REVIEW

Hormone replacement therapy in postmenopausal women

Toshiyuki Yasui, Hirokazu Uemura, Masaya Takikawa, and Minoru Irahara

Department of Obstetrics and Gynecology, The University of Tokushima School of Medicine, Tokushima, Japan

Abstract : Hormone replacement therapy (HRT) is effective for relieving vasomotor symptoms such as hot flash and vaginal atrophy and for preventing bone loss in postmenopausal and bilaterally ovariectomized women. However, compliance with HRT was reported to be low despite the benefits of HRT. In addition, results of several recent large-scale randomized clinical trials have demonstrated that protection from cardiovascular disease is not an indication for treatment with estrogen and progestin in postmenopausal women.

Recent studies have demonstrated that low-dose HRT is safe and effective for prevention of postmenopausal bone loss. Low-dose HRT has also been shown to be effective for reducing the number and severity of hot flashes, improving vaginal atrophy, and inducing favorable changes in lipids, lipoproteins and hemostatic factors. Moreover, low-dose regimens of CEE (conjugated equine estrogen) and MPA (medroxyprogesterone acetate) result in higher rates of amenorrhea and endometrial protection compared with the conventional dose of HRT. Low-dose HRT may improve the compliance rate and may be more effective than conventional-dose HRT for reducing the risk of breast cancer. On the other hand, it has been shown that transdermal estrogen treatment reduces the incidence and severity of hot flashes and that long-term treatment with transdermally administered estrogen is effective for protection against osteoporosis. Transdermal administration of estrogen is recommended in postmenopausal women with hypertriglycemia because this treatment has little effect on lipid metabolism.

The serum estradiol level was reported to be closely related to estrogenic effects on various tissues. An HRT regimen should be based on the needs of each patient. Serum estradiol levels in women should be maintained at appropriate levels for benefits and not be excessively high in order to prevent side effects. Selection of the most appropriate regimen of HRT (dose, route of administration and schedule) for the needs of the individual are important factors to increase the rate of continuation with HRT. J. Med. Invest. 50 : 136-145, 2003

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BENEFITS AND RISKS IN HRT

The effectiveness of estrogen replacement therapy (ERT) for relief of vasomotor symptoms such as hot flash and vaginal atrophy and for prevention of bone loss in postmenopausal and bilaterally ovariectomized women is well established (1-3). In postmenopausal women with hypercholesterolemia, estrogen is effective for reducing the levels of total cholesterol and low-density lipoprotein-cholesterol (LDL-C) and for increasing the level of high-density lipoprotein-cholesterol (HDL-C)(4, 5). Supplementation of estrogen was also demonstrated to improve endothelium-dependent vasodilatation in postmenopausal women due to augmentation of nitric oxide production (6). In addition, estrogen was reported to be associated with reduced

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Address correspondence and reprint requests to Toshiyuki Yasui, M.D., Ph.D., Department of Obstetrics and Gynecology, The University of Tokushima School of Medicine, Tokushima 770-8503, Japan and Fax : +81-88-631-2630.

risk of Alzheimer's disease (7). In women with an intact uterus, treatment with estrogen and progestin as hormone replacement therapy (HRT) is needed to reduce the incidence of endometrial hyperplasia observed with unopposed estrogen and to reduce the risk of endometrial cancer.

In USA and several countries in Europe, more than 30% of postmenopausal women are receiving HRT. However, compliance with HRT has been reported to be low despite the various benefits of HRT. Many studies have shown that a large percentage of postmenopausal women receiving HRT discontinue treatment within 5 years. Thorp *et al*. reported that only 42% of new HRT drug users continuously took HRT drugs during the first year (8). Ettinger *et al*. demonstrated that the probability of continuation in older women aged 65 years or older was only 38% after 12 months treatment (9). MacLennan *et al*. reported that the ratio of current and past use of HRT drugs in South Australian women was 50 to 60% (10). In addition, the rate of long-term compliance was shown to be lower. Purdie reported that only 48% of women who started HRT were continuing 2 years later (11). Coope *et al*. reported that only 15% of women had continued HRT for over 5 years (12). The most common reasons for discontinuation of HRT have been reported to be side effects such as uterine bleeding, breast tenderness, fear of cancer and anxiety about thrombosis (9, 13).

In Japan, the total sales of estrogen products have increased threefold over the past decade. However, the percentage of postmenopausal women receiving HRT is still smaller than the percentages in Europe and USA. In the Department of Obstetrics and Gynecology of Tokushima University Hospital, the rates of compliance with HRT after one, three and five years in postmenopausal and bilaterally ovariectomized women treated with HRT were 65.4%, 48.5% and 36.9%, respectively (14). The compliance rate was significantly lower in women with an intact uterus than in hysterectomized women. In addition, the rate of early discontinuation of HRT was high ; 43% of the women discontinued HRT after only one visit to our out-patient clinic. Anxiety about HRT and no relief of symptoms were the major reasons for stopping HRT in the first year after beginning HRT, while the percentage of women who discontinued HRT due to side effects such as unacceptable uterine bleeding and breast tenderness increased after one year of HRT.

REPORTS OF THE WOMEN'S HEALTH INITIATIVE

Several recent large-scale randomized clinical trials such as the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) trial have shown that there is no apparent benefit of HRT for risk of atherosclerosis and that protection from cardiovascular disease is not an indication for the use of HRT in postmenopausal women (15, 16). The Women's Health Initiative (WHI) trial, a randomized controlled primary prevention trial in which 16,608 postmenopausal women (50-79 yr. old) with intact uteri participated, was stopped in July, 2002 on the basis of assessment that the overall health risks exceeded health benefits after an average follow-up period of 5.2 years (17). As shown in Table1, this planned 8.5-year randomized clinical trial showed that women taking estrogen (conjugated equine estrogen : CEE) at a dosage of 0.625mg/day and progestin (medroxyprogesterone acetate : MPA) at a dosage of 2.5mg/day were at increased risk for myocardial infarction, stroke, venous thromboembolism and breast cancer compared with women taking a placebo. Although there were decreased risks of osteoporotic fractures and colorectal cancer in the hormone treatment group, an unfavorable global risk-benefit profile was found in this group. The estrogen-alone trial is scheduled to continue until March, 2005. Moreover, the UK Medical Research Council announced that the Women's International Study of long Duration Oestrogen after Menopause (WISDOM) had to be stopped in October, 2002 for scientific and practical reasons (18).

Table 1. Clinical outcomes

Outcomes	Hazard ratio
Coronary heart disease	1.29
Stroke	1.41
Venous thromboembolic disease	2.11
Invasive breast cancer	1.26
Colorectal cancer	0.63
Hip fracture	0.66
Global index	1.15

The global index represents the first event for each participant from among the following types : CHD, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture and death due to other causes. (Writing group for the WHI investigators, JAMA 288, 2002)

In the WHI trial, only one drug regimen, CEE at a dosage of 0.625mg/day and MPA at a dosage of 2.5mg/day, was tested in postmenopausal women. In the report

presenting results of the WHI, it was stated as a limitation of the study that the results do not necessarily apply to lower dosages of these drugs or to estrogens and progestins administered through the transdermal route. Several problems characteristic of the subjects in this trial were also discussed in that report. The women who enrolled in the WHI trial were 50 to 79 years old at the time of recruitment, but participants were not typical users of HRT drugs. In the WHI trial, 36% of the women who underwent HRT had hypertension, 49% were current or past smokers and 34% were obese (body mass index> 30kg/m^2). Therefore, not all women were healthy. Further analysis of the WHI data may be necessary.

LOW-DOSE HRT

The most commonly prescribed estrogen for HRT is conjugated equine estrogen (CEE : Premarin®, Wyeth), which is usually taken orally at a dosage of 0.625mg/day. Medroxyprogesterone acetate (MPA : Provera®, Upjohn) for endometrial protection is the most commonly used progestin for HRT, with typical dosages of 2.5mg/day when taken daily and 5 to 10mg/day for a cycle of 10 to 14 days when administered sequentially. CEE was reported to be effective in preventing bone loss and reducing fracture rates when given orally at a daily dose of 0.625mg, and relatively small doses of CEE (less than 0.625mg/day) were originally found to be ineffective in preventing osteoporosis (19). However, recent studies have demonstrated that low-dose HRT is safe and effective for prevention of postmenopausal bone loss (20, 21). Dosages of estrogens that are considered to be low are shown in Table 2 (20). Ettinger *et al*. and Webber *et al*. demonstrated that CEE at a daily dose of 0.31mg with calcium supplementation of 1,000 mg/day was effective in preventing postmenopausal bone loss (22, 23). Mizunuma *et al*. reported that HRT using 0.31 mg of CEE can increase lumbar bone mineral density (BMD) in Japanese postmenopausal women (24). Recker *et al*. demonstrated that continuous low-dose HRT with CEE (0.3mg) and MPA (2.5mg) combined with adequate calcium and vitamin D supplementation provides a bone-sparing effect that is similar or superior to that provided by higher-dose HRT regimens in elderly postmenopausal women (25). Prestwood *et al*. also reported that low-dose estrogen treatment with calcium and vitamin D decreased bone resorption and increased bone mass in older women (26). As shown in Figure 1, Lindsay *et al*., who recently carried out a large-scale, randomized, placebo-controlled study, demonstrated that lower doses of CEEs (0.45 and 0.3mg/day) prevented the loss of spine and hip BMD and reduced bone turnover (27).

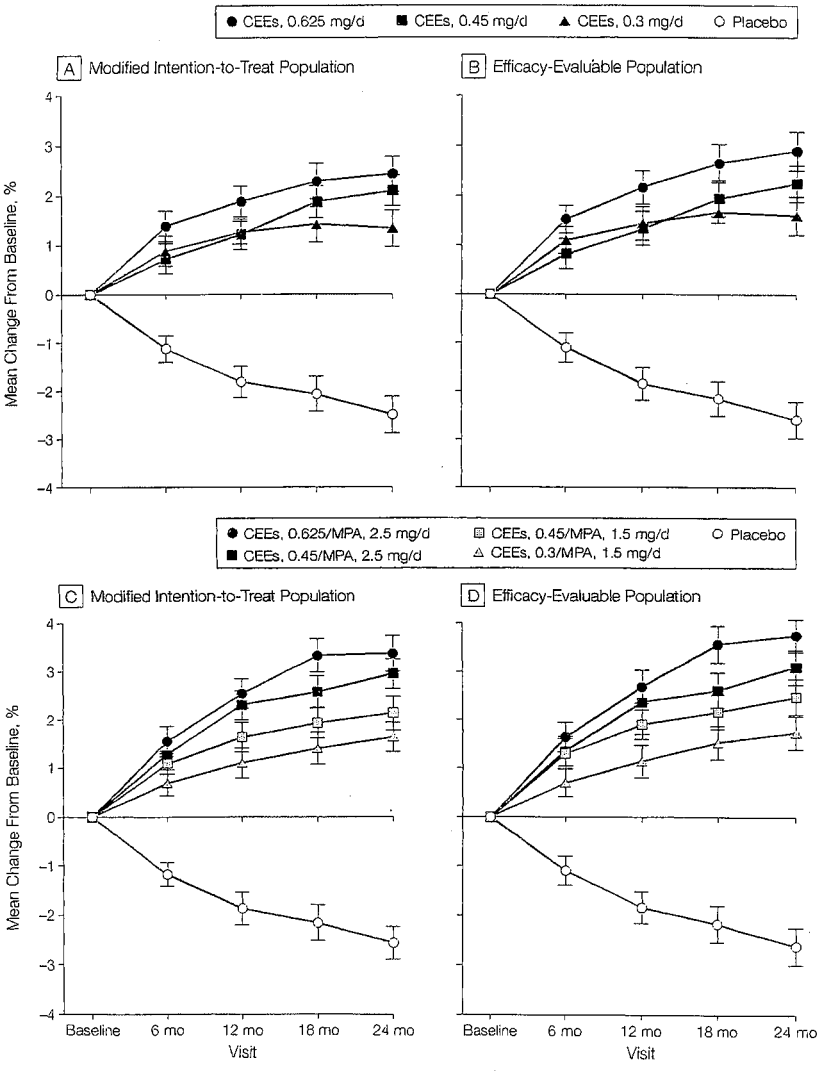

Fig.1. Spine bone mineral density changes for modified intention-to-treat and efficacy-evaluable populations for conjugated equine estrogens (CEEs) alone and CEEs-medroxyprogesterone acetate (MPA) groups.
Adjusted mean percentage changes (SE) in spine BMD over time are shown for the modified intention-to-treat (A and C) and efficacy-evaluable (B and D) populations for both the CEEs alone (A, B) and CEEs-MPA groups (C, D). The placebo group is displayed in all graphs. Changes were significantly different ($p<0.05$) from baseline and placebo for all active treatment groups at all time points.
(Lindsay et al., JAMA 287, 2002)

Table 2. Low-dose estrogen preparations

	Estrogen	Dosage (mg/day)
Oral	Conjugated equine estrogen	0.3
	Esterified estrogen	0.3
	Micronized estradiol	0.5
Transdermal	17 β-Estradiol	0.025

Differences of opinion exist on estrogen dosages that qualify as "low dose". In the USA, dosages below 0.625 mg conjugated equine estrogens (CEE)(or equivalent) are generally considered low dose. Outside the USA, some clinicians define therapy with 0.625mg/day CEE (or equivalent) as low-dose. (Lobo *et al.*, Climacteric 4, 2001)

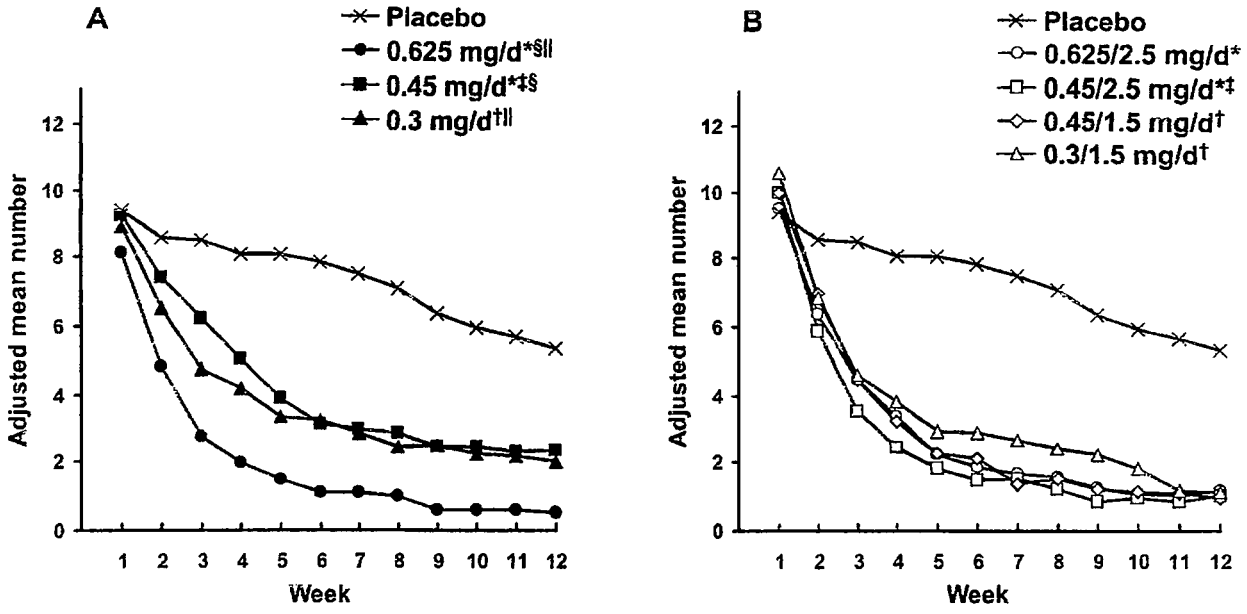

Fig.2. Mean daily number of hot flashes by week are shown for the eight treatment groups. A:The placebo and the CEE alone groups. B : The placebo and the CEE/MPA groups. Data are adjusted for baseline. All values for mean number of hot flashes (unadjusted) were significantly less than baseline ($p<0.05$), except CEE 0.3/MPA 1.5 at week one.
*Difference from placebo was significant ($p<0.05$) from weeks 2 through 12.
† Difference from placebo was significant ($p<0.05$) from weeks 3 through 12.
‡ Difference from CEE 0.45 and CEE 0.45/MPA 2.5 was significant ($p<0.05$) at weeks 3,4,5 and 9.
§ Difference between CEE 0.625 and CEE 0.45 was significant ($p<0.05$) from weeks 2 through 12.
‖ Difference between CEE 0.625 and CEE 0.3 was significant ($p<0.05$) at weeks 4,5,6,9,10 and 12.
(Utian *et al.*, Fertil Steril 75, 2001)

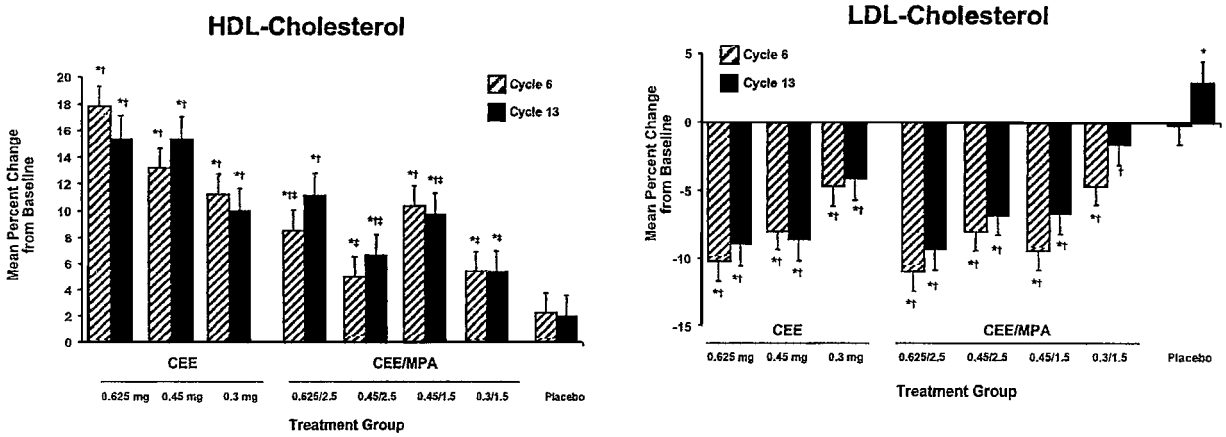

Fig.3. Mean percent changes from baseline (±SE) are shown for HDL-C (left panel) and LDL-C (right panel) for all treatment groups after cycle 6 and cycle 13.*$p<0.05$ vs. baseline ; † $p<0.05$ vs. placebo ; ‡ $p<0.05$ vs. comparable dose of CEE alone
(Lobo *et al.*, Fertil Steril 76, 2001)

Low-dose HRT was also effective in decreasing the number and severity of hot flashes and in improving vaginal atrophy in postmenopausal women (Fig.2)(28) in addition to inducing favorable changes in lipids, lipoproteins and hemostatic factors (Fig.3)(29). A recent Nurses Health Study report noted that administration of low-dose HRT reduced the incidence of cardiovascular disease (30). Sanada *et al*. reported that low-dose CEE plus MPA similar to conventional-dose CEE plus MPA augmented endothelial function in forearm resistance arteries and decreased malondialdehyde-modified LDL levels (31). Goudev *et al*. revealed that low-dose HRT with 17β-estradiol and norethisterone acetate reduced the serum levels of intercellular adhesion molecules, vascular cell adhesion molecules and P-selectin, which are associated with cardiovascular risk (32). Moreover, low-dose regimens of CEE and MPA result in higher rates of amenorrhea, no bleeding and endometrial protection compared with 0.625mg CEE and 2.5mg MPA per day (33, 34). These findings suggest that low-dose HRT may improve the compliance rate because low-dose HRT causes minimal spotting and breast tenderness and less progestogen-related adverse effects and possibly reduces the risk of cancer. The establishment of low-dose formulaions with potentially fewer side effects is important for enhancing patient acceptance and continuance of HRT. Recently, low-dose HRT has also been shown to result in a better quality of life (35).

In Japan, CEE at a dosage of 0.3125mg was not available in principle. Serum estradiol levels in subjects in the present study who were treated with CEE and MPA every other day were found to be significantly lower than those in subjects who were treated every day (36), and treatment with CEE and MPA every other day could be regarded as low-dose HRT. We showed that HRT with CEE and MPA every other day was effective for relieving vasomotor symptoms and preventing bone loss and was associated with fewer side effects, such as unscheduled bleeding or breast tenderness, while it showed no beneficial effects on lipid profile (36). HRT administered every other day at a low dose is also a choice of treatment for preventing unscheduled uterine bleeding and breast tenderness.

TRANSDERMAL ESTROGEN TREATMENT

Estrogen administered transdermally has been shown to reduce the incidence and severity of hot flashes (37). Long-term treatment with transdermal estrogen has been effective for preventing osteoporosis (38). However, the effect of transdermal estrogen therapy on lipid metabolism was reported to be weak because estrogen administered transdermally is absorbed directly into the systemic circulation, avoiding hepatic first-pass metabolism, while estrogen administered orally directly enters hepatic circulation and affects lipid metabolism in the liver. Thus, changes in lipid profiles in the case of treatment with transdermal estrogen are smaller than those in the case of treatment with oral estrogen.

On the other hand, hypertriglyceridemia is also a risk factor for coronary heart disease. McNamara *et al*. suggested that the plasma triglyceride level is the single most important factor affecting the size of LDL particles (39). Oral estrogen therapy with CEE was reported to increase the plasma concentration of triglyceride and reduce the size of LDL particles, while transdermal estrogen therapy was demonstrated to decrease the plasma concentration of triglyceride and increase the size of LDL particles (40). Small sizes of LDL particles are associated with increased risk of coronary heart disease because they are more susceptible to oxidative modification, an initial step in the atherosclerotic process. Thus, transdermal estrogen treatment is recommended for postmenopausal women with hypertriglyceridemia.

ESTROGEN THRESHOLD HYPOTHESIS

The serum estradiol level was reported to be closely related to the estrogenic effects on various tissues (41, 42). As shown in Fig.4, the hierarchy of the most-sensitive to least-sensitive estrogen-responsive process is in the order of calcium turnover, gonadotropin secretion, vasomotor symptoms, vaginal epithelial growth, lipid production and liver protein production such as sex hormone-binding globulin production (41). In a similar manner, estradiol-dependent disease processes also appear to have a hierarchy of responsiveness to estradiol. Breast cancer can be very sensitive to the growth-promoting effect of estradiol at concentrations as low as 10 to 20pg/ml. To reduce myoma volume in premenopausal women by 50%, serum estradiol concentrations in the range of 15 to 25pg/ml must be achieved. A serum estradiol level about 30pg/ml induces regression of endometriotic lesions. The hierarchy of the most-sensitive to least-sensitive estrogen-response disease processes appears to be in order of breast cancer, myomas and endometriosis.

A relation between estradiol level and BMD of the lumbar spine in postmenopausal women who have been continuously taking esterified estrogen medication has been demonstrated (43). However, it is not known whether there is a relation between serum estradiol level

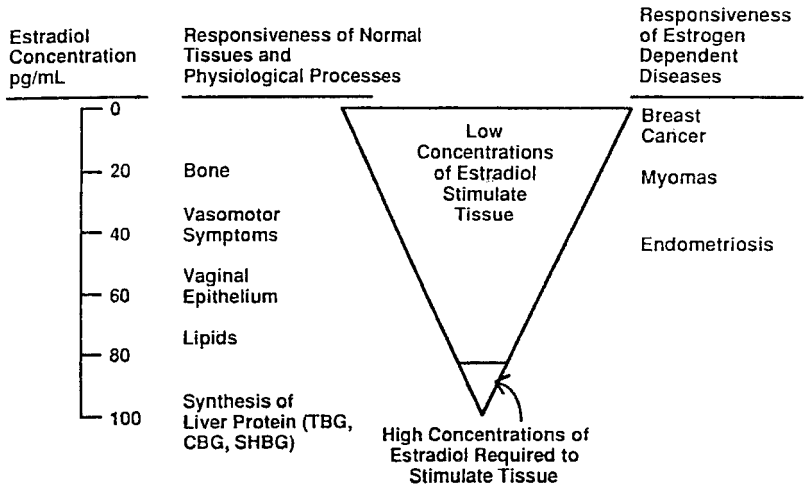

Fig.4. Hierarchy of tissue and disease response to various concentrations. Calcium metabolism and bone may be more sensitive to estradiol than vaginal epithelium and lipid metabolism. TBG: thyroid-binding globulin; CBG: cortisol-binding globulin; SHBG: sex hormone-binding globulin
(Barbieri *et al*., Am J Obstet Gynecol 166, 1992)

and BMD in women treated with CEE. CEE, which is the most commonly prescribed drug for HRT worldwide, is a unique complex of at least 10natural estrogens. Thus, precise measurement of serum estradiol levels in women receiving oral CEE is difficult. For postmenopausal women receiving CEE for HRT, extraction of sex steroid hormones from serum before the assay is needed for measurement of serum levels of estradiol. We have developed a highly sensitive and specific assay using high-performance liquid chromatography (HPLC) for purification and a radioimmunoassay (RIA) for measurement of serum estrone and estradiol levels, and reported the precise levels of estrone and estradiol in women undergoing oral CEE treatment (44). The mean serum estradiol level measured by HPLC-RIA was 22.8pg/ml, while that measured using a conventional RIA kit was 76.2 pg/ml. We also measured serum levels of estradiol in postmenopausal women receiving CEE (0.625mg) and MPA (2.5mg) every other day and every day, and we showed that there was a relation between serum estradiol level and BMD of the lumbar spine (45).

ENDOGENOUS ESTROGEN

The need for estrogen replacement therapy may depend on the amount of endogenous estrogen being synthesized and estrogen threshold for a relevant organ (e.g., brain, bone and heart). Thus, the level of endogenous estrogen is also an important factor in the administration of exogenous estrogen such as HRT. Endogenous estrogen level is known to be closely related with body mass index (46). Women who are heavier or who have a greater body mass index have been reported to have higher levels of estrogen, due to the aromatization of gonadal steroid hormone precursors in fat and muscle tissue (47-50).

Recent studies using highly sensitive methods to measure serum estradiol levels have provided evidence of beneficial effects of very low levels of circulating estrogens on bone. Cummings *et al*. found that women 65 years of age or older with low but detectable levels of serum estradiol (ranging from 5 to 9 pg/ml) had a significantly lower risk of hip or vertebral fractures than did women with undetectable levels (less than 5pg/ml) (51). In a different sample of women randomly selected from the same cohort, Ettinger *et al*. found that women with estradiol levels below 5pg/ml had substantially less BMD at all sites measured than did women with levels in the range of 10 to 25pg/ml (52). Thus, higher endogenous estradiol levels are associated with increased bone density, reduced bone loss and reduced fracture incidence in elderly women. In addition, low endogenous estradiol levels in postmenopausal women were found to be related to appearance of hot flash (53). On the other hand, the relative risk for breast cancer in women with very high endogenous estradiol levels was significantly higher than that in women with very low estradiol levels (54). The results of the MORE trial showed that the risk of breast cancer in women with an endogenous estradiol level of greater than 10pmol/l was higher than that in women with an undetectable estradiol level (55).

The relation between endogenous estrogen and its effect on various tissues in Japanese postmenopausal women is not clear. We precisely measured the level of endogenous estrogen by the HPLC-RIA method whose sensitivity of estrone and estradiol levels was 5 and 2pg/ml, respectively. A study of the relation between endogenous estrogen level and BMD of the lumbar spine in postmenopausal women revealed that

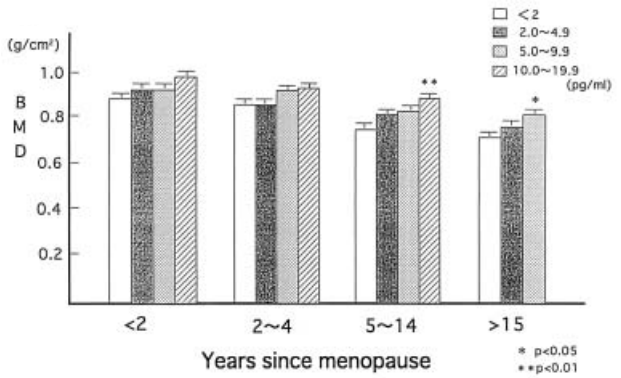

Fig.5. Bone mineral density grouped by level of endogenous estradiol.

women with estradiol levels below 2pg/ml for whom more than 5years had passed since menopause had less spine BMD than did women with levels in the range of 10 to 20pg/ml (Fig.5)(56).

INDIVIDUALIZED HRT

It was reported that ERT reduces the risk of edentulism and protects against loss of teeth (57). ERT was also reported to have a protective effect on lenses in postmenopausal women (58). In addition, Zandi *et al*. suggested that the higher risk of Alzheimer's disease for women than for men in old age might disappear if women were to undergo long-term postmenpausal HRT (Fig.6)(59). Thus, there is great interest in further development of low-dose HRT and transdermal estrogen therapy. These regimens with fewer side effects in addition to various effects on several tissues, will be important for the future of HRT.

An appropriate HRT regimen should be selected to suit the individual in terms of risks, benefits and preferences (60). Various basic characteristics of individuals such as endogenous estrogen level, BMI, smoking and the state of glucose metabolism are important, and selection of the most appropriate regimen of HRT (dose, route of administration and schedule) for the needs of the individual are important factors for continuation of HRT. Alternative treatments, such as herbal medicines and soy proteins for improvement of vasomotor symptoms and selective estrogen receptor modulators and bisphosphonate for maintenance of bone mineral density, may be also selected. A plan for treatment over a 1-year period should be made, and adjustments may be made after 1 year with consideration given to individual needs, benefits and risks based on results of examination.

Clinicians should become experts in tailoring HRT to accord with the characteristics and needs of each woman.

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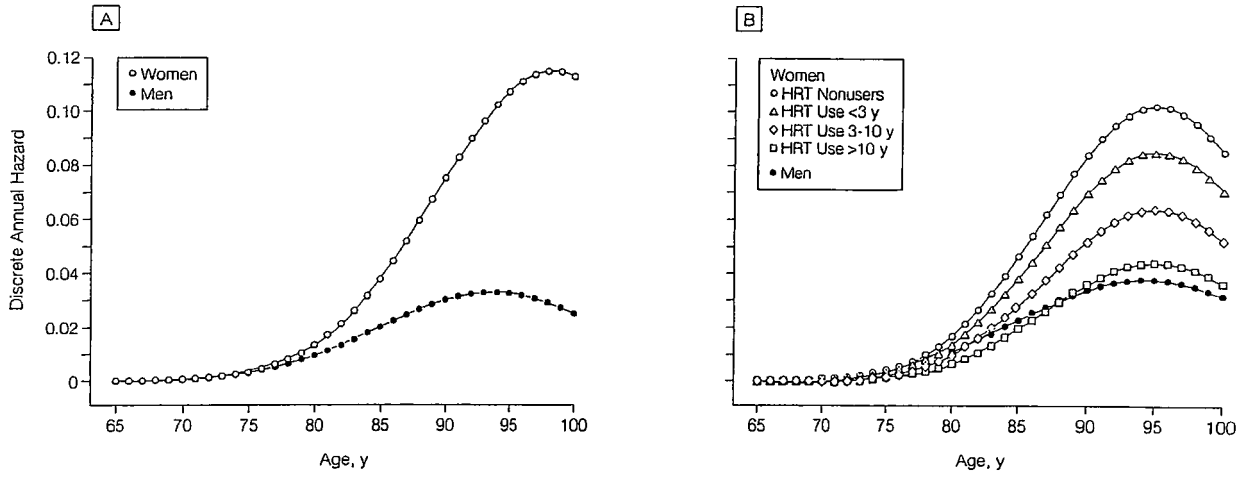

Fig.6. Estimated discrete annual hazard of Alzheimer disease for men and women by age, and by duration of hormone replacement therapy use for women. Both figures indicate risks estimated for an individual with the mean value of 13 years of education and no e4 alleles at POE. A : The curves depict the annual hazards predicted by fitting the base model including an age-by-sex interaction term. B : The curves depict the annual hazards predicted by fitting model 7 to the women with available hormone replacement therapy exposure information and, in filled circles, the corresponding annual hazards for men after omitting the terms for HRT. (Zandi *et al*., JAMA 288, 2002)

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