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Correlations between the Fatty Acid Composition of Serum Phospholipids and Blood Pressure

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ABSTRACT

Studies of the relationship between the composition of serum fatty acids and blood pressure are complex and controversial. Fatty acids, important constituents of biological membranes, could potentially affect vasoreactivities including blood pressure. In this study the compositions of fatty acids in serum phospholipids were compared between three types of hypertensive subjects (men, pre-menopausal women, and post-menopausal women) and their respective normotensive controls. Serum lipids were extracted and phospholipids were separated by thin layer chromatography. The percentage of palmitic acid (16 : 0) in serum phospholipids was significantly higher and the percentage of stearic acid (18 : 0) was significantly lower in all three hypertensive groups, compared with their corresponding control groups. Only in the group of post-menopausal women, palmitic acid was closely associated with increases in both systolic (SBP) and diastolic blood pressure (DBP), while stearic acid was associated with decreases in both SBP and DBP. The polyunsaturated fatty acids in serum phospholipids behaved differently from saturated fatty acids. The ratios of products / precursor fatty acids, such as ΣLCPUFAω6/18 : 2ω6, 20 : 4ω6/18 : 2ω6, ΣLCPUFAω3/18 : 3ω3 and 22 : 6ω3/20 : 5ω3, were all clearly associated with both SBP and DBP in hypertensive, post-menopausal women. Desaturation and elongation in fatty acid metabolism could affect the bioavailability of eicosanoid precursors. Changes in the constituent fatty acids of phospholipids and eicosanoid precursors may also influence fluidity, ionic transport, hormone receptors and enzyme activities in biological membranes. In conclusion, both systolic and diastolic blood pressure in post-menopausal women was positively associated with the level of palmitic acid, and negatively associated with the level of stearic acid, in serum phospholipids. The relationships between serum phospholipid-ω6 and ω3 series fatty acids and blood pressure in women, especially in post-menopausal women, require further investigation by taking into consideration hormonal status and eicosanoid metabolism. Further study is needed to determine the value of dietary manipulation of fatty acid constituents of serum phospholipids, relating to hypertension in women.

KEY WORDS: serum phospholipid-fatty acids, menopause, essential hypertension.

INTRODUCTION

The relationships between serum fatty acids or serum phospholipid-fatty acids and blood pressure have been studied, and still remain as a complex and enigmatic issue.[1-7] Fatty acids are important constituents of cell membranes and have crucial effects on membrane permeability, fluidity and binding activities of receptors; all of these elements are important in maintaining normal blood pressure in human bodies.[8-11] It has been proposed that the types of fatty acids available for eicosanoid synthesis may potentially have an impact on the complex balance between the prostacyclins and thromboxanes which influence vasoreactivities.[8)12-16] Among the saturated fatty acids, it was found that palmitic acid (16 : 0) was positively,[1)8] and stearic acid (18 : 0) was negatively, associated with blood pressure.[3] More complicated results have been reported with polyunsaturated fatty acids. The precursor polyunsaturated fatty acids such as linoleic acid (18 : 2ω6) and a-linolenic acid (18 : 3ω3) often behave differently from the product polyunsaturated fatty acids such as arachidonic acid (20 : 4ω6), eicosapentaenoic acid (20 : 5ω3) and docosahexaenoic acid (22 : 6ω3).[1)3)7)8] Due to differences in genetic factors, the varieties in dietary patterns, and other confounding factors such as body mass index (BMI), smoking and hormonal status, it is a complex matter to find a concrete association between serum fatty acids and blood pressure in the general population.[17] In this study the compositions of fatty acids in serum phospholipids were investigated in men, and in pre-menopausal and post-menopausal women. In addition, the ratios of product and precursor polyunsaturated fatty acids were compared.

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METHODS AND MATERIALS

1 Subjects

Forty one men and fifty seven women who visited the Cardiovascular Center at Severance Hospital, Yonsei University, Seoul, Korea, participated in this study between January and December 1996. Subjects consisted of normotensive controls (25 men, 14 pre-menopausal women, and 11 post-menopausal women) and hypertensive patients (16 men, 19 pre-menopausal women, and 13 post-menopausal women). Patients were excluded from this study if they were suffering from chronic diseases or taking steroids, nonsteroidal anti-inflammatory drugs, antiplatelet agents, lipid-lowering drugs or contraceptive pills. Essential hypertensive patients were defined as those without any previous treatments who had a systolic blood pressure (SBP) greater than 140 mmHg or a diastolic blood pressure (DBP) greater than 90 mmHg. Healthy subjects without any clinical history of heart disease, diabetes mellitus or hypertension were selected as the normotensive control groups. This study was approved by the Medical Ethics Committee of the College of Medicine, Yonsei University, and all subjects were outpatients who gave their written informed consent to participate.

2. Fatty acid analysis

Lipids were extracted from two hundred ml of each serum sample by the Folch method,[18] and phospholipids were separated from the extracted lipids by thin layer chromatography (TLC). The phospholipid portion was scraped off immediately after the TLC procedure and was methylated, using the method of Lepage and Roy.[19] The methylated fatty acid esters were quantified by gas chromatography (GC), using Hewlett Packard 6890A equipment. For the GC separation, a bonded fused-silica capillary column (OmegawaxTM 250) was used. The GC oven temperature was held at 180℃ for 5 minutes and was increased to 210℃ in 2℃/min increments. The temperature of the injection and detector ports was maintained at 280℃. Helium was used as a carrier gas at a flow rate of 0.8 ml/min and with a split ratio of 10 : 1. Methyl esters of the various fatty acids were identified by comparing their retention times with those of the standards supplied by Sigma Chemical of the U.S. The peaks of the standard fatty acid fractions were quantified using a Hewlett Packard 3365A series III Chemstation integrator.

3. Statistical analysis

The results were analyzed using the Strategic Application Software (SAS) package, version 6.12. The subjects were divided into three groups: men, pre-menopausal women, and post-menopausal women. In all three groups, the fatty acid composition of serum phospholipids was expressed as mean percentages and SEM. Differences in percentages of specific fatty acids between the hypertensive and the control groups were compared by the Student's *t*-test. Correlation coefficients were calculated for the relationships between serum phospholipid-fatty acids and blood pressure levels, using Pearson's correlation.

RESULTS

1. General characteristics of the subjects

Table 1 shows the general characteristics of the subjects studied. Mean ages of the hypertensive subjects were similar to those of the controls in all three groups. Mean systolic blood pressures of the control and hypertensive subjects were: 119.2 mmHg vs 154.4 mmHg for men, 114.3 vs 156.2 for pre-menopausal women, and 116.0 vs 154.3 for post-menopausal women, respectively. Mean Diastolic blood pressures of the control and the hy-

Table 1. General characteristics of subjects

	Men		Pre-menopausal women		Post-menopausal women	
	Control (n = 25)	Hypertension (n = 16)	Control (n = 14)	Hypertension (n = 19)	Control (n = 11)	Hypertension (n = 13)
Age (year)	39.1 ± 1.57	41.7 ± 0.97	39.7 ± 1.03	40.4 ± 1.47	53.3 ± 0.82	55.0 ± 0.72
Body mass index (kg/m^2)	25.2 ± 0.32	24.8 ± 0.41	23.8 ± 0.31	23.6 ± 0.61	25.2 ± 0.43	24.2 ± 0.46
Fasting blood glucose (mg/dl)	86.1 ± 2.34	83.2 ± 1.71	84.0 ± 0.97	81.1 ± 3.12	85.6 ± 2.12	82.4 ± 2.33
Total cholesterol (mg/dl)	184.1 ± 2.31	181.6 ± 4.50	172.4 ± 1.28	179.9 ± 4.92	188.5 ± 3.22	188.1 ± 4.00
HDL-cholesterol (mg/dl)	38.2 ± 0.97	39.9 ± 1.49	44.3 ± 0.87	45.8 ± 2.77	47.3 ± 1.39	44.3 ± 1.81
LDL-cholesterol (mg/dl)	111.3 ± 2.87	110.5 ± 4.04	109.2 ± 2.76	111.4 ± 5.00	119.1 ± 2.97	116.1 ± 4.35
Triglyceride (mg/dl)	151.0 ± 11.34	155.4 ± 10.51	111.2 ± 4.88	113.5 ± 10.48	147.1 ± 10.52	138.5 ± 13.68
Systolic blood pressure (mmHg)	119.2 ± 7.01	154.4 ± 13.52**	114.3 ± 10.32	156.2 ± 22.00**	116.0 ± 10.27	154.3 ± 18.90**
Diastolic blood pressure (mmHg)	80.0 ± 4.66	101.2 ± 9.68**	73.1 ± 8.04	95.2 ± 7.56**	77.2 ± 6.91	96.2 ± 7.70**

Values are mean ± SEM.
The values of hypertension group are significantly different from those of the paired control group at **$p < 0.01$ by Student's *t*-test.

pertensive subjects were: 80.0 vs 101.2 for men, 73.1 vs 95.2 for pre-menopausal women, and 77.2 vs 96.2 for post-menopausal women, respectively. The differences in blood pressures between all three hypertensive groups and their respective control groups were statistically significant. No differences were found between the control and the hypertensive subjects in the mean values of BMI, fasting blood glucose, total serum cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides.

2. Saturated fatty acids in serum phospholipids

The fatty acid compositions of serum phospholipids in men, pre-menopausal women, and post-menopausal women are shown in Table 2. Among the saturated fatty acids, the mean percentage of palmitic acid (16 : 0) was significantly higher, and that of stearic acid (18 : 0) was significantly lower, in the hypertensive subjects compared to the controls in all three subject groups. Moreover, Pearson's correlation test results showed that, only in post-menopausal women, was palmitic acid closely associated with an increase in both systolic and diastolic blood pressure while stearic acid was associated with a decrease in both systolic and diastolic blood pressure (Fig. 1).

3. Monounsaturated and polyunsaturated fatty acids in serum phospholipids

Among levels of monounsaturated fatty acids in serum phospholipids, only oleic acid (18 : 1) was found to be significantly lower in hypertensive, post-menopausal women, as compared with their normotensive controls. Among ω6 series polyunsaturated fatty acids, levels of arachidonic acid (20 : 4ω6) and dihomogammalinoleic acid (20 : 3ω6) were significantly higher in pre- and post-menopausal, hypertensive women compared to their controls. Also, linoleic acid (18 : 2ω6) showed a significantly lower value in post-

Table 2. Percentage of fatty acid composition in serum phospholipids among subjects

Fatty acids	Men		Pre-menopausal women		Post-menopausal women	
	Control (n = 25)	Hypertension (n = 16)	Control (n = 14)	Hypertension (n = 19)	Control (n = 11)	Hypertension (n = 13)
SFAs	52.4 ± 0.54	52.3 ± 1.32	50.1 ± 0.43	46.7 ± 1.28	57.3 ± 0.74	55.9 ± 1.70
12 : 0	0.2 ± 0.02	0.2 ± 0.03	0.2 ± 0.02	0.2 ± 0.03	0.2 ± 0.02	0.2 ± 0.04
14 : 0	0.5 ± 0.03	0.5 ± 0.06	0.5 ± 0.03	0.5 ± 0.04	0.6 ± 0.02	0.5 ± 0.04
16 : 0	33.7 ± 0.72	36.2 ± 1.59*	32.2 ± 0.51	34.3 ± 1.08*	34.0 ± 2.17	36.8 ± 1.30*
18 : 0	16.2 ± 0.29^{b}	13.7 ± 0.48*	15.8 ± 0.31^{b}	10.1 ± 0.22*	20.9 ± 0.81^{a}	16.9 ± 0.63*
20 : 0	0.4 ± 0.02	0.3 ± 0.02	0.4 ± 0.02	0.4 ± 0.03	0.3 ± 0.04	0.4 ± 0.03
22 : 0	0.7 ± 0.04^{a}	0.8 ± 0.14	0.9 ± 0.05^{a}	0.7 ± 0.07	0.5 ± 0.10^{b}	0.6 ± 0.06
24 : 0	0.8 ± 0.07	0.7 ± 0.09	0.8 ± 0.05	0.6 ± 0.06	0.8 ± 0.10	0.6 ± 0.04
MUFAs	11.9 ± 0.33	11.9 ± 0.34	12.7 ± 0.35	11.6 ± 0.46	13.7 ± 0.38	11.4 ± 0.55
16 : 1	1.0 ± 0.07	1.1 ± 0.10	1.1 ± 0.07	1.1 ± 0.08	1.3 ± 0.03	1.4 ± 0.08
18 : 1	9.4 ± 0.25	9.5 ± 0.37	9.7 ± 0.23	9.1 ± 0.38	11.1 ± 0.47	8.8 ± 0.51*
20 : 1	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.02	0.2 ± 0.02
22 : 1	0.2 ± 0.02	0.2 ± 0.02	0.3 ± 0.02	0.2 ± 0.03	0.2 ± 0.02	0.2 ± 0.01
24 : 1	1.1 ± 0.08^{ab}	1.0 ± 0.08	1.5 ± 0.11^{a}	1.0 ± 0.11	0.8 ± 0.14^{b}	0.9 ± 0.10
PUFAs	33.6 ± 1.23	33.7 ± 2.16	34.6 ± 1.98	39.4 ± 2.01	27.0 ± 0.49	30.3 ± 2.85
Σω6series	28.2 ± 0.74	26.8 ± 1.27	28.1 ± 0.69	31.0 ± 1.01	23.3 ± 0.65	22.3 ± 1.73
18 : 2	18.7 ± 0.57	17.3 ± 0.83	18.8 ± 0.47	20.1 ± 0.44	17.1 ± 0.78	12.0 ± 0.99**
18 : 3	0.1 ± 0.02	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.02	0.2 ± 0.02	0.1 ± 0.02
20 : 3	2.3 ± 0.17^{a}	2.3 ± 0.16	2.1 ± 0.08^{a}	3.0 ± 0.27*	1.4 ± 0.07^{b}	3.0 ± 0.27*
20 : 4	6.6 ± 0.29^{a}	6.6 ± 0.46	6.7 ± 0.29^{a}	7.4 ± 0.41*	4.0 ± 0.59^{b}	6.8 ± 0.33**
22 : 4	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.01	0.2 ± 0.02	0.1 ± 0.01	0.2 ± 0.02
22 : 5	0.3 ± 0.09^{b}	0.3 ± 0.09	0.1 ± 0.01^{c}	0.1 ± 0.01	0.5 ± 0.01^{a}	0.2 ± 0.06*
Σω3series	5.4 ± 0.93^{a}	6.9 ± 0.63	6.5 ± 0.41^{a}	8.4 ± 0.79*	3.7 ± 0.52^{b}	8.1 ± 0.94**
18 : 3	0.2 ± 0.05	0.3 ± 0.02*	0.2 ± 0.02	0.3 ± 0.02	0.2 ± 0.02	0.2 ± 0.02*
20 : 3	0.07 ± 0.03	0.09 ± 0.03	0.04 ± 0.01	0.04 ± 0.004	0.05 ± 0.002	0.05 ± 0.005
20 : 5	0.9 ± 0.14	1.5 ± 0.12	1.3 ± 0.15	1.8 ± 0.24	1.3 ± 0.28	1.9 ± 0.26*
22 : 5	0.6 ± 0.04	0.8 ± 0.05	0.7 ± 0.05	0.9 ± 0.07	0.7 ± 0.08	1.0 ± 0.08*
22 : 6	3.6 ± 0.30^{b}	4.3 ± 0.34	4.4 ± 0.33^{b}	5.3 ± 0.37	1.5 ± 0.51^{a}	5.0 ± 0.53**
Others	2.1 ± 0.70	2.1 ± 1.27	2.7 ± 0.92	2.3 ± 1.25	2.0 ± 0.54	2.4 ± 1.70

Values are mean ± SEM.
The values of hypertension groups are significantly different from those of controls at *$p < 0.05$ and **$p < 0.01$ by Student's *t*-test.
Different superscripts a, b, c denote significant differences between controls at $p < 0.05$.
SFAs: saturated fatty acids, MUFAs: monounsaturated fatty acids, PUFAs: polyunsaturated fatty acids.

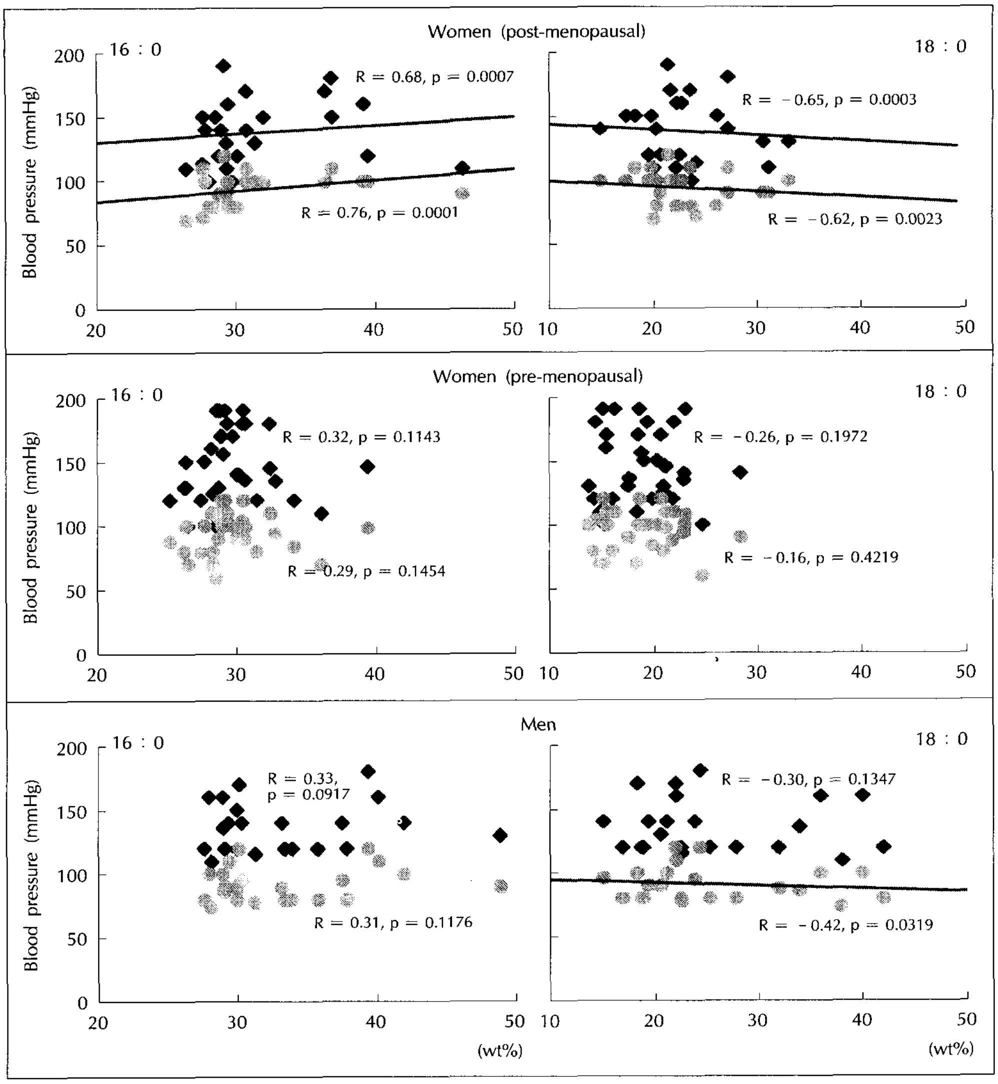

Fig. 1. Correlations of palmitic and stearic acids with systolic and diastolic blood pressure. ◆: Systolic blood presusre, ❋: Diastolic blood pressure

menopausal, hypertensive women, compared to their controls.

Table 3 shows the results of the Pearson's correlation tests, comparing blood pressure with levels of monounsaturated and polyunsaturated fatty acids in serum phospholipids. In post-menopausal subjects linoleic acid was negatively correlated with both SBP and DBP. Arachidonic acid, on the other hand, was positively correlated with SBP and DBP in post-menopausal subjects, but only with DBP in pre-menopausal subjects. Dihomogammalinoleic acid was positively correlated with DBP in both pre- and post-menopausal women.

The sum of all ω3 series fatty acids present in the serum phospholipids was higher in hypertensive women subjects that in their controls, as presented in Table 2. The following individual ω3 fatty acids showed significantly higher values in the hypertensive, post-menopausal subjects compared to the control subjects: linolenic acid (18 : 3ω3), eicosapentaenoic acid (20 : 5ω3), docosapentaenoic acid (22 : 5ω3) and docosahexaenoic acid (22 : 6ω3). In addition, significant correlations between these individual ω3 fatty acids and DBP were observed in post-menopausal women (Table 3).

DISCUSSION

Previous studies have reported a linear relationship between blood pressure and serum phospholipid-fatty acids,[1)3)6)] and this relationship was found to be independent of BMI,[1)] smoking, alcohol consumption and dietary fat intake.[3)] The extent to which plasma or serum phospholipid-fatty acids affect blood pressure, and the possible mechanisms of such an association, are not yet established.

The percentage of palmitic acid (16 : 0) in serum phospholipids was significantly higher, and that of stearic acid (18 : 0) was significantly lower, in all three hypertensive groups compared to their corresponding control groups (Table 2). For the post-menopausal woman group only, palmitic acid was closely associated with increases in both systolic and diastolic blood pressure, while stearic acid was associated with decreases in both SBP and DBP (Table 3). These opposite effects of palmitic and stearic acids have also been reported in cases of atherosclerosis,[20-22] although the pathophysiologies of hypertension and atherosclerosis differ somewhat.

In contrast to the above association between saturated fatty acids (16 : 0 and 18 : 0) and blood pressure in the hypertensive subjects of all three groups, the polyunsaturated fatty acid levels of serum phospholipids had a generally higher correlation with blood pressure in the female rather than in the male subjects. According to Simon *et al.*,[3] four fatty acids, namely 16 : 1, 18 : 2ω6, 22 : 4ω6 and 20 : 3ω9 in serum phospholipids, were significantly associated with blood pressure, independent of the effects of dietary fat intakes. Since dietary fat intakes were not measured in the present study, the possible influence of dietary fat intakes of the subjects on different serum phospholipid-fatty acid patterns could not be excluded.

Significantly different values of arachidonic acid (20 : 4ω6) and docosahexaenoic acid (22 : 6ω3) in hypertensive post-menopausal women can be partially explained by the lower values of these fatty acids in post-menopausal control subjects as compared to pre-menopausal female or male control subjects. The hormonal changes in menopause could influence the patterns of serum or erythrocyte membrane phospholipid-fatty acids.[23,24] Russo *et al.*,[8] using red blood cell membranes, reported that the ratios of fatty acids such as 20 : 4ω6/18 : 2ω6, 20 : 5ω3/18 : 3ω3 and 22 : 6ω3/20 : 5ω3 (indicative of desaturation and elongation in fatty acid metabolism) were significantly associated with blood pressure in hypertensive patients; these ratios were all higher in essentially hypertensive subjects in all age groups ($<$ 39 y, 40 – 59 y and $\geq$ 60 y).[8]

The products/precursor ratios such as ΣLCPUFAω6/

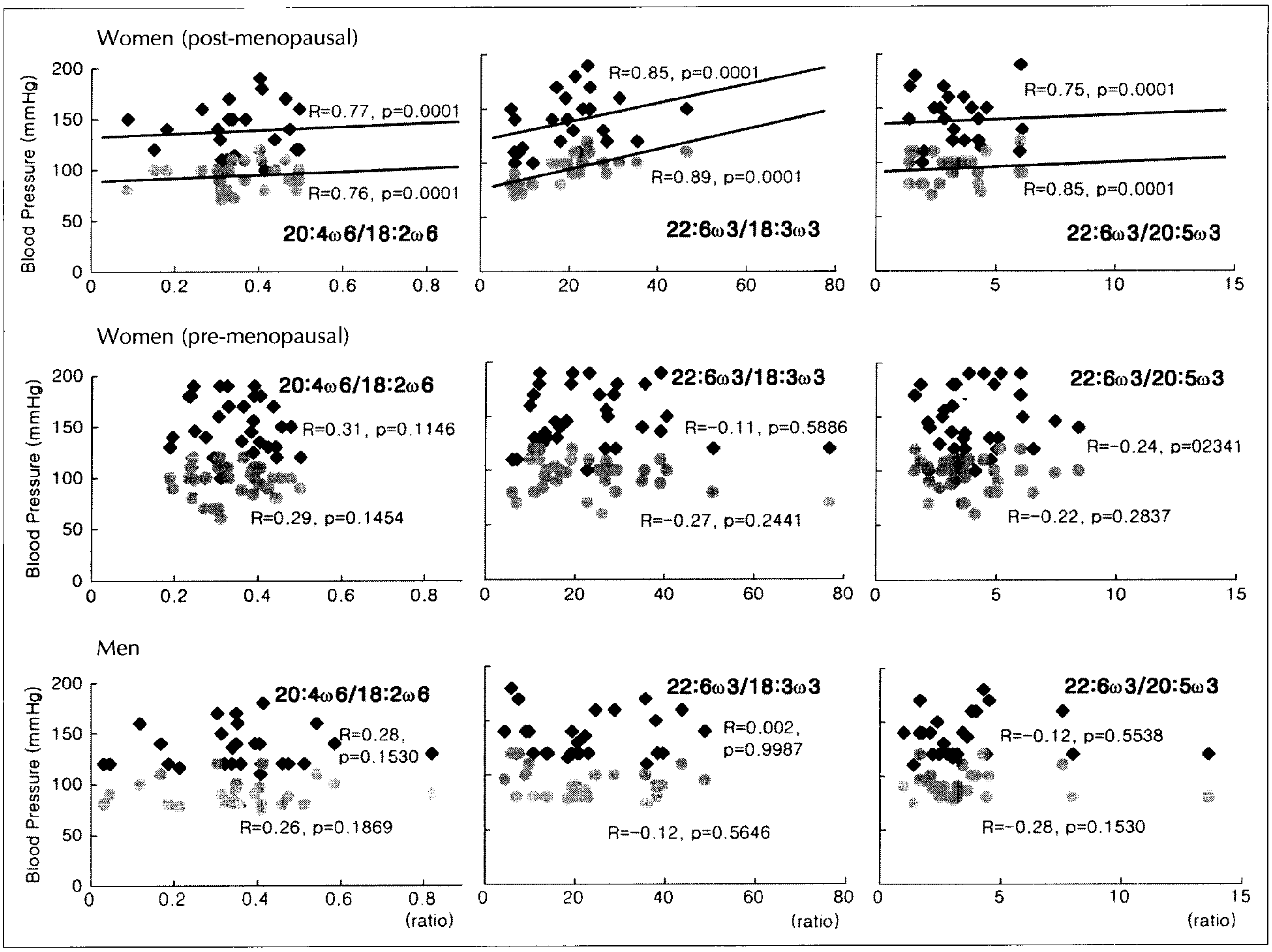

Fig. 2. Correlations between ratios of product/precursor fatty acids and systolic and diastolic blood pressure. ◆ : Systolic blood presusre, ❄ : Diastolic blood pressure

Table 3. Correlation coefficients between blood pressure and serum phospholipid monounsaturated and polyunsaturated fatty acids

Fatty acids	Men (n = 41)		Pre-menopausal women (n = 33)		Post-menopausal women (n = 24)	
	SBP	DBP	SBP	DBP	SBP	DBP
SFAs						
16 : 0	0.33	0.31	0.32	0.29	0.68	0.76
18 : 0	-0.30	-0.42*	-0.26	-0.16	-0.65*	-0.62*
MUFAs	0.13	0.29	-0.39	-0.32	-0.26	-0.29
PUFAs						
ω6 series						
18 : 2	-0.29	-0.25	0.19	0.24	-0.57*	-0.71**
18 : 3	0.08	0.31	-0.04	-0.07	-0.51*	-0.36
20 : 3	0.17	0.25	0.44	0.46*	0.44	0.64*
20 : 4	0.16	-0.15	0.14	0.62*	0.77**	0.72**
ω3 series						
18 : 3	0.47*	0.34	0.28	0.16	0.67*	0.66*
20 : 5	0.34	0.26	-0.04	0.19	0.40	0.66*
22 : 5	0.31	0.24	0.43	0.40	0.39	0.71**
22 : 6	0.31	0.26	0.32	0.24	0.75**	0.66*
ΣLCPUFAω6/18 : 2ω6	0.28	0.28	0.32	0.33	0.75**	0.75**
ΣLCPUFAω3/18 : 3ω3	0.11	-0.08	0.10	0.26	0.33	0.46*

SFAs: saturated fatty acids, MUFAs: monounsaturated fatty acids, PUFAs: polyunsaturated fatty acids, LCPUFA: longer chain polyunsaturated fatty acids, SBP: systolic blood pressure, DBP: diastolic blood pressure.
ΣLCPUFAω6 is (20 : 3 ω6 + 20 : 4ω6 + 22 : 4ω6 + 22 : 5ω6) and ΣLCPUFAω3 is (20 : 3ω3 + 20 : 5ω3 + 22 : 5ω3 + 22 : 6ω3).
*, **: significantly correlated at *$p < 0.05$ and **$p < 0.01$.

18 : 2ω6, 20 : 4ω6/18 : 2ω6 and 22 : 6ω3/20 : 5ω3 were all clearly associated with both SBP and DBP in hypertensive post-menopausal women (Fig. 2 and Table 3). Desaturation and elongation in fatty acid metabolism could affect bioavailability of eicosanoid precursors, and this could also be related to vascular functions and blood pressure. The changes in constituent fatty acids of phospholipids and in eicosanoid precursors may also affect some elements of biological membranes such as fluidity, ionic transport, hormone receptors and enzyme activities.

Evidence suggests that estrogen may increase activities of cyclooxygenase and prostacyclin synthase by increasing protein synthesis.[25)26)] This hormonal effect on enzymes involved in fatty acid metabolism such as cyclooxygenase and phospholipase A_2 may result not only in abnormal eicosanoid production but also in phospholipid metabolism including changes in bioavailability of eicosanoid precursors. There are discrepancies among the results of studies on vasoactive prostaglandin production.[26-32)] Also, it has been suggested that an imbalance between prostacyclin and thromboxane A_2 may affect vascular activity known to be involved in hypertension and coronary vasospasm.[33-36)]

In conclusion, both systolic and diastolic blood pressure in post-menopausal women was positively associated with the level of palmitic acid, and negatively associated with the level of stearic acid, in serum phospholipids. The relationships between serum phospholipid-ω6 and ω3 series fatty acids and blood pressure in women, especially in post-menopausal women, require further investigation by taking into consideration hormonal status and eicosanoid metabolism. Further study is needed to determine the value of dietary manipulation of fatty acid constituents of serum phospholipids, relating to hypertension in women.

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