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Influence of Menopause on High Density Lipoprotein-Cholesterol and Lipids

It has been generally accepted that high density lipoprotein cholesterol (HDL-C) level decreases with menopause in women. However, recent reports show different results. There is very little data concerning perimenopausal women. To verify these findings, lipids and lipoprotein(a) [Lp(a)] levels were compared among pre-, peri- and postmenopausal women of similar mean ages. Postmenopausal women had higher HDL-C levels than premenopausal women (p<0.001) and there was no difference between peri- and postmenopausal women. LDL-C level in perimenopausal women was lower than in postmenopausal women (p<0.001) and higher than in premenopausal women with borderline significance (p=.051). Total cholesterol levels showed stepwise elevation from premenopause to postmenopause. Perimenopausal women had lower Lp(a) levels than postmenopausal women (p<0.0005) and similar levels to premenopausal women. Lp(a) levels between 0.1 to 10.0 mg/dL were the most prevalent in pre- and perimenopausal women, and those between 10.1 to 20.0 mg/dL in postmenopausal women. In conclusion, menopause itself is associated with the elevation of HDL-C level, and the postmenopausal increase of coronary artery disease is not related to postmenopausal change of HDL-C level. Perimenopausal status, although transient, may favor Lp(a) and lipid profiles for delaying atherosclerosis.

Key Words: *Hormones; Female; Lipoproteins; Lipids; Menopause*

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INTRODUCTION

Cardiovascular morbidity and mortality are very low in premenopausal women compared with men and postmenopausal women of similar ages. Those increase steeply after menopause and no difference is observed in the eighth decade between men and women (1). Estrogen replacement therapy (ERT) in postmenopausal women lowers the incidence of cardiovascular disease mortality (2). Therefore, menopause is thought to be a risk factor for atherosclerosis.

One of the proposed mechanisms for postmenopausal increase of cardiovascular disease is the change in lipid profiles such as increases of low density lipoprotein cholesterol (LDL-C) and lipoprotein(a) [Lp(a)], and decrease of high density lipoprotein cholesterol (HDL-C) concentrations (3-5). However, recent trials have shown different results on the change of HDL-C level after menopause. In the Atherosclerosis Risk in Communities (ARIC) Study (5), HDL-C levels of postmenopausal women aged 45 to 49 were similar to those of premenopausal women with the same age interval. After surgical menopause, HDL-C levels showed a trend for elevation although it was statistically insignificant due to the small number of subjects (6).

HDL-C levels are associated with age. In women, HDL-C levels increase progressively to the sixth decade, and then decrease (5, 7). Therefore, age may influence HDL-C levels, leading to discrepancies among studies.

Many investigators have been interested in the comparisons of lipid levels between pre- and postmenopausal women (3-5). The duration of transitional period between pre- and postmenopause, perimenopause varies. During this period, follicle stimulating hormone (FSH) level is elevated, and estrogen level reveals low normal range. This status is consistent with that of postmenopausal women taking hormone replacement therapy because the dose of estrogen is so low that FSH level is partially suppressed and blood estrogen level reaches low normal range. However, there is little data (8, 9) on lipid changes during perimenopause although it might be sufficient in preventing cardiovascular disease with minimal

complication of female sex hormones.

Lp(a), an atherogenic particle, is closely related to female sex hormones (10-12). The levels are higher in postmenopausal women than in premenopausal women (5) and hormone replacement therapy in postmenopausal women lowers Lp(a) level (13). However, Lp(a) levels in perimenopausal women were not reported.

This study was conducted to clarify Lp(a) and lipid profiles during perimenopausal status and reevaluate HDL-C levels between pre- and postmenopausal women of similar age.

MATERIALS AND METHODS

Study population

A total of 1,679 women who visited the hospital for periodic health examination were enrolled. They were divided into three groups by menstrual status and FSH level; premenopausal (n=485, regular menstruation and/or FSH≤10 mU/L), perimenopausal (n=373, 10<FSH<40 mU/L), and postmenopausal (n=821, amenorrhea over one year without gynecological diseases and/or FSH≥40 mU/L) groups. Mean ages were 47.1±2.6, 47.2±3.1 and 47.2±2.9 years, respectively. Subjects with diseases that influence lipid levels, such as diabetes mellitus, chronic liver disease, infectious diseases or other endocrine diseases, were excluded. None was taking hormonal preparation or hypolipidemic drugs.

Measurement

Concentrations of total cholesterol and triglyceride were determined by enzymatic method using an automatic analyzer (Hitachi7150, Naka, Japan). The concentrations of HDL-C, LDL-C and VLDL-C were determined by electrophoretic methods using an HDL Cholesterol Supply Kit (Helena Laboratory, Beaumont, TX, U.S.A.). The lipoproteins were separated according to their electrophoretic mobility on cellulose acetate in Tris-barbital buffer, pH 8.8 and fractions were visualized with production of quinoneimine by enzymatic method. The relative percentage of each fraction was obtained by scanning in a densitometer equipped with a 500 or 505 nm filter (Helena Laboratory). HDL-C, VLDL-C and LDL-C levels were calculated by multiplying each ratio by the total cholesterol concentration.

The concentration of apolipoprotein(a) [Apo(a)] was determined by 2-site immunoradiometric assay using a commercial radioimmunoassay kit (Pharmacia, Uppsala, Sweden) as previously described (14, 15). In brief, it was based on the direct sandwich technique in which 2 monoclonal antibodies were directed against separate antigenic determinants on the Apo(a) molecule. The approximate concentration of Lp(a) protein was calculated multiplying by a conversion factor of 0.7 proposed by the kit manufacturer. Interassay coefficients of variation were 5.8% and 7.2% for the high (mean 45.7 mg/dL) and low (mean 12.3 mg/dL) controls, respectively. Intraassay coefficient of variation was 2.6%.

FSH level was measured by immunoradiometric assay using a radioimmunoassay kit (Serono Diagnostic, Rome, Italy).

Statistical analysis

Data were expressed as mean±SD. The data were stored on an IBM computer using dBASE III plus (Borland Co, Scotts Valley, CA, U.S.A.). Statistical analysis was performed with the Social Package for Social Science (SPSS Inc., Chicago, IL, USA). To analyze Lp(a), VLDL-C and triglyceride, the Kruskal-Wallis test was used to evaluate the differences among groups, and the Mann-Whitney U test between groups. For other variables, analysis of variance was used to evaluate the differences among groups, and the unpaired t-test between groups. Statistical significance was $p<0.05$.

RESULTS

HDL-C levels were higher in postmenopausal women (1.80±0.44 mM/L) compared with premenopausal women (1.71±0.43 mM/L, $p<0.001$). There was no difference between peri- (1.80±0.46 mM/L) and postmenopausal women ($p=0.98$). Perimenopausal women also had higher levels than premenopausal women ($p<0.005$) (Table 1, Fig. 1). Perimenopausal women (2.98±0.67 mM/L) had lower LDL-C levels than postmenopausal women (3.17±0.70 mM/L, $p<0.001$) and higher levels than premenopausal women (2.89±0.65 mM/L) with borderline significance ($p=0.051$) (Table 1, Fig. 1).

Total cholesterol level showed the stepwise increases from premenopausal to postmenopausal women. Postmenopausal women (5.33±0.89 mM/L) had higher total cholesterol levels than perimenopausal women (5.13±0.95 mM/L, $p=0.001$), who had higher levels than premenopausal women (4.88±0.87 mM/L, $p<0.001$). Triglyceride revealed similar changes with HDL-C. Premenopausal women (1.15±0.69 mM/L) had lower levels than peri- (1.33±0.91 mM/L, $p<0.0005$) and postmenopausal women (1.34±0.78 mM/L, $p<0.0001$), both of whom had similar levels ($p=0.89$) (Table 1, Fig. 1).

Perimenopausal women (21.3±20.7 mg/dL) had lower Lp(a) levels than postmenopausal women (24.6±21.9

Table 1. Lipoprotein(a), lipid profiles, and biochemical parameters in pre-, peri-, and postmenopausal women

	Premenopausal (n=485)	Perimenopausal (n=373)	Postmenopausal (n=821)	ANOVA *p* value
Age (years)	47.1±2.6	47.2±3.1	47.2±2.9	0.91
BMI (Kg/m^2)	2.38±0.26	2.38±0.28	2.34±0.27‡,¶	0.07
Cholesterol (mmol/L)	4.88±0.87	5.13±0.95*	5.33±0.89*$^{,\parallel}$	0.000
(mg/dL)	(190.0±33.9)	(199.7±37.1)	(207.4±34.7)	
HDL-C (mmol/L)	1.71±0.43	1.80±0.46†	1.80±0.44*	0.002
(mg/dL)	(66.5±16.8)	(70.1±17.8)	(70.0±17.3)	
LDL-C (mmol/L)	2.89±0.65	2.98±0.67	3.17±0.70*,§	0.000
(mg/dL)	(112.5±25.4)	(116.0±26.1)	(123.6±27.2)	
VLDL-C (mmol/L)	0.28±0.22	0.35±0.34†	0.35±0.29*	0.0000
(mg/dL)	(10.9±8.5)	(13.5±13.3)	(13.7±11.3)	
Triglyceride (mmol/L)	1.15±0.69	1.33±0.91*	1.34±0.78*	0.0000
(mg/dL)	(102.0±60.7)	(117.7±80.2)	(118.3±69.1)	
Lipoprotein(a) (mg/dL)	20.2±16.7	21.3±20.7	24.6±21.9*,§	0.0001

BMI; body mass index, HDL-C; high density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, VLDL-C; very low density lipoprotein cholesterol
*p<0.001, $^{\dagger}p$<0.005, $^{\ddagger}p$<0.05 compared with premenopausal women
$^{\S}p$<0.001, $^{\parallel}p$<0.005, $^{\P}p$<0.05 compared with perimenopausal women

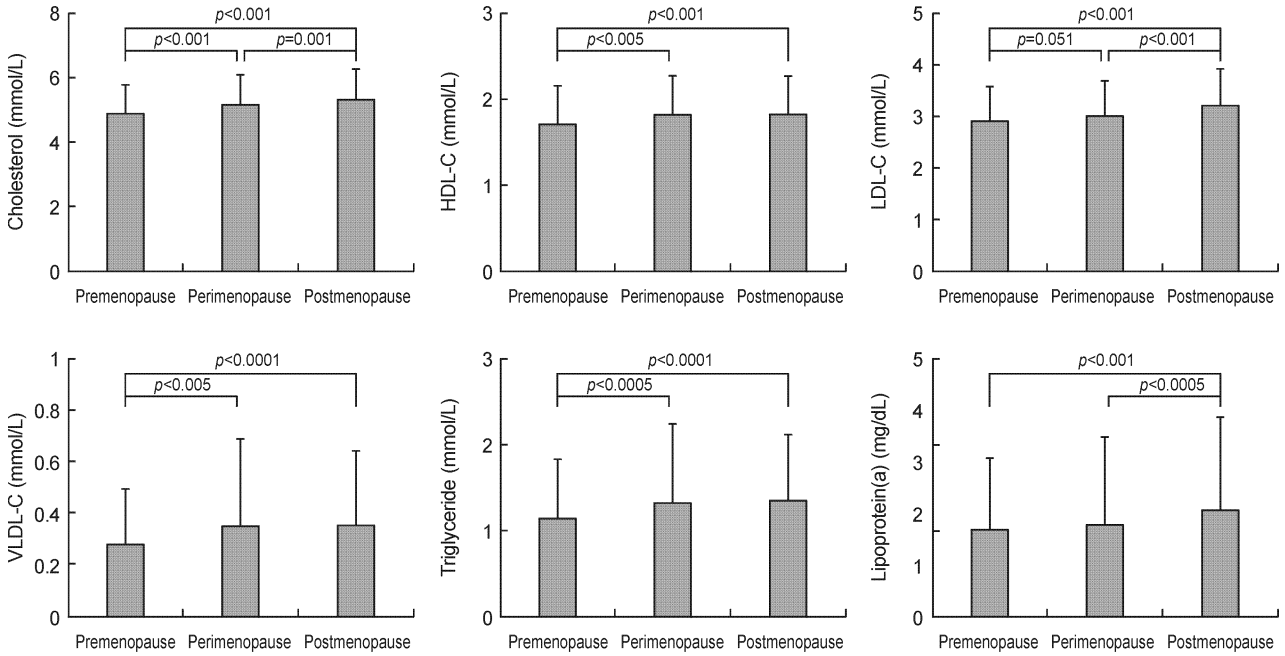

Fig. 1. Comparison of lipid and lipoprotein levels among pre-, peri-, and postmenopausal women. HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol.

mg/dL, p<0.0005) and similar levels with premenopausal (20.2±16.7 mg/dL, p=0.39) women (Table 1, Fig. 1). Lp(a) levels were higher in postmenopausal women than in premenopausal women (p<0.001). Lp(a) levels between 0.1 to 10.0 mg/dL were the most prevalent in pre- and perimenopausal women, and those between 10.1 to 20.0 mg/dL and between 20.1 to 30 mg/dL followed. In postmenopausal women, the levels between 10.1 to 20.0 mg/dL were the most frequent (Fig. 2).

Body mass index was higher in pre- (23.8±2.6 kg/m^2, p<0.05) and perimenopausal women (23.8±2.8 kg/m^2, p=0.01) than in postmenopausal women (23.4±2.7 kg/m^2).

DISCUSSION

This cross-sectional study showed that menopause

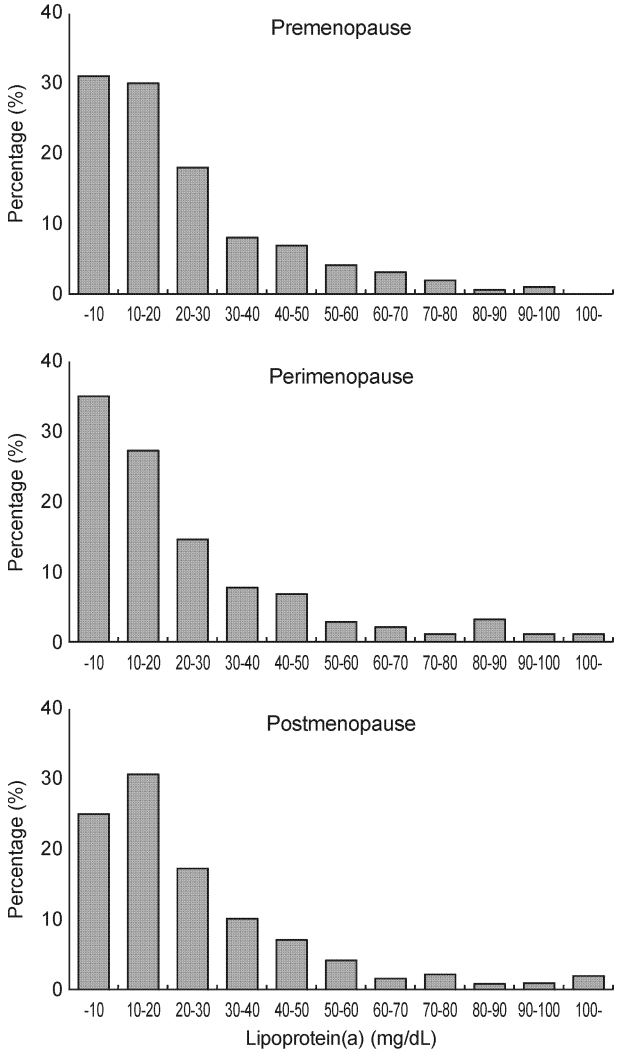

Fig. 2. Percentage distribution of lipoprotein(a) levels in pre-, peri, and postmenopausal women.

itself is associated with increase of HDL-C level and that perimenopausal status is unique in favoring Lp(a) and lipid profiles for delaying atherosclerosis.

The incidence of cardiovascular disease of premenopausal women in the fifth decade is only one-tenth of men and one-third of postmenopausal women of a similar age. After menopause the incidence increases steeply and no difference is observed in the eighth decade between men and women (1). ERT in postmenopausal women reduced mortality by coronary artery disease by 30-70% in most but not all case-control and cohort studies (2) although these investigations were not randomized trials. Therefore, menopause, loss of female sex hormone, is thought to be a risk factor for atherosclerosis. The proposed mechanisms for this phenomenon are change of lipid profiles, such as increase of LDL-C and Lp(a) and decrease of HDL-C, impairment of vasomotor tone, alterations of thrombotic or thrombolytic system and others (3-5, 16).

It has been generally accepted without direct evidence that menopause decreases HDL-C level. There has been indirect evidence supporting this hypothesis. First, several (3, 17) but not all cross-sectional (1, 5) and prospective longitudinal studies (18) showed that postmenopausal women had lower HDL-C levels than premenopausal women. This difference was significant after adjusting for age (3). Second, ERT in postmenopausal women increased HDL-C level (15, 19, 20). However, we think that these evidences do not indicate that HDL-C level is lowered after menopause.

In previous cross-sectional studies, postmenopausal women were older than premenopausal women (3, 17). HDL-C levels increase progressively with age to the sixth decade and then decrease in women (5, 7). In PEPI trial (21), HDL-C levels decreased by 1.9% after 3 year follow-up in postmenopausal women taking placebo. Therefore, low HDL level in postmenopausal women might not result from the loss of female sex hormone, but from the aging process. Age-adjustment is also invalid because HDL-C levels in middle aged women initially increase and then decrease with aging. To rule out the effect of age, we sampled three groups with similar mean ages and showed that menopause itself does not reduce HDL-C level.

Several reports that considered the age of subjects showed similar or even higher HDL-C levels in postmenopausal women compared with premenopausal women. In the ARIC Study (5) and Framingham Study (1), significant differences of HDL-C levels were not observed between pre- and postmenopausal women in fixed age intervals. However, in each age interval, the distribution of age might be right-skewed in premenopausal women and left-skewed in postmenopausal women, resulting in higher mean age in postmenopausal women than in premenopausal women. If this difference is corrected, postmenopausal women might have higher HDL-C levels than premenopausal women. In another study (9), HDL-C levels were higher in older postmenopausal women than in younger premenopausal women, although the authors did not emphasize this finding.

Prospective studies, observing lipid profiles after surgical menopause, showed that HDL-C levels were not changed (22) or elevated (23). In the previous study by the authors (6), HDL-C levels showed a trend for elevation after surgical menopause although it was not statistically significant due to the small number of cases. Longitudinal studies, observing the serial changes of lipid profiles from premenopause to natural menopause, showed inconsistent results on HDL-C levels (8, 18, 24).

Therefore, menopause itself is not associated with the reduction of HDL-C level. Low HDL-C levels in post-

menopausal women in most previous reports may not be due to menopause, but due to weight gain, lack of activity, reduced alcohol intake and associated metabolic diseases in old women.

The elevation of HDL-C with ERT in postmenopausal women cannot be a basis for the hypothesis that menopause decreases HDL-C levels. In cross-sectional studies, postmenopausal women taking estrogen had higher HDL-C levels than postmenopausal women not taking estrogen and also premenopausal women (5, 18). Similarly, the previous study by the authors (6) mentioned above showed that with ERT, HDL-C levels further increased and were significantly higher than preoperative premenopausal levels. Therefore, the elevation of HDL-C level with ERT is not a return to premenopausal status but the therapeutic effect of estrogen.

The differences of LDL-C and Lp(a) levels between pre- and postmenopausal women are consistent with previous reports (3-5).

Many studies have compared Lp(a) and lipid levels between premenopausal and postmenopausal women (3-5). The duration of transitional period between pre- and postmenopause, perimenopause varies. However, only a few reports (8, 9) investigated the perimenopausal status because it seems to be only a transitional period between pre- and postmenopausal status without clinical significance. During perimenopausal period, FSH level is elevated and estrogen level is in the low normal range. These values are similar to those of postmenopausal women taking hormone replacement therapy (20).

A high Lp(a) concentration had been thought to be an independent risk factor for coronary artery disease (10-12) and cerebrovascular disease (25, 26). Now, there are controversies because recent trials showed inconsistent results (27). High Lp(a) levels cannot be lowered by general measures and hypolipidemic agents (28, 29) except for nicotinic acid (30). Lp(a) levels are closely correlated with female sex hormones. Postmenopausal women had higher Lp(a) levels than premenopausal women (5). Natural or surgical menopause is associated with increase of Lp(a) levels (6,31). Hormone replacement therapy in postmenopausal women reduces Lp(a) level (6, 13). However, there have been no reports on Lp(a) during perimenopausal period. Therefore, we compared Lp(a) and lipid profiles in perimenopausal women with those in pre- and postmenopausal women.

In this study, perimenopausal women have lower LDL-C and Lp(a) levels than postmenopausal women and similar levels with premenopausal women. In addition, perimenopausal women have higher HDL-C levels than premenopausal women. Considering only Lp(a) and lipid profiles, perimenopausal status may be more protective than premenopausal status for atherosclerotic diseases.

As a result of the differences of these subfractions, total cholesterol increased stepwise from premenopausal to postmenopausal women. In contrast to the differences of cholesterol, triglyceride levels were higher in perimenopausal women than in premenopausal women. However, this finding may not indicate an atherogenic tendency for perimenopausal status because perimenopausal women have higher HDL-C level than premenopausal women and the role of high triglyceride level in atherosclerosis is controversial, especially in subjects with high HDL-C levels (32).

There are several limitations to this study. To make mean ages similar among three groups, the premenopausal group contained more premenopausal women continuing menstruation until old age and postmenopausal group contained more women with premature menopause compared with the general population. However, we think this may not influence the results of this study. As indirect evidence, there were no significant differences in HDL-C levels between younger and older halves in both pre- and postmenopausal women (data not shown). Because the definition of perimenopause is ambiguous, we defined perimenopausal women by FSH levels. If other criteria of perimenopause are used, the results may be different from our observations.

Several factors including diet, exercise, smoking, alcohol, and medications influence HDL-C level. In this study, the subjects taking cholesterol lowering drug and female hormonal preparation were excluded and other factors were not examined. The well-designed study will be needed to confirm the result.

HDL-C concentrations measured by the electrophoretic method show higher values than those measured by precipitation methods (33). Therefore, HDL-C levels were higher in this study than in most other studies. To verify electrophoretic method, we compared the electrophoretic method with precipitation methods, using heparin-manganese ($r=0.80$) and phosphotungstate-magnesium ($r=0.92$). Mean HDL-C levels measured by the electrophoretic method were higher by 13.7% and 23.6% than those of precipitation methods, respectively.

In summary, menopause is associated with the elevation of HDL-C levels and the concept concerning the relationship between HDL-C and menopause must change. Postmenopausal increase of coronary artery disease may not be related directly to postmenopausal HDL-C changes. Perimenopause is a transient but unique status. Perimenopausal women have Lp(a) and lipid levels that may favor delaying atherosclerosis than those of premenopausal women. We think that further intensive studies must be done on this characteristic status not only in the fields of lipids but also in those of other phenomena including vasoreactivity and others.

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