risk factors, excluding age, did not significantly correlate with the progression of IMT (data not shown). This result parallels that of previous studies that smoking is the major risk factor for the development of atherosclerosis and CVD. Inflammatory response may be involved in the progression of IMT in male smokers. In the current study, a significant increase in the serum IL-6 level was observed even in female smokers. Therefore, inflammatory response may be also involved in the progression of IMT in female smokers. Although a significant association between IL-6 and the progression of IMT was not detected, our previous study with more subjects showed that IMT was associated with serum...
IL-6 concentration in men, but not in women. An increased number of the subjects may reveal direct association between inflammation and the progression of IMT.

Cessation of smoking is an important approach for various health problems in women. Women face particular problems linked to smoking. It is a risk factor of female-specific cancers and affects menstrual function (e.g., abnormal vaginal bleeding and early menopause). Smoking also affects fertility and is involved in the etiologies of adverse pregnancy outcomes, such as increased risk of spontaneous abortion, ectopic pregnancy, low birth weight and sudden infant death syndrome, and also long-term adverse effects on the growth and development of...
the children.\textsuperscript{5,33} Moreover, the risk of CVD increases in female smokers.\textsuperscript{9} The present study clearly showed that smoking promotes subclinical atherosclerosis by progression of IMT in women. It is important to clarify the effects of smoking cessation on IMT in a further study.

**Study Limitations**

Generally, physical exercise and eating habit are also important factors in visceral fat accumulation. Although questions on exercise and eating habit were included in our study, neither showed any significant correlation with VFA (data not shown). There might be a more appropriate way to research these factors. In addition, the relatively small numbers of subjects might lead to failure to detect a significant difference of VFA between male smokers and never-smokers. However, the sample size of women was smaller than that of men, but female subjects clearly showed a significant association between smoking and visceral fat accumulation.

In conclusion, VFA was significantly high in female smokers and smoking was the major risk factor for visceral fat accumulation, especially in women. Smoking also associated with subclinical atherosclerosis and CVD risk, not only in men but also women.

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