Effect of Age at Menopause on Blood Pressure in Postmenopausal Women

Yoichi Izumi, Koichi Matsumoto, Yukio Ozawa, Yuji Kasamaki, Atsushi Shinndo, Masakatsu Ohta, Madet Jumabay, Tomohiro Nakayama, Eise Yokoyama, Hiroaki Shimabukuro, Hiroshi Kawamura, Zuheng Cheng, Yitong Ma, and Masum Mahmut

Background: A major mechanism of hypertension in many postmenopausal women is deficiency of female gonadal steroids. A long postmenopausal period may thus represent one factor that influences the prevalence of hypertension because of long periods of estradiol loss.

Methods: When we conducted a medical survey in northwestern China, we also asked 150 postmenopausal female subjects to provide age at menopause in a questionnaire. Age at menopause ranged from 37 to 57 years for all subjects. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) in all subjects were obtained from 24-h ambulatory blood-pressure monitoring.

Results: An inverse correlation was identified between age at menopause and SBP and DBP, and a positive correlation was found between postmenopausal period and either SBP or DBP. Blood pressure, age at menopause, and postmenopausal period were not significantly related to body mass index, plasma renin activity, glomerular filtration rate, or urinary excretion values of sodium and potassium.

Conclusions: Our results clearly demonstrated that higher blood-pressure levels in postmenopausal women depend on age at menopause and postmenopausal period, but not subjects’ age, suggesting that a longer absence of female gonadal steroids represents a major factor contributing to increased blood pressure in elderly women.

Key Words: Age, menopause, blood pressure, postmenopausal women.
become salt-sensitive. The mechanisms involved in blood-pressure increases after menopause are therefore complex.

Data obtained from elderly female subjects in our survey were analyzed to determine relationships between blood pressure, age at menopause, and postmenopausal duration.

Methods

In total, 310 healthy adults from three ethnic groups were recruited by random selection of resident cards from the local government offices in Hotan (Hotan Prefecture, southern part of Xinjiang in China) and Balikun (Balikun Prefecture, northwest of Xinjiang). The Ethics Committee of Xinjiang Medical University approved all study protocols. All subjects provided informed consent to participate in this study. In total, 150 women were retained for this study after excluding subjects with incomplete data regarding blood and urinary parameters or incomplete questionnaires. No subjects had previously received antihypertensive agents or female gonadal steroid. Subjects from the three ethnic groups (elderly Han in Hotan and Balikun, age range, 65 to 70 years, n = 42; elderly Kazakh in Balikun, age range, 65 to 70 years, n = 74; and elderly Uygur in Hotan, age range, 65 to 70 years, n = 34) were hospitalized for 4 days at local medical centers in Hotan or Balikun. Han subjects from both regions participated, to examine whether any differences existed in the prevalence of hypertension according to environment for subjects from the same ethnic background. Subjects arrived at the hospital in the evening of the first day of hospitalization. All subjects underwent a physical examination, including measurements of body weight and height. Subjects were asked their age at first menstruation and age at menopause in the questionnaire. On the morning of the second day of hospitalization, 24-h urine collection was initiated to determine urine volume and sodium and potassium excretion levels. Venous blood was drawn on day 3, after the end of the urine collection cycle and before breakfast, to determine plasma renin activity (PRA), serum glucose, and creatinine. Ambulatory blood-pressure monitoring (ABPM) was performed using a TM2421 monitor (A&D Corp., Tokyo, Japan) fixed to each subject to continuously monitor blood pressure for 24 h. Traditional Islamic meals were provided by the hospital during hospitalization. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) obtained during 24-h monitoring were used as blood-pressure values in the present study. Office blood pressure was measured in the right arm while subjects were seated in the office, and was recorded as the average of three measurements, each taken after a 5-min rest before the start of 24-h ABPM. Hypertension was defined as office SBP ≥140 mm Hg or DBP ≥90 mm Hg. Urinary sodium and potassium and serum creatinine were measured using an RA-2000 automatic analyzer (Technicon Instruments, Tarrytown, NY). Radioimmunoassay kits were used to measure PRA (Beijing North Biotechnology Institute, Beijing, China). To evaluate renal function, the glomerular filtration rate (GFR) was calculated, based on serum creatinine value (SCr; mg/dL), body weight (BW; kg), and age (years), as follows: $GFR = (140 - \text{age}) \times BW \times 0.85)/(72 \times SCr)$, as described by Cockcroft and Gault.

Body mass index (BMI) was calculated as follows: $BMI = BW/(height (in meters))^2$. Postmenopausal period was determined by subtracting age at menopause from age at the time of the present study.

All values are shown as mean ± standard error of the mean (SEM). All statistical calculations were performed using SPSS for Windows software, version 11.5 (SPSS, Chicago, IL). Intragroup comparisons were determined using one-way ANOVA with Tukey post hoc testing. Multiple regression analysis was performed using SBP and DBP as dependent variables, and age, age at menopause, postmenopausal period, and ethnicity as independent variables. Values of $P < .05$ were considered statistically significant.

Results

The SBP and DBP were significantly higher in Kazakh subjects $(133.7 ± 2.3$ mm Hg and $76.4 ± 1.3$ mm Hg) than in the other two groups (Han, $126.3 ± 2.7$ mm Hg and $71.9 ± 1.4$ mm Hg; Uygur, $123.7 ± 2.9$ mm Hg and $70.8 ± 1.4$ mm Hg). The prevalence of hypertension according to environment for subjects from the same ethnic background is shown in Table 1. Han and Uygur had a significantly higher prevalence of hypertension than Kazakh subjects. A comparison of systolic blood pressure and diastolic blood pressure between the Han, Kazakh, and Uygur groups, classified according to age and postmenopausal period, is shown in Fig. 1. The SBP and DBP were significantly higher in Kazakh women than in Han or Uygur women. The SBP and DBP of Han and Uygur women did not differ significantly.

FIG. 1. Mean systolic blood pressure (SBP) (A) and diastolic blood pressure (DBP) (B) as measured by ambulatory blood-pressure monitoring, age at menopause (C), and postmenopausal period (D) in the three different ethnic groups. Han; KAZ = Kazakh; UIG = Uygur. *$p < .05$, **$p < .01$, ***$p < .001$. 
68.7 ± 1.1 mm Hg; Fig. 1A,B). No significant differences in SBP or DBP were identified between Han and Uygur subjects. Age at menopause was significantly lower in Kazakh subjects (43.7 ± 0.5 years) than in Han (48.7 ± 0.7 years) or Uygur (49.0 ± 0.5 years) subjects (Fig. 1C). No significant differences were observed in age at menopause between Han and Uygur subjects. The postmenopausal period was significantly higher in Kazakh subjects (23.4 ± 0.6 years) than in Han (18.2 ± 0.9 years) or Uygur (18.3 ± 0.6 years) subjects (Fig. 1D). No significant differences in postmenopausal period were seen between Han and Uygur subjects, and no significant differences in age at first menstruation existed between any groups (data not shown). No significant differences in SBP or DBP, age at menopause, or postmenopausal period were observed between the two Han groups from Balikun and Hotan. When all subjects were divided into hypertensive group (HT) and normotensive group (NT) according to office blood pressure, no significant differences in age were seen between HT (67.62 ± 0.28 years) and NT (67.07 ± 0.19 years) (Fig. 2A). However, age at menopause was significantly lower in HT (44.62 ± 0.66 years) than in NT (46.97 ± 0.47 years; P < .005) (Fig. 2B). When data from the three groups were analyzed together using multiple regression analysis, age at menopause was inversely correlated with SBP (r = 0.30, P < .0001; Fig. 3A) and DBP (r = 0.32, P < .0001; Fig. 3B). Postmenopausal period also correlated with SBP (r = 0.30, P < .0001; Fig. 4A) and DBP (r = 0.28, P < .001; Fig. 4B). Postmenopausal period inversely correlated with GFR (r = 0.23, P < .005; Fig. 4C). Clinical characteristics of study subjects from the three ethnicities are shown in Table 1. Body mass index and urinary sodium excretion values were lowest in Uygur subjects (P < .001 versus Han and Kazakh subjects, and P < .01 versus Han and Kazakh subjects, respectively), and urinary potassium excretion was lowest in Kazakh subjects (P < .05 versus each of the other two groups). The GFR and PRA were lowest in Kazakh subjects (P < .05 versus Han and Uygur subjects, and P < .01 versus Han and Uygur subjects, respectively). The SBP, DBP, age at menopause, and postmenopausal period were not significantly related to BMI, urinary sodium or potassium excretion values, and PRA, according to multiple regression analysis. No differences in SBP, DBP, age at menopause, or postmenopausal period were found between Han subjects from the Hotan and Balikun regions.

**Discussion**

A high prevalence of hypertension is a natural part of aging in postmenopausal women. Postmenopausal period is well-established as one risk factor for cardiovascular disease in women. As one example of this phenomenon, the prevalence of hypertension is higher in males who are 30 to 45 years old than in females of similar age, while the prevalence of hypertension in females after this age increases to levels similar to those exceeding that in males. The postmenopausal increase in blood pressure in females...
is mainly caused by a loss of sex steroids, indicating that estrogen exerts protective effects against increases in blood pressure. Animal experiments showed a blood-pressure increase in ovariectomized female rats, and estrogen replacement in these rats restored vascular contraction to the levels seen in intact female rats, supporting the role of estrogen abolishment in causing postmenopausal hypertension. Some mechanisms of the protective effects of estrogen on cardiovascular disease were described. Estrogen inhibits the renin-angiotensin system, decreasing the expression of AT1 receptors in animal experiments. Another vasoconstrictor, endothelin, also appears to be suppressed by estrogen. In addition, relationships between postmenopausal hypertension and changes in insulin sensitivity and salt sensitivity were reported, suggesting that complex mechanisms play a role in rises in blood pressure due to the loss of estrogen in females, together with the mechanisms mentioned above. In the present study, no significant relationships between blood pressure and either urinary sodium or potassium excretion values were observed. Postmenopausal period was inversely correlated with GFR. However, SBP and DBP were not significantly related to GFR, suggesting a weak relationship between changes in renal function and changes in blood pressure in this study. Nevertheless, a longer postmenopausal period tended to be associated with lower renal function and higher blood pressure.

An increase in sympathoadrenal responsiveness was also observed, and was attenuated during oral HRT after menopause. Conversely, the production of vasodilators, endothelial nitric oxide, and PGI2 is stimulated by estrogen. Menopause induces a loss of gonadal steroids and abolishes the above mechanisms tending to protect against cardiovascular disease. As a result, the mechanisms causing the increase in blood pressure also increase these activities, whereas the mechanisms by which increases in blood pressure are suppressed lower these activities in postmenopausal women.

Clinical evidence has accumulated, and estrogen replacement therapy was shown to suppress the incidence of cardiovascular disease, including hypertension in women. The present results indicate that the above therapy is reasonable, because HRTs such as estrogen administration represent an artificial product for women to receive during the premenopausal period. However, several reports described either serious adverse effects (eg, thrombo-embolic accident or breast cancer) as a result of HRT or no significant benefit of this therapy against cardiovascular disease.

Multiple regression analysis in this study showed that lower menopausal age and longer postmenopausal period were related to higher blood pressure, independent of age and ethnicity. In addition, this analysis indicated no relationships among factors such as blood pressure, age at menopause, and postmenopausal period to BMI, GFR, PRA, and sodium and potassium excretion values. Blood pressure was only related to age at menopause and postmenopausal period, indicating that higher age at menopause lowers the prevalence of hypertension. We determined serum estradiol and testosterone levels in all subjects, and no significant relationships were observed between these sex hormones and either blood pressure or age at menopause (data not shown).

The question remains regarding how to naturally prolong the period of menstruation, without resorting to artificial methods such as HRT. Hardy and Kuh reported on social and environmental conditions across the life course...
and age at menopause.26 Age at menopause and psychological factors are closely related.

In conclusion, long postmenopausal period clearly represents one factor that influences the prevalence of hypertension due to a long period of estrogen loss. Therefore, hormone replacement therapy should theoretically be recommended for patients with hypertension, based on the present results. However, we should carefully take into account the fact that hypertension in postmenopausal women is not always caused by a loss of estrogen. In fact, we can select several alternative antihypertensive agents when clinically treating for such hypertension, because the mechanisms of hypertension among postmenopausal women are not uniform. Even if risk of hypertension is increased due to younger age at menopause, most such females can still maintain a long life if appropriate treatment is implemented early.

References