A Cross-Sectional Observation on The Association of Menopause with Coronary Risk Factors in Japanese Female Workers

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Abstract: A Cross-Sectional Observation on The Association of Menopause with Coronary Risk Factors in Japanese Female Workers: Yuka Noborisaka, et al. Department of Hygiene, Kanazawa Medical University—Biological risk factors for coronary heart disease (CHD), i.e., blood pressure, serum lipids and uric acid (UA), blood glucose and hemoglobin A1c, together with serum hepatic enzymes, were measured in 260 female workers consisting of 118 40-year-olds, 102 50-y.o. and 40 60-y.o., and the age-related differences were compared with male workers of the same age. The association of menopause with the risk factors and serum hepatic enzymes was also evaluated. Serum total cholesterol (Tch), triglycerides (TG), UA, alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) levels were higher in the females in higher age groups, much more noticeably than in the males. Serum Tch was lower in the females aged 40 y than in the males, but higher in the females aged 50 and 60 y. Other parameters remained better in the females in all three age groups. A significant association of menopause was found with a higher serum Tch level and was suggested with higher serum ALT and GGT levels. Tch was highest in women ≤5 years from menopause while ALT and GGT were highest in women 5 to 9 years from menopause, suggesting a quick change in serum Tch and gradual changes in serum hepatic enzymes after menopause. These adverse changes in serum lipids and hepatic enzymes after menopause should be taken into consideration in industrial health care for middle-aged women.

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Key words: Female workers, Coronary risk factors, Age, Menopause, Serum lipids, Hepatic enzymes

The number of women working in industry in Japan has increased from 15 million to 20 million during the last 10 years, and in 1995 more than 60% of the female workers were composed of middle-aged persons above 35 years of age. Menopause affects a variety of psychological and physical health conditions in middle-aged women. As the number of middle-aged women increases, the health problems associated with menopause will increase in importance in industrial health care, but little attention has been paid to these problems in Japan. At most, attention has been mainly paid to the psychological problems rather than the physical ones, because women during the peri-menopausal period tend to complain of various vague and uncomfortable symptoms such as facial flushing, palpitation, easy fatigability and mood changes.

Coronary heart disease (CHD) has long been recognized as a disease of men after middle-age, but the implication of CHD in women's health has recently been emphasized in the United States1, 2) and United Kingdom3) because CHD is the leading cause of death in those countries, with more than a fourth of women dying of CHD there. It has also been demonstrated in those countries that although total CHD mortality is higher in men than in women, the increase with advancing age is more marked in women than in men after 50–60 years of age. This may be related to the fact that women have a beneficial profile of serum lipids in comparison with men at a younger age, but tend to lose the benefit after menopause4–10).

The death rate from CHD in Japan at present is much lower than in the US or UK. CHD mortality in Japanese women in 1994 was 42.7 per one hundred thousand of the population, but it was not much lower than that in men with 50.8, and the differences between men and women in CHD mortality decreased after 50–60 years of age11), similarly to those in the US and UK. Although evidence of significant effects of menopause on CHD risk in Japanese women remains to be provided, some
previous studies\textsuperscript{12–14} showed the adverse effects of menopause on serum lipid profiles in Japanese women, suggesting the need to consider the effects of menopause on CHD risk as a health care problem in women working in industry. The aim of this preliminary cross-sectional study is to show the association of menopause with biological risk factors for CHD in middle-aged women recruited from an occupational population.

**Subjects and Methods**

The subjects of this study were middle-aged female workers in a metal products factory who received a health check-up in a hospital. The employees in this factory are encouraged to undergo the health check-up every ten years after their 40th birthday. The subjects were thus composed of 118 women aged 40 years, 103 50-y.o. and 43 60-y.o., but one 50-y.o. and three 60-y.o. women were excluded from the study because they were receiving medications for chronic illness such as hypertension, hyperlipidemia and diabetes mellitus. Two hundred and sixty age-matched men were randomly recruited as controls from among 852 male workers in the same factory who also received the health check-up in the hospital and were not taking any medications.

Both the male and female subjects had their blood pressure (BP) taken with a sphygmomanometer while in the sitting position after resting 15 min or more on a chair, according to the standard method recommended by the Japanese Circulatory Disease Control Association\textsuperscript{15, 16}. Venous blood samples collected in the morning after a 12-h fast were analyzed for biochemical parameters known to relate to CHD risk, i.e., serum lipids of total cholesterol (Tch), HDL-cholesterol (HDLc) and triglycerides (TG), and uric acid (UA) and glucose (Glc), together with serum hepatic enzymes of asparate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) with an automatic analyzer, Hitachi 7450, Japan. Hemoglobin A1c (HbA1c) was also measured with an analyzer, HLC-723 GHb II, Toso, Japan.

The data on alcohol and cigarette consumption were collected by means of a questionnaire, but none of the female subjects drank alcohol regularly or smoked. Data on menstruation status, i.e., regular, irregular, date of the last menstruation, history of ovariostereis and use of hormonal replacement in the female subjects, were also collected during the health check-up by means of a questionnaire. Menopause was defined here as when one year or more had elapsed since the last menstruation.

The differences between men and women and among the three age groups in the means of these biochemical parameters were analyzed for the effects of body mass index (BMI: kg/m\textsuperscript{2}), and the association of menopause with the mean values adjusted for the effects of age and BMI, were tested by a generalized linear model (GLM) analysis with a statistical program package delivered by the SAS Institute, USA. Statistical significance was defined as $p<0.05$, and $0.05<p<0.10$ was regarded as of borderline significance.

**Results**

The means and standard deviations of BMI, systolic and diastolic BP (SBP and DBP), and other biochemical parameters possibly related to CHD in the male and female subjects divided into the three age groups are summarized in Table 1. A two-way analysis of variance showed that the mean BMI was significantly higher in the higher age groups in both men and women without a significant gender difference.

SBP and DBP were also higher in the higher age groups, and were somewhat higher in men than in women. The differences in the age groups were highly significant, but the gender differences did not reach a significant level after adjusting BMI levels by a GLM analysis. Significant differences in the age groups were found in serum AST, Tch and HbA1c while significant gender differences were found in serum ALT, GGT, TG, Tch, HDLc and UA levels. TG, UA and hepatic enzymes were significantly higher and HDLc was lower in men than in women. Tch was lower in women aged 40 y, but it was higher in those aged 50 and 60 y than in men. Significant interactive effects of aging and gender on the parameters were found in serum Tch, TG, UA and GGT, which meant that age-related differences in these parameters were significantly more marked in women than in men.

Data on menstruation status are summarized in Table 2. Among 118 women aged 40 y, 96 (81\%) recognized regular menstruation, 14 (12\%) complained of irregularity, and 8(6\%) were in menopause. Menopause in one of the 8 women was caused by oophorectomy. Regular menstruation was found in 15 (15\%) of 102 women aged 50 y, irregularity in 30 (30\%), and menopause in 57 (56\%), including one operative case. All the 40 women aged 60 y were in menopause including one case of oophorectomy. As shown in the table, one woman aged 40 y and two 50 y were receiving hormone replacement therapy, and were excluded from the following analyses for the association of menopause with the parameters possibly related to CHD.

One hundred and fifty-five women (110 aged 40 y and 45 aged 50 y) were categorized as “premenopause” including regular and irregular menstruation, 38 women (3 aged 40 y and 35 aged 50 y) as “<5 years since menopause”, 34 women (3 aged 40 y, 13 aged 50 y and 18 aged 60 y) as “5–9 years since menopause” and 27 women (6 aged 50 y and 21 aged 60 y) as “≥10 years since menopause.”

Least square means of the biochemical parameters in women divided into the four menstruation categories and three age groups are shown in Table 3. A significant
difference in the means among the four menstruation categories was found in serum Tch levels, and a borderline significant difference was found in serum ALT and GGT levels, after adjusting for the effects of age and BMI. No significant association of menopause was found with the other parameters although serum TG was somewhat higher and HDLc was somewhat lower in the 50-y.o. women who were <5 and 5–9 years since menopause in comparison with the premenopausal women.

The least square means and standard errors of the serum Tch, ALT and GGT are illustrated in Fig. 1, where the differences between two categories were tested by a protected least square difference method. As shown in the figure, serum Tch showed the highest value in the women in <5 years since menopause, and was significantly different from the value for premenopausal women and women 5 years or more after menopause. No significant difference was, however, found between the premenopausal women and those 5 years or more after menopause. On the other hand, the two serum hepatic enzymes were higher in women who were longer after menopause except for those who were 10 years or more after menopause, and the highest value was found in the women 5–9 years after menopause.

**Discussion**

According to summary reports from the US and UK, serum lipid profiles regarding CHD risk were better in...
Fig. 1. Least square means and standard errors for serum Tch, ALT and GGT levels divided by categories of menstruation status. Premenopausal women are coded 0, women <5 years from menopause 1, those 5 to 9 years 2, and those ≥10 years 3. The difference among the categories in least square means were tested by a protected least square difference method. *: p<0.05, **: p<0.01.

Table 2. Numbers of women divided by categories of menstruation status in the three age groups of 40, 50 and 60-y.o.

<table>
<thead>
<tr>
<th>Menstruation Status</th>
<th>Age group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 y.o</td>
<td>50 y.o</td>
</tr>
<tr>
<td>Premenopause</td>
<td>110</td>
<td>45</td>
</tr>
<tr>
<td>Regular</td>
<td>96</td>
<td>15</td>
</tr>
<tr>
<td>Irregular</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Postmenopause+</td>
<td>8</td>
<td>57</td>
</tr>
<tr>
<td>&lt;5 yrsb</td>
<td>3</td>
<td>36 (1)c</td>
</tr>
<tr>
<td>5–9 yrs</td>
<td>4 (1)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>≥10 yrs</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Operatived</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>102</td>
</tr>
</tbody>
</table>

+: Menopause was defined as being present when one year or more had elapsed since the last menstruation. b: Years elapsed from the last menstruation. c: The number in parenthesis shows women who have been receiving hormone replacement therapy. d: Menopause caused by oophorectomy.

Table 3. Least square means of blood pressure and serum biochemical parameters related to coronary heart disease in women divided by age groups and categories of menstruation status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Premenopause</th>
<th>Postmenopause</th>
<th>Statistical resultsb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 y.o (n=110)</td>
<td>50 y.o (n=45)</td>
<td>&lt;5 yrs&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>122</td>
<td>124</td>
<td>112</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70.3</td>
<td>74.2</td>
<td>68.3</td>
</tr>
<tr>
<td>AST (U/l)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16.5</td>
<td>18.0</td>
<td>21.8</td>
</tr>
<tr>
<td>ALT (U/l)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12.1</td>
<td>13.1</td>
<td>19.5</td>
</tr>
<tr>
<td>GGT (U/l)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.0</td>
<td>8.4</td>
<td>8.7</td>
</tr>
<tr>
<td>TG (mg/dl)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>75</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td>Tch (mg/dl)</td>
<td>195</td>
<td>202</td>
<td>219</td>
</tr>
<tr>
<td>HDLc (mg/dl)</td>
<td>59.1</td>
<td>57.0</td>
<td>55.4</td>
</tr>
<tr>
<td>UA (mg/dl)</td>
<td>3.90</td>
<td>3.91</td>
<td>3.79</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.42</td>
<td>5.44</td>
<td>5.24</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Years elapsed from the last menstruation. <sup>b</sup>: Significant differences in the means of parameters among the four categories of menstruation status were tested by a generalized linear model analysis, adjusted for age and body mass index. <sup>c</sup>: Geometric mean.
women than in men until 40 y. After 50 years of age, however, serum Tch and LDL-cholesterol (LDLc) levels became higher in women than in men. Serum TG was increased and HDLc was lowered with age in women, but they remained better than in men throughout life. The 3rd and 4th National Surveys of Circulatory Disorders in Japan reported similar findings: serum Tch and TG were lower in women than in men aged 40 y or below, but increased more markedly in older women than in men, and Tch was higher in women aged 50 y or above and TG in women was almost equal to those in men after 60 years of age. On the other hand, serum HDLc was higher in women than in men in all age groups, but in women it decreased gradually with age.

As shown in Table 1, the present male and female workers had age-related serum lipid profiles similar to those noted in previous reports, i.e., serum Tch was lower in the women aged 40 y, but higher in those aged 50 and 60 y than in men, whereas TG remained lower and HDLc remained higher in women than in men in all three age groups, although TG was higher and HDLc was much lower in higher age groups in women. Similar gender differences in age-related serum lipid profiles have been observed in some other Japanese studies and in a Chinese study, where both fat intake and CHD mortality were much lower than in the US and UK. The gender difference in serum lipid profiles may at least partly be attributable to the gender difference in some lifestyle factors, mainly alcohol and cigarette consumption which was much higher in men than in women, but the results also suggest a kind of strong hormonal regulation of serum lipid levels in women.

The present study showed higher levels of serum hepatic enzymes and UA in women in higher age groups, which paralleled the age-related difference in serum TG levels. Our previous studies showed that increases in serum hepatic enzymes, especially serum GGT, were closely related to increases in blood pressure and serum lipids and glucose levels, even in non-drinkers. Increases in serum hepatic enzymes may reflect the progression of hepatic steatosis. Hepatic fat infiltration is closely related to intra-abdominal or visceral fat accumulation which is known to relate to CHD, probably mediated via insulin resistance and hyperinsulinemia. These are the reasons why we measured serum hepatic enzyme levels in the present study. Although we did not measure plasma insulin in this study, the increases in serum hepatic enzymes and UA may relate to the increase in plasma insulin in women with age.

As shown in the results of GLM analyses, an association of menopause was found with serum Tch levels and was suggested with serum hepatic enzymes of ALT and GGT in the present female subjects. Serum TG levels were somewhat higher and HDLc levels were lower in the postmenopausal women, though these were not significantly different from those in the premenopausal women. This statistical association between menopause and serum lipids levels was basically in accordance with the previous findings showing that menopause caused a noticeable increase in serum Tch and small increases in TG and decreases in HDLc levels.

No attention was paid to the influence of menopause on serum hepatic enzymes in previous studies. As noted above, increases in serum hepatic enzymes may be a reflection of fat accumulation in the abdominal cavity and liver, a characteristic of android-type fat distribution. Body fat distribution in premenopausal women is very different (gynoid-type) from that in men (android-type), but it was reported that fat distribution becomes more android after menopause. Therefore, the increases in serum ALT and GGT in postmenopausal women may reflect the changes in body fat distribution after menopause.

The postmenopausal increase in serum Tch was conspicuous in the women less than 5 years from menopause. It became less clear in those 5 or more years after menopause. On the other hand, increases in serum hepatic enzymes were more gradual, and became most noticeable in the women 5 to 9 years after menopause. These results suggest that serum Tch changes relatively quickly after menopause but hepatic enzymes change more slowly. In Japanese people above middle age, the effects of birth cohorts on serum lipid levels have been demonstrated; those are higher in the younger rather than in the older above 60 y, probably due to the differences in their dietary habits. Thus the differences in birth cohorts may have influenced the present findings of lower serum Tch in the women 5 or more years after menopause in comparison with those less than 5 years after menopause, which could not be excluded from this cross-sectional observation.

Further investigation is required to confirm these findings, but the adverse changes in serum lipid profiles and hepatic enzymes in postmenopausal women should be taken into consideration in industrial health care for women.

References
3) Khaw KT, Sharp I. Coronary heart disease in women. The scale of the problem: should we be concerned? In: