Effect of human placental extract on menopausal symptoms, fatigue, and risk factors for cardiovascular disease in middle-aged Korean women

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Abstract

Objective: In Korea, human placental extract (HPE) has recently been used to treat various diseases (chronic liver diseases, menopause syndrome, chronic fatigue, skin pigment diseases, etc.), but evidence-based studies are not yet sufficient. The aim of this study was to examine the effects of HPE on menopausal symptoms, fatigue, and risk factors for cardiovascular disease in middle-aged Korean women in a randomized controlled trial.

Design: Korean women, aged 40 to 64 years, with menopausal symptoms and fatigue were recruited as participants. The women were randomly assigned to a placebo group or an HPE group. The HPE group received subcutaneous injections of HPE in the abdomen for 8 weeks, whereas the placebo group received normal saline. Then, the Menopause Rating Scale, and Fatigue Severity Scale, and Visual Analog Scale were administered, and risk factors for cardiovascular disease were assessed.

Results: The Menopause Rating Scale total baseline score was not different between the two groups; however, the score of the HPE group decreased significantly at 8 weeks compared with that of the placebo group ($P = 0.033$). Fatigue Severity Scale and Visual Analog Scale scores of the placebo group did not change, whereas the scores of the HPE group decreased significantly during the study period (Fatigue Severity Scale, $P = 0.002$; Visual Analog Scale, $P = 0.001$). The baseline 17β-estradiol level was not significantly different between the two groups, but the 17β-estradiol level of the HPE group was significantly increased at 8 weeks compared with that of the placebo group ($P = 0.031$). No changes in risk factors for cardiovascular disease were observed in either group.

Conclusions: Menopausal symptoms and fatigue in middle-aged Korean women improved after 8 weeks of HPE treatment, whereas risk factors for cardiovascular disease did not change during the study period.

Key Words: Human placental extract – Menopausal symptoms – Fatigue.

Human placenta had often been used in the past in folk remedies in Asian countries. In 1959 the therapeutic components were successfully extracted from human placenta in Japan and given the commercial name Laennec; the hydrolysate of human placenta was marketed as human placental extract (HPE) in Japan and was approved as a therapeutic agent for cirrhosis of the liver. In Japan there have been many studies on the effect of HPE on liver regener-ation[1-4]; however, almost all studies have limitations because the studies were carried out only in animals.

In Korea HPE has been approved for improvement of liver function and menopausal symptoms since the importa-tion of Laennec from Japan in 2003. Currently HPE is widely used in primary care practice in Korea for improve-ment of fatigue and skin whitening as well as for improve-ment of liver function and menopausal symptoms.

The pathogenesis of skin whitening was shown to be due to the antimelanocyte effect of HPE.[5,6] Conversely, some studies show conflicting results, such as a melanogenesis effect of HPE.[7-10] Therefore, the effect of HPE on melano-genesis remains to be clarified.

Menopausal symptoms and fatigue are some of the most common symptoms in patients seen in primary care practice, and fatigue is accompanied by menopausal symptoms in middle-aged women. Many patients in Korea have been taking HPE to improve these symptoms; however, research evidence of these effects is lacking. Therefore, we attempted to verify the effects.

We conducted a randomized controlled trial to determine whether HPE improved menopausal symptoms and fatigue in middle-aged women. We also investigated the effect of HPE on risk factors for cardiovascular disease (CVD), including blood pressure, fasting plasma glucose (FPG), insulin, insulin resistance index, lipid levels, and high-sensitivity C-reactive protein (hs-CRP) level, because the risk of CVD increases in middle-aged women.[11-13]

METHODS

Study participants

This study was approved by the institutional review board of Ajou University Hospital, Suwon, Republic of Korea.

We posted a public notice to recruit research participants (40- to 64-y-old women with menopausal symptoms or fatigue) on the notice board of Ajou University Hospital between March and July 2006. The purpose and protocol of the study were explained to potential volunteers. We selected women who had a total score of 5 or more on the Menopause Rating Scale (MRS) (mild to more menopausal symptoms).

Initial screening included a medical history and physical examination. Women with a history of chronic renal disease, with plasma creatinine levels more than 1.5 mg/dL, with a history of cirrhosis of the liver, other hemorrhagic diseases, any cancer, and medications such as thrombolytic agents or estrogen therapy were excluded. Eighty-four women were enrolled and were randomly assigned (by number-adaptive randomization) to a placebo group (n = 41) or an HPE group (n = 43). The sample size calculations were based on the following assumptions: (1) a standardized effect size of 0.80, (2) statistical power of 95%, and (3) a two-sided type I error of 5%. Two participants were added to the HPE group. Therefore, there were 41 participants in the placebo group and 43 participants in the HPE group.

Data collection and measurements

We measured the height and weight of the women at baseline and at the end of the study and calculated body mass index (BMI) (weight [kg]/height [m^2]). Blood pressure was measured with a mercury blood pressure gauge in the sitting position at rest.

Metabolic variables assessed at baseline and at the end of the study included hemoglobin, platelet count, white blood cell count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and hs-CRP concentrations. We calculated the insulin resistance index using the homeostasis model assessment of insulin resistance[14] and the Quantitative Insulin Sensitivity Check Index.[15] Hormone levels such as follicle-stimulating hormone (FSH) and estradiol (E$_2$) were also measured.

FPG, total cholesterol, and triglyceride level were measured with an enzymatic colorimetric method (TBA-200FR, Toshiba, Tokyo, Japan); insulin, with an immunoradiometric assay kit (Dinabot, Tokyo, Japan); and hs-CRP, with a latex-photometric immunoassay (TBA-200FR, Toshiba). FSH was measured with an immunoradiometric assay kit (Biosource, Brussels, Belgium), and E$_2$ was measured with a radioimmunoassay kit (DPC, Los Angeles, CA). The kit used to determine the E$_2$ level cannot detect values below 20 pg/mL; therefore, values less than 20 pg/mL are shown as 20 pg/mL.

Menopausal symptom and fatigue questionnaires

To assess the degree of menopausal symptoms, we used an international version of the MRS, which was translated into Korean.[16] The MRS was initially published in German and then translated first into English as the international version when it became well accepted internationally. Currently the MRS is available in 10 languages, including Asian languages such as Indonesian,[17] and it is a valuable tool for assessing the health-related quality of life of women in the menopausal transition.[17-19]

The MRS consists of 11 items, each rated on a scale of 0 (none) to 4 points (very severe) depending on the severity of complaints perceived by the woman completing the scale. The composite score (MRS total) is the sum of three domain scores: psychological (MRS psychological), somatovegetative (MRS somatic), and urogenital (MRS sexual). An MRS total score of 0 to 4 indicates no symptoms; 5 to 7, mild symptoms; 8 to 15 moderate symptoms; and 16 or more, severe symptoms.

We used the Fatigue Severity Scale (FSS) to measure fatigue severity.[20,21] The usefulness of this scale was recently investigated in Korea; using the FSS index of 3.22 as the cutoff point, sensitivity was 84.1% and specificity was 85.7% for the fatigue and control groups.[22] The FSS contains nine items, each of which is ranked for degree of severity using a scale of 1 (none) to 7 (very severe); the score is the average of the nine items. We also used the Visual Analog Scale (VAS) to assess the degree of fatigue, using a scale of 0 (no fatigue) to 10 (very severe fatigue).

Study protocol

We used Laennec, the hydrolysate of human placenta commercially marketed under the trade name of HPE, supplied by Green Cross Japan Bio Products Ltd, Korea. HPE is an aqueous extract of human placenta that is used for improvement of chronic liver diseases with the approval of the Korean Food and Drug Administration.

Human placentas collected at the time of full-term delivery were immediately placed in ice. The placentas were then cut into pieces, extracted with water, and the aqueous extract was sterilized and sealed in ampules. Before this procedure fresh placentas were tested for human immunodeficiency virus and hepatitis B and C viruses. In addition, product sterilization and virus tests were performed before and after the ampules were filtered.

We randomly analyzed one ampule of Laennec for viruses, cytokines, and hormones. In the virus analyses,

TABLE 1. *Cytokines and hormones levels in randomly selected ampules of human placental extract (Laennec)*

Cytokine	Level
Interleukin-1α	0.67 pg/mL
Interleukin-1β	<0.01 pg/mL
Interleukin-2	6.14 pg/mL
Interleukin-4	<0.01 pg/mL
Interleukin-6	<0.01 pg/mL
Interleukin-8	<0.01 pg/mL
Interleukin-10	<0.01 pg/mL
VEGF	<0.01 pg/mL
TNF-α	<0.01 pg/mL
Interferon gamma	<0.01 pg/mL
EGF	<0.01 pg/mL
MCP-1	<0.01 pg/mL
Hormones	
Estradiol	94 pg/mL
FSH	2.8 mIU/mL
Testosterone	<0.2 ng/mL
IGF-1	<10 μIU/mL
DHEA-S	<6 μg/dL

VEGF, vascular endothelial growth factor; TNF, tumor necrosis factor; EGF, epidermal growth factor; MCP, monocyte chemotactic protein; FSH, follicle-stimulating hormone; IGF, insulinlike growth factor; DHEA-S, dehydroepiandrosterone sulfate.

polymerase chain reaction of hepatitis B and C viruses, reverse-transcriptase polymerase chain reaction of human immunodeficiency virus 1, and VDRL tests were all negative. Cytokines were analyzed using automated biochip array technology (Randox Laboratories Ltd, Antrim, UK) (Table 1). Hormone levels (FSH, E_2, testosterone, insulinlike growth factor I, dehydroepiandrosterone sulfate) in the ampules of Laennec also were measured (Table 1): FSH and E_2 were measured by the same methods as described above; testosterone level, with a radioimmunoassay kit (DPC); insulinlike growth factor I, with an immunoradiometric assay kit (DSL, Webster, Texas); and dehydroepiandrosterone sulfate, with a radioimmunoassay kit (Radiam, Barcelona, Spain).

The women were randomly assigned to receive subcutaneous injection of either placebo (normal saline) or HPE for 8 weeks. During the first 2 weeks, 4 mL was injected twice weekly. During the second 2 weeks, 2 mL was injected twice weekly, and during the last 4 weeks, 2 mL each was injected once weekly. The women visited the hospital 12 times during the 8 weeks, so the total amount injected was 32 mL. We could differentiate HPE from placebo because Laennec is a brownish liquid and normal saline is colorless. But, we covered the eyes of the women during injection so that they did not see the liquid (single-blind method).

Statistical analysis

We used SPSS software for Windows version 11.5. The extreme values, lower than or equal to the first quartile minus three times or higher or equal to the third quartile plus three times, were excluded from exploratory data analysis. We used independent-samples t tests for comparison of HPE with placebo at baseline characteristics and used analysis of covariance (ANCOVA) for adjusted age and BMI. We used independent-samples t tests for comparison of HPE with placebo at the end of study period and

difference of change. We used paired-samples t tests for the difference in FSS and MRS scores between baseline and after the study within groups. The VAS scores did not have a normal distribution; therefore, we used the Wilcoxon test for the difference in the VAS during the study period within groups and used the Mann-Whitney U test for change difference in VAS between the two groups. All values are mean ± SD. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Baseline clinical characteristics

Six women (three from each group) did not complete the study because they withdrew for personal reasons. Therefore, 78 women participated in the final analysis (40 in the HPE group and 38 in the placebo group).

The mean age of the HPE group (51.6 ± 7.5 y) was younger than that of the placebo group (55.0 ± 5.4 y) (P = 0.023; Table 2). The proportion of menopausal women (last menstrual period more than 6 mo ago) between the two groups was not significantly different (19 in the HPE group and 25 in the placebo group, P = 0.103 by a χ^2 test). There were no significant differences between the HPE and placebo groups in the proportion of diseases associated with CVD at baseline, including hypertension, diabetes, and hyperlipidemia.

Weight was not significantly different between the HPE and placebo groups. The BMI of the HPE group (23.4 ± 2.4 kg/m^2) was lower than that of the placebo group (24.9 ± 2.6 kg/m^2) (P = 0.012; Table 2); however, the difference was not significant after adjustment for age (P = 0.054 by ANCOVA).

TABLE 2. *Comparison of clinical and biochemical characteristics between the two study groups at baseline*

	Placebo (n = 38)	HPE (n = 40)	P	P^a
Age (y)	55.0 ± 5.4	51.6 ± 7.5	0.023	
Weight (kg)	59.5 ± 6.7	56.9 ± 6.7	0.096	
BMI (kg/m²)	24.9 ± 2.6^b	23.4 ± 2.4	0.012	
Hemoglobin (g/dL)	13.2 ± 0.9	12.7 ± 1.1	0.060	0.151
Platelet (× 10³/μL)	255.2 ± 54.4	261.9 ± 60.9	0.610	0.614
WBC (× 10³/μL)	6.323 ± 1.309	5.986 ± 1.592^{bc}	0.317	0.898
Creatinine (mg/dL)	0.77 ± 0.10	0.76 ± 0.09	0.539	0.430
AST (U/L)	21.4 ± 4.3	19.6 ± 3.5^c	0.047	0.133
ALT (U/L)	21.8 ± 8.1	17.3 ± 3.4^d	0.002	0.014^e
γ-GTP (U/L)	18.8 ± 10.1^d	17.7 ± 9.0^c	0.624	0.860
FSH (mIU/mL)	42.0 ± 27.5	36.2 ± 31.4	0.384	0.989
E₂ (pg/mL)	20.0 ± 0.0^f	43.3 ± 42.4^d	0.004	0.065

Mean ± SD. HPE, human placental extract; BMI, body mass index; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP; gamma glutamyl transpeptidase; FSH, follicle-stimulating hormone; E₂, estradiol.
^{a}Comparison of placebo and HPE after adjusting for age and BMI by analysis of covariance.
^{b}Data missing.
^{c}Data excluded for one woman due to extreme value within group.
^{d}Data excluded for two women due to extreme values within group.
^{e}Statistically significant P value after adjusting for age and BMI.
^{f}Data excluded for nine women due to extreme values within group.

AST and ALT levels of the HPE group were lower than those of the placebo group ($P = 0.047$ and 0.002, respectively), but the difference in AST levels was not significant after adjusting for age and BMI. AST and ALT levels of both groups were in the normal range.

The FSH level was not significantly different between the HPE and placebo groups. Two women in the HPE group and nine women in the placebo group had extreme values of E_2; therefore, these women were excluded from the analysis of E_2 levels. E_2 levels of all women in the placebo group (after nine women were excluded) were 20 pg/mL, and this level was lower than the mean E_2 of the HPE group (43.3 ± 42.4 pg/mL); nevertheless, there was no significant difference after adjusting for age and BMI ($P = 0.065$).

There were no significant differences between the HPE and placebo groups in baseline characteristics, including blood pressure, hemoglobin, platelet count, white blood cell count, creatinine, gamma glutamyl transpeptidase, FPG, insulin, insulin resistance index (homeostasis model assessment of insulin resistance, Quantitative Insulin Sensitivity Check Index), total cholesterol, triglyceride, high-density lipoprotein cholesterol, and hs-CRP levels. All these values were within normal range.

Clinical characteristics after study period

Weight after study period was not significantly different between the HPE and placebo groups, and the BMI of the HPE group (23.4 ± 2.3 kg/m^2) was lower than that of the placebo group (24.7 ± 2.6 kg/m^2). However, the difference in BMI was not significant after adjusting for age ($P = 0.087$ by ANCOVA).

The ALT level of the HPE group at the end of study period was lower than that of the placebo group; however, the difference was not significant after adjusting for age and BMI ($P = 0.323$). ALT levels of both groups were within the normal range.

The FSH level at the end of study period was not significantly different between the two groups. The E_2 levels of all women in the placebo group (one woman was excluded because of missing data and eight women for extreme values) at the end of study period were 20 pg/mL. The E_2 level of the placebo group was lower than that of the HPE group (47.8 ± 39.3 pg/mL), and this differrence remained significant after adjusting for age and BMI ($P = 0.031$). The exact mean level of E_2 was lower than 20 pg/mL because E_2 levels lower than 20 pg/mL could not be measured by the kit used. However, they are reported here as 20 pg/mL.

There were no significant differences between the two groups in hemoglobin, platelet count, white blood cell count, creatinine, AST, and gamma glutamyl transpeptidase levels. All these values were within normal range.

Change of menopausal symptoms

We excluded women who had extreme values of FSH and E_2 concentrations at baseline or 8 weeks from the analysis of MRS.

The mean total MRS score was not different between the HPE and placebo groups at baseline (HPE: 20.7 ± 7.5, placebo: 21.9 ± 7.5; $P = 0.515$). The mean total MRS scores of both groups at baseline were in the range of severe menopausal symptoms. There were no significant
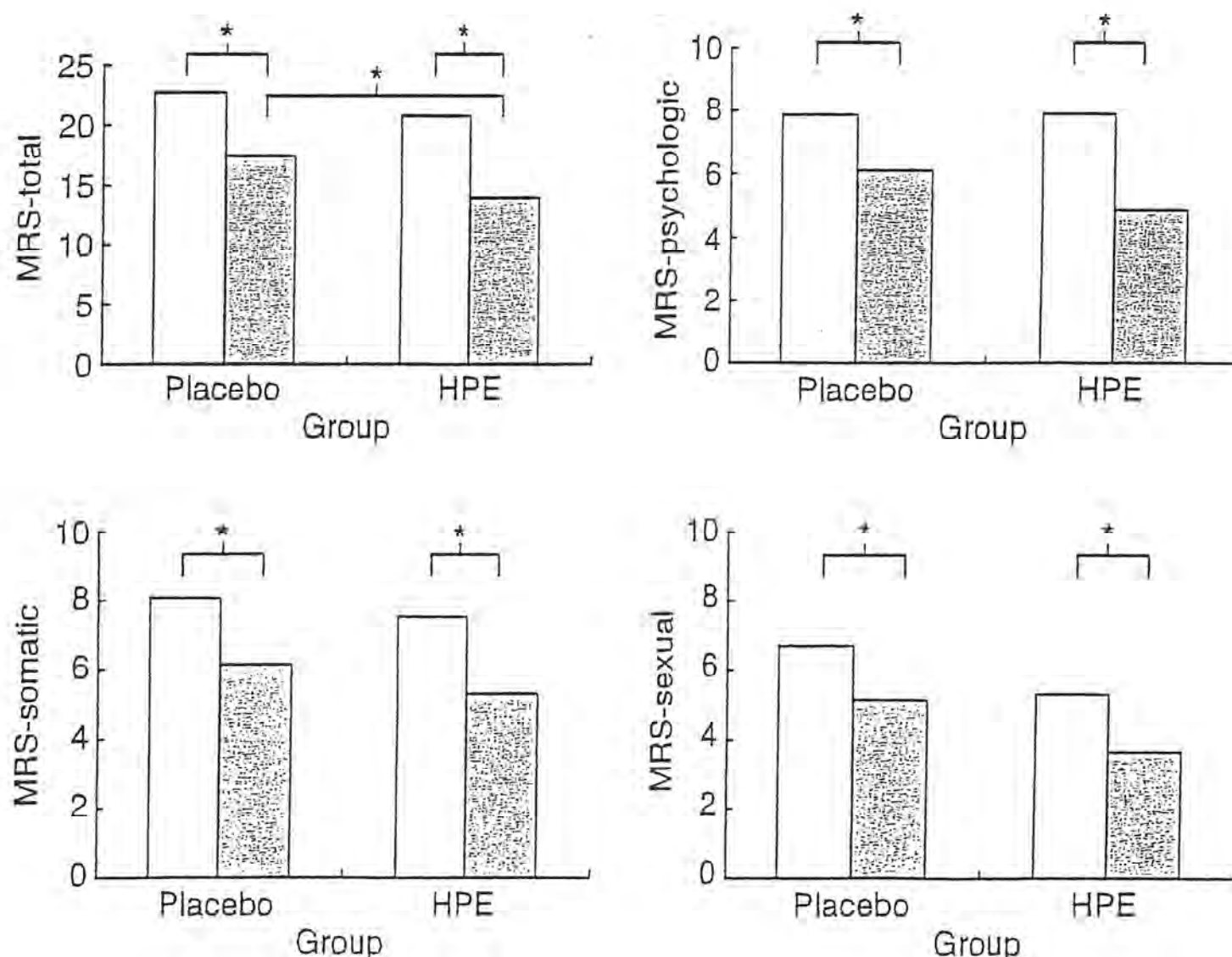

FIG. 1. Change in Menopause Rating Scale (MRS) score in the two study groups. *$P < 0.05$. HPE, human placental extract.

differences between the HPE and placebo groups in the mean scores on subscale: MRS psychological (HPE: 7.8 ± 3.3, placebo: 7.6 ± 3.7; $P = 0.736$), MRS somatic (HPE: 7.4 ± 2.9, placebo: 7.9 ± 3.0; $P = 0.525$), and MRS sexual (HPE: 5.4 ± 3.5, placebo: 6.5 ± 2.1; $P = 0.145$) (Fig. 1).

The mean total MRS score (13.6 ± 7.9) of the HPE group at 8 weeks was significantly lower than that of the placebo group (17.8 ± 7.6) ($P = 0.033$). This significance still remained after adjusting for age and BMI ($P = 0.046$ by ANCOVA). There were no significant differences between the HPE and placebo groups in the mean scores on subscales: however, the scores of the HPE group showed a lower tendency than those of the placebo group (MRS psychological: HPE 4.9 ± 3.4, placebo 6.3 ± 3.1, $P = 0.089$; MRS somatic: HPE 5.2 ± 3.1, placebo 6.6 ± 3.5, $P = 0.089$; MRS sexual: HPE 3.5 ± 2.9, placebo 4.9 ± 3.0; $P = 0.061$) (Fig. 1).

The mean total MRS and three subscale scores in the two groups at the end of the study period were significantly lower than the scores at baseline (all $P < 0.05$ by paired-samples t tests). There were no significant differences between the two groups in mean change of total MRS and the three subscale scores during the study period (MRS total: HPE -6.9 ± 8.0, placebo -5.2 ± 7.4, $P = 0.418$; MRS psychological: HPE -3.0 ± 3.7, placebo -1.8 ± 3.9, $P = 0.201$; MRS somatic: HPE -2.2 ± 2.7, placebo -1.9 ± 2.5, $P = 0.691$; MRS sexual: HPE -1.7 ± 3.3, placebo -1.6 ± 3.2, $P = 0.900$).

Change in fatigue

In the HPE group the FSS score (3.2 ± 1.4) at the end of the study period was significantly decreased from baseline (3.9 ± 1.3) ($P = 0.002$ by paired-samples t tests; Fig. 2A). However, the FSS score in the placebo group was not significantly different between baseline and the end of the study period (3.1 ± 1.1 at baseline, 3.4 ± 1.4 at the end; $P = 0.196$ by paired-samples t tests). There was a significant difference between the two groups in the mean change in FSS score during the study period (HPE: -0.7 ± 1.3, placebo: 0.3 ± 1.2, $P = 0.001$ by independent-samples t tests).

The VAS score in the HPE group was significantly decreased (5.3 ± 2.0 at baseline and 4.0 ± 2.1 at the end;

$P = 0.001$ by the Wilcoxon test; Fig. 2B); however, the placebo groups did not show any significant change during the study period (4.7 ± 1.4 at baseline and 4.7 ± 1.9 at the end; $P = 0.850$ by the Wilcoxon test). There was a significant difference between the two groups in the mean change in VAS during the study period (HPE: -1.4 ± 2.1, placebo: -0.1 ± 1.8; $P = 0.028$ by the Mann-Whitney U test).

Changes in risk factors for CVD

There were no significant changes in risk factors for CVD in the two groups during the study period, including blood pressure, FPG, insulin, insulin resistance index (homeostasis model assessment of insulin resistance, Quantitative Insulin Sensitivity Check Index), lipid levels (total cholesterol, triglycerides, high-density lipoprotein cholesterol), and hs-CRP (Table 3).

DISCUSSION

In the present study the menopausal symptoms and fatigue were found to be improved in middle-aged Korean women after they received HPE for 8 weeks. HPE did not affect risk factors for CVD such as blood pressure, FPG, insulin, insulin resistance index, lipid levels, and hs-CRP level.

The mean total MRS and three subscale scores in both the HPE and placebo groups were significantly decreased during the 8-week study period, showing a placebo effect on menopausal symptoms. Nevertheless, the decreased scores of the HPE group were significantly lower than the decreased scores of the placebo group at the end, indicating that the menopausal symptoms of the HPE group improved more. There was no difference in the E_2 baseline concentrations between the two groups, but the E_2 concentration of the HPE group was significantly higher than that of the placebo group during the 8-week study period, possibly because of the effect of E_2 concentration of HPE on the improvement of menopausal symptoms.

The reason why the E_2 levels of the HPE group were affected was suggested by hormone analysis of randomly selected HPE ampules, which showed 94 pg/mL. However, this amount was too small compared with the amount of traditional estrogen therapy in menopausal women. HPE is a
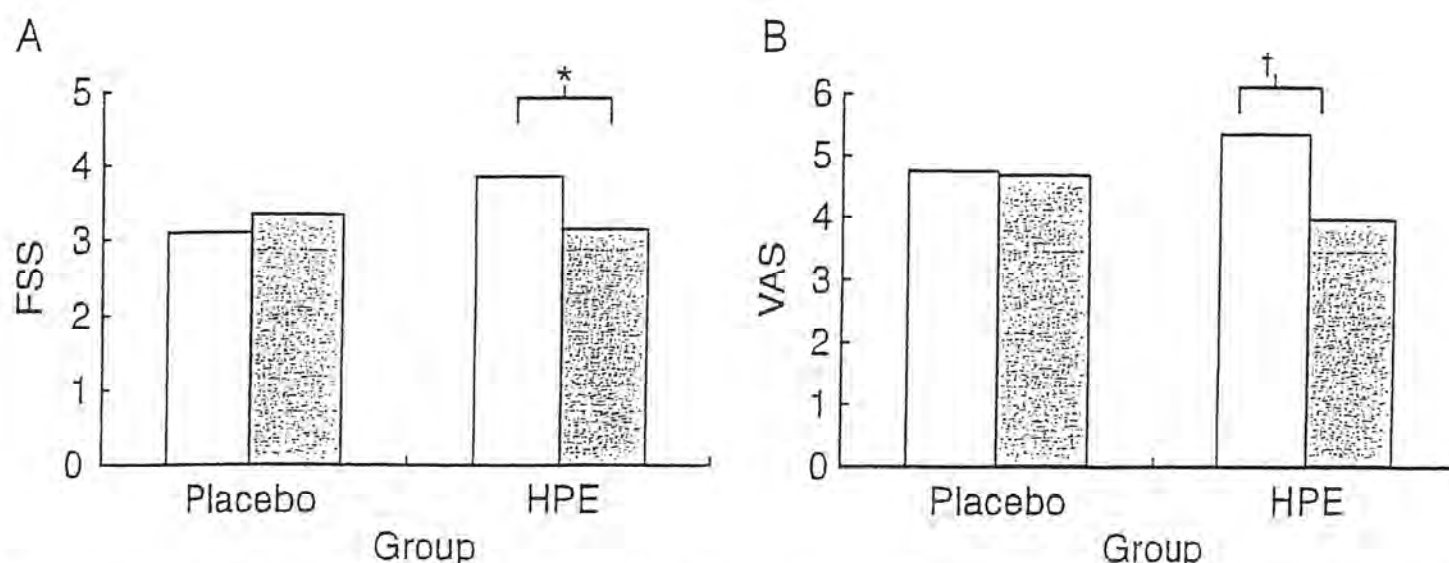

FIG. 2. Change in Fatigue Severity Scale (FSS) score (A) and Visual Analog Scale (VAS) (B) of fatigue in the two study groups. *$P < 0.05$ by paired-sample t test. †$P < 0.05$ by Wilcoxon test. HPE, human placental extract.

TABLE 3. *Change in risk factors of cardiovascular disease in the two study groups*

	Placebo (n = 38)			HPE (n = 40)			
	Baseline	End	Difference[a]	Baseline	End	Difference[a]	P (placebo vs HPE)[b]
SBP (mm Hg)	119.3 ± 13.6	117.6 ± 11.0[c]	−2.3 ± 13.8	117.6 ± 14.3	115.8 ± 10.6[c]	−1.8 ± 12.1	0.866
DBP (mm Hg)	79.5 ± 5.9	77.3 ± 6.6[c]	−2.2 ± 5.5	76.5 ± 9.0	76.0 ± 7.5[c]	−0.3 ± 8.5	0.247
FPG (mg/dL)	96.9 ± 11.1	94.2 ± 6.0[d]	−0.8 ± 7.1	93.3 ± 7.4[c]	92.7 ± 7.2	−0.7 ± 7.2	0.944
Insulin (μIU/mL)	7.2 ± 3.5[c]	5.3 ± 2.9[c]	−2.0 ± 3.0	6.1 ± 3.7[e]	5.3 ± 3.2	−1.0 ± 3.2	0.161
HOMA-IR	1.89 ± 1.22	1.28 ± 0.73[c]	−0.64 ± 1.12	1.42 ± 0.91[e]	1.21 ± 0.76	−0.24 ± 0.82	0.079
QUICKI	0.36 ± 0.03	0.38 ± 0.04[c]	0.03 ± 0.04	0.37 ± 0.04	0.39 ± 0.04	0.01 ± 0.04	0.148
Total cholesterol (mg/dL)	196.3 ± 31.5[d]	199.7 ± 39.9	1.5 ± 28.4	184.2 ± 29.5	189.8 ± 32.1	5.6 ± 25.7	0.510
Triglyceride (mg/dL)	137.6 ± 73.3[d]	130.9 ± 64.3	−10.8 ± 70.5	118.7 ± 60.9	123.0 ± 66.6	4.4 ± 44.1	0.274
HDL cholesterol (mg/dL)	56.7 ± 13.8	56.5 ± 11.9	−0.2 ± 7.5	58.2 ± 12.1	57.6 ± 12.7	−0.6 ± 6.3	0.766
hs-CRP (mg/dL)	0.07 ± 0.06	0.08 ± 0.06[d]	0.01 ± 0.07	0.06 ± 0.06[f]	0.06 ± 0.05[d]	−0.00 ± 0.40	0.306

Mean ± SD. HPE, human placental extract; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, Quantitative Insulin Sensitivity Check Index; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein.
[a]Change from baseline (after baseline).
[b]P values are for the comparison between groups (change from baseline).
[c]Data missing for one woman.
[d]Data for two women excluded due to extreme values within group.
[e]Data for one woman excluded due to extreme value within group.
[f]Data for four women excluded due to extreme values within group.

complex material; therefore, we do not agree with the contention that only E_2 contained in HPE contributed to the increase in E_2 levels in women who received HPE, and further studies are needed.

We showed that women who received HPE had significant improvement in FSS and VAS scores during the study period, whereas the women in the placebo group did not show any significant improvement on these scales during this period.

Chronic fatigue is a common problem in patients visiting primary care practices.[23,24] Many patients with fatigue visit the hospital; however, objective diagnosis is difficult because the symptoms of fatigue are nonspecific.[25] Emotional stress is one of the common major causes of chronic fatigue, in addition to abnormal immune function, immune activation, and various microbial infections.[26]

Earlier studies[27,28] suggested that HPE has anti-inflammatory properties, thereby resulting in fatigue improvement. HPE significantly inhibits carrageenin and prostaglandin E_1-induced edema in rats. This degree of HPE effect was almost the same as that in the diclofenac sodium-treated group.[27] HPE has been used in many countries for the treatment of chronic wounds,[29-31] and it improves or eradicates oral mucositis in cancer patients who undergo chemotherapy and/or radiotherapy.[32,33] Therefore, the anti-inflammatory properties of HPE improve chronic inflammation, which is one of the causes of chronic fatigue syndrome. The second possible reason for the HPE effect on fatigue could be its ability to improve immunity. One of the causes of chronic fatigue is impaired immune function, and 6.14 pg/mL interleukin-2 was found in randomly sampled HPE ampules. Interleukin-2 is a cytokine used to improve immune function, and a high dose of this cytokine is used in anticancer therapy.[34] A future study is needed to determine the change in cytokine levels after women receive HPE. Finally, one plausible additional cause is that HPE is a rich

source of various bioactive substances, such as RNA, DNA, peptides, amino acids, proteins, lipids, and enzymes.[35,36] The anabolic effect of these components is to assist energy production, thereby improving fatigue. Also, fatigue takes a favorable turn simultaneously with menopausal symptoms because menopausal symptoms and fatigue occur together.[37]

We did not observe a change in hs-CRP level in our present study. hs-CRP is an inflammation marker known to explain the instability of the atherosclerotic plaque that develops in CVD. Furthermore, hs-CRP has a greater ability to predict development of CVD than traditional risk factors.[38,39] The average hs-CRP level in the women in this study was in the normal range at baseline because extreme values of hs-CRP levels at baseline were excluded from analysis. Therefore, the change in hs-CRP level within the normal range was not significant during the study period. Four women with extreme hs-CRP levels who were excluded exceeded the normal range found in our hospital laboratory (0.02-0.22 mg/dL): The values of the four women were 3.93, 0.59, 0.50, and 0.46 mg/dL. All these women received HPE, and their values decreased after the study period: Three of the four women had hs-CRP levels within the normal range at the end (one woman with rheumatoid arthritis had 3.93 mg/dL at baseline and 1.78 mg/dL at the end).

These effects showed the possibility of using HPE to lower hs-CRP levels. However, the number of women in our study with an increased hs-CRP level at baseline was very small; therefore, further study on the effect of HPE in women with abnormal hs-CRP levels is needed. Additionally, a clinical study on the role of HPE in protecting against CVD is needed because HPE also inhibits platelet aggregation.[27,40]

The risk factors for CVD, ie, blood pressure, FPG, insulin, insulin resistance index, lipid levels, and hs-CRP level, were not changed in the present study. Therefore, HPE did not affect the risk of CVD in middle-aged women in the