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M. Dören

Effects of HRT on bone mineral density and fracture incidence – a review

Abstract

Estrogen replacement therapy (ERT) is generally regarded as first choice for prevention of osteoporosis in women apart from life style modifications. Natural and synthetic estrogens at least preserve bone mineral density (BMD) in a dose-dependent fashion independent of age and mode of administration. Maximum effects are achievable with daily use of 2 mg estradiol, 0.625 mg conjugated equine estrogens, 1.25 mg estrone, 50 µg transdermal patch estradiol, and 1–2 mg estradiol gel. Progestogens neither attenuate nor augment the effect of estrogens. Tibolone 2.5 mg daily, a synthetic steroid related to norethisterone acetate, also preserves BMD. Observational studies suggest a hip fracture risk reduction by at least 25 % in ever users of non-contraceptive estrogens. There are no designated fracture trials available for any estrogen. The recommendation to use estrogen as first line pharmacological prevention for postmenopausal osteoporosis, given both the lack of direct evidence by fracture trials and the rare use of estrogen in (late) postmenopausal women is not well supported. Fracture trials of women including the very elderly need to be conducted in order to overcome shortcomings of the current level of evidence for ERT compared with other drugs approved for the prophylaxis of postmenopausal osteoporosis.

Introduction

It is general opinion that estrogens are the first choice for prevention of postmenopausal osteoporosis. At least two meta-analyses [1, 2] assessed the impact of estrogen replacement therapy (ERT) on bone mineral density (BMD) in controlled clinical trials. All studies found a positive impact on bone both in early healthy and in late postmenopausal women with osteoporosis (WHO criteria). Doses of 2 mg estradiol, 0.625 mg conjugated equine estrogens (CEE), and 1.25 mg estrone daily had the greatest impact, lower doses were less effective. The impact of a given estrogen appeared to be attenuated at the hip compared with the lumbar spine, few studies assessed femoral BMD. Age did not attenuate the impact of hormone replacement therapy (HRT), there was no measurable effect of any progestin on BMD. These analyses could not assess whether various types and doses of estrogen were indeed equivalent because small sample sizes did not allow for valid comparisons. For clinical practice it would be important to know which compounds are best for bone and not only to be assured that any HRT is better than placebo or no treatment, which is the current state of knowledge. Another shortcoming is the fact that it is unknown whether BMD results allow for conclusions regarding fracture risk in the old.

Bone mineral density – evidence from clinical trials

Recent 3- and 10-year trials confirmed that HRT in early postmenopausal women preserves BMD or at least diminishes the rate of bone loss (Table 1 [3–5]). Estradiol matrix patches [6] and gel [7] are also effective. The PEPI-trial showed that increases of femoral BMD were less compared with lumbar BMD, a finding supported by one 3.5-yr-trial in older women [8]. There is no solid evidence of a bone-specific advantage for continuous combined HRT [5]. Oral estriol is not generally thought of in the context of osteoporosis; however, doses above 4–6 mg daily seem to be different from placebo [9]. Some studies in Chinese and Japanese women suggested effects of low-dose estriol [10,11].

Antiresorptive agents such as etidronate and alendronate, approved for treatment of established osteoporosis, were combined with HRT for primary [12] and secondary prevention [13] of osteoporosis in trials, the results of which suggested additive effects on BMD. These strategies and the combination of HRT and a bone forming agent such as monofluorophospate [14] were suggested for women at high(er) risk for osteoporosis.

Essentially data upon specific effects of progestins and progesterone are also limited. Bone loss may be reduced by NETA 5–10 mg daily [15]. One study showed a greater impact on lumbar BMD by a regimen including continuous NETA compared with sequential MPA in the presence of similar estradiol levels induced by both study regimens [16]. In the PEPI trial, there were no BMD differences between women treated with 0.625 mg CEE daily and either sequential 10 mg MPA or 200 mg micronised progesterone daily, respectively [5]. A 1-year study did not show any impact of transdermal progesterone on BMD [17]. Tibolone, a syn-

thetic steroid structurally related to NETA, also preserves BMD in postmenopausal women including osteoporotic patients [18, 19].

Fracture – evidence from clinical trials

There are no designated, adequately powered HRT/ERT fracture studies. The first study which assessed radiologic vertebral deformities in ovariectomized women showed use of mestranol, a synthetic estrogen used in contraception, prevented height loss within a follow-up of nine years [20]. One long-term study, conducted in patients hospitalized for chronic diseases given a high estrogen dose, reported the absence of fractures compared with the control group [21]. The HERS trial, a randomized, double-blind, placebo-controlled cardiovascular secondary prevention study in late postmenopausal women, did not suggest differences in the rates of any type of fracture, a prespecified secondary endpoint, within the average follow-up of 4.1 years in 2,763 women treated with continuous combined CEE and MPA or placebo, respectively

Table 1: Controlled long-term studies of HRT: Bone mineral density in early postmenopausal women – primary prevention

Authors	Intervention	Size n¶	Follow-up years	Outcome BMD increase from baseline lumbar spine	hip[a]
Eiken et al. 1995 [3]*	A) Continuous E (2 doses) + sequential P per 28-day cycles 2 mg E_2/d x 12 d + 2 mg E_2 + 1 mg NETA/d x 10 d + 1 mg E_2/d x 6 d	11	10	+15.9 %	na
	B) Continuous E + P 2 mg E_2 + 1 mg NETA/d	19	10	+11.1 %	na
	C) Placebo	29	10	–4.7 %	na
Komulainen et al. 1999 [4]	A) Sequential E (21 days) + sequential P per 28 day cycles 2 mg E_2-Val/d x 21 d + 1 mg CPA/d x 11 d	74	5	+1.5 %	–0.4 %
	B) HRT A plus seasonal (winter) 300 IU Vit D_3 + 93 mg Ca^{2+}/d	88	5	+1.8 %	–0.6 %
	C) Seasonal (winter) 300 IU Vit D_3 + 93 mg Ca^{2+}/d	101	5	–4.6 %	–4.4 %
	D) Ca^{2+} 93 mg/d	104	5	–4.7 %	–4.4 %
PEPI 1996 [5]#	A) Estrogen-only 0.625 mg CEE/d	94	3	+5.1 %	+2.6 %
	B) Continuous E + sequential P 0.625 mg CEE/d + 10 mg MPA/d x 12/month	137	3	+4.8 %	+2.5 %
	C) Continuous E + sequential P 0.625 mg CEE + 200 mg MP/d x 12/month	131	3	+4.2 %	+1.5 %
	D) Continuous E + P 0.625 mg CEE + 2.5 mg MPA/d	144	3	+5.1 %	+2.0 %
	E) Placebo	124	3	–2.7 %	–2.0 %

¶ evaluable number of patients
[a] PEPI 1996: total hip BMD; Komulainen et al. 1999: proximal femur BMD
* double-blind, placebo-controlled or the initial 2 years with consecutive open-label follow-up,
# % change reported for adherent women
BMD: bone mineral density; d: day; na: not available; E: estrogen compound, P: progestogen compound, E_2: estradiol, NETA: norethisterone acetate, E_2-Val: estradiol valerate, CPA: cyproterone acetate, Ca^{2+}: calcium, CEE: conjugated equine estrogens, MPA: medroxyprogesterone acetate MP: micronized progesterone

[22]. One relatively small controlled 5-year trial, however, suggested a reduction of peripheral fractures, after adjustment for previous fracture and baseline femoral neck BMD, in early postmenopausal women treated with 2 mg estradiol valerate daily and sequential cyproterone acetate [23].

Discussion

Apart from an increasing number of BMD studies, much of the impetus to advocate HRT/ERT for primary prevention of postmenopausal osteoporosis is derived from observational studies. One meta-analysis case-control and cohort studies, most of them conducted with unopposed CEE, concluded that ERT lowers the risk of hip fractures by 25 % [24]. Data on combined HRT regimens were generated in a large Swedish population-based case-control study. The risk for hip fractures decreased by 4 % for estrogen-only and by 11 % for combined estrogen and progestin regimens for every year of use [25]; fracture protection was lost five years after discontinuation of HRT. The efficacy of ERT was not restricted to early postmenopausal women. Fracture risk reduction by ERT/HRT remains to be established in designated fracture trials. These trials are feasible as demonstrated for bisphosphonates such as alendronate [26], risedronate [27] and the selective estrogen receptor modulator raloxifene [28]. Fractures trials are essential because fractures have a profound impact on quality of life. Crucially, currently both clinical trials and observational studies suggest that the effect of HRT is attenuated at the hip. Hip fractures mainly occur in women > 75 years of age, when HRT rarely is an issue in clinical practice [29].

Decision making which medical intervention to choose for prevention of osteoporosis needs to take into account risks and benefits of long-term HRT. Major non-bone related benefits and risks are largely based on observational studies which suggest a risk reduction for coronary heart disease [30] without current evidence of benefits for secondary prevention [22], an increase of both breast cancer risk [31], and venous thromboembolism [22] apart from the well-known beneficial impact on climacteric symptoms.

Conclusions

Published evidence consistently demonstrates a dose-dependent beneficial impact on BMD of various HRT regimens including estradiol compounds, CEE, and tibolone, which is not restricted to a particular postmenopausal age. The ideal time for both onset and optimal duration of therapy is currently unknown. Progestogens do not attenuate or augment the effects of estrogen. There are no fracture studies to examine the impact of any HRT. Observational studies suggest that HRT decreases the risk for hip fracture by at least 25 % in ever users of estrogen. Thus, it is reasonable to ask why ERT/HRT should be continued to be recommended as first line prevention measure for postmenopausal women, given both the lack of direct evidence regarding the endpoint fracture and the rare use of ERT/HRT in late postmenopausal women most susceptible to fractures [32]. Fracture studies with various types and doses of oral and non-oral estrogen compounds, possibly integrating strategies to prevent future (impact of) falls [33] and dietary modifications, should be considered to overcome the shortcomings of the current level of evidence.

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