LIFESTYLE HAS SIGNIFICANT EFFECTS ON ATHEROSCLEROSIS IN THE POPULATION AS YOUNG AS BELOW 40 YEARS OLD

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Abstract The epidemiological research was carried out to investigate the relationship between brachial-ankle pulse wave velocity (baPWV) and atherosclerosis-related factors. Subjects were 1,730 Iwaki residents (Aomori Prefecture, Japan) who participated in the Iwaki Health Promotion Project between 2005 and 2010. They were divided into different genders and age group. The results were analyzed using multiple linear regression analysis with baPWV as a dependent variable, and atherosclerosis-related factors as independent variables. In male of the youngest age group, baPWV was found to have a significant positive correlation with the number of cigarette consumption per day. In female of the youngest age group, baPWV was found to have significant positive correlations with triglyceride and glucose levels, and a significant negative correlation with frequency of exercise. Therefore, cigarette smoking in young male was suggested to be a major risk factor, and exercise habit in young female was suggested to be a preventive factor of atherosclerosis.

Key words: atherosclerosis; atherosclerosis-related factors; brachial-ankle pulse wave velocity; obesity; blood pressure.
Introduction

Atherosclerosis is characterized by a condition in which the arterial wall loses its flexibility, causing stiffening of the arterial wall. Some of the major atherosclerotic diseases include cerebrovascular disease and cardiac disorders which account for the 2nd and 3rd highest crude mortality rates in Japan.\(^1\)

Initially, the morphological changes of atherosclerosis appears asymptptomatically at an early stage of life. However, the condition progresses with age causing a variety of vascular diseases such as ischemic cardiac disease and cerebrovascular diseases.

Atherosclerosis is additionally known to be the result of various factors including lifestyle.\(^2\) The known related risk factors include age,\(^3\) gender,\(^4\) blood pressure,\(^5\) cigarette smoking,\(^6\) diabetes mellitus or obesity,\(^7\) and other general lifestyle habits.\(^8\) In other words, the presence and degree of these factors in young persons will make a difference in the degree of atherosclerosis in their future, which will also affect the lifestyle-related diseases (ischemic cardiac disease and cerebrovascular diseases etc), QOL and even their life expectancy.

A method by which atherosclerosis could be accurately evaluated was unavailable in the past. Other methods such as carotid echography and the evaluation of the eyeground arteries were available only for examining subdivided atherosclerosis patients.\(^9\) The assessment of blood pressure has been commonly used as an index of atherosclerosis, although it has a major downside of being easily affected by the measurement conditions, especially the psychological factors. In many epidemiological studies, these factors were considered as an obstacle for the completion of detailed deliberation regarding atherosclerosis and other clinical conditions in addition to various diseases.\(^10-12\)

In recent years, the pulse wave velocity (PWV) method has been recognized as an effective index for atherosclerosis.\(^13\) Among the various PWVs, brachial-ankle pulse wave velocity (baPWV) is not only an easy, non-invasive method, but has also been reported to reflect the stiffness of the arteries, and has been strongly correlated with cardiovascular diseases caused by atherosclerosis.\(^14, 15\) Thus, baPWV has become a common method to evaluate atherosclerosis in many clinical studies, especially in epidemiological investigations. However, long-term cohort baPWV studies have not yet been conducted, as its introduction into clinical practice is relatively new.\(^16\) In the present study, we have investigated an association between baPWV and atherosclerosis-related factors in 1,730 volunteers who participated in the Iwaki Health Promotion Project.

Subjects and Methods

1. Subjects and investigation method

The subjects were 1,730 volunteers (660 males and 1,070 females) who participated in the Iwaki Health Promotion Project between 2005 and 2010. All of the subjects were residents in Iwaki area in Aomori Prefecture, located in northern Japan (Table 1).

2. Investigated items

a. Lifestyle and background of subjects

The data on lifestyle and background of the subjects were obtained from a self-completion questionnaire and each answer was confirmed during an individual interview with an investigational team member. Items included in the questionnaire were age, gender, smoking habit, history of cigarette smoking and number of cigarette smoked per day, drinking habit including amount of alcohol consumption per day, total hours of work per week, exercise habit
including frequency of exercise per week, and certain lifestyle-related diseases which might affect atherosclerosis (hypertension, diabetes mellitus and dyslipidemia).

b. Blood biochemistry

Enzymatic methods were used to measure the levels of serum glucose, total cholesterol, triglyceride, and HDL cholesterol. All blood samples were taken under fasting condition. LDL cholesterol was excluded from the investigated items because direct measurement method of LDL cholesterol had not been common at the starting part of this study (2005). Given that diagnostic criteria of metabolic syndrome in Japan do not include HbA1c, it was also excluded from the investigated items in this study.

c. Body mass index (BMI)

BMI was calculated for each subject according to his/her height and weight. Height was measured using a height ruler, and weight was determined using a body composition scale (Multi-frequency body composition scale, MC-190 TANITA, Tokyo).

d. Blood pressure

Blood pressure was measured with a manometer. The value of diastolic pressure was not eligible for an investigated item for systolic and diastolic pressure provided multi-collinearity when multiple linear regression was done.

e. baPWV

Brachial-ankle PWV was measured using a volume-plethysmographic apparatus (form PWV/ABI, COLIN Co. Ltd., Tokyo, Japan). In addition to recording the limb lead ECG, mechano-cardiograms were simultaneously recorded by attaching blood pressure cuffs with a tonometric sensor to the upper arms and ankles. Brachial-ankle PWV was calculated by time-phase analysis. The time interval between the wave front of the brachial waveform and that of the ankle waveform was defined as the time interval between the brachium and ankle (ΔTba). The distance between sampling points of baPWV was calculated automatically according to the height of the subject. The path length from the suprasternal notch to the brachium (Lb) was obtained from superficial measurements and was expressed using the following equation: Lb = 0.2195 × height of the patient (in cm) -2.0734. The path length from the suprasternal notch to the ankle (La) was obtained from superficial measurements and was expressed using the following equation: La = (0.8129 × height of the patient (in cm) + 12.328). Finally, the following equation was used to obtain baPWV: baPWV = (La- Lb) / ΔTba 17. In this study, the average of left and right values of baPWV was used.

3. Ethical consideration

The purpose of the current study was thoroughly explained verbally to all subjects

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Males</th>
<th>Females</th>
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</thead>
<tbody>
<tr>
<td>20–39</td>
<td>103 (15.6)</td>
<td>163 (15.2)</td>
</tr>
<tr>
<td>40–59</td>
<td>275 (41.7)</td>
<td>380 (35.5)</td>
</tr>
<tr>
<td>60~</td>
<td>282 (42.7)</td>
<td>527 (49.3)</td>
</tr>
<tr>
<td></td>
<td>660 (100)</td>
<td>1070 (100)</td>
</tr>
</tbody>
</table>

n(%)
prior to the study, including their rights to withdraw from the research at anytime as well as protection of their personal information, and written informed consent was obtained from each subject. This study was approved by the ethics committee of the Hirosaki University Graduate School of Medicine (reference number 2011-033).

4. Statistical analysis

Brachial-ankle PWV has been reported to vary both by age and gender\(^9\). Thus, subjects were subgrouped by gender, then into 3 age groups as follows: 20-39 years old (the youngest group), 40-59 years old (the middle age group) and 60+ years old (the eldest group).

The investigated items such as age, BMI, baPWV, systolic blood pressure, serum glucose level, total cholesterol level, working hours, exercise habit of subjects among three age groups were compared using a one-way analysis of variance. The prevalence of lifestyle-related diseases among three age groups were compared using chi-square test.

In order to determine the relationship between baPWV and atherosclerosis-related factors, baPWV was used as the dependent variable, and the duration of cigarette smoking, BMI, frequency of exercise, serum glucose, total cholesterol, triglyceride and HDL cholesterol were used as the independent variables when multiple linear regression was performed. The atherosclerosis-related factors were listed as the items related to fat and sugar metabolisms and lifestyle-related items\(^10\). Also, age, systolic blood pressure, working hours, amount of alcohol consumption, and having atherosclerosis-related diseases (hypertension, diabetes mellitus and dyslipidemia) were used as corrected items for both gender. Furthermore, menopause was used as a corrected item for women. As for smoking habit, three categories such as "non-smoker", "more than one cigarette per day", and "ex-smoker" were set from two items – "smoking habit", and the "number of cigarette smoked per day". Alcohol drinking habit was further categorized into either "non-drinker", "more than 1g per day" or "ex-drinker". The working hours category was further categorized into either "none", "less than 40 hours per week", "between 40 hours and 50 hours per week", "between 50 and 60 hours per week" and "more than 60 hours per week". Exercise habit was further categorized into either “none”, “once per week”, “2-3 times per week”, “4-5 times per week” or “almost every day”.

SPSS ver.12.0J (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. All data were separated according to gender, and values were considered significant at p<0.05.

Results

1. Characteristics of subjects

In males, baPWV, systolic blood pressure and serum glucose level were shown to increase significantly with age (p<0.05 all) (Table 2-1). In females, baPWV, systolic blood pressure, levels of serum glucose and triglyceride significantly increased with age (Table 2-2).

2. Physical activities

In males, those who were in the middle age group were found to have the longest working hours, and it was lower in the eldest age group (Table 2-1). In females, working hours tended to become less as the age increased (Table 2-2). In general, there were a large number of both males and females who had no exercise habit.

3. Lifestyle

A large number of males were current and ex-smokers in the youngest age group (68.9%
and 11.7% respectively) (Table 2-1). Also, many males were found to drink alcohol in all age groups (68.0% in the youngest age group, 76.4% in the middle age group and 72.3% in the eldest age group) (Table 2-1).

However, most of females were non-smokers in all age groups (61.3% in the youngest age group, 78.4% in the middle age group and 96.4% in the eldest age group), and a higher number of females in the youngest groups tended to have a drinking habit (46.0% in the youngest age group, 27.4% in the middle age group and 9.3% in the eldest age group) (Table 2-2).

### 4. Medical conditions

For both genders, the prevalence of hypertension, diabetes mellitus and dyslipidemia tended to be higher in the eldest age groups, and the percentage of subjects with hypertension was highest in those who were significantly higher in the eldest age group than in other two groups (p<0.01 each) (Table 3).

### 5. Relationships between baPWV and atherosclerosis-related factors

For males in the youngest age group.

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**Table 2-1 Characteristics of the subjects (Males, n=660)**

<table>
<thead>
<tr>
<th></th>
<th>20~39 (years)</th>
<th>40~59 (years)</th>
<th>60 or over (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.7±5.0</td>
<td>50.0±5.7</td>
<td>* 69.3±6.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2±3.6</td>
<td>23.7±2.8</td>
<td>23.4±3.0</td>
</tr>
</tbody>
</table>
| baPWV (cm/sec)         | 1283.9±150.7  | 1454.5±245.1  | * 1898±410.6       |†
| Systolic blood pressure (mmHg) | 117.1±12.6  | 123.8±16.4    | * 135.5±18.1       |†
| Glucose (mg/dl)        | 80.0±9.3      | 89.6±22.4     | * 95.7±22.2        |†
| Total cholesterol (mg/dl) | 184.6±32.2  | 203.4±30.6    | * 192.2±32.5       |†
| Triglyceride (mg/dl)   | 109.2±65.2    | 111.3±63.7    | 97.9±55.5          |
| HDL-cholesterol (mg/dl)| 57.8±12.8     | 58.8±15.1     | 58.2±16.0          |

<table>
<thead>
<tr>
<th>Working hours (hours/week)</th>
<th>20~39 (years)</th>
<th>40~59 (years)</th>
<th>60 or over (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>16 (15,5)</td>
<td>39 (14,2)</td>
<td>72 (25,5)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>16 (15,5)</td>
<td>36 (13,1)</td>
<td>49 (17,4)</td>
</tr>
<tr>
<td>40~49</td>
<td>48 (46,6)</td>
<td>117 (42,5)</td>
<td>98 (34,8)</td>
</tr>
<tr>
<td>50~59</td>
<td>10 (.9,7)</td>
<td>34 (12,4)</td>
<td>36 (12,8)</td>
</tr>
<tr>
<td>60±</td>
<td>13 (12,6)</td>
<td>49 (17,8)</td>
<td>27 (.9,6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency of exercise‡‡</th>
<th>20~39 (years)</th>
<th>40~59 (years)</th>
<th>60 or over (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>69 (67,0)</td>
<td>223 (81,1)</td>
<td>197 (69,9)</td>
</tr>
<tr>
<td>Once/week</td>
<td>14 (13,6)</td>
<td>24 (.8,7)</td>
<td>16 (.5,7)</td>
</tr>
<tr>
<td>2-3 times/week</td>
<td>10 (.9,7)</td>
<td>11 (.4,0)</td>
<td>29 (10,3)</td>
</tr>
<tr>
<td>4-5 times/week</td>
<td>3 (.9,7)</td>
<td>7 (.2,5)</td>
<td>20 (.7,1)</td>
</tr>
<tr>
<td>Every day</td>
<td>7 (.6,8)</td>
<td>10 (.3,6)</td>
<td>20 (.7,1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking habit‡‡</th>
<th>20~39 (years)</th>
<th>40~59 (years)</th>
<th>60 or over (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non smoker</td>
<td>20 (19,4)</td>
<td>70 (25,5)</td>
<td>118 (41,8)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>71 (68,9)</td>
<td>125 (45,5)</td>
<td>72 (25,5)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>12 (11,7)</td>
<td>80 (29,1)</td>
<td>92 (32,6)</td>
</tr>
<tr>
<td>Cigarette consumption</td>
<td>202 ±10,4</td>
<td>204 ±9,0</td>
<td>199 ±11,2</td>
</tr>
<tr>
<td>Smoking period (years)</td>
<td>128 ±5,6</td>
<td>247 ±9,8</td>
<td>372 ±13,3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drinking habit</th>
<th>20~39 (years)</th>
<th>40~59 (years)</th>
<th>60 or over (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Drinker</td>
<td>29 (28,2)</td>
<td>59 (21,5)</td>
<td>60 (21,3)</td>
</tr>
<tr>
<td>Current drinker</td>
<td>70 (68,0)</td>
<td>210 (76,4)</td>
<td>204 (72,3)</td>
</tr>
<tr>
<td>Ex-drinker</td>
<td>4 (.3,9)</td>
<td>6 (.2,2)</td>
<td>18 (.6,4)</td>
</tr>
</tbody>
</table>

| Alcohol consumption (g/day)| 121 ±495.6    | 136.4 ±754.9  | 98.6 ±414.6        |

Mean ± SD or n (%)

Compared with 20~39 (years); * p<0.05
Compared with 40~39 (years); † p<0.05
BMI : Body Mass Index
baPWV: brachial ankle pulse wave velocity
Chi square test; ‡‡ p<0.01
baPWV was positively correlated with "number of cigarette smoked per day" ($\beta=0.321$, $p<0.05$) (Table 4). In the middle age group, no significant relationship was observed between baPWV and any atherosclerosis-related factors. However, BMI was the only factor that was found to have a significant inverse correlation with baPWV ($\beta=-0.206$, $p<0.01$) in the eldest age group.

For females in the youngest age group, baPWV values were significantly positively correlated with serum glucose ($\beta=0.168$, $p<0.05$) and triglyceride ($\beta=0.228$, $p<0.01$) (Table 4). A significant inverse correlation was observed between baPWV and frequency of exercise ($\beta=-0.140$, $p<0.05$) in the same age group. For the middle and eldest age groups, BMI ($\beta=-0.029$, $p<0.01$ for the middle age group and $\beta=-0.126$, $p<0.01$ for the eldest age group) was inversely correlated with baPWV.

### 6. Comparison of BMI among participants with lifestyle-related diseases

Figure 1 shows comparisons of BMI among participants with hypertension, diabetes mellitus and dyslipidemia according to age groups. There was not any participant with these three diseases in the youngest age group.
In males, we did not detect any differences in BMI between the middle age group and the eldest age group. In females, BMI of those with hypertension in the middle age group was significantly higher than that in the eldest age group (p<0.05).

**Discussion**

In males of the youngest age group, "number
of cigarette smoked per day had a significant positive correlation with baPWV, suggesting that an increasing number of cigarettes smoked per day resulted in an elevated baPWV. In previous studies, cigarette smoking has been reported to affect the cardiovascular system by increasing systolic blood pressure and heart rate\cite{20, 21}. Continuous smoking has been reported to cause progression of atherosclerosis\cite{22}. Furthermore, it has also been reported that exposure to cigarette smoke at an early stage of life may increase premature development of atherosclerosis\cite{23}. The result of the current study supported these previous results. Furthermore, 68.9% of the young male subjects who participated in the current study claimed to be current smokers and there is therefore an immediate need to develop countermeasures against the smoking habit.

For both genders in the eldest group, BMI was found to have a significant inverse correlation with baPWV. Such results are few in previous studies\cite{24}. The possible reason is that a large proportion of subjects have atherosclerosis-related diseases in this age group, and resulted in a decreased body weight as well as ageing.

For females, the exercise frequency was found to have a significant inverse correlation with baPWV in the youngest age group, indicating that many of those who had an exercise habit tended to have a low baPWV, which is in accord with previous studies\cite{25}. It has also been reported that regular exercise can reduce the risk of atherosclerosis-associated cardiovascular diseases, especially in females\cite{26}. In addition, the risk of cardiovascular diseases can also be reduced by being physically active from a young age\cite{27}. Furthermore, the amount of daily physical exercise and/or regular exercise were reported to strengthen vascular functions\cite{28-30}. Therefore, regular physical exercise was suggested to have preventive effects against atherosclerosis. In the present study, 87% of the female residents in Iwaki area who participated in the investigation were found to have no exercise habit. Such results suggested that regular exercise or having an exercise habit are effective ways to prevent atherosclerosis even among females, especially when they are young.

For females in the youngest age group, the serum glucose level and triglyceride level were found to have significant positive correlations with baPWV. According to previous studies, metabolic risk factors of coronary heart disease were stated as total cholesterol, triglyceride and abnormal glucose tolerance\cite{31}. It is one of the most important points from the results of the current study is that the management of dyslipidemia and diabetes mellitus or obesity is needed in the youngest generations.
For the middle age group in both genders, the results tended to show an average between the youngest and eldest age groups.

The most important finding of the current study was the significant associations between lifestyle and baPWV in the age group which was previously considered to be too young to have effects on atherosclerosis. In other words, those who are below 40 years of age with certain lifestyle are already at the risk of atherosclerosis.

Another important point is that the association between obesity and baPWV (atherosclerosis) in the eldest age group demonstrated opposite results from previous studies for both genders (i.e., baPWV increased and BMI decreased as a result of having lifestyle-related diseases as well as aging).

The results obtained from the current study reconfirmed the importance of improving and maintaining a desirable lifestyle from a young age. In addition, the relationship between baPWV and obesity in the elderly should be carefully analyzed during evaluation\(^2\). There are some limitations in this study. Firstly, self-completion questionnaire performed in this study did not include therapeutic histories of hypertension, diabetes mellitus and dyslipidemia. Certain medications, such as angiotensin converting enzyme inhibitors and statins, have influence on progress of atherosclerosis. Secondly, prevalence of hypertension, diabetes mellitus and dyslipidemia was based on self-completion questionnaire so that it could be different from accurate histories of participants.

Acknowledgements

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References

9) Hulthe J, Wikstrand J, Emanuelsson H, Wiklund


