ESTROGEN THERAPY IN POSTMENOPAUSAL OSTEOPOROSIS WHAT WE KNOW AND WHAT WE DON'T*

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SUMMARY. - Replacement estrogen therapy is of proven efficacy for the prevention and treatment of postmenopausal bone loss. Oral and transdermal 17β estradiol have provided similar benefits in clinical studies. The lowest effective doses are 0.625 mg per day for conjugated estrogens, 2 mg per day for oral 17β estradiol, 1.5 µg per day for 17β estradiol gel, and 50-µg 17β estradiol patch per day. Bone mineral density should be monitored if lower doses are used. Several epidemiologic studies found that a decrease in the incidence of osteoporotic fractures was achieved only when the duration of estrogen replacement therapy exceeded seven years. It follows that replacement therapy should be started at cessation of menses, if possible. However delayed replacement therapy (i.e., at 65 years of age) is unquestionably effective.

RÉSUMÉ. - *Estrogénothérapie et ostéoporose post-ménopausique : les certitudes et les problèmes.* - Le traitement estrogénique substitutif est reconnu comme efficace dans la prévention et le traitement de l'ostéoporose post-ménopausique. Le 17 β estradiol peut être administré par voie orale ou transcutanée avec, dans les études cliniques, une efficacité comparable. Des doses minimales efficaces ont été établies : 0,625 mg pour les estrogènes conjugués équins, et, pour le 17β estradiol, 2 mg pour la voie orale, 1,5 mg pour le gel et 50 µg pour le patch. Lors de l'utilisation de doses inférieures la surveillance densitométrique est nécessaire. Selon plusieurs études épidémiologiques seuls les traitements prolongés (au moins à 7 ans) peuvent réduire l'incidence des fractures ostéoporotiques. Dans la pratique cela pose le problème du moment optimal d'instauration du traitement hormonal. Il est logique de le débuter à la ménopause. Un début dit tardif (à 65 ans) du traitement hormonal garde néanmoins toute son efficacité.

Key words: **Estrogen - Osteoporosis - Menopause - Densitometry.**

Mots clés : **Estrogènes - Ostéoporose - Ménopause - Densitométrie.**

The efficacy of hormone replacement therapy in the prevention and treatment of postmenopausal osteoporosis is widely recognized [1]. Other benefits include favorable effects on many immediate and delayed postmenopausal changes. Lipid parameters improve and this, together with a direct effect on blood vessel walls, probably reduces the cardiovascular risk. Studies are under way to determine whether hormone replacement therapy protects against Alzheimer's disease. The breast cancer risk in patients under hormone replacement therapy has been investigated in many studies, with conflicting results [1,2].

Rheumatologists are frequently called upon to provide advice regarding the appropriateness of hormone replacement therapy in a postmenopausal patient [3]. This advice should be based on a number of «bone» criteria, which are discussed below.

WHICH ROUTE OF ADMINISTRATION?

Estrogens can be given orally (conjugated estrogens or 17β estradiol) or transdermally (17β estradiol in a gel or patch). Both these routes are

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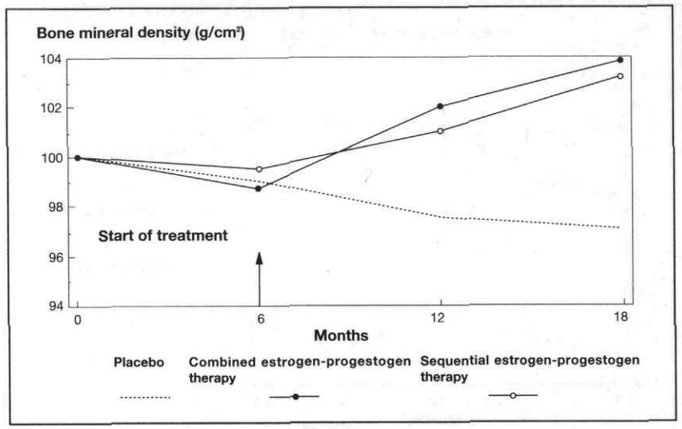

Fig. 1. - Change in bone mineral density at the spine (% of baseline). Comparison of continuous and sequential oral therapy. From Munk-Jensen et al. [5].

associated with a transient increase in bone mass. This effect was demonstrated as early as 1981 by a study of continuous sequential therapy with 4 mg then 1 mg of oral 17β estradiol [4]. Subsequently, a prospective, randomized, placebo-controlled study in 151 women [5] showed that oral estradiol in a dose of 2 mg per day for 18 months produced a 3 to 4% increase in bone mass, which translated into a 5 to 6% advantage over the placebo group (Fig. 1). In a prospective open study in 40 women who were less than five years postmenopausal [6], 1.5 mg per day of 17β estradiol as a gel, plus a progestogen ten days per month, induced a 5% increase in bone mass over a two-year period. Also, a prospective two-year study of the same treatment versus estriol [7] in 39 women demonstrated an annual bone mass increase of 1.2% with an arrest in bone loss at the femur. An open controlled study [8] found similar effects with 0.625 mg/day conjugated estrogens (n=17) or 1.5 mg/day 17β estradiol in a gel (n=20) given for two years, with an increase in spinal bone mass of 4.1% and 5.6% in these two groups, respectively (Fig. 2). In a prospective randomized study in 118 oophorectomized women [9], a 50 µg 17β estradiol patch applied each day 24 days per month produced a 2.8% increase in vertebral bone mass over a one-year period; similar results were obtained with 0.625 mg/day conjugated estrogens given orally 27 days per month. Two randomized studies [10,11] found comparable effects on bone mineral density with a 17β estradiol patch (one 50-µg patch per day for 28 days, with addition of 0.25 mg/day norethisterone acetate for 14 days) and with 0.625 mg/day oral conjugated estrogens for 28 days, with addition of 0.15 mg/day norgestrel for 12 days: bone mineral density was increased at the spine and femoral neck by about 2.5% after 18 months and 1% after three years, with no significant differences between the oral and transdermal routes (Fig..3). Effects on bone mass have also been similar with the gel and patch forms of 17β estradiol. For instance, in an open controlled study [12], 94 postmenopausal women were divided into three groups that were comparable in terms of time since menopause, height, and weight. Two groups received 17β estradiol in a patch or gel, respectively, and the third group served as the control. The 17β estradiol dose was one 50-µg patch per day or 1.5 mg in a gel per day, 21 days per month, with a progestogen during the last ten days of the sequence (progesterone, dihydrogesterone, or promegestone). After two years, a comparable increase in bone mass was seen in the two treatment groups (4.4% with the patch and 5.2% with the gel), whereas bone mass decreased by 4% in the control group (Fig. 4).

HOW LONG?

Three years is the longest follow-up in available prospective bone mineral density studies. Some evidence that bone loss may resume at a slow rate after several years under hormone replacement therapy has been reported [13,14], and further work on this point is needed.

The optimal duration of hormone replacement therapy should be determined based on expected effects on the fracture risk. Case-control and cohort studies have suggested an up to 50% decrease in the fracture risk under replacement therapy, with the effect being most marked at the femoral neck [1,15-21]. In one study [16], the relative risk of fracture was 0.8 to 0.9 during the first four years of replacement therapy but fell to 0.4-0.5 after five

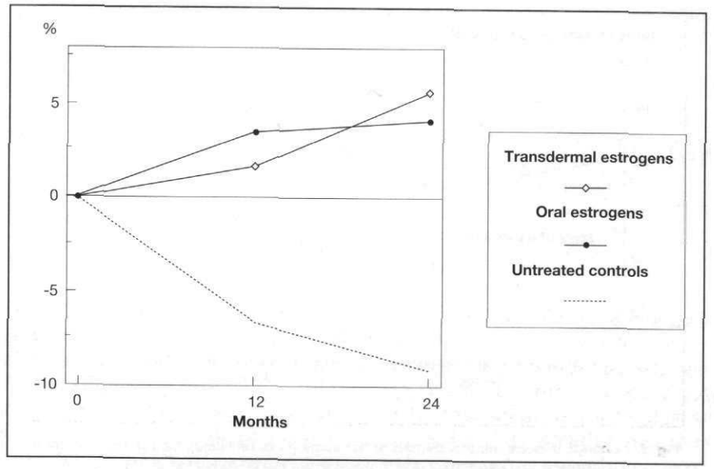

Fig. 2. - Change in bone mineral density at the spine (% of baseline). Comparison of oral estrogens (0.625 mg/day conjugated estrogens) and transdermal estrogens (1.5 mg/day of estradiol in a gel). From Palacio S. et al. [8].

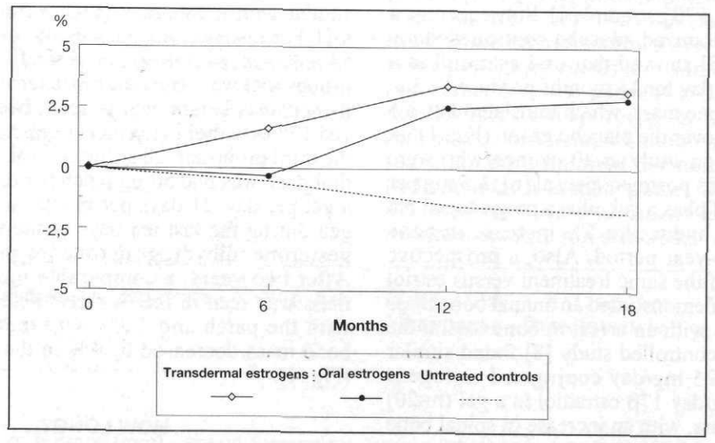

Fig. 3.- Change in mean bone mineral density at the spine (% of baseline). Comparison of oral conjugated estrogens (0.625 mg/day) and transdermal estradiol (one 50-µg patch per day). From Stevenson JC et al. [10].

years. This time-course was confirmed in a subsequent study [17], in which the relative risk fell to 0.42 after five years. An analysis of bone mineral density data from the Framingham study [22] found that hormone replacement therapy was associated with significant increases in spinal and femoral bone mass versus controls only when the treatment duration was longer than seven years. All these results were obtained in patients given conjugated estrogens or 17β estradiol without progestogens. Only 2.8% of the women studied by Cauley et al. [20] had received combined estrogen-progestogen therapy. In a 1990 prospective cohort study [19], in contrast, combined therapy was used by 41% of the patients.

WHEN TO START?

At cessation of menses

Bone loss occurs at a faster rate during the first few years after the menopause, suggesting that hormone replacement therapy should be started as

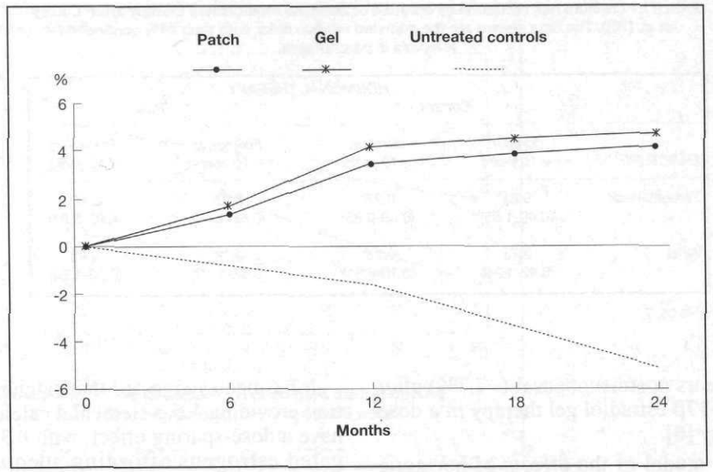

Fig. 4. - Change in bone mineral density at the spine. Comparison of estradiol in a gel (1.5 mg/day) and in a patch (50 µg/day). From Ribot C. et al. [12].

soon as menstruation ceases. In one study [23], for instance, bone was lost at the spine and femur at an annual rate of 1.5% during the first two years after the menopause, versus 0.5% ten years after the menopause. In addition, the period of rapid bone loss is probably characterized by permanent alterations in the microarchitecture of bone trabeculae. An epidemiological study [20] found that the reduction in fracture risk was most marked with long-term therapy started at cessation of menses.

Bone continues to be lost lifelong, however: at the proximal femur, for instance, the annual rate of bone loss ranged from 0.5 to 0.8% according to the measurement site in a group of subjects aged 68 to 98 years [24]. This explains why the decrease in bone mass at the proximal femur exceeds 50% toward the end of a woman's lifespan. Studies using recently identified sensitive and specific markers for bone turnover [25] have shown that the increase in bone turnover seen at the menopause as a result of estrogen deprivation remains unchanged more than ten years later. Increased bone turnover was shown to be a more significant determinant of osteoporosis in women who were more than 20 years postmenopausal than in women who had recently ceased menstruating [26]. These data suggest that treatment with antiosteoclast agents may be appropriate for reducing bone turnover in osteoporotic women who are more than ten years postmenopausal.

After cessation of menses

Epidemiological studies consistently found that the beneficial effects of hormone replacement therapy on bone became gradually less marked with advancing age. In the MEDOS study [29], treatment for at least five years decreased the risk of femoral neck fracture in patients younger than 80 years (relative risk, 0.51) but not in those older than 80 years. Similarly, a 25-year follow-up study that compared 245 treated women with a group of controls found that estrogen therapy given for a mean of 17 years was associated with a reduced fracture risk in women younger than 80 years but not in those older than 80 years [21].

Hormone replacement therapy slows the rate of bone loss only for as long as it is given, although no rebound effect is seen at treatment discontinuation [4]. In some studies [16,18], the relative risk of femoral neck fracture began to increase two years after treatment discontinuation. Another study suggested that stopping the treatment erased its beneficial effects, even if it had been given for many years [20]. From an epidemiological viewpoint, hormone replacement therapy started at the menopause should be continued lifelong (Table I).

Estrogen therapy started after 65 years of age has beneficial effects, including significant decreases in bone turnover markers [28] and an increase in bone mass [29-31]. In a group of women with a mean age of 65 years (range, 54-72 years), annual bone mass increases of 5.3% at the spine, 7.6% at the trochanter, and 1% at the radius were seen during 17β estradiol patch treatment (100 µg/day, 21 days per month) combined with medroxyprogesterone acetate 10 days per month [32]. Another study found similar bone mass increases in women less than five years postmenopausal (+5%) and

TABLE I. - **Fracture risk reduction by duration of hormone replacement therapy (from Cauley et al. [20]). The data shown are the adjusted relative risks, with their 95% confidence intervals in parentheses.**

	HORMONAL THERAPY			
	Current		Past	
FRACTURE	duration < 10 years	duration > 10 years	Follow-up < 10 years	Follow-up > 10 years
Femoral neck	0.81 (0.40-1.65)	0.27* (0.08-0.85)	0.97 (0.65-1.46)	1.67 (0.92-3.01)
Wrist	0.75 (0.42-1.36)	0.25* (0.10-0.61)	0.79 (0.57-1.10)	0.90 (0.50-1.64)

*p<0.05.

more than ten years postmenopausal (+7.7%) after two years under 17β estradiol gel therapy in a dose of 1.5 mg per day [6].

A theoretical model of the effects of hormone replacement therapy on bone has been developed [13] that highlights the rapid obliteration of bone mineral density gains after treatment withdrawal, as well as the efficacy of delayed treatment. This last assumption is in keeping with a study demonstrating an immediate decrease in the vertebral fracture risk after treatment initiation at 65 years of age (Fig. 5). However, the model also makes the assumption that bone continues to be lost at a slow rate during long-term administration of estrogens, which remains unproven.

HOW MUCH?

Estrogens affect bone only when given above a threshold dose. Effects on bone have been documented with 0.625 mg/day oral conjugated estrogens, 2 mg/day oral 17β estradiol or estradiol valerate, 50 mg/day 17β estradiol in a patch, and 1.5 mg/day 17β estradiol in a gel [5,10,12,33,34]. Furthermore, the bone effects of estrogens are probably dose-dependent. For instance, a study of oral estrogen therapy found a greater increase in radial bone mass with 4 mg/day than with 2 mg/day [4]. Dose dependency probably also exists with transdermal 17β estradiol [35].

Identification of the lowest effective dose is an important goal that cannot be achieved based on epidemiological data because of the marked changes in prescribing patterns that have occurred over time, at least in the United States. For instance, in one study conjugated estrogens were given in a mean dose of 0.9 mg/day in the 1970s versus 0.5 mg/day starting in the 1980s [21]. In the same study, 81% of patients had received more than the recommended dose of 0.625 mg/day. The effect of the treatment on the fracture risk cannot be ascribed to a given dose.

It has been suggested that calcium supplementation providing 1.5 g elemental calcium per day may have a dose-sparing effect, with 0.3 mg/day conjugated estrogens affording adequate protection against bone loss [36]. This has not been confirmed. Neither has it been established that a dosage reduction after some time under therapy allows to maintain the initial gain. A prospective, randomized, placebo-controlled study in 127 recently oophorectomized women found that 17β estradiol in a dose of one 25 µg patch per day failed to prevent bone loss at the spine and radius [35]. However, the rate of bone loss is very high in surgically menopausal patients.

Until prospective bone mineral density studies of the effects of moderate doses are available (0.3 mg oral conjugated estrogens, 1 mg oral 17β estradiol, 37.5 or 25 µg 17ß estradiol in a patch, or 0.75 µg 17β estradiol in a gel), such doses cannot be recommended for the goal of preventing bone loss. If used, their effect should be monitored by bone mineral density measurements.

WHICH EFFICACY CRITERION?

Today, the only efficacy criterion suitable for use in clinical practice is the effect on bone mineral density. Reproducibility of bone mineral density measurements shortly after the menopause is about 1% at the spine and 1.5% at the proximal femur. Strictly speaking, only a change of at least 2.5-3% is proof of an actual change in bone mass. It follows that any beneficial effects on bone mineral density can be demonstrated only after 18 to 24 months under therapy. To sidestep this difficulty, surrogate markers that may allow earlier detection of treatment effects have been looked for. Serum estradiol assays are not widely available and must be done on samples taken at a given time after application of estrogen to the skin. In addition, the serum estradiol threshold above which bone effects occur varies widely across individuals, from 40 to 60 pg/ml.

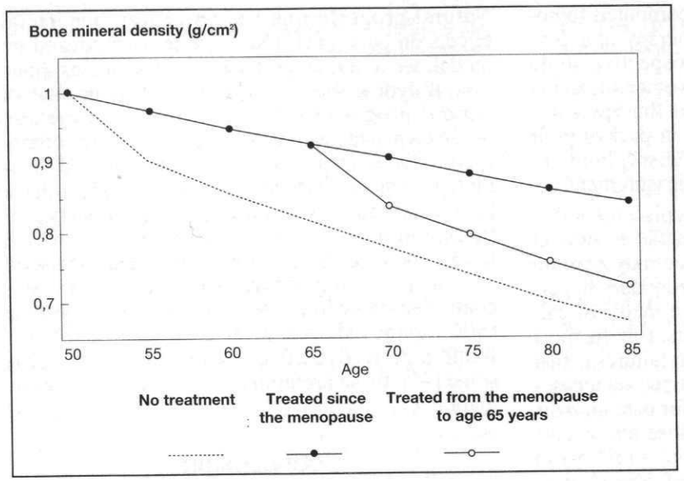

Fig. 5. - Suggested model of the effects on bone mineral density of hormone replacement therapy in an effective dose. From Ettinger and Grady [13]. A: discontinuation of the treatment at 65 years of age is followed by resumption of bone loss. B: initiation of treatment at 65 years of age is followed by an increase in bone mass.

More satisfactory surrogate markers may be biochemical markers for bone turnover (serum osteocalcin and urinary pyridinoline and collagen peptides) [28], whose levels were lower in postmenopausal women under hormone replacement therapy than in postmenopausal controls [25]. After three months under therapy, similar decreases in these markers were found with the oral route (0.625 mg/d) and the transdermal route (50 µg patch) [37]. At present, however, reproducibility is too low and normal values too uncertain to allow use of these markers as tools to guide therapeutic decisions in the individual patient. This will probably change in the near future: evidence has been obtained that an adequate decrease in bone turnover markers in patients under bisphosphonate therapy indicates satisfactory control of bone turnover and is associated with an increase in bone mass and a decrease in the fracture risk.

DO SOME PATIENTS FAIL TO RESPOND?

Opinion is divided on whether hormone replacement therapy fails to prevent bone loss in some patients [13,38]. Use of too low a dose or faulty technique during measurements of bone effects may mistakenly suggest a treatment failure. In one study [11], however, significant bone loss was documented at the femoral neck in 14% of patients who had been receiving effective doses of estrogens via the oral or transdermal route. Another study reporting individual values rather than means found

vertebral bone loss detectable by computed tomography during oral 17β estradiol therapy in a dose of 1 to 2 mg per day [39]. A retrospective study demonstrated bone loss in 21% of women receiving appropriate hormone replacement therapy [40], although this result was ascribed in part to poor reproducibility of the gadolinium absorptiometry method used for the bone density measurements.

There is no obvious reason why replacement therapy with a natural hormone might fail to protect against bone loss. Poor compliance may explain some apparent treatment failures. Secondary hyperparathyroidism due to an inadequate intake of calcium may be present in some patients. But the most likely explanation for most treatment failures is that the dose should probably be determined on a case-by-case basis. Patients at high risk for osteoporosis who cannot be given the estrogen dose that is currently recommended for bone loss prevention should be monitored by bone mineral density measurements.

HOW USEFUL IS CONCOMITANT PROGESTOGEN THERAPY?

Progestogens antagonize the effects of estrogens but have no harmful effects on bone and do not modify the beneficial bone effects of estrogens. Natural progesterone has no proven beneficial effects on bone [41]. Using the ovariectomized rat model, we found no protective effects against bone loss of dydrogesterone, a dehydro-stereoisomer of natural progesterone [42]. Norethisterone and medroxyprogesterone acetate, which are widely used in the United States, have demonstrated favorable effects on cortical bone [43,44], which have been ascribed to the androgen-like properties of these compounds. The 19 norpregnanes, which have a good metabolic safety profile, may be useful as bone protecting agents. A prospective placebo-controlled study in 23 women given promegestone (500 µg/day) shortly after cessation of menses found a protective effect against bone loss at the spine [45]; these preliminary results require confirmation.

CONCLUSION

Estrogen therapy is effective for preventing and treating postmenopausal osteoporosis. The transdermal route (gel or patch) is as effective as the oral route. However, the beneficial effects occur only if the estrogen is given long-term and in an effective dose. It follows that the products used must have an excellent safety profile. The results of studies of the efficacy of moderate doses are impatiently awaited.

REFERENCES

1. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B et al. Hormone therapy to prevent disease and prolong life in post menopausal women. Ann Int Med 1992; 117: 1016-37.
2. Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles or vertebral fracture and coronary heart disease among white post menopausal women. Ann Intern Med 1989; 149: 2445-8.
3. American College of Physicians. Guidelines for counseling post menopausal women about preventive hormone therapy. Ann Intern Med 1992; 117: 1038-41.
4. Christiansen C, Christensen MS, Transbol I. Bone mass in post menopausal women after withdrawal of oestrogen/gestagen replacement therapy. Lancet 1981; i: 459-61.
5. Munk-Jensen N, PorsNielsen S, Obel EP, Eriksen PB. Reversal of postmenopausal vertebral bone loss by estrogen and progestogen : a double blind placebo controlled study. BMJ 1988; 296: 1150-2.
6. Trémollières F, Pouillès JM, Ribot C. Preventive effects on postmenopausal bone loss of percutaneous 17β estradiol in early and late menopause. In : Christiansen C, Overgaard K, editors. Osteoporosis 3. Osteopress ApS 1990; 3: 1910-6.
7. Devogelaer JP, Lecart C, Nagant de Deuxchaisnes. The effect of percutaneous estradiol on post menopausal bone loss [Abstract]. Osteoporosis Int 1996; 6 suppl 1, PTu 571.
8. Palacios S, Menendez C, Jurado AR, Vargas JC. Effects of percutaneous oestradiol versus oral oestrogens on bone density. Maturitas 1995; 20: 209-13.
9. Castelo-Branco C, Pons F, Gonzalez-Merlo J. Bone mineral density in surgically post menopausal women receiving hormonal replacement therapy as assessed by dual photon absorptiometry. Maturitas 1993; 16: 133-7.
10. Stevenson JC, Cust MP, Gangar KF, Hillard TC, Lees B, Whitehead MI et al. Effects of transdermal versus oral hormone replacement therapy on bone density in spine and proximal femur in post menopausal women. Lancet 1990; 335: 265-9.
11. Hillard TC, Whitecroft SJ, Marsh MS, Ellerington MC, Lees B, Whitehead MI et al. Long-term effects of transdermal and oral hormone replacement therapy on postmenopausal bone loss. Osteoporosis Int 1994; 4: 341-8.
12. Ribot C, Trémollières F, Pouillès JM. Prevention of post menopausal bone loss by long-term parenteral administration of 17 β estradiol : comparison of percutaneous and transdermal route. In : De Luca H, Mazess R Editors. Osteoporosis. Physiological basis, assessment and treatment. Amsterdam: Elsevier, 1989: 137-45.
13. Ettinger B, Grady D. Maximizing the benefit of estrogen therapy for prevention of osteoporosis. Menopause 1994; 1: 19-24.
14. Sornay-Rendu E, Garnero P, Arlot ME, Delmas PD. Significant bone loss at the hip in women under hormone replacement therapy for more than 4 years. The OFELY prospective study. Osteoporosis Int 1996; 6 suppl 1: 92.
15. Hutchinson TA, Polansky SM, Feinstein AR. Postmenopausal oestrogens protect against fractures of hip and distal radius. A case-control study. Lancet 1979; ii: 705-9.
16. Weiss NS, Ure CL, Ballard JH, Williams AR, Daling JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. N Engl J Med 1980; 303: 1195-8.
17. Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen therapy and hip fractures. Ann Intern Med 1981; 9 : 28-31.

18. Kiel DP, Felson DT, Anderson JJ, Wilson PWF, Moskowitz MA. Hip fracture and the use of estrogens in postmenopausal women. The Framingham study. N Engl J Med 1987; 317: 1169-74.
19. Naessen T, Persson I, Adami HO, Bergstrom R, Bergkvist L. Hormone replacement therapy and the risk for first hip fracture. A prospective, population-based cohort study. Ann Intern Med 1990; 113: 95-103.
20. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. Ann Intern Med 1995; 122: 9-16.
21. Maxim P, Ettinger B, Spitalny GM. Fracture protection provided by long-term estrogen treatment. Osteoporosis Int 1995; 5: 23-9.
22. Felson DT, Zhang Y, Hannan MT, Kiel DP, Wilson PWF, Anderson JJ. The effect of postmenopausal estrogen therapy on bone density in elderly women. N Engl J Med 1993; 329: 1141-6.
23. Pouillès JM, Trémollières F, Ribot C. Effect of menopause on femoral and vertebral bone loss. J Bone Miner Res 1995; 10: 1531-6.
24. Hannan MT, Felson DT, Anderson JJ. Bone mineral density in elderly men and women : results from the Framingham Osteoporosis Study. J Bone Miner Res 1992; 7: 547-53.
25. Garnero P, Gineyts E, Arbault P, Christiansen C, Delmas PD. Different effects of bisphosphonate and estrogen therapy on free and peptide-bound bone cross-links excretion. J Bone Miner Res 1995; 10: 641-9.
26. Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD. Increased bone turnover in late post menopausal women is a major determinant of osteoporosis. J Bone Miner Res 1996; 11: 337-49.
27. Kanis JA, Johnell O, Gullberg B, Allander E, Dilsen G, Gennari C et al. Evidence for efficacy of drugs affecting bone metabolism in preventing hip fracture. Br Med J 1992; 305: 1124-8.
28. Prestwood KM, Pielbeam CC, Burleson JA, Woodiel FN, Delmas PD, Deftos LJ et al. The short term effects of conjugated estrogen on bone turnover in older women. J Clin Endocrinol Metab 1994; 79: 366-71.
29. Quigley MET, Martin PL, Burnier AM, Brooks P. Estrogen therapy arrests bone loss in elderly women. Am J Obstet Gynecol 1987; 156: 1516-21.
30. Christiansen C, Riis BJ. 17β estradiol and continuous norethisterone : an unique treatment for established osteoporosis in elderly women. J Clin Endocrinol Metab 1990; 71: 836-41.
31. Marx CW, Dailey III GE, Cheney C, Vint VC, Muchmore DB. Do estrogens improve bone mineral density in osteoporotic women over age 65? J Bone Miner Res 1992; 7: 1275-9.
32. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, Lane AW et al. Treatment of post menopausal osteoporosis with transdermal estrogen. Ann Int Med 1992; 117: 1-9.
33. Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of post menopausal bone loss. Obstet Gynecol 1984; 63: 759-63.
34. Selby PL, Peacock M. Dose dependent response of symptoms, pituitary, and bone to transdermal oestrogen in post menopausal women. BMJ 1986; 293: 1337-9.
35. Field CS, Ory SJ, Wahner HW, Herrmann RR, Judd HL, Riggs BL. Preventive effects of transdermal 17β estradiol and oral conjugated equine estrogens on osteoporotic changes after surgical menopause : a two-year placebo controlled trial. Am J Obstet Gynecol 1993; 168: 114-21.
36. Ettinger B, Genant HK, Cann CE. Postmenopausal bone loss is prevented by treatment with low-dosage estrogen with calcium. Ann Int Med 1987; 106: 40-5.
37. Reginster JY, Christiansen C, Dequinze B et al. Effect of transdermal 17β estradiol and oral conjugated equine estrogens on biochemical parameters of bone resorption in natural menopause. Calcif Tissue Int 1993; 53: 13-6.
38. Hassager C, Jensen SB, Christiansen C. Non-responders to hormone replacement therapy for the prevention of post menopausal bone loss : do they exist ? Osteoporosis Int 1994; 4: 36-41.
39. Ettinger B, Genant HK, Steiger P, Madvig P. Low-dosage micronized 17β estradiol prevents bone loss in post menopausal women. Am J Obstet Gynecol 1992; 166: 479-88.
40. Rozenberg S, Gevers R, Peretz A, Vandromme J, Robyn C, Ham H. Decrease of bone mineral density during estrogen substitution therapy. Maturitas 1993; 17: 205-10.
41. Riis BJ, Thomsen K, Strom V, Christiansen C. The effect of percutaneous estradiol and natural progesterone on postmenopausal bone loss. Am J Obstet Gynecol 1987; 156: 61-5.
42. Roux C, Kolta S, Chappard C, Morieux C, Dougados M, Vernejoul MC de. Bone effects of dydrogesterone in ovariectomized rats: a biologic, histomorphometric and densitometric study. Bone 1996; 19: 463-8.
43. Gallagher JC, Kable WT. Effect of progestin therapy on cortical and trabecular bone : comparison with estrogen. Am J Med 1991; 90: 171-8.
44. Horowitz M, Wishart JM, Need AT . Effects of norethisterone on bone related biochemical variables and forearm bone mineral in postmenopausal osteoporosis. Clin Endocrinol 1993; 39: 649-55.
45. Tremollières F, Pouillès JM, Ribot C. Effect of long term administration of progestogen on post menopausal bone loss: result of a two-year controlled randomized study. Clin Endocrinol 1993; 38: 627-31.

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