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Evaluation of Effectiveness and Safety of Natural Plants Extract (Estromon®) on Perimenopausal Women for 1 Year

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ABSTRACT
Objectives: This research was designed to investigate the effects of natural herbal product, Estromon®, which is the newly developed phytoestrogen for perimenopausal women.
Methods: A prospective randomized clinical trial was performed. A total 48 perimenopausal women were included into this study and divided either into Estromon® group(n=24) and placebo group(n=24). The treatment group was treated for 12 months with oral administration of two capsules of Estromon® twice a day. Bone mass density, serum bone markers, weight, BMI, serum lipid profile, human growth hormone, FSH and E2 were measured at baseline and 3, 6, 9, 12 months. Final analysis was conducted for 42 subjects who were medicated continuously for 12 months.
Results: The oral administration of two capsules of Estromon® twice a day for 3 months significantly improved climacteric symptoms about 5 times more than placebo group. (OR=5.04, 95% C.I. 1.40-18.14) In the group of 19 patients having taken Estromon®, alkaline phosphatase, as the bone marker, decreased from 73.35±21.02(IU/L) to 66.21±4.87(IU/L) after 12 months with statistical significance(paired t-test, $p<0.05$). Since osteocalcin also decreased (from 6.02±2.74ng/ml to 5.66±3.01ng/ml) in Estromon® group but increased (from 6.24±3.04ng/ml to 6.47±2.58ng/ml) in placebo group(Mann-Whitney Test $p<0.05$), bone density is expected to improved in long-term treatment. As for BMD of femur neck, it increased(2.24%:from 0.746±0.10g/cm2 to 0.763±0.13g/cm2) during 12 months of treatment in Estromon® group, but decreased(1.14%:from 0.743±0.10g/cm2 to 0.733±0.14g/cm2) in placebo group. And this difference had statistical significance ($p<0.05$, Mann-Whitney test). Mean serum human growth hormone level was increased more in Estromon® group(268%: from 0.25±0.21ng/ml to 0.92±0.97ng/ml) than placebo group(42% from 0.57±0.71ng/ml to 0.81±0.83ng/ml) after 1-yr treatment($p<0.05$, Mann-Whitney test). Among the subjects in Estromon® group, We found the reduction in serum triglyceride(119.10±54.72mg/dl to 92.16±49.94mg/dl) significantly($p<0.05$, paired t-test), but there were no changes in placebo group. Serum E2, FSH, Blood pressure, LDL, HDL, Total cholesterol and BMD for spines were not changed significantly in both groups after 12 months.
Conclusions: Therefore, perimenopausal women may have benefit from Estromon® as a phytoestrogen supplement especially for climacteric symptoms, femur neck BMD, serum triglyceride and human growth hormone without weight gain or any serious side effects.

- ***Key words***: Perimenopause, Postmenopause, Hormone Replacement Therapy, Phytoestrogen, *Cynanchum wilfordii*, *Phlomis umbrosa*

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It is well established that hormone replacement therapy is effective for the climacteric symptoms like insomnia, hot flush and night sweat and relieves depressive condition. The therapy is also known to prevent reproductive organ disorders like urinary incontinence and vaginal dryness and reduce the risk of osteoporosis and bone fracture (1, 2, 3). Estrogen replacement therapy has been widely used to resolve those conditions. However, estrogen replacement therapy showed some problems of higher risk of coronary artery disease (4, 5) and absently preventive effect of ischemic heart stroke of women in menopause (6, 7). Especially, many results of potential risk of breast cancer have been reported (4, 5, 7). In the report of Women's Health Initiative (WHI) in which about 16,000 of women had participated for five years, the study agent, the Prempro that is the combination of CEE with progesterone lowered the incidences of colon cancer by 37% and bone fracture by 24% while the incidence of breast cancer, heart disease, stroke and blood clotting are elevated by 26%, 29%, 41% and 100%, respectively (5). Because of these serious side effects, FDA recently issued a negative recommendation for long-term prescription of estrogen replacement therapy.

So, though HRT is a very effective measure, there are some problems to adopt the therapy as a long-term clinical use or for sole relief of climacteric symptoms.

In this connection, there have recently been increasing interests in phytoestrogen showing the partial effect of HRT in vivo without increasing risks of breast cancer and coronary artery disease. Particularly, many researches on isoflavone as a kind of phytoestrogen have been conducted (8,9). However Korean FDA recently refused to admit the effectiveness of isoflavone for climacteric symptoms with the advent of the safety of isoflavone. Some researchers reported that isoflavone doesn't show any effectiveness for hot flush(10-11) and another report described that soy bean supplements relieved hot flush but the authors concluded that the effect was not derived from phytoestrogen but other substances of soy bean (12). Unlike western counterparts, women of Korea, Japan and China intake much isoflavone from such daily diet as soy bean, tofu and bean sprouts while many of them in the oriental countries suffered from the menopausal syndrome. In this viewpoint, it is difficult to take isoflavones as an alternative to HRT.

In spite of many therapies with diverse natural plant extracts, there are few prospective study result of clinical studies by general hospitals in Korea. We conducted this study to observe the short-term changes of climacteric symptoms with the new product Estromon of plant estracts and nutritional ingredients (plant extracts were found to have the effect of increasing uterus weight (13)) and we also wanted to evaluate effects on bone density and lipid profile in a long period of 1 year.

STUDY GROUP AND METHOD

1. Study group

This study was conducted with 48 female patients with menopausal symptoms who visited family medicine clinic or climacteric disease clinic of Samsung Cheil hospital as a randomized double blind comparative clinical trial from May 2003 to Apr. 2004. This clinical study has been approved by IRB of Samsung Cheil hospital and complied with the Helsinki Declaration as revised in 1983. As inclusion criteria, patients were over 45 year old and diagnosed as menopausal syndrome with written consent for the trial. Exclusion criteria include acute or chronic diseases, or cancer. The patients were randomly allocated to 24 of study group (Estromon® group) and 24 of placebo group (corn starch placebo group). Informed consents were confirmed. After written consent of the patients, their eligibilities were reexamined and serial numbers were allocated to the patients. Patients with individual serial numbers are regarded as registered volunteers. Study and placebo materials were encapsulated in brown capsules and packed in the same bottles so that both doctors and patients may not know the difference from the external appearances.

2. Study method

1) Treatment of natural plant extracts

The ingredients of Estromon® were 41.78mg (13.26%) of *Phlomis umbrosa* extract, 13.26% of *Cynanchum wilfordii* extract, 45mg (14.29%) of *Angelica gigas* Nakai extract, 45mg (14.29%) of L-arginine, 15mg (4.76%) of L-lysine monohydrochloride, 12mg (3.81%) of soy bean extract, 93mg (29.52%) of Seaweed calcium, 0.375mg (0.12%) of dry formed Vitamin A, 3mg (0.95%) of dry formed Vitamin E (dl-tocopherol), 0.58% of Vitamin C (L-ascorbic acid), 3mg (0.95%) of Vitamin B1 (thiamine hydrochloride), 1mg (0.32%) of B6 (Pyridoxine hydrochloride), 0.0002% of B12 (Cyanocobalamine), 0.0025mg (0.0008%) of Vitamin D3 (Cholecalciferol), 0.038mg (0.012%) of biotin, 5.46375mg (1.73%) of nicotinamide, 3.73mg (1.18%) of ferrous lactate and 0.95 of magnesium stearate. It was formulated as (315mg) hard capsules. Patients are to administer the study material as 2 capsules twice a day for 48 weeks.

2) Observation and Test items

Age, time of menopause, pregnancy and its history and period of menopause of all patients were recorded. All patients visited the hospital at month 1, 3, 6, 9 and 12, were examined height, weight, waist, body-mass index, blood pressure(diastolic and systolic), pulse, compliance of study material and combination medications. Test items were estrogen (E2), follicular stimulating hormone (FSH), human growth hormone (hGH), lipid profile such as total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride, such bone markers as alkaline phophatase (ALP) and osteocalcin, bone density, and general hematology tests. Interviews on relief of climacteric symptoms for 3 months were done and recorded.

3) Data analysis

Patients who once had been dropped out could not be re-registered for the study and early drop out patients were not replaced. Examination variables for effectiveness were treated with PP(per-protocol) analysis basically. Patients for ITT analysis who satisfied following standards were included in PP analysis:

1. eligible to inclusion/exclusion criteria unless agreed by research members; 2. complied with the dosage of protocol over 70% per 12 month treatments; and 3. well complied with the study protocol without eligibility to any exclusion criteria.

Safety evaluation was performed by ITT (Intent-to-treat) analysis. LOCF (last-observation-carried-forward) method was used for omitted data. For ITT analysis any enrolled patient was included who has taken test material at least once and who visited the hospital at least once, and early drop-out patients were also included.
In order to evaluate effectiveness, examination variables were measured at week 0, week 4, week 12, week 24, week 36 and week 52 and differences from baseline were analyzed by Mann-Whitney test and Fisher's exact test. In two-tailed test the analysis was performed with 5% significance in case p value was less than 0.05. SPSS for Windows 10.0(SPSS Inc., Chicago, IL, USA) was used for the analysis.

3. Study Results

To evaluate the effectiveness and safety of Estromon® capsules, the safety was evaluated with 48 patients out of total 48 patients enrolled to the study. The effectiveness was evaluated for 42 patients who completed the whole study procedure complied to protocol for 52 weeks except 5 self denied patients and 1 patient having shown skin eruption.

1) General characteristics of the study group at baseline

Total enrolled patients were 48 and 6 patients were dropped out of the study. In result, 23 patients were in the placebo group and 19 patients were in Estromon® group out of the finally analyzed 42 study patients. Average age of the patients was 54 ranging from 46 to 66. Age distribution of the patients is noted on the Table 1 and 6 patients (14.3%) were over 61 year old.
At baseline of the study there were no significant differences of basic physical profiles, serum hormone concentrations, bone markers, serum human growth hormone, and serum lipid profiles between the study group and the placebo group but mean ossification rate was higher in the study group (Table 2).

2) Result of primary endpoint evaluation (interview on the improvement of menopausal symptoms)

■ Change of climacteric symptoms 3 months after the treatment of Estromon®

After 3 months of Estromon® treatment, the study group showed better improvement of various menopausal symptoms than placebo group with statistic significance (OR=5.04, 95% C.I. 1.4-18.1). More specifically, the improved symptoms include 9 cases of dyspareunia, 5 of hot flush, 1 of sleep disorder, 2 of mental awareness problem, 1 of joint pain, 1 of musculoskeletal disease, 2 of dyspepsia, 1 of urinary incontinence and 1 of fatigue, 23 cases in total out of 14 patients. The result of the improvement of climacteric symptoms is shown on the table 3.

Table 1. Demographic characteristics

Total patients		Number of patients
		42 (100%)
Age	46 ~ 50	13 (31.0%)
	51 ~ 60	23 (54.8%)
	61 ~ 66	6 (14.3%)

Table 2. Basic characteristics of subjects

	Case	Control	Total
	average	average	average
L2 BMD(g/cm^2)	0.943±0.14	0.834±0.15	0.883±0.15
L3 BMD(g/cm^2)	1.003±0.14	0.897±0.16	0.945±0.16
L4 BMD(g/cm^2)	1.044±0.15	0.922±0.17	0.977±0.17
L2-4 BMD(g/cm^2)	0.996±0.14	0.888±0.16	0.936±0.16
Neck BMD (g/cm^2)	0.746±0.10	0.743±0.10	0.744±0.10
Troch anter BMD (g/cm^2)	0.639±0.09	0.617±0.10	0.627±0.10
Inter trochanter BMD (g/cm^2)	1.047±0.15	1.021±0.12	1.033±0.13
Total neck BMD (g/cm^2)	0.866±0.12	0.856±0.09	0.861±0.10
Ward BMD (g/cm^2)	0.607±0.13	0.565±0.13	0.585±0.13
FSH (mlu/ml)	52.400±32.80	56.037±32.74	54.489±32.46
E2 (pg/ml)	27.565±32.25	21.292±24.12	24.020±27.79
Osteocalcin(ng/ml)	6.020±2.74	6.241±3.04	6.147±2.89
βcross lab(ng/ml)	0.470±0.21	0.591±0.30	0.540±0.27
Alkaline Phospate(IU/L)	73.350±21.02	74.407±27.33	73.957±24.59
hGh(ng/ml)	0.250±0.21	0.573±0.71	0.461±0.60
IGF-1(ng/ml)	265.556±76.82	271.438±48.87	234.760±63.37
Fasting Glucose(mg/dl)	99.400±22.58	103.296±11.30	101.638±16.93
Cholesterol(mg/dl)	182.750±36.19	203.000±38.68	194.383±38.59
HDL (mg/dl)	46.850±8.44	46.815±13.13	46.830±11.26
LDL (mg/dl)	112.080±33.75	133.156±33.02	124.187±34.61
Triglyceride(mg/dl)	119.100±54.72	115.148±37.63	116.830±45.18
Weight(kg)	57.332±5.84	57.243±6.12	57.279±5.94
Height(cm)	157.300±3.74	153.852±5.41	155.319±5.03
WtoH	0.808±0.04	0.834±0.04	0.824±0.04
BMI(kg/m^2)	23.133±1.79	24.123±2.12	23.714±2.03
Systolic Pressure(mmHg)	117.000±13.89	113.038±17.67	114.711±16.13
Diastolic Pressure(mmHg)	76.474±8.32	73.846±10.75	74.956±9.78

p >0.05, Mann-Whiteney test

FSH; Follicuar Stimulating Hormone, hGH; human Growth Hormone,

HDL; High Density Lipoprotein, LDL; Low Density Lipoprotein,

WtoH; Waist to Hip Ratio, BMI; Body Mass Index

Table 3. Change of climacteric symptoms 3 months after study commence

		change of climacteric symptoms		Total
		No improvement	Improvement	
Placebo Group	case(n)	18	5	23
	(%)	78.3%	21.7%	100.0%
Study Group	case(n)	10	14	24
	(%)	41.7%	58.3%	100.0%
Total	case(n)	28	19	47
	(%)	59.6%	40.4%	100.0%

OR = 5.04(95% C.I. ; 1.4 - 18.1)

Fisher's Exact Test

■ Change in the patients with climacteric symptoms before the treatment of Estromon®
Among the patients with climacteric symptoms at baseline, patients of the study group showed more improvement of the symptoms in numbers than the placebo group did. However, it was not statistically significant (OR = 6.67, 95% C.I. 0.49 – 91.3) (Table 4).

Table 4. Change in the patients with climacteric symptoms at baseline after treatment for 3months

		change of climacteric symptoms		Total
		No improvement	Improvement	
Placebo Group	case(n)	5	1	6
	(%)	83.3%	16.7%	100.0%
Study Group	case(n)	3	4	7
	(%)	42.9%	51.7%	100.0%
Total	case(n)	8	5	13
	(%)	61.5%	38.5%	100.0%

OR = 6.67 (95% C.I. 0.49 - 91.3)
Fisher's Exact Test

3) Evaluation of secondary endpoint (evaluation of effectiveness after 12 months)
The changes of variables of 12 months of Estromon® treatments are shown on Table 5.
Femoral neck bone density increased from mean 0.746±0.10g/cm^2 at baseline to mean 0.763±0.13g/cm^2 at month 12 by 0.017±0.03 g/cm^2 (2.24%) in the study group but decreased by 0.01±0.04 (1.14%) from mean 0.743±0.10g/cm^2 at baseline to mean 0.733±0.14g/cm^2 at month 12 in the control group. The treatment showed statistically significant increase in femoral neck bone density ($p<0.05$, Mann-Whiteney test).
Serum osteocalcin concentration was decreased in the study group (mean 6.02±2.74ng/m1 at baseline and mean 5.66±3.01ng/ml at month 12) but was increased in the control group at month 12 (mean 6.24±3.04ng/ml at baseline and mean 6.47±2.58ng/ml at month 12). The changes were different significantly ($p<0.05$, Mann-Whitney Test)(Fig 1.).
Serum ALP concentration changed from 74.41±27.3 IU/L to 71.00±32.54 IU/L, but the difference was not significant ($p>0.05$, paired t-test). However, the concentration of the study group decreased from 73.35±21.02 at baseline to 66.21±4.87IU/L with statistic significance ($p<0.05$, paired t-test). In comparing the difference between the two groups, the decrease of study group was bigger than that of control group with borderline significance (p=0.08, Mann-Whitney Test)
Serum hGH concentrations increased from mean 0.25±0.21ng/ml at baseline to mean 0.92±0.97ng/ml at month 12 by 268% in the study group while it increased by 42% from mean 0.57±0.71ng/ml at baseline to mean 0.81±0.83ng/ml at month 12 in the control group with statistic significance ($p<0.05$, Mann-Whitney Test).
Change of serum triglyceride and total cholesterol concentrations are noted in Figure 2 and 3. In serum triglyceride, there was no significant change in the control group (115.15±37.63mg/dl at baseline and 104.39±52.56mg/dl at month 12) ($p>0.05$, paired t-test), but the study group showed significant decrease from 119.1±54.72mg/dl at baseline to 92.16±49.94mg/dl at month 12 ($p<0.05$, paired t-test). The difference between the two groups was at borderline significance. (p=0.66, Mann-Whitney Test)
Serum total cholesterol did not show significant changes in both two groups and there was not increase of serum cholesterol in the study group after 12 months ($p>0.05$, Mann-Whitney Test).
In the change of weight and BMI, the variables of patients were not of significant change in both groups after 12 months. The difference between the two groups could not be observed. Changes of weight after Estromon® treatment is noted on the Figure 4.
In terms of the absolute and comparative changes of several variables between baseline and month 12, there was no significant statistic difference between baseline and month 12 and between the two groups on serum estrogen, follicular stimulating hormone (FSH), low density lipoprotein (LDL), high density lipoprotein (HDL) and spinal bone density ($p>0.05$, Mann-Whitney test).

Table 5. Change of the variables for 12 months of treatment with Estromon®

	Case			Control			Total		
	post treatment	pre treatment	Mean diffence(%)	post treatment	pre treatment	Mean diffence(%)	post treatment	pre treatment	Mean diffence(%)
L2 BMD (g/cm2)	0.937 ±0.131	0.943 ±0.14	0.12 ±0.04	0.822 ±0.150	0.834 ±0.15	0.012 ±0.05	0.871 ±0.150	0.883 ±0.15	0.012 ±0.04
L3 BMD (g/cm2)	0.983 ±0.150	1.003 ±0.14	0.021 ±0.03	0.88 ±0.155	0.897 ±0.16	0.017 ±0.05	0.926 ±0.159	0.945 ±0.16	0.019 ±0.04
L4 BMD (g/cm2)	1.039 ±0.154	1.044 ±0.15	0.005 ±0.05	0.914 ±0.163	0.922 ±0.17	0.008 ±0.03	0.971 ±0.169	0.977 ±0.17	0.006 ±0.04
L2-4 BMD (g/cm2)	0.987 ±0.139	0.996 ±0.14	0.009 ±0.03	0.768 ±0.154	0.888 ±0.16	0.12 ±0.03	0.926 ±0.156	0.936 ±0.16	0.01 ±0.03
Neck BMD (g/cm2)	0.763 ±0.110	0.746 ±0.10	-0.017 ±0.03*	0.733 ±0.094	0.743 ±0.10	0.01 ±0.04*	0.752 ±0.101	0.744 ±0.10	-0.008 ±0.04
Trochanter BMD (g/cm2)	0.636 ±0.092	0.639 ±0.09	0.003 ±0.02	0.607 ±0.100	0.617 ±0.10	0.01 ±0.07	0.624 ±0.096	0.627 ±0.10	0.003 ±0.05
Inter trochanter BMD (g/cm2)	1.027 ±0.145	1.047 ±0.15	0.02 ±0.4	0.988 ±0.123	1.021 ±0.12	0.033 ±0.05	0.996 ±0.132	1.033 ±0.13	0.037 ±0.0
Total neck BMD (g/cm2)	0.865 ±0.114	0.866 ±0.12	0.001 ±0.04	0.853 ±0.215	0.856 ±0.09	0.003 ±0.22	0.846 ±0.175	0.861 ±0.10	0.015 ±0.16
Ward BMD (g/cm2)	0.605 ±0.115	0.607 ±0.13	0.002 ±0.05	0.56 ±0.129	0.565 ±0.13	0.005 ±0.03	0.577 ±0.123	0.585 ±0.13	0.008 ±0.04
FSH(mlu/ml)	51.8 ±34.30	52.4 ±32.80	0.6 ±23.03	57.59 ±31.53	56.037 ±32.74	-1.553 ±14.63	54.97 ±32.53	54.489 ±32.46	-0.481 ±18.80
E2(pg/ml)	27.97 ±34.03	27.565 ±32.25	-0.405 ±34.14	24.87 ±43.62	21.292 ±24.12	-3.578 ±48.11	26.27 ±39.14	24.02 ±27.79	-2.25 ±41.74
Osteocalcin (ng/ml)	5.66 ±3.01	6.02 ±2.74	0.36 ±2.43**	6.47 ±2.58	6.241 ±3.04	-0.229 ±2.99*	6.1 ±2.78	6.147 ±2.89	0.047 ±2.72
βcross lab (ng/ml)	0.39 ±0.19	0.47 ±0.21	0.08 ±0.14*	0.54 ±0.29	0.591 ±0.30	0.051 ±0.27*	0.47 ±0.26	0.54 ±0.27	0.07 ±0.22
Alkaline Phospate (IU/L)	60.42 ±14.87	73.35 ±21.02	12.93 ±13.11**	71 ±32.54	74.407 ±27.33	3.407 ±11.58**	66.21 ±26.34	73.957 ±24.59	7.747 ±12.63
hGh(ng/ml)	0.92 ±0.97	0.25 ±0.21	-0.67 ±0.54*	0.81 ±0.83	0.573 ±0.71	-0.237 ±0.82*	0.86 ±0.89	0.461 ±0.60	-0.399 ±0.77
IGF-1(ng/ml)	254.05 ±63.14	265.556 ±76.82	11.506 ±36.64	268.65 ±111.69	271.438 ±48.87	2.788 ±42.88	262.05 ±92.19	234.76 ±63.37	-27.29 ±39.84
Fasting Glucose (mg/dl)	96.84 ±11.11	99.4 ±22.58	2.56 ±20.04	96.96 ±10.66	103.296 ±11.30	6.336 ±9.71	96.9 ±10.73	101.638 ±16.93	4.738 ±15.28
Cholesterol (mg/dl)	187.89 ±39.27	182.75 ±36.19	-5.14 ±21.30	208.3 ±46.68	203 ±38.68	-5.3 ±26.56	199.07 ±44.18	194.383 ±38.59	-4.687 ±23.97
HDL (mg/dl)	54.89 ±14.63	46.85 ±8.44	-8.04 ±8.11	52.65 ±14.38	46.815 ±13.13	-5.835 ±10.44	53.67 ±14.36	46.83 ±11.26	-6.84 ±9.38
LDL (mg/dl)	114.57 ±34.90	112.08 ±33.75	-2.49 ±23.81	134.77 ±42.83	133.156 ±33.02	-1.614 ±28.19	125.63 ±40.29	124.187 ±34.61	-1.443 ±25.93
Triglyceride (mg/dl)	92.16 ±49.94	119.1 ±54.72	26.94 ±52.91†	104.39 ±52.56	115.148 ±37.63	10.758 ±56.09†	98.86 ±51.14	116.83 ±45.18	17.97 ±54.57
Weight(kg)	57.5 ±5.86	57.332 ±5.84	-0.168 ±1.62	57.23 ±6.80	57.243 ±6.12	0.013 ±1.53	57.35 ±6.32	57.279 ±5.94	-0.071 ±1.58
WtoH	0.89 ±0.06	0.808 ±0.04	-0.082 ±0.04	0.9 ±0.05	0.834 ±0.04	-0.066 ±0.04	0.89 ±0.05	0.824 ±0.04	-0.066 ±0.04
BMI (kg/m^2)	23.38 ±1.91	23.133 ±1.79	-0.247 ±26.34	23.99 ±2.38	24.123 ±2.12	0.133 ±30.75	23.72 ±2.17	23.714 ±2.03	-0.006 ±28.73

*p < 0.05 (Mann-Whiteney test) **p = 0.08 (Mann-Whiteney test) †p = 0.66 (Mann-Whiteney test)
FSH; Follicuar Stimulating Hormone, hGH; human Growth Hormone, HDL; High Density Lipoprotein, LDL; Low Density Lipoprotein, WtoH; Waist to Hip Ratio, BMI; Body Mass Index

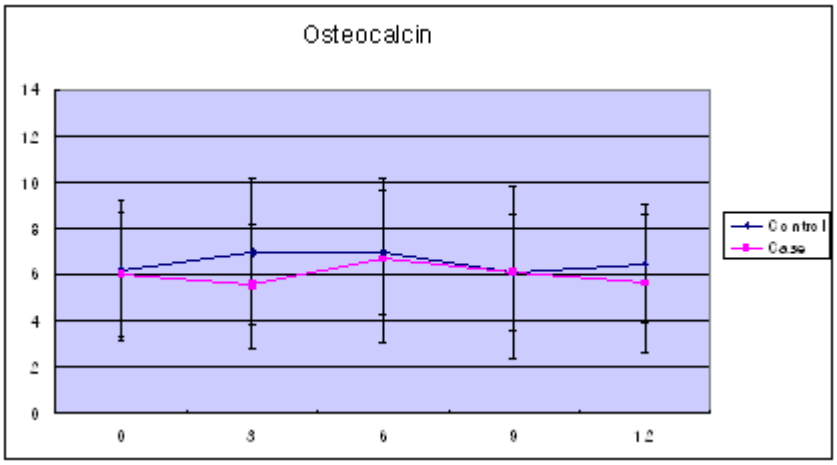

Fig. 1. Change of serum osteocalcin

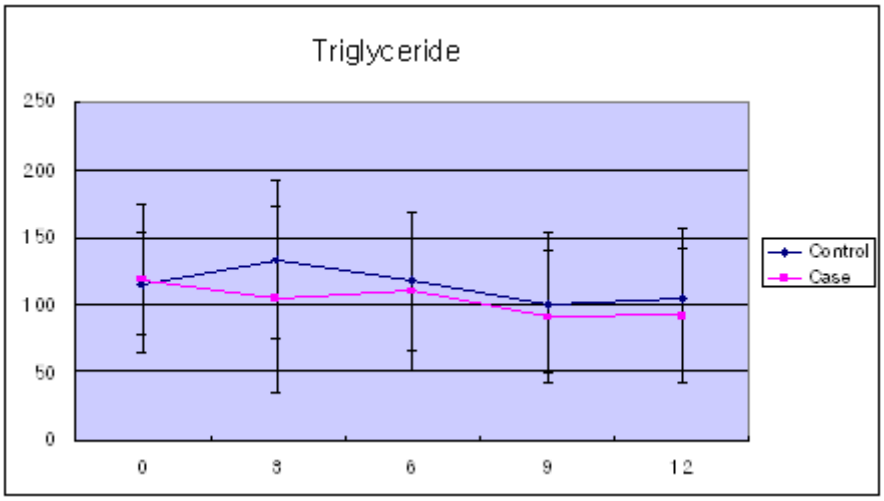

Fig. 2. Change of serum triglyceride

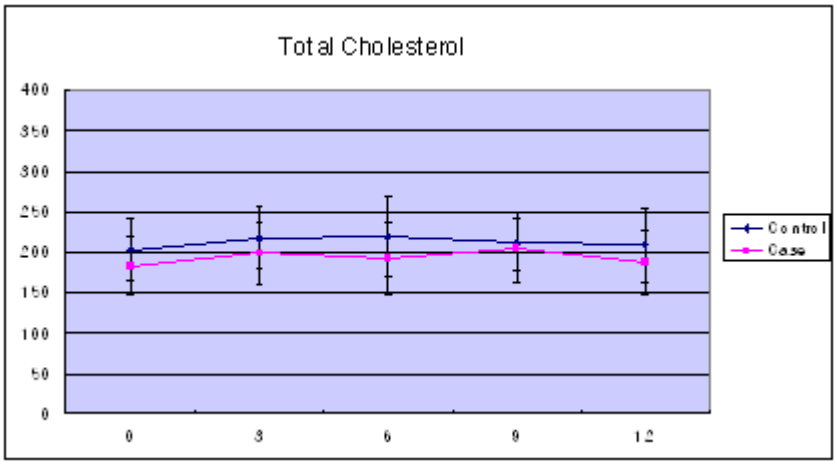

Fig. 3. Change of serum total cholesterol

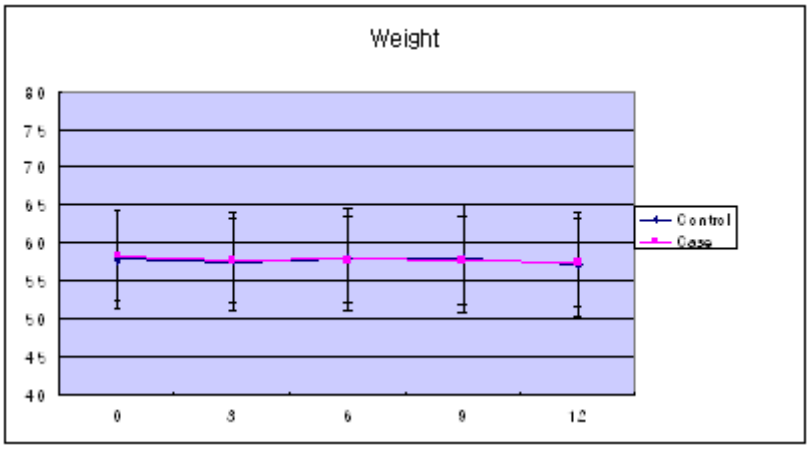

Fig. 4. Change of weight

DISCUSSION

One of the main reasons of menopausal women receiving HRT is to relieve such diverse climacteric symptoms as hot flush, vaginal dryness, joint pain and etc. It is well established that hormone replacement therapy is effective for the climacteric symptoms like hot flush, insomnia, night sweat and relieves memory loss and depressive condition (1, 2, 3, 14, 15, 16). This therapy has been used in clinical area in a long period of time. However estrogen replacement therapy showed some problems of higher risk of breast cancer and coronary artery disease (4, 17, 18, 19, 20). Though HRT is a very effective measure, there are some problems to adopt the therapy as a long-term clinical use or for sole relief of climacteric symptoms besides for the improvement of BMD. In this regard, phytoestrogen as an alternative to HRT have been attracting more interests.

In the patients with menopausal symptoms at baseline, 57.1 % of the study group and 16.7% of the control group were relieved from their symptoms at month 3 (OR=6.67, 95% C.I. 0.49-91.33). In the patients who were not concerned about menopausal symptoms at baseline, 58.3 % of the study group and 21.7% of the control group answered improvements at month 3 (OR=5.04, 95% C.I. 1.40-18.14). As symptom improvement, the total 23 cases of 9 cases of dyspareunia, 5 of hot flush, 1 of sleep disorder, 2 of mental awareness problem, 1 of joint pain, 1 of musculoskeletal disease, 2 of dyspepsia, 1 of urinary incontinence and 1 of fatigue in 14 patients of study group were relieved.

In terms of the absolute and comparative changes of several variables between baseline and month 12, there was no significant statistic difference between the two groups on blood pressure, serum E2, FSH, total cholesterol, LDL and HDL.

In the change of weight and BMI, the change between before and after treatment could not be observed. As described before, serum triglyceride level did not change at month 12 in control group while it has shown the decrease of borderline significance at month 12 by the treatment of Estromon® ($p=0.66$).

According to these results, it is meaningful not to be able to observe the weight increase that is commonly observed with estrogen replacement therapy. In addition, it is also important for serum triglyceride to decrease by Estromon® while HRT increases the level. Serum hGH concentrations increased by 268% from 0.25±0.21ng/ml at baseline to mean 0.92±0.97ng/ml at month 12 in the study group while it increased by only 42% in the control group with statistic significance ($p<0.05$). If a long-term treatment is sustained, it is expected to have the positive effects of human growth hormone such as the enhancement of bone growth, enhancement of gonadotropic hormone secretion, and increase of estradiol secretion (22, 23, 24, 25, 26).

It can be considered that the mechanism of the effects of Estromon® come from sole or complex interactive actions of diverse plant compounds, amino acids, vitamins and minerals. Cynanchum wilfordii is Estromon®'s main raw material contains more than 1.2% of 2,3,5,4'-tetrahyydroxylstilbene-2-0-β-D-glucoside acting as stilbene derivatives. The stilbene derivatives inhibit the damage of DNA, protein, LDL, and cell membrane lipid, and the phenolic ring makes similar binding to estrogen/ER binding to act as agonist and/or antagonist to estrogen (27). On the other hand, there have been no reports that Phlomis umbrosa or Cynanchum wilfordii does not contain the main phytoestrogenic ingredients like coumestrans, isoflavones, genistein, daidzein,

biochanin A, and formononetin (27, 28). Therefore, Estromon® 's mechanism is thought to be indirect action in connection to receptors like selective estrogen receptor modulator (SERM) rather than direct action as isoflavone does. It is necessary to do additional research to confirm the mechanism.

Phlomis umbrosa contains saponin including triterpene glycosides, and Cynanchum wilfordii contains saponin including wilforside and cyanuricuoside(29, 30). Therefore, it can be considered that the saponin activates steroid, among others, estrogen receptor to improve diverse menopausal symptoms (31, 32). In addition, Estromon® contains Angelica gigas, and its decursin acts as coumarin derivatives of phytoestrogen to be able to induce the development of sex organs and help express progesterone and lutenizing hormone receptor (33).

Regarding ossification metabolism, femoral neck bone density was increased by 0.017±0.03 (2.24%) from mean 0.746±0.10g/cm2 at baseline to average 0.763±0.13g/cm2 at month 12 in the study group but showed decrease of 14% in the control group. The BMD improved with statistical significance ($p<0.05$). It is noticeable result considering that most HRT does not improve femoral bone density as well as it does spinal bone density. Serum osteocalcin concentration was decreased in the study group (mean 6.02±2.74ng/m1 at baseline and mean 5.66±3.01ng/ml at month 12) but was increased in the control group at month 12 (mean 6.24±3.04ng/ml at baseline and mean 6.47±2.58ng/ml at month 12). The changes were different significantly ($p<0.05$). Serum ALP concentration also decreased from 73.35±21.02 at baseline to 66.21±4.87 in Estromon® group with borderline significance ($p<0.05$, paired t-test) ($p=0.08$, Mann-Whitney Test). The improvement of the above bone markers enables us to consider that it helps improve bone density in case of long term treatment.

In result, Estromon® can be used to relieve climacteric symptoms as a comparatively safe measure without the increase of body weight. Although it is hard to say Estromon® can be used as a sole agent for improving bone density, it can help treat menopausal syndrome effectively if parallel treatment with other anti-osteoporosis agents is made. With regard to the improved bone markers after the treatment, it is necessary to analyze the change of bone density with bigger scale of study group for longer period of time.

CONCLUSION

Treatment with Estromon® for 3 months in patients with menopausal symptoms showed improvement of climacteric symptoms including hot flush, joint pain and exocrine secretion.

In the treatment of Estromon® for 12 months, human growth hormone was significantly increased, the effect of improvement of bone metabolism markers was shown, and the increase of femoral bone density was observed. However, after Estromon® treatment, the increase of weight and BMI was not shown, the increase of serum triglyceride concentration as is commonly observed with HRT was not observed, rather, the concentration was decreased. In result, while side effects that is common with HRT were not observed for 12 month long treatment, the improvement of menopausal symptoms was confirmed. The treatment of menopausal women with Estromon® is observed to be effective and safe for the improvement of symptoms.

Even if it is hard to say Estromon® can be used as a sole agent for improving bone density now, it can help treat menopausal syndrome effectively if parallel treatment with other anti-osteoporosis agents is made. And, it is necessary to analyze the change of bone density in an additional study with bigger scale of study group for longer period of time.

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