Transdermal 17β-estradiol for Preventing Postmenopausal Bone Loss

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To the Editor,

We were interested to read the report by Yang et al, "A clinical trial of 3 doses of transdermal 17β-estradiol for preventing postmenopausal bone loss: a preliminary study".[1] The authors provided a useful clinical observation, showing that the use of low-dose estradiol gel at the dose of 1.25 g/day (equivalent to 17β-estradiol 0.75 mg/day) could effectively prevent bone loss in postmenopausal women after a 12-month treatment period.

We were greatly concerned, however, about the recommendation from the authors. Postmenopausal osteoporosis following vertebral and/or non-vertebral fracture is an important health issue because it results in a significant increase in morbidity and mortality in postmenopausal women. For decades, conventional hormone therapy (HT), mainly with estrogen plus progestin (EPT), has been the mainstay therapy not only for relieving climacteric symptoms but also for preventing and treating postmenopausal osteoporosis.[2] However, because the significant risk is greater than the benefit, with a resultant low acceptable benefit/risk ratio, HT should not be recommended as a therapeutic strategy for preventing and treating osteoporosis in routine practice in postmenopausal women without vasomotor symptoms.[3] We were disappointed to read the authors' positive recommendation of HT for the cardiovascular system. In the text, the authors commented that HT could reduce morbidity and mortality from cardiovascular disease, although the authors cited 4 published articles to support their recommendation. From the results of the Women's Health Initiative (WHI), one can conclude that, in women with osteoporosis and cardiovascular risk factors, HT should be avoided in favor of alternative antiresorptive agents,[4] and that HT remains an option only for short-term early use around the menopause in symptomatic younger women with high risk of fracture.[4] The post-WHI turmoil was actually focused on the risks of therapy, although data from more recent publications "surprisingly" indicated that risk may vary with type of hormone, dosage, route of administration, duration of treatment, and patient age, suggesting that the use of HT and the increased cardiovascular risk is still doubtful.[5–7]

We are interested to know why the authors used estriol 2 mg/day as their control group. A number of small-scale trials of poor methodologic design have been conducted to assess the efficacy of estriol, which is widely used in Japan and Europe as HT, mostly together with other estrogens, for the treatment of urogenital atrophy or climacteric symptoms.[8] The effectiveness of the treatment of climacteric symptoms with estriol use only is doubtful. In addition, 3 studies failed to detect significant protection from bone loss,[9–12] although 2 other studies favored the effectiveness of bone protection in the use of estriol.[13,14]

Finally, we do not agree with the authors' conclusion that the therapeutic effect of estradiol gel on bone mass was more prominent in the surgical menopausal groups at the dosage of 2.5 g/day. In addition, we look forward to learning the reason why the authors suggested the effectiveness dose of estradiol gel as 1.25 g/day. From either Figure 1 or Figure 2, the most effective dose for increasing bone mass density was 5 g/day.[1] We already know the fact that the increased bone mass density is not equal to the increased bone quality.[15]

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References

1. Yang TS, Chen YJ, Liang WH, Chang CY, Tai LC, Chang SP, Ng HT. A clinical trial of 3 doses of transdermal 17β-estradiol for preventing postmenopausal bone loss: a preliminary study. *J Chin Med Assoc* 2007;70:200–6.
2. Wang PH, Horng HC, Cheng MH, Chao HT, Chao KC. Standard and low-dose hormone therapy for postmenopausal women—focus on the breast. *Taiwan J Obstet Gynecol* 2007; 46:127–34.
3. Levine JP. Pharmacologic and nonpharmacologic management of osteoporosis. *Clin Cornerstone* 2006;8:40–53.
4. Sambrook P, Cooper C. Osteoporosis. *Lancet* 2006;367:2010–8.
5. Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, Kuller LH, et al; WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med* 2007;356:2591–602.
6. Haney AF, Wild RA. Options for hormone therapy in women who have had a hysterectomy. *Menopause* 2007;14:592–7.
7. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77.
8. Cirigliano M. Bioidentical hormone therapy: a review of the evidence. *J Womens Health (Larchmt)* 2007;16:600–31.
9. Takahashi K, Manabe A, Okada M, Kurioka H, Kanasaki H, Miyazaki K. Efficacy and safety of oral estriol for managing postmenopausal symptoms. *Maturitas* 2000;34:169–77.
10. Takahashi K, Okada M, Ozaki T, Kurioka H, Manabe A, Kanasaki H, Miyazaki K. Safety and efficacy of oestriol for symptoms of natural or surgically induced menopause. *Hum Reprod* 2000;15:1028–36.
11. Yang TS, Tsan SH, Chang SP, Ng HT. Efficacy and safety of estriol replacement therapy for climacteric women. *J Chin Med Assoc* 1995;55:386–91.
12. Lindsay R, Hart DM, MacLean A, Garwood J, Clark AC, Kraszewski A. Bone loss during oestriol therapy in post-menopausal women. *Maturitas* 1979;1:279–85.
13. Terauchi M, Obayashi S, Aso T. Estriol, conjugated equine estrogens, and alendronate therapy for osteoporosis. *Int J Gynaecol Obstet* 2006;92:141–2.
14. Minaguchi H, Uemura T, Shirasu K, Sato A, Tsukikawa S, Ibuki Y, Mizunuma H, et al. Effect of estriol on bone loss in postmenopausal Japanese women: a multicenter prospective open study. *J Obstet Gynaecol Res* 1996;22:259– 65.
15. Recker RR, Kendler D, Recknor CP, Rooney TW, Lewiecki EM, Utian WH, Cauley JA, et al. Comparative effects of raloxifene and alendronate on fracture outcomes in postmenopausal women with low bone mass. *Bone* 2007;40:843–51.

REPLY

A Clinical Trial of 3 Doses of Transdermal 17β-estradiol for Preventing Postmenopausal Bone Loss: A Preliminary Study

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To the Editor,

We would like to respond to the letter from Wen-Ling Lee, Hsiang-Tai Chao and Peng-Hui Wang. First, thank you for your important comments on our paper.

Second, you mention that recent randomized clinical trials of postmenopausal hormone therapy (HT) have informed clinical decision-making, but several key questions remain unanswered. Observation studies suggest that HT prevents coronary heart disease

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(CHD), whereas randomized clinical trial has not confirmed a cardioprotective effect. A major difference between participants in observational studies and those in clinical trials is timing of initiation of HT in relation to menopause onset. Women taking postmenopausal hormones in observational studies typically start therapy in early postmenopause, whereas clinical trial participants are often randomly assigned to hormones long after menses have ceased. In the United States, the average age at menopause is 51 years. The 20-year Nurses' Health Study (NHS) is 1 of the largest prospective investigations of HT and CHD incidence. The baseline ages of NHS participants ranged from 30 to 55 years, and approximately 80% of cohort members who opted to use HT did so within 2 years of menopause. Among 70,533 postmenopausal participants, current use of HT was associated with a relative risk of a major coronary event of 0.61 (95% confidence interval, 0.52–0.71). In contrast, the mean baseline ages of the Women's Health Initiative (WHI) study and the Heart and Estrogen/progestin Replacement Study (HERS) were 63 and 67 years, respectively; the majority of these women had been postmenopausal for more than a decade at the time of enrolment.

Administration of exogenous hormones immediately after oophorectomy, during the early stages of atherosclerosis, reduced the extent of plaque by 50%.[1] Most atherosclerosis progression (imaging) trials in humans have been conducted among women with significant coronary lesions at baseline and have not shown estrogen to be effective in slowing the rate of arterial narrowing.[2,3] However, 1 study of younger postmenopausal women (50–59 years old) showed that the calcified plaque burden in the coronary arteries was lower in women assigned to estrogen than in those assigned to placebo.[4] The Estrogen in the Prevention of Atherosclerosis Trial (EPAT), which did not require participants to have significant lesions at entry, found that micronized 17β-estradiol did retard the progression of carotid atherosclerosis.[5] Subgroup analysis of WHI data also revealed that women who had initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause.[6]

Transdermal estrogen may be less thrombogenic than oral estrogen. The data from recent case-control studies in France and the Estrogen and Thromboembolism Risk (ESTHER) study showed that transdermal estrogen was not associated with venous thromboembolism. There is now a critical mass of data to support the hypothesis that time since menopause and route of estrogen administration may importantly influence the benefit–risk ratio associated with HT. Thus, a 5-year randomized trial (the Kronos Early Estrogen Prevention Study) will evaluate the effectiveness of low-dose oral estrogen and transdermal estradiol in preventing progression of atherosclerosis in recently postmenopausal women.

Third, we used estriol 2 mg/day as the control group to prevent a high dropout rate in the HT study. According to our experience, if we use placebo control for early postmenopausal women, the dropout rate would be about 40–50%.

Fourth, effective low dose is the current trend for HT. Current evidence from controlled trials indicates that low-dose HT appears effective and safe. This makes it a good choice for the alleviation of climacteric symptoms, and for this purpose, long-term administration of low-dose HT does not seem to impose serious health risks.[7,8] Thus, we suggest estradiol gel of 1.25 g/day.

References

1. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res* 2002;53: 605–19.
2. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, Ouyang P, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288:2432–40.
3. Hodis HN, Mack WJ, Azen SP, Lobo RA, Shoupe D, Mahrer PR, Faxon DP, et al; Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial Research Group. Hormone therapy and the progression of coronary artery atherosclerosis in postmenopausal women. *N Engl J Med* 2003; 349:535–45.
4. Manson JE, Allison MA, Rossouw JE, Carr JJ, Langer RD, Hsia J, Kuller LH, et al; WHI and WHI-CACS Investigators. Estrogen therapy and coronary artery calcification. *N Engl J Med* 2007;356:2591–602.
5. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, Selzer RH, et al; Estrogen in the Prevention of Atherosclerosis Trial Research Group. Estrogen in the prevention of atherosclerosis: randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;135:939–53.
6. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, Ko M, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77.
7. van de Weijer PH, Mattsson LA, Ylikorkala O. Benefits and risks of long-term low-dose oral continuous combined hormone therapy. *Maturitas* 2007;56:231–48.
8. Cagnacci A, Generali M, Pirillo D, Baldassari F, Volpe A. Effects of low- or high-dose hormone therapy on fasting and post-methionine homocysteine levels in postmenopausal women. *Climacteric* 2006;9:388–95.