

# Correlation Pattern of Serum Lipid Parameters and a Biological Anti-Oxidant Potential Between Premenopausal and Perimenopausal Healthy Women

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## Abstract

**Objectives.** Improved understanding of the associations among cardiometabolic, antioxidative, and menopausal status is crucial to prevent cardiovascular disease (CVD). For preventing the development of CVD in women, the association of serum lipid profile and antioxidant parameters during menopausal transition is of interest. The aim of the study is to evaluate the correlation between lipid and antioxidant levels especially in premenopausal and perimenopausal women.

**Methods.** A total of 130 CVD-free healthy women; the premenopausal group (n = 51, mean 41 years) and perimenopausal group (n = 79, mean 49 years) were studied. A biological antioxidant potential (BAP) test was utilized for measuring antioxidant levels. The association between lipid and BAP levels was examined by linear correlation analyses.

**Results.** The perimenopausal group showed a significantly higher low-density lipoprotein cholesterol (LDL-C) level than the premenopausal group (mean 123 vs. 111 mg/dL,  $p < 0.05$ ), while there were no significant differences in triglyceride, high-density lipoprotein cholesterol and BAP levels between the groups. A significant inverse correlation existed between LDL-C and BAP levels in the perimenopausal group ( $\beta = -0.30$ ,  $p < 0.05$ ), but not in the premenopausal group.

**Conclusions.** The correlation patterns between lipid parameters and antioxidant levels demarcated the premenopausal from perimenopausal stage. Increased LDL-C associated with decreased antioxidant levels in perimenopausal women may call early attention for cardiovascular health.

Key words: antioxidants, estrogen, FSH, LDL cholesterol, perimenopause

## Introduction

A cardiovascular disease (CVD) risk in premenopausal women was well documented to be lower than postmenopausal women [1]. One possible explanation for it is due to the sex hormonal changes during menopausal transition [2], and another is due to the alteration of serum lipid profile, for instance an increase of low-density lipoprotein (LDL) cholesterol (LDL-C) [3-5]. Acceleration of atherogenic lipid

profile is currently recognized among postmenopausal women, and so in preventing CVD, there is an increasing importance on understanding the characteristics of lipid profile especially at earlier stages of menopausal transition such as perimenopause [4]. Little information is, however, available about the characteristics especially in perimenopausal women. In particular, antioxidant

conditions were not sufficiently mentioned as a part of the pathophysiology of CVD development in perimenopausal women [5].

In general, antioxidant conditions are known to be associated with the CVD development [6] and positively associated with symptoms and clinical manifestations related to menopause [7]. Recently, a biological antioxidant potential (BAP) test has been used as an easy handling and reliable assay in the clinical setting to measure total antioxidant capacity, which can identify the ability to reduce ferric ions to ferrous ions [8, 9]. The BAP test are widely recognized and used in clinical studies just as the ferric-reducing ability plasma assay [9] and the test is used to study oxidative stress-related diseases [10]. Given an importance to discuss the association between blood lipid profile and BAP levels besides generic CVD-related parameters during menopausal transition for preventing CVD development, the present study aimed to investigate their correlation patterns between premenopausal and perimenopausal healthy women.

## Methods

### Studied subjects

A total of 130 Japanese women, who were diagnosed in the premenopausal group ( $n = 51$ , mean 41 years) and in perimenopausal group ( $n = 79$ , mean 49 years) were enrolled in this study. The study was approved by the institutional ethics committee and informed consent was obtained from all subjects. Subjects were recruited from women who were visiting our clinic for general medical examinations. Eligible subjects were healthy with no history of CVD, acute infectious disease, or severe liver/kidney disease, and were non-smokers, who were not taking medications including antioxidant supplements. Body mass index (BMI), mean blood pressure (MBP) and blood parameters were measured during a fasting period. Blood was sampled from premenopausal women during the follicular phase.

For a precise determination of menopausal status, subjects were diagnosed into premenopausal and perimenopausal groups based on the classification of the Stages of Reproductive Aging Workshop (STRAW) [11]. According to the classification, the premenopausal group corresponded to the reproductive stage (Stage -3), and the perimenopausal group corresponded to the early and late menopausal transition stage (Stage -2 to -1).

### Blood parameters

The serum levels of LDL-C, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C),

estradiol ( $E_2$ ) and follicle-stimulating hormone (FSH) were measured with standard methods. Hemoglobin A1c (HbA1c) level was measured with a high-performance liquid chromatographic method. These analyses were supplied in a single laboratory facility certified in Japanese laboratory system (Mitsubishi BCL Laboratory Co. Ltd., Tokyo, Japan). The BAP tests were implemented by the Free Radical Analytical System (Diacron, Grosseto, Italy) according to the analytical manual. In brief, a 20  $\mu$ L of blood sample was dissolved in a colored solution obtained by mixing a source of ferric ions ( $FeCl_3$ , ferric chloride) with a chromogenic substrate (a sulphur-derived compound). After a 5-minute incubation, the intensity of the discolored change was assessed by a photometer, and the amount of reduced ferric ions calculated. The BAP unit was expressed as mol/L of reduced Fe/L.

### Statistical analyses

The difference between the groups was examined by student t-test. A simple correlation between outcome (lipid parameters) and other variables was examined by a Pearson's correlation test, and subsequently, a stepwise multiple regression analysis was performed in order to extract the variables correlated with outcome variables (lipid parameters). The data of TG,  $E_2$  and FSH were log-transformed for these analyses because of their skewed distributions. A  $p$ -value  $< 0.05$  was considered significant.

## Results

As listed in **Table 1**, the perimenopausal group showed a significantly higher level of age, MBP, LDL-C, HbA1c and FSH, as well as a significantly lower level of  $E_2$ , than the premenopausal group. There were no significant differences in TG, HDL-C and the BAP levels between the groups.

As listed in **Table 2**, simple correlation tests and stepwise multiple-regression analyses revealed a significant positive correlation between LDL-C and TG or HbA1c levels in the perimenopause group. Furthermore, there found to be a significant inverse correlation between LDL-C and BAP levels in the perimenopause group. Any relative significant correlations of LDL-C with other parameters were not observed in the premenopause group.

Similar analyses revealed a significant positive correlation between TG and LDL-C, as well as a significant inverse correlation between TG and HDL-C levels in the perimenopause group. Any relative significant correlations of TG with other parameters were not observed in the premenopause group.

Similar analyses revealed a significant positive correlation between HDL-C and FSH, as well as a significant inverse correlation between HDL-C and BMI or TG levels in the perimenopause group. Any relative significant correlations of HDL-C with other parameters were not observed in the premenopause group.

## Discussion

The present study investigated the association of serum lipid parameters with the BAP, besides generic CVD-related parameters, in premenopausal and perimenopausal healthy women. While most correlations between lipid parameters and generic CVD-related parameters were as expected, the significant inverse correlation pattern between LDL-C and BAP levels was found in perimenopausal women, but not in premenopausal women. This seems to demarcate a potential antioxidant linkage with the CVD development between the premenopausal and perimenopausal stage.

A high blood cholesterol, especially LDL-C, concentration is a CVD risk [2]. The incident CVD after menopause can be partly induced by changes in the blood lipid levels that occur following menopausal transition [12]. In the present study, of note, an inverse correlation between LDL-C and BAP levels was found only in the perimenopausal stage. While the increased trend of LDL-C with menopausal

transition was also observed in the present study, this appears to be consistent with the result that such an increase level of LDL-C is significantly associated with damage to antioxidant molecules [13]. Even though the LDL-C level was not so high in perimenopausal women of the present study, speculatively, LDL-C and/or LDL particle might be oxidatively modified under the perimenopausal state [12]. Importantly, the present study finding may also provide a proper timing for the management of LDL-C levels in women [14].

**Table 1.** Subject characteristics

Parameter	Premenopausal group (n = 51)	Perimenopausal group (n = 79)	P
Age, years	41 ± 6	49 ± 3	< 0.01**
BMI, kg/m <sup>2</sup>	20.9 ± 2.8	21.1 ± 3.2	0.74
MBP, mmHg	89 ± 12	95 ± 15	< 0.01**
LDL-C, mg/dL	111 ± 32	123 ± 32	0.04*
TG, mg/dL	79 (58-106)	85 (62-123)	0.19
HDL-C, mg/dL	71 ± 15	73 ± 12	0.52
HbA1c, %	5.2 ± 0.3	5.3 ± 0.3	0.02*
BAP, μM	1995 ± 238	2026 ± 198	0.43
Estradiol, pg/mL	78 (50-128)	43 (15-97)	< 0.01**
FSH, mIU/mL	5.6 (3.3-8.9)	30.0 (9.5-70.3)	< 0.01**

BMI: body mass index, MBP: mean blood pressure, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, HbA1c: hemoglobin A1c, BAP: biological anti-oxidant potential, FSH: follicular stimulating hormone.

Statistical significance (t-test): P < 0.05. Data are the mean ± standard deviation or the median (inter-quartile range).

**Table 2.** Correlations between lipid and other parameters

Parameter	LDL-cholesterol				Triglyceride				HDL-cholesterol			
	Premenopausal group		Perimenopausal group		Premenopausal group		Perimenopausal group		Premenopausal group		Perimenopausal group	
	r (P)	β (P)	r (P)	β (P)	r (P)	β (P)	r (P)	β (P)	r (P)	β (P)	r (P)	β (P)
Age, years	0.28 (0.05)	0.26 (0.06)	0.07 (0.54)	NE	0.25 (0.08)	0.19 (0.20)	0.06 (0.60)	NE	-0.05 (0.75)	NE	0.05 (0.64)	0.10 (0.30)
BMI, kg/m <sup>2</sup>	-0.01 (0.98)	NE	0.14 (0.22)	NE	0.16 (0.26)	NE	0.05 (0.66)	NE	-0.30 (0.04*)	-0.23 (0.10)	-0.43 (< 0.01**)	-0.39 (< 0.01**)
MBP, mmHg	-0.06 (0.68)	NE	0.10 (0.39)	NE	0.07 (0.63)	NE	0.10 (0.39)	NE	-0.11 (0.46)	NE	-0.09 (0.48)	NE
LDL-C, mg/dL	-	-	-	-	0.20 (0.16)	0.19 (0.19)	0.43 (< 0.01**)	0.36 (< 0.01**)	0.19 (0.18)	0.23 (0.10)	-0.09 (0.44)	NE
TG, mg/dL	0.20 (0.16)	NE	0.43 (< 0.01**)	0.27 (< 0.01**)	-	-	-	-	-0.20 (0.16)	-0.18 (0.19)	-0.23 (0.04*)	-0.25 (0.02*)
HDL-C, mg/dL	0.19 (0.18)	NE	-0.09 (0.44)	NE	-0.20 (0.16)	-0.23 (0.11)	-0.23 (0.04*)	-0.23 (0.03*)	-	-	-	-
HbA1c, %	0.20 (0.16)	0.18 (0.19)	0.48 (< 0.01**)	0.38 (< 0.01**)	0.04 (0.81)	NE	0.20 (0.09)	NE	0.08 (0.50)	NE	0.08 (0.50)	0.12 (0.23)
BAP, μM	-0.19 (0.19)	NE	-0.36 (< 0.01**)	-0.30 (< 0.01**)	-0.18 (0.20)	NE	-0.21 (0.06)	NE	-0.15 (0.30)	NE	0.24 (0.03*)	0.12 (0.24)
Estradiol, pg/mL	-0.01 (0.92)	NE	-0.31 (< 0.01**)	NE	0.14 (0.30)	NE	-0.25 (0.03*)	-0.18 (0.11)	-0.25 (0.08)	-0.17 (0.23)	-0.17 (0.14)	NE
FSH, mIU/mL	-0.03 (0.86)	NE	0.22 (0.05)	0.14 (0.13)	-0.14 (0.32)	NE	0.16 (0.16)	NE	0.11 (0.45)	NE	0.31 (< 0.01**)	0.23 (0.03*)

NE: not extracted, BMI: body mass index, MBP: mean blood pressure, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, HbA1c: hemoglobin A1c, BAP: biological anti-oxidant potential, FSH: follicular stimulating hormone.

Statistical significance: p < 0.05. Data are r-coefficients (by a Pearson's correlation test) and β-coefficients (by a stepwise multiple regression analysis). Triglyceride, estradiol, and FSH levels were log-transformed in these analyses because of their skewed distributions.

An increase of LDL-C can be caused by not only a simple biological aging but an alteration of sex hormones with menopausal transition [12], and the change in sex hormones is assumed to affect the correlation between LDL-C and BAP levels. A reduction of LDL-C was, indeed, documented in subjects with hormone replacement therapy using exogenous estrogens [15]. In the present study,  $E_2$  was not significantly extracted as an independent parameter of LDL-C. This might be partially due to a significant but small increase of LDL-C in perimenopausal women relative to that in premenopausal women in the present study.

A decrease of antioxidative conditions can also stem from an alteration of sex hormones during menopausal transition, and blood antioxidant capacity and antioxidant enzyme expression at a gene level were documented to positively correlate with  $E_2$  levels [16-18]. On the other hand, the association between (anti)oxidative stress-related markers and sex hormones has been still controversially reported; that is, urinary isoprostane excretion was not correlated with endogenous estrogen levels in perimenopausal women [19] or total antioxidant ability was not correlated with  $E_2$  levels during menopausal transition [20]. In the present study, expectedly, perimenopausal women exhibited a lower level of  $E_2$  than premenopausal women, while BAP levels were not significantly correlated with  $E_2$  both in premenopausal and perimenopausal women. Our present results were likely to coincide with the later studies [19, 20]. The discrepant results might be due to the difference in (anti)oxidative stress-related marker types measured across studies (the BAP test reflects a global antioxidative condition [8, 9] and there are currently few studies using this test). There is also a thought that the blood  $E_2$  level is much lower than the necessary concentration of chemical antioxidants [21]. Thus, the relationship between the antioxidant system and  $E_2$  levels has to be more investigated in humans.

The beneficial effect of hormone replacement therapy on the CVD development in earlier stages of menopausal transition was reported [22, 23]; however, there is currently no full explanation and a long-term debate about the benefit and risk for CVD by hormone replacement therapy [24, 25]. Although our present study showed no apparent significant correlation between  $E_2$  and LDL-C or BAP levels, further investigations on changes in various biochemical factors, including lipids and (anti)oxidative stress-related markers, by hormone replacement therapy may provide relevant consideration of the therapeutic effect on the CVD development.

The present study had several limitations. The sample size was relatively small, the study design was cross-sectional, and CVD outcomes were not evaluated. While a single anti-oxidant biomarker was used in the present study, comparative studies using the other anti-oxidant biomarkers would be interesting. A prospective study in a larger population with long-term follow-up periods and/or intervention trial with various anti-oxidant biomarkers and antioxidants would be necessary to confirm the results of the present study.

In conclusion, the present study investigated the association of serum lipid parameters with the BAP level between premenopausal and perimenopausal healthy women. There was an increase of LDL-C associated with antioxidant conditions in perimenopausal women, and this might present us to require early attention for the management of cardiovascular health from this stage.

## Competing Interests

The authors have declared that no competing interest exists.

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