Change in Ankle-Brachial Index Over Time in a Screened Japanese Cohort
– The Okinawa Peripheral Arterial Disease Study –
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Background: The temporal change in ankle-brachial index (ABI) in the general population, especially in those aged <40 years, remains unclear.

Methods and Results: ABIs of 23,673 individuals were measured in 1-day health checkups between 2003 and 2010. Among them, 1,117 participants aged 28–76 years (mean 53±9 years) whose ABI was measured at least twice within an interval of ≥4 years (mean: 4.9 years) were selected for this study. Baseline ABI was the lowest at age <40 years and increased with age. ABI significantly increased in participants aged <40 and 40–49 years, but not in participants aged 50–59 and ≥60 years. ABI increased in participants with borderline-low baseline ABI (0.9<ABI<1.0, 0.09; P<0.001) and normal baseline ABI (1.0<ABI<1.2, 0.006; P=0.017). ABI decreased in participants with high-normal baseline ABI (1.2<ABI<1.4, −0.04; P<0.001). Stepwise multivariate analysis revealed that ABI change was independently associated with baseline ABI (β=−0.566), height (β=0.162), body mass index (β=0.093), and sex (women, β=−0.08).

Conclusions: ABI was lowest at age <40 years and increased with age. In participants aged <50 years, ABI significantly increased over the mean observation period of 4.9 years.

Key Words: Atherosclerosis; Blood pressure; Cardiovascular diseases; Peripheral vascular disease

The ankle-brachial index (ABI) is the ratio of the systolic blood pressure (BP) measured at the ankle to that in the arm. A cutoff ABI value ≤0.90 has good sensitivity and excellent specificity for lower-extremity arterial stenosis >50% on digital subtraction angiography. The ABI is also an indicator of future cardiovascular events and death. Both a low ABI (≤0.9) and a borderline-low ABI (0.9<ABI<1.0) are associated with endothelial dysfunction, an increased risk of myocardial infarction, stroke, and both overall death and cardiovascular-related death. Several studies have reported differences in the normal ABI values according to sex and ethnicity. However, the same cutoff value has been used for the diagnosis of peripheral arterial disease (PAD) regardless of sex, ethnic group, and age. Lower-extremity PAD is mostly an atherosclerotic disease and predominantly affects patients at high risk of cardiovascular diseases. Therefore, ABI screening is recommended for patients with suspected lower-extremity PAD, who are defined as individuals with ≥1 of the following: exertional leg symptoms, non-healing wounds, aged ≥65 years, or ≥50 years with a history of smoking or diabetes.

Previous studies have reported that the ABI decreases with age, most likely because of increased prevalence and progression to lower-extremity PAD. However, we recently reported that the ABI was lowest at age <40 years, and increased with age until 60–69 years in both sexes among subjects of a screened cohort. In participants aged 21–39 years, 18% of women and 8% of men had a borderline-low ABI. For both men and women aged <60 years the prevalence of hypertension was significantly lower in participants with borderline-low ABI compared with those with 1.0<ABI<1.4. We assumed that young adults did not always have arterial stenosis despite borderline-low ABI. We reported that the ABI positively correlated with systolic BP, pulse pressure, and the brachial-ankle pulse wave velocity (baPWV), indices of arterial stiffness. A high-normal ABI (1.2<ABI<1.4) was also associated with target organ damage, including proteinuria, only in participants aged <60 years. In contrast, a low ABI was associated with proteinuria only in participants aged ≥60 years. Therefore, we hypothesized that ABI increases with age and arterial
stiffening and decreases when flow-limiting atherosclerotic arterial stenosis occurs in a lower limb. The aim of this study was to evaluate the ABI change (ΔABI) over time in a younger population.

Methods

Subjects
The present study was an observational, longitudinal, single-center study. Participants were recruited from the 1-day health center study. Participants were recruited from the 1-day health evaluation of the general population held by the Okinawa General Health Maintenance Association. A total of 91,962 individuals participated and for 23,673 participants, the ABI was voluntarily measured as an optional checkup between July 2003 and March 2010. Some individuals attended checkup multiple times during this period, so we enrolled subjects who participated at least twice over a 4-year interval (ie, visit 1 in 2003–2005 and visit 3 in 2008–2010). Participants with an ABI ≥ 1.4. The reliability and reproducibility of this instrument in measuring ABI are similar to that of the Doppler probe.13

Data Collection
Individual medical histories were determined using self-administered questionnaires and were confirmed by physician interview. Trained nurses measured BP using a standard mercury sphygmomanometer after the participants sat quietly for 15 min. Blood was drawn after an overnight fast. Hypertension was defined as the systolic BP ≥ 140 mmHg and/or the diastolic BP ≥ 90 mmHg, or the current use of any antihypertensive medication. Body mass index (BMI, kg/m²) was calculated as the body weight divided by the square of the height. Diabetes was defined as fasting blood sugar level ≥ 150 mg/dl, triglycerides level ≥ 250 mg/dl, h-density-lipoprotein-cholesterol level < 40 mg/dl, hemo-globin A1c level (HbA1c) ≥ 6.5%, and/or taking of any medication for diabetes. Dyslipidemia was defined as serum total cholesterol level ≥ 220 mg/dl, serum triglyceride level ≥ 150 mg/dl, high-density-lipoprotein-cholesterol level < 40 mg/dl, and/or taking of any medication for dyslipidemia. Smoking was defined as current, past, or never as determined by interview.

Statistical Analysis
All parametric values are expressed as the mean ± standard deviation (SD). Comparisons between quantitative variables were performed with Student’s t-test. The difference in the measured values between visit 1 and visit 3 were assessed using a paired t-test. Two-sided tests with P<0.05 were considered to be significant. If a clinically worthwhile effect for ABI is 0.0214 and the between subjects’ standard deviation is 0.05,15 we estimated the sample size is 100 with an 80% power and 5% significance. All statistical analyses were performed using JMP (version 10.0.0). The difference in the mean values between groups was tested using the Tukey-Kramer test. Stepwise forward multiple linear regression analyses were performed to determine independent predictors of ΔABI. Independent variables considered in the models were those that were found to be clinically relevant (eg, age; sex; BMI; height; baseline ABI; baseline baPWV; current smoking status; presence of hypertension, diabetes mellitus, and dyslipidemia).

Table 1. Baseline Characteristics of Study Subjects by Sex and ABI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women (n=608)</th>
<th>Men (n=509)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>35</td>
<td>13</td>
<td>0.009</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50±7*</td>
<td>53±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151±5</td>
<td>152±5</td>
<td>0.464</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23±3</td>
<td>24±3</td>
<td>0.034</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>11 (4)</td>
<td>139 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0 (0)</td>
<td>22 (4)</td>
<td>0.408</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>11 (31)</td>
<td>232 (44)</td>
<td>0.240</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>2 (6)</td>
<td>29 (5)</td>
<td>0.629</td>
</tr>
<tr>
<td>baPWV (m/s)</td>
<td>13.46±2.21</td>
<td>14.21±2.65</td>
<td>0.024</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115±13</td>
<td>112±15</td>
<td>0.004</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71±9</td>
<td>74±10</td>
<td>0.034</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.4±0.1</td>
<td>5.6±0.0</td>
<td>0.477</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>202±28</td>
<td>209±33</td>
<td>0.463</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>68±14*</td>
<td>63±14</td>
<td>0.020</td>
</tr>
<tr>
<td>Triglycerides (log10)</td>
<td>4.4±0.5</td>
<td>4.5±0.5</td>
<td>0.282</td>
</tr>
</tbody>
</table>

Values are mean±SD or %. *P<0.05, **P<0.01 vs. 1.0≤ABI<1.2 group. ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; SBP, systolic blood pressure.
Change in ABI Over Time

Baseline Characteristics
The mean age of participants was 53±10 years (range, 28–76 years). For women, participants with a borderline-low ABI were found to be younger and have higher HDL-cholesterol, and lower baPWV values than those with normal ABI. Participants with high-normal ABI were found be older and to have a higher prevalence of hypertension than those with normal ABI (Table 1). For men, participants with a borderline-low ABI were found to be younger than those with a normal ABI. Participants with a high-normal ABI were found to have a higher prevalence of hypertension and diabetes as well as higher systolic BP, and diastolic BP than those with normal ABI.

Change in ABI Over Time
The mean duration between visit 1 and visit 3 was 4.9±0.3 years (range, 4.0–5.9 years). The frequency of baseline borderline-low ABI was highest in participants aged <40 years and decreased with age in both sexes (Figure 1A). Figure 1B shows the distribution of ∆ABI by sex. The mean ∆ABI was quite small and exhibited no significant difference over 4.9 years (0.003±0.06, P=0.096). Baseline ABI was the lowest at age <40 years and increased with age until 60–69 years (Figure 2A) as we previously reported.11 ABI significantly increased at visit 3 only in participants aged <40 years (0.02±0.07, P<0.01) and 40–49 years (0.01±0.07, P<0.01). ∆ABI decreased in participants aged 50–59 years (~0.001±0.06, P=0.660) and ≥60 years (~0.004±0.06, P=0.852), but the difference was not statistically significant. Only 1 participant had an ABI ≤0.9 (0.93–0.84) and no individuals had an ABI ≥1.4 at visit 3. We also examined 3 serial ABI measurements by age category in 825 participants (Figure 2B). In participants aged <40 years and 40–49 years, the ABI was significantly higher at visits 2 and 3 vs. visit 1. In participants aged ≥60 years, the ABI decreased at visit 3. In participants aged ≥60 years, the ABI did not change over time.

Determinants of ∆ABI
Stepwise forward multiple regression analyses revealed that baseline ABI, height, sex, and BMI were independent determinants of ∆ABI, accounting for 31% of the variability of ∆ABI. Baseline height and BMI were positively associated with ∆ABI, and baseline ABI and sex (female) were negatively associated with ∆ABI (Table 2).
Table 2. Determinants of Change in Ankle-Brachial Index (ΔABI) in Study Subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate correlations</th>
<th>Stepwise multiple regression model (r²=0.31, P&lt;0.001)</th>
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<tbody>
<tr>
<td></td>
<td>R²</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>0.008</td>
<td>0.003</td>
</tr>
<tr>
<td>Height</td>
<td>0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.002</td>
<td>0.186</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.008</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.001</td>
<td>0.239</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>&lt;0.001</td>
<td>0.671</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.001</td>
<td>0.257</td>
</tr>
<tr>
<td>Baseline ABI</td>
<td>0.253</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>baPWV</td>
<td>0.002</td>
<td>0.125</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

Discussion

We observed that ΔABI over the mean observation period of 4.9 years was quite small as in previous reports, and increased only in individuals who were aged <40 years and 40–49 years. In participants aged ≥60 years, ΔABI decreased, but was not statistically significant. Therefore, the results in this study are in agreement with those of our previous cross-sectional study that showed that ABI was lowest in individuals aged <40 years, increased with age until 60–69 years, and decreased thereafter.

Several previous studies have reported the prevalence of PAD in Japan. The prevalence of an ABI <0.9 was 1.5% in men and 0.7% in women ≤60 years, and 3.6% in men and 3.3% in women ≥60 years in subjects aged ≥40 years. The Hisayama study, the prevalence of ABI ≤0.9 was 1.47% in the 3,061 subjects aged ≥40 years. We previously reported that the prevalence of ABI ≤0.9 was 0.5% (n=67) in a screened cohort of Japanese (n=13,211). In this study, the prevalence of an ABI ≤0.9 was 0.4% (n=4) at baseline, which is much lower than the prevalence in previous reports, and only 1 subject progressed to an ABI ≤0.9 from a borderline-low ABI. One reason for this lower prevalence of ABI ≤0.9 may be that the study subjects were much younger, as 34% of the participants were aged <50 years.

Several studies have investigated ΔABI over time. In the cross-sectional Edinburgh Artery Study, the mean ABI decreased with age in both sexes in subjects aged 55–74 years. In a longitudinal study, a decrease of 0.03 was observed over 5 years, and only 0.01 over 12 years was observed in 695 subjects aged 55–74 years in a population-based study. In a group of 750 Spanish volunteers aged 60–79 years, ABI decreased 0.02 over 4 years.

A few longitudinal studies reported that a certain percentage of subjects had an increase in ABI over time. In a multi-ethnic study of atherosclerosis, 1.3% participants with 0.9<ABI≤1.4 developed an ABI ≥1.4 at the 3-year follow-up. The risk factors for progression to ABI ≥1.4 were the male sex, as well as a higher baseline BMI and ABI. Lahoz et al reported that a decrease in ABI >10% was observed in 22% and an increase of ABI >10% was observed in 16% of participants. Compared with the participants with ΔABI <10%, participants with an increase of ΔABI >10% had higher rates of low HDL-cholesterol levels and Framingham risk score, but a lower baseline ABI and rate of β-blocker medication. However, the multivariate analysis showed no significant variables associated with an increase of ΔABI >10%. The mechanism for the increase in ABI has yet to be elucidated, but an abnormally high ABI (≥1.4) has been thought to be related to calcification of the arterial media. This is more frequent in individuals with diabetes, end-stage renal disease, and advanced age.

In the present study, no individuals exhibited a baseline or follow-up ABI ≥1.4. In addition, ΔABI increased only in the subjects aged <40 and 40–49 years, who did not have higher prevalence of diabetes or renal failure.

The BP waveform amplifies as it travels distally from the heart, resulting in a progressive increase in systolic BP and may be the case in the ABI. Both arterial stiffness and reflected waves contribute to systolic BP amplification. The amplification of pressure in the upper limbs is different from that below the aorta in the femoral and more distal arteries. The reflected wave returning from the lower body provides a substantial contribution to the contour of the brachial pressure wave, and is responsible for the secondary late systolic surge. In contrast, the reflection from the upper limb has little effect on the lower body pulse, indicating that the age-related increase in systolic BP amplification might be more enhanced in the ankle than in the elbow, and could result in age-related increases of the ABI. Previous studies have demonstrated a positive correlation between height and ABI as a consequence of the progressive systolic BP increase with greater distance from the heart. Sex differences in the ABI have been reported in previous studies, including ours, and height is sometimes considered the reason. However, we and others have reported that the influence of height on ABI is small and not significant after adjusting for sex. The relationship between height and ΔABI over time has not been reported to date. However, high stature may be correlated with an age-dependent increase of ABI because of a greater number of
bifurcations in the lower limbs than in the upper limbs, leading to an amplification of systolic BP via increased reflected waves. Previous studies have reported that PWV is the highest in the arms during adolescence compared with the aorta and lower extremities, but age-related changes in PWV are the most gradual in the arms. These results indicate that age-related changes in systolic BP might be slowest in the arms compared with the aorta and lower extremities, which could lead to age-related increases in the ABI.

In this study, BMI was positively associated with ΔABI over time via multiple linear regression analyses. In the ARIC study, BMI was higher in the subjects with an ABI >1.3 than in those with 0.9 ≤ ABI < 1.3. The MESA study also reported that BMI was a risk factor for progression to an ABI ≥ 1.4. In that study, neither diabetes nor renal failure was associated with an increase of ABI above 1.4. Tabara et al reported a positive correlation between ABI and the femoral muscle cross-sectional area, which is also associated with BMI. They concluded that a large muscle mass might act as a resistance to cuff compression of the arteries, and thus caused an artifactual elevation of the ankle systolic BP. We analyzed the relationship between changes in body weight and ABI. There was no significant relationship between them (P=0.367), even adjusted for sex and age (P=0.367). This result indicated that a change in muscle mass may not be a potent determinant of ΔABI. The ΔABI over time was significantly associated with baseline ABI: the higher the value, the higher the probability of decrease, and vice versa. These results may indicate statistical convergence to an average value that would lead to an overestimate of the real variation. In this study, however, ΔABI significantly increased in participants aged <40 years and 40–49 years, but ΔABI did not decrease in the 50–59 years and ≥60 years age groups. We analyzed 3 serial ABI measurements and revealed that the ABI significantly increased at both visit 2 and visit 3 compared with baseline, in participants aged <40 years and 40–49 years. In participants aged 50–59 years and ≥60 years, the ABI did not change significantly at visit 2 compared with baseline. Therefore, we believe that the ΔABI over time in participants aged <50 years is different from that of regression to a mean value.

Study Limitations
Participants in this study were self-selected and might have been more concerned about their health than the general population. In addition, the value of ΔABI was quite small compared with previous studies. Therefore, we need a much larger sample size and a longer follow-up to detect the apparent ΔABI over time. The numbers of participants with borderline-low ABI and high-normal ABI were not enough to evaluate the effects of age and cardiovascular risk factors on ΔABI over time by ABI categories. We did not perform other examinations, such as computed tomography angiography, magnetic resonance angiography, and ultrasound duplex scan; therefore, we did not evaluate the prevalence of false-normal results. We did not evaluate the effects of drugs, such as antihypertensive and statins, which may have an influence on arterial stiffness and wave reflections. Because ethnicity affects the ABI value, further studies are needed to establish whether these results apply to any other ethnicities.

Conclusions
ABI was lowest at age <40 years and increased with age. In participants aged less than 50 years, ABI significantly increased over the mean observation period of 4.9 years, indicating that borderline-low ABI in low-risk younger subjects does not always indicate lower limb arterial stenosis.

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Conflict of Interests / Disclosures / Funding Sources
None.

References


