ORIGINAL CONTRIBUTION

Changes in Cardiovascular Risk Factors Related with Menopause in Rural Japanese Women

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To examine menopause-related changes in cardiovascular risk factors in women, we analyzed the data of a 1981-84 cross-sectional study of rural Japanese women aged 40-69 years and a 4.3-year subsequent follow-up of premenopausal women. In the cross-sectional study, mean serum total cholesterol was higher in women aged 50 and over than in women aged 40-44 years. Women showed a significantly higher serum cholesterol level than men for aged 50 and over. For women aged 45-49, in which 50% of women turned into postmenopausal status, postmenopausal women showed a significantly higher cholesterol level than premenopausal women: 194 mg/dl vs. 183 mg/dl, respectively ($p < 0.05$). Blood pressure levels were lower in women than in men, but the sex difference was smaller for aged 50 and over. Mean body mass index and skinfold thickness were higher in women than in men. During the follow-up period, women showed a significant increase in mean serum total cholesterol (16 mg/dl) and subscapular skinfold thickness (2 mm) while men did not. Triceps skinfold thickness did not change in either sex. Blood pressure levels increased for both women and men in a similar magnitude. In conclusion, we found the increase in serum total cholesterol and the change in body fat distribution related with menopause in Japanese women. Whether these menopause-related risk factor changes would raise the risk of subsequent cardiovascular disease require further studies. *J Epidemiol*, 1995; 5: 23-28.

menopause, serum total cholesterol, skinfold thickness, blood pressure, cross-sectional study, follow-up study

Menopause is one of the major physical changes related with health for women¹⁾. Several epidemiological studies of Caucasian women in the United States and European countries indicated that menopause increased the risk of coronary heart disease and total mortality²⁻⁷⁾. These health-adverse effects were in part explained by an increase of blood pressure^{3,4)} and serum lipids^{3-5,7,8)} and changes in body fat distribution⁹⁾.

Previous data of Caucasian women may not be applicable to Japanese women because serum cholesterol levels are much lower in Japanese than in Caucasians^{10,11)}, and blood pressure levels are higher in Japanese than in Caucasians¹²⁾. There have been three cross-sectional studies¹³⁻¹⁵⁾ and one follow-up studies¹⁵⁾ on menopause-

related changes in cardiovascular risk factors in Japanese women. These studies indicated that serum total cholesterol and triglyceride were higher in postmenopausal women than in premenopausal women cross-sectionally¹³⁻¹⁵⁾, and that serum total cholesterol increases after menopause prospectively¹⁵⁾. However, none of these studies has examined menopause-related changes in serum lipids, blood pressure and body fat distribution simultaneously.

To examine menopause-related changes in these cardiovascular risk factors in women, we analyzed cross-sectional and follow-up data in a rural Japanese population.

Received August 30, 1994; accepted December 5, 1994

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MATERIALS AND METHODS

Study Population

The surveyed population was men and women aged 40-69 living in a rural community of Akita Prefecture, located in the northeast area of Japan. Common occupations in this community were rice farmers and/or workers for light industry. We included men for the analyses because men was regarded as "control" to examine changes in cardiovascular risk factors related with menopause for women.

Cross-sectional analysis

A cross-sectional population survey was conducted for women and men aged 40-69 living in the community between 1981 and 1984. The number of census population, participants and participation rates were shown in Table 1. Participation rates for aged 40-69 were 90% in women and 78% in men in average.

Menopausal status was examined by interview. Menopause was defined as a cease in menstruation during the past six months. Among 787 postmenopausal women, 16(2%) women were reported to have surgical menopause.

Serum total cholesterol was measured by the Liebermann-Burchard method with a Technicon Autoanalyzer II¹⁶⁾ in the laboratory at the Center for Adult Diseases, Osaka. Quality control of the laboratory was maintained by combined internal controls and external standardization by the Centers for Disease Control in Atlanta, Georgia^{17,18)}. Systolic and diastolic blood pressures were measured by trained physicians using a standard mercury sphygmomanometer on the right arm of seated participants after at least a 5-minute rest. Blood pressures were measured twice when the first measurement of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and otherwise measured once. Values of the first measurement were used for the analyses. Height in stocking feet and weight in light clothing were

measured. Body mass index was calculated as body weight (kg) divided by square of height (m²). Skinfold thickness was measured at the right triceps and the right subscapular areas using a Eiken skinfold caliper (Meiko Inc., Tokyo, Japan).

Age-specific mean values of serum total cholesterol, resting blood pressures, body mass index and skinfold thickness were compared between women and men. For women aged 45-49, these mean values were also compared between pre- and postmenopausal women.

Follow-up study

A follow-up study was conducted to examine individual changes in cardiovascular risk factors related with menopause. We identified 203 premenopausal women in the 1981-84 cross-sectional survey who participated in the follow-up surveys after 1 to 8 years (in average 4.3 years) until they turned into postmenopausal status. Age range of premenopausal women was 40 to 58 years in the 1981-84 survey. Age- and follow-up year-matched men (n=203) from the 1981-84 survey were selected randomly for comparison with women. During the follow-up, no woman had surgical menopause. Serum total cholesterol, resting blood pressures, body mass index and skinfold thickness were examined 1 to 8 year later, again.

Statistical analysis

Student's t-test (independent t-test) was used to compare mean values of cardiovascular risk factors between women and men or between pre- and postmenopausal women in the cross-sectional analyses. Paired t-test was used to examine changes in mean values of 203 women and 203 men between in the 1981-84 survey and in the follow-up survey. Sex differences in individual changes in the follow-up study were tested by independent t-test. All p-values for statistical significance were two-tailed. P values of 0.05 or less were considered significant.

Table 1. The number of census population and participants, and participation rates by sex and age, women and men ages 40-69.

Age group	Women			Men		
	Census population (n)*	Participants (n)	Participation rates (%)	Census population (n)*	Participants (n)	Participation rates (%)
40-44	224	215	96	201	144	72
45-49	240	211	88	222	170	77
50-54	247	225	91	230	182	79
55-59	231	199	86	196	163	83
60-64	196	174	89	144	121	84
65-69	159	149	94	145	103	71
Total	1,297	1,173	90	1,138	883	78

* The average of population in 1980 and 1985

RESULTS

Age-related changes in cardiovascular risk factor levels in women and men, a cross-sectional study

Figures 1-3 illustrates mean values of cardiovascular risk factors by sex and age from the 1981-84 cross-sectional study. The proportion of postmenopausal women was 9% in aged 40-44, 34% in aged 45-49, 82% in aged 50-54 and 99% in aged 55 or more. Women showed a sharp increase

Figure 1. Plots of mean serum total cholesterol by sex and age in 1981-1984. Sex differences: * $p < 0.05$, *** $p < 0.001$

Figure 2. Plots of mean systolic and diastolic blood pressures by sex and age in 1981-1984. Sex differences: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

in mean serum cholesterol level between aged 40-44 and 50-54 (the difference: $p < 0.001$), and stable thereafter, whereas men showed a stable serum cholesterol level across the age range 40-69 (Figure 1). Women showed a significantly higher serum cholesterol level than men for aged 50 and over. Furthermore, in women aged 45-49, in which 50% of women turned into postmenopausal status, postmenopausal women showed a significantly higher cholesterol level than premenopausal women: 194 mg/dl vs. 183 mg/dl, respectively ($p < 0.05$).

Women showed an increase in mean values of systolic and diastolic blood pressures with age, and sex difference in blood pressure levels became smaller with increased age (Figure 2). The sex difference in blood pressure levels was no more significant for aged 45 and over in mean systolic blood pressure and for aged 60 and over in mean diastolic blood pressure.

Women showed a slight increase in mean body mass index with age between the aged 40-44 and 55-59 years, and

Figure 3. Plots of mean body mass index and subscapular skinfold thickness by sex and age in 1981-1984. Sex differences: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 2. Changes in mean values of blood pressures, serum total cholesterol, body mass index and skinfold thickness between menopausal status in women and men matched with age and follow-up year.

Variables	Menopausal status	Women (n=203)				Men (n=203)				Sex differences in change (p-value)**
		Mean	SD	Change	p-value*	Mean	SD	Change	p-value*	
Age (years)	I	46.8	3.6	4.3	<0.001	47.1	3.8	4.3	<0.001	0.575
	II	51.1	3.1			51.4	3.6			
Serum total cholesterol (mg/dl)	I	183.7	36.2	16.3	<0.001	185.4	31.0	-2.2	0.249	<0.001
	II	200.0	36.7			183.1	30.6			
Systolic blood pressure (mmHg)	I	128.1	17.9	5.6	<0.001	130.5	18.3	5.4	<0.001	0.906
	II	133.7	19.3			135.9	21.7			
Diastolic blood pressure (mmHg)	I	77.3	10.8	4.1	<0.001	82.3	13.0	2.4	<0.001	0.098
	II	81.4	11.2			84.7	12.6			
Body mass index	I	23.7	3.0	0.2	0.033	23.2	2.8	0.0	0.719	0.153
	II	23.9	3.0			23.2	2.8			
Subscapular skinfold thickness (mm)	I	18.4	7.4	1.8	<0.001	11.9	5.8	-0.1	0.712	<0.001
	II	20.2	7.7			11.8	4.8			
Triceps skinfold thickness (mm)	I	16.2	6.1	0.4	0.299	6.7	3.5	0.3	0.234	0.816
	II	16.6	6.0			7.0	3.2			

I: Pre-menopausal status II: Post-menopausal status

*: Differences in individual changes in the selected variables were tested by paired t-test.

**: Sex differences in individual changes in the selected variables were tested by independent t-test.

a decline in the older ages while men showed a consistent decline (Figure 3). The sex difference in mean body mass index was significant for aged 50 and over.

Mean subscapular skinfold thickness was stable with age for women and declined slightly with age for men. Women showed a consistently higher subscapular skinfold thickness over the age range (Figure 3). A similar pattern on the sex difference was observed in triceps skinfold thickness (not shown in Figure).

Individual changes in cardiovascular risk factors related with menopause, a follow-up study

Table 2 shows changes in mean values of serum total cholesterol, blood pressures, body mass index and skinfold thickness at pre- and postmenopausal status. Mean values of these variables for men matched with age and follow-up year, were also presented.

During the follow-up, women showed a 16 mg/dl increase in mean serum total cholesterol while men showed a 2 mg/dl decline. The sex difference in individual changes in serum total cholesterol was highly significant.

There was a significant increase in systolic and diastolic blood pressure levels for both sexes and the magnitude of the increase in blood pressure levels was similar between women and men. The result was similar when persons with antihypertensive medication use in either at baseline and follow-up examination (n=34 for both men and women) were excluded from the analysis.

Women showed a slight increase in mean body mass index while men did not. Mean value of subscapular skinfold thickness increased for women, but declined for men. The sex difference in individual changes in sub-

capular skinfold thickness was highly significant. Mean value of triceps skinfold thickness did not change significantly in either sex.

DISCUSSION

A substantial increase in serum total cholesterol was seen in women between the ages 40-44 and 50-54 in the cross-sectional study, and a consistent increase was observed between pre- and postmenopausal status in the follow-up study. Because serum total cholesterol did not change in age-matched men, the increase in women is likely due to menopause.

Mechanism for a postmenopausal increase in serum total cholesterol level is not yet established. However, recent in-vivo studies in both animals and humans have shown that the synthesis of LDL-cholesterol receptors decreases after menopause, leading to higher serum LDL-cholesterol concentrations¹⁹.

Our result was consistent with previous reports of cross-sectional and follow-up studies^{13-15,20-30}. The present study indicated that a 16 mg/dl increase in serum total cholesterol was associated with menopause. A similar magnitude of an increase in serum total cholesterol was observed in previous prospective studies: 12 mg/dl in for Caucasians in the Framingham study²⁰ and 16-18 mg/dl for Caucasians in the Goeteborg study²², and 10 mg/dl for Japanese in the Hisayama study¹⁵.

There was a significant increase in subscapular skinfold thickness between pre- and postmenopausal status although an increase in subscapular skinfold thickness with age was not evident in cross-sectional study. On the

other hand, triceps skinfold thickness did not change between pre- and postmenopausal status. Thus, there was a change in fat distribution, i.e. increased central fat distribution associated with menopause. Recent prospective studies indicated the increased risk of coronary heart disease and total mortality with increased central obesity³¹⁻³³.

Mechanisms for the change in fat distribution due to menopause supposed to be as follows. Termination of estrogen secretion from ovaries after menopause results in a decline in blood estrogen concentration³⁴. Blood androgens, especially testosterone level, however, do not decline so much after menopause³⁴. This situation increases androgenic activity relative to estrogenic activity. Because estrogens stimulate production of sex hormone binding globulin in the liver³⁵, sex hormone binding globulin decreases after menopause. The decreased level in sex hormone binding globulin leads to an increased levels of free testosterone in blood, which in turn increases androgenic activity further³⁶. Increased androgenic activity results in an increased activity of adipose tissue lipoprotein lipase, leading to an enlargement of adipocyte size in particular for abdominal adipocytes because the number and/or affinity of testosterone receptors are larger in abdominal adipocytes than adipocytes of other areas^{37,38}.

According to the follow-up in average 4.3 years, an increase in blood pressure levels was observed in women between pre- and postmenopausal status, but a similar increase was also seen in men. The cross-sectional study, however, indicated a slope of systolic blood pressure increase with age between 40 and 69 was steeper in women than in men although the sex difference was not statistically significant. Therefore, it is possible that an effect of menopause on blood pressure levels may appear in older ages such as 65 and over. Nevertheless, the blood pressure increase during the relatively short period of time between pre- and postmenopausal status was likely due to aging but not due to menopause. A study of two Belgian districts³⁹ showed that menopause was accompanied by a steeper rise of systolic blood pressure with age, and by an increase in the absolute level of diastolic blood pressure, which was independent on age. However, the result should be interpreted cautiously because of a cross-sectional design. Two prospective studies, the Framingham study²⁰ and the Goeteborg study²² reported no significant change in blood pressure levels related with menopause like most cross-sectional studies^{13-15,21,24,25,32,33,40-42}.

The increase in serum total cholesterol and the change in body fat distribution related with menopause in rural Japanese women may be associated with the increased risk of coronary heart disease. However, it should be noted that serum total cholesterol level in Japanese women was not so high as Caucasian women^{10,11}. Mean body mass index was much lower in Japanese women than in

Caucasian women¹². Therefore, whether menopause-related risk factor changes would raise the risk of subsequent cardiovascular disease requires further studies.

ACKNOWLEDGMENTS

This study was supported in part by fund of University of Tsukuba Project Research, 1993 and Grant-in-Aid for Scientific Research 06770274 from the Ministry of Education, Science, and Culture, 1994. Authors thank Dr. Saburo Kojima, Mrs. Kishi M, Mrs. Yamazaki T and other staffs of surveys from the Center for Adult Diseases, Osaka and in Ikawa Town.

REFERENCES

1. Radwanska E. The role of reproductive hormones in vascular disease and hypertension. *Steroids*, 1993; 58: 605-610.
2. Gordon T, Kannel WB, Hjortland MC, et al. Menopause and coronary heart disease: The Framingham Study. *Ann Intern Med*, 1978; 89: 157-161.
3. Matthews KA, Meilahn E, Kuller LH, et al. Menopause and risk factors for coronary heart disease. *N Engl J Med*, 1989; 321: 641-646.
4. Weiss NS. Relationship of menopause to serum cholesterol and arterial blood pressure: The United States' Health Examination Survey of adults. *Am J Epidemiol*, 1972; 96: 237-241.
5. Knapp RG, Sutherland SE, Keil JE, Rust PF, Lackland DT. A comparison of the effects of cholesterol on CHD mortality in black and white women: Twenty-eight years of follow-up in the Charleston Heart Study. *J Clin Epidemiol*, 1992; 45: 1119-1129.
6. Peter T, Harper R, Luxton M, et al. Acute myocardial infarction in women. The influence of age on complications and mortality. *Med J Aust*, 1978; 1: 189-191.
7. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: A 26-year follow-up of the Framingham population. *Am Heart J*, 1986; 111: 383-390.
8. Snowdon DA, Kane RL, Lawrence Beeson W, et al. Is early natural menopause a biologic marker of health and aging? *Am J Public Health*, 1989; 79: 709-714.
9. Folsom AR, Kaye SA, Sellers TA, et al. Body fat distribution and 5-year risk of death in older women. *JAMA*, 1993; 269: 483-487.
10. Johnson CL, Riskind BM, Sempos CT, et al. Declining serum total cholesterol levels among US adults: The National Health and Nutrition Examination Surveys. *JAMA*, 1993; 269: 3002-3008.
11. Shimamoto T, Komachi Y, Inada H, et al. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation*, 1989; 79: 503-515.
12. Baba S, Pan WH, Ueshima H, et al. Comparison of blood pressure levels and body mass index in Japanese and US National Surveys. *J Hypertens*, 1986; 4: S24-S26.
13. Shibata H, Matsuzaki T, Hatano S. Relationship of relevant factors of atherosclerosis to menopause in Japanese women. *Am J Epidemiol*, 1979; 109: 420-424.
14. Shibata H, Haga H, Suyama Y, Kumagai S, Seino T. Serum total and HDL cholesterol according to reproductive status in Japanese females. *J Chron Dis*, 1987; 40: 209-213.
15. Fujii I, Ueda K, Yanai T, et al. Changes in various blood

- chemical constituents in relation to menopause. The Hisayama Study. *Jpn J Geriatr*, 1986; 23: 50-58 (in Japanese).
16. Technicon Method No SE4-0026FC4: Cholesterol (direct). Tarrytown, NY. Technicon Instruments Corporation, 1974.
 17. Manual of laboratory operations, Lipid Research Clinics Program: Lipid and lipoprotein analysis. Bethesda, MD, US Department of Health and Welfare Publication, 1974; 1: 75-628.
 18. Nakamura M, Morita M, Yabuuchi E, et al. The evaluation of cholesterol and triglyceride standardization program by WHO-CDC. *Rinsho Byori*, 1982; 30: 325-332 (in Japanese).
 19. Arca M, Vera GL, Grundy SM. Hypercholesterolemia in postmenopausal women. Metabolic defects and response to low-dose Lovastatin. *JAMA*, 1994; 271: 453-459.
 20. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease. *Ann Intern Med*, 1976; 85: 447-452.
 21. Hjortland MC, McNamara PM, Kannel WB. Some atherogenic concomitants of menopause; The Framingham Study. *Am J Epidemiol*, 1976; 103: 304-311.
 22. Lindquist O, Bengtsson C. Serum lipids, arterial blood pressure and body weight in relation to the menopause: results from a population study of women in Goeteborg, Sweden. *Scand J Clin Lab Invest*, 1980; 40: 629-636.
 23. Lindquist O. Intraindividual changes of blood pressure, serum lipids and body weight in relation to menstrual status: results from a prospective population study of women in Goeteborg, Sweden. *Prev Med*, 1982; 11: 162-172.
 24. Baired DD, Tyroler HA, Heiss G, Chambless LE, Hames CG. Menopausal change in serum cholesterol. Black/white differences in Evans County, Georgia. *Am J Epidemiol*, 1985; 122: 982-993.
 25. Wu Z, Wu X, Zhang Y. Relationship of menopausal status and sex hormones to serum lipids and blood pressure. *Int J Epidemiol*, 1990; 19: 297-302.
 26. Bonithon-Kopp C, Scarabin PY, Darne B, Malmejac A, Guize L. Menopause-related changes in lipoproteins and some other cardiovascular risk factors. *Int J Epidemiol*, 1990; 19: 42-48.
 27. Campos H, Wilson PWF, Jimenez D, et al. Differences in apolipoproteins and low-density lipoproteins subfractions in postmenopausal women on and off estrogen therapy: results from the Framingham Offspring Study. *Metabolism*, 1990; 39: 1033-1038.
 28. Demirovic J, Sprafka JM, Folsom AR, Laitinen D, Blackburn H. Menopause and serum cholesterol: Differences between blacks and whites. The Minnesota Heart Study. *Am J Epidemiol*, 1992; 136: 155-164.
 29. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga PL. Weight gain at the time of menopause. *Arch Intern Med*, 1991; 151: 97-102.
 30. Posner BM, Cupples LA, Miller DR, et al. Diet, menopause, and serum cholesterol levels in women: the Framingham Study. *Am Heart J*, 1993; 125: 483-489.
 31. van Beresteijn ECH, Korevaar JC, Huijbregts PCW, et al. Perimenopausal increase in serum cholesterol: a 10-year longitudinal study. *Am J Epidemiol*, 1993; 137: 383-392.
 32. Stern MP, Haffner SM. Body fat distribution and hyperinsulinemia as risk factors for diabetes and cardiovascular disease. *Arteriosclerosis*, 1986; 6: 123-130.
 33. Donahue RP, Abbott RD, Bloom E, Reed DM, Yano K. Central obesity and coronary heart disease in men. *Lancet*, 1987; 8537: 821-824.
 34. Jones HW, Wentz AC, Burnett LS. Novak's textbook of gynecology. 11th ed. Williams & Wilkins, Baltimore, Hong Kong, London, and Sydney, 1988.
 35. Anderson DC. Sex-hormone-binding globulin. *Clin Endocrinol (Oxf)*, 1974; 3: 69-96.
 36. Rosenfield RL. Studies of the relation of plasma androgen levels to androgen action in women. *J Steroid Biochem*, 1975; 6: 695-702.
 37. Evans DJ, Hoffman RG, Kalkhoff RK, Kissebah AH. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. *J Clin Endocrinol Metab*, 1983; 57: 304-310.
 38. Zamboni M, Armwllini F, Milani MP, et al. Body fat distribution in pre- and post-menopausal women: metabolic and anthropometric variables and their inter-relationships. *Int J Obes*, 1992; 16: 495-504.
 39. Staessen J, Bulpitt CJ, Fagard R, Lijnen P, Amery A. The influence of menopause on blood pressure. *J Hum Hypertens*, 1989; 3: 427-433.
 40. Kotchen JM, McKean HE, Kotchen TA. Blood pressure trends with aging. *Hypertension*, 1982; 4 (Suppl 3): 3-128-3-134.
 41. Harlan WR, Hull AL, Schmodder RL, et al. Blood pressure and nutrition in adults: The National Health and Nutrition Examination Survey. *Am J Epidemiol*, 1984; 120: 17-28.
 42. van Beresteijn ECH, van 't Hof MA, de Waard H. Contributions of ovarian failure and aging to blood pressure in normotensive perimenopausal women; A mixed longitudinal study. *Am J Epidemiol*, 1989; 129: 947-955.