The Effects of Smoking on the Relationship Between Metabolic Syndrome and Arterial Stiffness

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Abstract: It has been reported that arterial stiffness assessed by pulse wave velocity (PWV) can predict cardiovascular morbidity and mortality. Metabolic syndrome and smoking are independently associated with increased risk of cardiovascular disease. The purpose of this study was to evaluate the effect of smoking on the relationship between metabolic syndrome and arterial stiffness. We retrospectively enrolled 1,530 men on whom brachial-ankle pulse wave velocity (baPWV) measurement had previously been performed as part of health screening at Kosin University Hospital. We found that PWV was positively correlated with the following variables: age (r=0.391, P<0.0001), systolic blood pressure (r=0.438, P<0.0001), diastolic blood pressure (r=0.377, P<0.0001), low-density lipoprotein (LDL) (r=0.068, P=0.008) and high-density lipoprotein (HDL) (r=0.027, P=0.287), whereas BMI was negatively correlated, although without statistical significance (r=-0.026, P=0.309). Among current smokers, PWV decreased with increasing BMI (from 1,387.9 to 1,311.6), and increased with increasing HDL (from 1,342.7 to 1,385.4). On the other hand, among never smokers, PWV increased with increasing BMI (from 1,382.3 to 1,458.8), and decreased with increasing HDL (from 1,391.2 to 1,369.7). PWV was inversely associated with BMI and HDL, and these differences are likely due to smoking.

Key words: arterial stiffness, pulse wave velocity, metabolic syndrome, smoking.

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Introduction

The prevalence of metabolic syndrome is increasing worldwide, naturally with differences according to ethnicity and national characteristics [1]. Numerous studies have indicated an association of metabolic syndrome with increased cardiovascular morbidity and mortality [2]. The U.S National Cholesterol Education Program (NCEP) defined metabolic syndrome as having 3 or more of the following 5 cardiovascular risk factors: central obesity, elevated triglycerides, decreased high-density lipoprotein (HDL) cholesterol, systemic hypertension and elevated fasting glucose. Apparently, these risk factors have a synergistic effect on cardiovascular events [3].

Arterial stiffness is documented as an independent predictor of cardiovascular morbidity and mortality [4]. A useful, non-invasive method for evaluating arterial stiffness is pulse wave velocity (PWV) [5], and brachial-ankle (ba) PWV in particular has been widely used in clinical research because of its relative simplicity [6–8].

There is a lot of evidence on the relationship between a person’s PWV and metabolic syndrome [9–12]. Interestingly, some studies have shown differences between men and women. In women, most risk factors for metabolic syndrome correlated with PWV, whereas no significance was found for these relationships in men [13, 14].

For this study, we hypothesized that these differences are due to smoking, because there are many more male smokers than female smokers. Unfortunately, due to the significantly smaller number of women in our sample group, we included only men in the final analysis. Our study objectives were: first, to evaluate the relationships between metabolic-syndrome related variables with PWV; second, to analyze the effects of metabolic-syndrome related variables on the PWV, according to smoking status. We hypothesized that the relationships between the risk factors for metabolic syndrome and the PWV in non-smoking men are similar to those in women from previous studies.

Methods

Study population

A total of 1,583 individuals who had undergone PWV for health screening at Kosin University Hospital, from January 2009 to June 2010 were retrospectively enrolled. Out of the total sample of 1,583 individuals, 1,530 were men and 53 were women. The data for women were excluded from our analyses because the sample size was too small. The Institutional Review Board of Kosin University Gospel Hospital approved the study.

General health examination

All the patients received a questionnaire that enquired about any personal or family history of diabetes, hypertension, hepatitis or tuberculosis. The questionnaire also included life style factors such as smoking status, alcohol ingestion and exercise. Smoking status was classified as follows: current smoker - one who currently smokes; former smoker - one with a past history of smoking; and never smoker - one with no history of smoking. We had no precise data to be able
to calculate smoking pack-years.

Brachial blood pressure was obtained with the subject in a sitting position after resting for more than 5 minutes. Experienced staff measured the height, weight and abdominal circumference (AC) of each participant. After an overnight fast, serum glucose, total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol levels were measured.

**PWV Measurement**

The PWV was measured using a volume-plethysmographic device (Colin Co., Komaki, Japan) which simultaneously measures blood pressure, ankle-brachial pressure index (ABI), electrocardiographic indices, and heart rate. All the subjects were examined in the supine position, and the cuff was wrapped around both brachia and ankles after at least 5 minutes of rest. The PWV was calculated by dividing the distance by the pulse transit time. The transit time was calculated between the fronts of the brachial and ankle waveforms. The distance between the brachium and the ankle was estimated based on subject height. We used the right PWV in analyses because the right and left PWV values are significantly correlated [15].

**Statistical Analysis**

Values are expressed as mean with standard deviation. The average of PWV according to body mass index (BMI) and HDL were compared by analysis of variance (ANOVA), according to smoking status. Correlations between PWV and the risk factors for metabolic syndrome were tested using Pearson’s correlation test, where the right PWV was used for convenience. Linear regression results were displayed in scatter plots. Multiple linear regressions were performed to measure the magnitude of the effects of the risk factors for metabolic syndrome on PWV, according to smoking status. Backward elimination multiple regression analysis was performed to choose independent variables and best-fit models. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

**Results**

The characteristics of all the subjects are shown in Table 1. The mean age of the subjects was 47.38 years. The mean values of the right (Rt.) and left (Lt.) PWV were 1,373.27 ± 201.50 and 1,376.36 ± 210.83. Table 2 and Fig. 1 show the correlations between PWV and metabolic-syndrome-related risk factors. Age, BP (systolic and diastolic), and LDL were statistically significantly positively correlated with PWV. BMI was negatively correlated, although not strong enough to reach statistical significance (*r* = −0.026, *P* = 0.309). On the other hand, HDL was positively correlated, although it was not was statistically significant.

The subjects were classified according to their smoking status. There were 633 current smokers, 242 former smokers, 362 never smokers and 293 subjects that did not respond to the question. Among the current smokers, PWV decreased as BMI increased (Fig. 2A), whereas
Table 1. Mean subject characteristics including factors of metabolic syndrome and pulse wave velocities

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.38 ± 7.82</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.40 ± 6.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.12 ± 2.71</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.11 ± 2.71</td>
</tr>
<tr>
<td>AC (cm)</td>
<td>84.20 ± 7.48</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>130.67 ± 16.26</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80.46 ± 11.42</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>96.49 ± 21.64</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>47.58 ± 10.98</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>118.01 ± 31.42</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>152.58 ± 99.66</td>
</tr>
<tr>
<td>Rt. PWV (cm/sec)</td>
<td>1373.27 ± 201.50</td>
</tr>
<tr>
<td>Lt. PWV (cm/sec)</td>
<td>1376.36 ± 210.83</td>
</tr>
</tbody>
</table>

SD: standard deviation, PWV: pulse wave velocity, BMI: body mass index, AC: abdominal circumference, BP: blood pressure, FBS: fasting blood sugar, HDL: high density lipoprotein, LDL: low density lipoprotein (n=1530)

Table 2. Test of correlation between brachial-ankle pulse wave velocity (PWV) and various factors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pearson’s correlation coefficient (n=1530)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Age</td>
<td>0.391</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.438</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.377</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.026</td>
</tr>
<tr>
<td>AC</td>
<td>0.028</td>
</tr>
<tr>
<td>FBS</td>
<td>0.194</td>
</tr>
<tr>
<td>HDL</td>
<td>0.027</td>
</tr>
<tr>
<td>LDL</td>
<td>0.068</td>
</tr>
<tr>
<td>TG</td>
<td>0.071</td>
</tr>
</tbody>
</table>

R: Pearson’s correlation coefficient, BP: blood pressure, BMI: body mass index, AC: abdominal circumference, FBS: fasting blood sugar, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride

Fig. 1. Correlation between pulse wave velocity (PWV) and metabolic-syndrome-related risk factors.
PWV increased as BMI increased in the never smokers (Fig. 2B). Figure 3A shows that PWV increased as HDL increased in the current smokers, while Fig. 3B shows that PWV decreased as HDL increased in the never smokers.

Table 3 shows the average values of PWV according to BMI and HDL by smoking status. In the current smokers, mean PWV significantly decreased with increasing BMI ($P=0.006$). According to multiple regression analyses, age, systolic BP, BMI, AC, fasting blood sugar (FBS) and LDL were statistically significant predictors of PWV among the current smokers, while only age and systolic BP were statistically significant predictors among the never smokers (Table 4).
Therefore, the is one of the most important factors in the pathophysiology of cardiovascular disease [16, 17].

The tendency of HDL could be explained by the fact that lipid profiles are affected by both age, systolic BP, BMI, AC, FBS and LDL had positive correlations with PWV in both the current and never smokers. These issues had a negative correlation between BMI and PWV, while the correlation among the never smokers was positive. In current smokers, it is possible that heavier smokers will have a more reduced smoking status.

Moreover, on the acute effects of smoking on arterial stiffness, Kubozono et al. reported a dose-response relationship between smoking and arterial stiffness and showed that the daily consumption of cigarettes was independently correlated with the annual rate of increased PWV [23]. It is known that the main effects of smoking on body weight are mediated by nicotine. Nicotine is the release of several hormones which suppress appetite and increase satiety [27, 30, 31]. The results of the present study are consistent with this evidence, where the current smokers had a negative correlation between BMI and PWV, while those with BP, FBS, LDL, and triglyceride (TG) were the same among both men and women [13]. We believe that these results are due to smoking, which is more prevalent in men than in women.

Cigarette smoking is a major risk factor for cardiovascular disease [18–20] and is the most

**Table 3.** Mean PWV according to BMI and HDL group in each smoking status

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>BMI &lt;25</th>
<th>25–30</th>
<th>&gt;30</th>
<th>P</th>
<th>HDL &lt;40</th>
<th>40–50</th>
<th>&gt;50</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current (n=633)</td>
<td>1387.9</td>
<td>1333.9</td>
<td>1311.6</td>
<td>0.006*</td>
<td>1342.7</td>
<td>1369.1</td>
<td>1385.4</td>
<td>0.169</td>
</tr>
<tr>
<td>Former (n=242)</td>
<td>1363.6</td>
<td>1388.6</td>
<td>1307.6</td>
<td>0.481</td>
<td>1342.8</td>
<td>1418.7</td>
<td>1348.4</td>
<td>0.019</td>
</tr>
<tr>
<td>Never (n=362)</td>
<td>1382.3</td>
<td>1374.0</td>
<td>1458.8</td>
<td>0.498</td>
<td>1391.2</td>
<td>1386.4</td>
<td>1369.7</td>
<td>0.708</td>
</tr>
</tbody>
</table>

a : BMI<25 and 25<BMI<30

**Table 4.** Multiple linear regression analysis of PWV on metabolic variables, according to smoking status

<table>
<thead>
<tr>
<th>Variables</th>
<th>Current smoker (n=633)</th>
<th>Never smoker (n=362)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R² β ± SE    P</td>
<td>R² β ± SE    P</td>
</tr>
<tr>
<td>Age</td>
<td>7.32 ± 0.82 &lt;0.0001</td>
<td>9.74 ± 1.03 &lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>5.23 ± 0.44 &lt;0.0001</td>
<td>4.95 ± 0.51 &lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.34 -19.52 ± 0.38 &lt;0.0001</td>
<td>0.39 3.10 ± 1.30 0.017</td>
</tr>
<tr>
<td>AC</td>
<td>3.10 ± 1.30 0.017</td>
<td></td>
</tr>
<tr>
<td>FBS</td>
<td>1.08 ± 0.31 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>0.53 ± 0.21 0.012</td>
<td></td>
</tr>
</tbody>
</table>


**Discussion**

This study was performed to investigate the effect of smoking in the relationships between the PWV and the risk factors for metabolic syndrome. It is well known that metabolic syndrome is associated with increased cardiovascular morbidity and mortality [2] and that arterial stiffness is one of the most important factors in the pathophysiology of cardiovascular disease [16, 17]. Therefore, the notion of a relationship between the factors of metabolic syndrome and PWV is quite reasonable. However, an interesting finding of previous studies was that this predicted relationship was only observed in women and not in men [13, 14]. In particular, the associations between PWV and BMI and HDL were the opposite, while those with BP, FBS, LDL, and triglyceride (TG) were the same among both men and women [13]. We believe that these results are due to smoking, which is more prevalent in men than in women.

Cigarette smoking is a major risk factor for cardiovascular disease [18–20] and is the most
common cause of premature death from cardiovascular and respiratory disease and cancer in the United States [21]. The mechanism of cardiovascular disease includes endothelial dysfunction, impaired lipoprotein metabolism and abnormal thrombo-hemostasis [22]. Cigarette smoking causes arterial stiffness, and this effect can be measured using PWV. Tomiyama et al. reported a dose-response relationship between smoking and arterial stiffness and showed that the daily consumption of cigarettes was independently correlated with the annual rate of increased PWV [23]. Moreover, on the acute effects of smoking on arterial stiffness, Kubozono et al. reported that active male smokers who smoked 1 cigarette for 5 minutes had increased PWV and cardio-ankle vascular indices, compared to their measurements taken before smoking [24].

It is known that most people tend to gain weight after quitting smoking [25]. This often explains why some smokers don’t try to quit, especially women [26]. The average body weight of smokers is 4-5 kg less than that of non-smokers [27]. In other studies, the average BMI of smokers was shown to be at least 1 kg/m² lower than that of non-smokers [28, 29]. The pathophysiology of the effect of cigarette smoking on body weight is not completely understood, although it is known that the main effects of smoking on body weight are mediated by nicotine. Nicotine is a sympathomimetic agent that increases energy expenditure by approximately 10% and promotes the release of several hormones which suppress appetite and increase satiety [27, 30, 31].

The results of the present study are consistent with this evidence, where the current smokers had a negative correlation between BMI and PWV, while the correlation among the never smokers was positive. In current smokers, it is possible that heavier smokers will have a more reduced body weight compared to the “less heavy” smokers. Therefore, lower body weight in smokers is a possible indication of increased arterial stiffness. This explanation, however, is insufficient because the never smokers also showed a positive correlation between BMI and PWV (although not statistically significant). This suggests that there are other factors that affect the relationship between BMI and PWV, such as muscle mass, physical activity and basal metabolism, which could possibly be explained by the “obesity paradox”. The “obesity paradox” supposes that obesity and high cholesterol may, counter-intuitively, be protective and associated with greater survival in certain groups of people, such as very elderly individuals or those with certain chronic diseases. It further postulates that normal to low body mass index or normal values of cholesterol may be detrimental and associated with higher mortality in asymptomatic people [32]. Further research is required in this area.

The tendency of HDL could be explained by the fact that lipid profiles are affected by both BMI and smoking. In a study that used both obese and non-obese subjects divided into smoking and non-smoking groups, Mizuno et al. reported that smokers had larger waist circumferences than never smokers among the obese subjects, suggesting that smoking may lead to increased abdominal fat accumulation [33]. However, the question that remains from this study is why, among the lipid profile factors, it affected only the HDL cholesterol. LDL, TG and total cholesterol had positive correlations with PWV in both the current and never smokers. These issues should be themes for future research.

It is interesting to note from our results that while age, systolic BP, BMI, AC, FBS and LDL were statistically significant predictors of PWV among the current smokers, only age and sys-
tolic BP were statistically significant predictors among the never smokers. It may be said that in current smokers, metabolic syndrome has considerable effects on the PWV, whereas in never smokers, factors other than metabolic syndrome are likely to affect the PWV.

This study has critical limitations, the most important of which is the absence of data for women. The outcomes may have been more persuasive if we had been able to demonstrate results in female smokers, similar to those found among male smokers. The other limitation of the study was selection bias. This study was performed using health screening data. In this hospital, health screening is performed in almost all workers. Thus, the subjects of this study were relatively young and healthy people with a job. Lastly, this was a retrospective study, so we could not control for subjects who smoked just before the examination. In the analysis of PWV, they were considered to contribute to the acute effects of smoking.

Despite these limitations, our findings will be useful for understanding the effects of metabolic syndrome and smoking on arterial stiffness. They could also partly explain the reasons behind the inverse relationships between PWV and metabolic factors such as BMI and HDL among men.

Conclusions

Metabolic syndrome could be a useful predictor of arterial stiffness in currently smoking men, but not in men that have never smoked. In the future, more research is required to investigate the effects of metabolic syndrome and smoking on arterial stiffness in both men and women.

Conflicts of Interest

None of the authors of this paper has a conflict of interest in its compilation.

References

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メタボリックシンドロームと動脈硬化の関連性への喫煙の影響

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要旨:
動脈硬化を脈波伝播速度を用いて評価することで,心血管疾患の罹患率および死亡率が予測できることが報告されている。
メタボリックシンドロームと喫煙は,それぞれ心血管疾患のリスクを高めることも知られている。

今回の研究目的は,メタボリックシンドロームと動脈硬化の関連性への喫煙の影響を評価することである。

これまでに高神大学病院の健康診断において,上腕・足首脈波伝播速度 (baPWV)を測定した男性(1,530名)を対象に,レトロスペクティブに調査した。

PWVと正の相関を認めた変数は:年齢 (r = 0.391, P < 0.0001), 収縮期血圧 (r = 0.438, P < 0.0001),拡張期血圧 (r = 0.377, P < 0.0001), LDLコレステロール (r = 0.068, P = 0.008)とHDLコレステロール (r = 0.027, P = 0.287)であった。

BMIとPWVの関係は,有意ではなかったが,負の相関を認めた (r = -0.026, P = 0.309)。

現在喫煙者では, PWVはBMIが増加するにつれて低下し(1,387.9から1,311.6), HDLコレステロールが増加するにつれて上昇した(1,342.7から1,385.4)。

一方,非喫煙者では, PWVはBMIが増加するにつれて上昇し(1,382.3から1,458.8), HDLコレステロールが増加するにつれて低下した(1,391.2から1,369.7)。

PWVは, BMI, HDLと逆の関連性が見られ,これらの差は喫煙の影響によると考えられる。

キーワード: 动脈硬化, 脈波伝播速度, メタボリックシンドローム, 喫煙

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メタボリックシンドロームと動脈硬化の関連性への喫煙の影響

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要 旨：動脈硬化を脈波伝播速度を用いて評価することで、心血管疾患の罹患率および死亡率が予測できることが報告されている。メタボリックシンドロームと喫煙は、それぞれ心血管疾患のリスクを高めることも知られている。今回の研究目的は、メタボリックシンドロームと動脈硬化の関連性への喫煙の影響を評価することである。これまでに高神大学病院の健康診断において、上腕・足首脈波伝播速度（baPWV）を測定した男性（1,530名）を対象に、レトロスペクティブに調査した。PWVと正の相関を認めた変数は：年齢（r = 0.391, P < 0.0001）、収縮期血圧（r = 0.438, P < 0.0001）、拡張期血圧（r = 0.377, P < 0.0001）、LDLコレステロール（r = 0.068, P = 0.008）とHDLコレステロール（r = 0.027, P = 0.287）であった。BMIとPWVの関係は、有意ではなかったが、負の相関を認めた（r = -0.026, P = 0.309）。現在喫煙者では、PWVはBMIが増加するにつれて低下し（1,387.9から1,311.6）、HDLコレステロールが増加するにつれて上昇した（1,342.7から1,385.4）。一方、非喫煙者では、PWVはBMIが増加するにつれて上昇し（1,382.3から1,458.8）、HDLコレステロールが増加するにつれて低下した（1,391.2から1,369.7）。PWVは、BMI、HDLと逆の関連性が見られ、これらの差は喫煙の影響によると考えられる。

キーワード：動脈硬化、脈波伝播速度、メタボリックシンドローム、喫煙。

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