Appendix C: Evidence on HRT and Bone Loss

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A large number of controlled clinical trials have demonstrated that hormone replacement therapy (HRT) is able to reduce the rate of bone loss in postmenopausal women. Most of the controlled clinical trials of HRT on bone mass have been for a duration of three or fewer years (table C- 1). The first pages of table C-1 ("HRT and Bone Mineral Density: Clinical Trials of 3 or Fewer Years") provide details of the design and results of each of the studies. The percentage change in bone mass from the baseline measurement to the end of the study is provided so that we may compare bone mass data that are given in disparate units (e.g., bone mineral content (usually measured in grams per centimeter (g/cm)) and bone mineral density (usually measured in grams per square centimeter (g/cm^2)).

Virtually all of these studies have shown that HRT, begun soon after menopause, maintains or increases bone mass within the first three years after menopause. Although HRT may reduce the rate of bone loss after menopause, HRT is not able to substantially restore bone mass that is lost. The increases in bone mass seen with initiation of therapy soon after menopause are small, generally in the range of 1 to 3 percent of the total bone mass.

A number of investigators have questioned whether there is a significant subgroup of postmenopausal women who fail to respond to HRT (16). Recent analyses have found that the proportion of women who fail to respond to hormone replacement therapy is relatively small (20).

Only a handful of studies of HRT and bone mineral density have followed women more than three years after initiation of therapy (table C-2), and these studies have shown that HRT maintains bone mass or reduces the rate of bone loss in postmenopausal women compared with placebo. In a retrospective cohort study, Meema and colleagues contacted postmenopausal women who had a bone mass measurement at a university clinic four to 10 years previously and asked them to volunteer for a second bone mass measurement (36). Eighty two volunteers were identified, 29 of whom had been treated continuously with estrogens. After an average followup period of six years, the estrogen-treated women showed no significant changes in bone mass and cortical thickness, whereas untreated women had significant decreases in bone mass and cortical thickness. In a cross-sectional study, Moore examined the bone mineral density of 65 postmenopausal women between 55 and 75 years of age who were at least 10 years from menopause (37). Long-term estrogen users were defined as those women who had begun therapy within five years of menopause and

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 1 of 7)

Study	Number of part' 'p	Duration of monitoring of bone	Type of	Results	
Aitke (' 973)	68 treated; 56 controls	1 years	Ten treated patients and 10 controls two months post-oophorectomy; 41 treated patents and 39 controls three years post-oophorectomy; and 17 treated patients and 17 controls six years post oophorectomy. Treated patients received mestranol in an average daily dose of 20 mcg.	Placebo: ▪ Two months post-oophorectomy ▪ Three years post-oophorectomy ▪ Six years post-oophorect Mestranol-treated patients: ▪ Two months post-oophorectomy ▪ Three years post-oophorectomy ▪ Six years post-oophorectomy	 -3.9 % -0.3 % -0.9 % -0.1 % 2.4 % -0.9 %
Recker 19/7)	18 treated; 20 controls; 22 Ca CO_3 2,600mg	2 years	Patients divided into three groups: Group I received placebo; Group II received conjugated equine estrogen, 0.625mg, and methyl testosterone, 5mg, 21 days of each month; Group III received 2,600mg calcium carbonate daily	Control Hormone-treated Calcium-carbonate treated	-5.75% -1.32% -3.65%
Lindsay (' 978a)	10 mestranol; 10 gestranol; 10 placebo	1 year	Patients randomized to three groups; Group I: mestranol 40mg/day; Group II: gestranol hexanoate (Depostat) 200mg IM every month for 3 months, then every 3 months; Group III: placebo	Mestranol Gestranol Placebo	+1.33% +0.22% -3.76%
Christiansen 1980)	2' Trisequens orte; 103 placebo	2	315 women randomized to seven treatment groups and placebo group: all patients received 500mg calcium daily; hormone replacement therapy group (21 patients) received Trisequens forte; 264 patients completed study	Placebo HRT	-3.3 % +2.5 %
Christiansen (1981a)	23 placebo; 21 1,25$(OH)_2$ D_3 ; 21 1,25$(OH)_2$ D_3 + hormones; 19 hormones	1 year	One control group and three treatment groups: 1,25$(OH)_2$ D_3 (0.25mg/d); Trisequens forte; 1,25$(OH)_2$ D_3 (0.25mg/d) + Trisequens forte; placebo control Trisequens: estradiol, estriol, and norethisterone acetate	1,25$(OH)_2$ D_3 Placebo 1,25$(OH)_2$ D_3 + hormones Hormones	-2.1±0.5% -2.0±0.5% +0.5±0.5% +1.5±0.5%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 2 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Christiansen (1981 b)	part I: 43 treated; 51 controls. Part II: 35 treated, 42 controls	3 years, Part I: first two years of study; Part II: third year of study	Patients treated with Trisequens forte (17-beta-estradiol (4mg) and estriol (2mg) days 1-12, 17-beta-estradiol (4mg) estriol (2mg) and norethisterone acetate 1 mg days 13-22, 17-beta-estradiol (1 mg) and estriol (0.5mg) days 23-28), All patients received 500mg calcium per day.	Part I: HRT (g/cm) Placebo Part II: HRT Placebo HRT Placebo	 2.5% -3.8% 3.7% *0.2%* *-2.4%* -5.7%
Finn Jensen (1 982)	31 treated; 43 controls	18 mo. (6 mo. run-in period)	Patients divided into four groups, 1,25$(OH)_2D_3$(0.50 mg/d) + 500mg calcium, 19 patients; Trisequens + 500mg calcium, 11 patients; 1 ,25$(OH)_2D_3$(0.50mg/d) + Trisequens + 500mg calcium: 20 patients; 500mg calcium 24 patients	Post six month run-in period, 1,25 + calcium calcium + hormones 1,25 + hormones + calcium calcium	 *-1.91 %* *+3.62%* *+3.06%* *-0.39%*
Lindsay (1984)	887 treated patients divided among four groups; 21 controls	2 years	Patients assigned to either placebo group or to CEE at one of four dosage levels: 0,15mg/day, 0.3mg/day, 0.625 mg/day, and 1.25mg/day	Placebo 0.15mg/d 0.30mg/d 0.625mg/d 1.25mg/d	-8.23% -8.51 % -5.01 % -0.24% -0.00%
Christiansen (1984)	2 treatment groups and one placebo group, E_2+E_3 +P: 22 patients; E_2+P: 20 patients; placebo group: 23 patients	1 year	Two treatment groups, 17 beta-estradiol and norethisterone acetate; 17 beta-estradiol, estriol, and norethisterone acetate, placebo group Daily doses used were, 17-beta-estradiol 2mg from days 1-22, 1 mg from days 23-28, estriol: 1 mg days 1-22, 0.5mg days 23-28, norethisterone acetate, 1 mg days 13-22. All patients received 500mg/d calcium,	E_2+P E_2+E_3+P Placebo	+0.52% +1.53% -3.3%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 3 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Caniggia (1984)	22 patients group 1: (n=5) 1,25$(OH)_2D_3$, group 2: (n=5) estradiol valerate, group 3: (n=7) 1,25$(OH)_2$ D & estradiol valerate group 4: (n=5) placebo	1 year	Four groups: l ,25 $(OH)_2D_3$ (0.5mcg) ■ ,25 $(OH)_2D_3$ 0.5mcg+ estradiol valerate (2mg/d) ■ stradiol valerate (2mg/d) n placebo No statistical analysis of data.	Placebo 1 ,25$(OH)_2D_3$ 1 ,25$(OH)_2D_3$+-E_2 E_2	-8.O% +9.O% +6.0% +9.0%
Gotfredsen (1986)	52 treated, 52 controls	1 year	Treated patients received either 17-beta-estradiol, either percutaneously (one daily dose of 5g, corresponding to 3mg 17-beta-estradiol) or orally (sequentially administered oral 17-beta-estradiol 2mg and for 10 days each cycle 1 mg cyproterone acetate).	Placebo: Head Chest Arms Pelvis Legs Spine HRT: Head Chest Arms Pelvis Legs Spine DPA lumbar spine. HRT Placebo DPA total spine. HRT Placebo SPA forearm HRT Placebo	 -5. O+-1.5% -7.0+-2.0% -3.0+-1.0% -5.5+-1.5% -4.3+-0.3% -3.0+-2.5% + *1 . 7 + - 1 . 3 %* +2.3+-2.0% +0.3+-0.5% -1.0+-2.0% -0.7+-0.25% -2.1+-1.5% + 1.0% 0.0% 0.0% -2.5% o o% -2.0%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 4 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Riis (1987a)	1 placebo controls; 14 calcium; 11 estrogen	2 years	Patients randomly allocated to three groups; percutaneous 17 beta-estradiol 3mg/d for 24 days each 28 day cycle; calcium carbonate 2,000mg per day; placebo. Code was partly broken after one year of treatment and estrogen group received cyclic supplementation of progesterone 200mg from days 13 through 24.	Proximal forearm: Estrogen Calcium Placebo Total body (g): Estrogen Calcium Placebo Distal forearm: Estrogen Calcium Placebo Spine: Estrogen Calcium Placebo	 +0.0% -4.0% -6.0% -0.5% -5.5% -8.0% -1.0% -6.0% -8.2% +3.8% -3.0% -1.8%
Riis (1987b)	29 treated; 28 placebo	2 years	Patients received either 3mg percutaneous estradiol or placebo; code was broken after one year of treatment, and women receiving estradiol continued with a cyclic addition of progesterone, whereas those with placebo continued to receive placebo.	Proximal HRT Placebo Distal HRT Placebo Spine HRT Placebo	 -0.5% -6.0% 0.0% -7.5% +5.5% -2.3%
Civitelli 1988)	11 conjugated estrogens; 10 placebo	1 year	Patient treated with CEE 1.25mg/day; all patients daily intake was maintained in the range of 800-1,000mg of calcium	Femoral shaft Placebo CEE vertebral bodies Placebo CEE	-2.22% +8.3% -2.89% +9.12%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 5 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Munk-Jensen (1988)	50 continuous estrogen and progestogen; 50 sequential estrogen and progestogen, 51 placebo	18 months (including 6 mo. run-in period)	Group 1, continuous estradiol 2mg and norethisterone acetate 1 mg; group 2, cyclic estradiol 2mg and 10 days per month 1 mg norethisterone acetate; group 3, placebo. 6 month run-in period where all patients were untreated	Distal forearm, Estrogen and progesterone (continuous) Estrogen and progesterone (sequential) Placebo Lumbar spine: Estrogen and progesterone (continuous) Estrogen and progesterone (sequential) Placebo	 -0.8+-0.6% -2.0+-O.5% -5.6+-0.55% **+4,2+-.8%** +3.2+-0.55% -2.6±0.45%
Riis (1988)	21 treated, 22 controls	2 years	Patients assigned to either continuous 17-β-estradiol, 2mg, and norethisterone acetate, 1 mg, or placebo	Forearm (prox,). HRT Placebo Forearm (distal): HRT Placebo Spine: HRT Placebo	 **+1.0+-1.9%** **-4.5+-2.7%** **+0.8+-3.8%** **-7.5+-3.8%** +5.4+-7.7% -3.7+-8.0%
Genant (1 990)	94 treated; 28 placebo-controls	1 year	30 patients treated with 0.3mg estrone sulfate; 32 patients treated with 0.65mg estrone sulfate, 32 patients treated with 1.25mg estrone sulfate. Purpose of study was to determine minimum effective dose of estrogens. All patients given 1,000mg elemental calcium supplementation	0.3mg estrone sulfate 0.625mg estrone sulfate 1.250mg estrone sulfate Placebo	-3.22% +1.38% +2.62% -0.82%
Lindsay (1990)	22 estrogen treated; 18 controls	2 years	All treated and controls given calcium to bring their total intake to 1,500mg/d, treated patients received CEE 0.625 mg/d, and those with an intact uterus received medroxyprogesterone 5 to 10mg for 12-14 days a month	Vertebrae. Controls Treated Hip: Controls Treated	 -7.6% +6.4% -4.13% +9.2%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 6 of 7)

Study	Number of participants	Duration of monitoring of bone density	Type of treatment	Results	
Resch (1990)	9 treated, 9 controls	1 year	Nine patients treated with Trlsequens; nine patients treated with placebo, all patients received 500mg calcium; Trisequens is estradiol (2mg) and norethisterone acetate (1 mg)	HRT Placebo	+8.84% 0.0%
Stevenson (1990)	66 treated, 30 controls	18 mos.	33 patients treated with transdermal 17β estradiol 0.05mg daily with transdermal norethisterone acetate 0.2mg to 0.3mg per day for 14 days a cycle; 33 patients treated with oral CEE 0.625mg daily with dl-norgestrel 0.15mg daily for 12 of the 28 days	Transdermal: Spine (L2-L4) Femoral neck Wards triangle Trochanteric Oral HRT: Spine Femoral neck Wards triangle Trochariteric Untreated: Spine Femoral neck Wards triangle Trochanteric	 +3. 14% +3. 14% +1.0% 0.0% +1.71% +1.00% +2.00% +2.66% -1.93% -3.16% -4.32% -2.15%

TABLE C-1: HRT and Bone Mineral Density: Selected Clinical Trials of 3 or Fewer Years (Page 7 of 7)

Study	Number of part pa	Duration of monitoring of bone d	Type of treatment	Results	
(1991)	13 placebo; 16 CEE; 20 medroxyprogesterone; 16 CEE/medroxyprogesterone	2 years	Patients were randomized into four groups: placebo; CEE 0.6mg; medroxyprogesterone 20mg; medroxyprogesterone 10mg/CEE 0.3 mg	Spine density:	
				CEE	2.10±1.50%
				Progest.	-4.58±1.30%
				CEE+progest.	0.88±2.58%
				Placebo	-7.22±2.39%
				Radial density:	
				CEE	-1.30±0.49%
				Progest.	-1.89±0.55%
				CEE+progest.	-0.05±1.06%
				Placebo	-4.12±2.07%
				Average cortical width:	
				CEE	-1.28±0.68%
				Progest.	-2.19±0.60%
				CEE+progest.	-2.24±0.58%
				Placebo	-6.53±1.11%
				Quantitative CT:	
				CEE	-3.64±2.36%
				Progest.	-10.1±3.01%
				CEE+progest.	-3.66±3.31%
				Placebo	-7.44±3.23%

SOURCE: Office of Technology Assessment, 1995.

TABLE C-2: HRT and Bone Mineral Density: Study Duration Greater Than 3 Years

Study	Number of participants	Study design	Duration of monitoring bone mass	Type of treatment	Results	
Meema, et al. (1 975)	29 control 53 treated	Retrospective cohort	4 to 10 years followup (6 years average followup)	Most frequently used hormone preparations were conjugated equine estrogens (0.625mg or 1.25 mg) usually administered cyclically	Castrates: Estrogen-treated Untreated Natural menopause: Estrogen-treated Untreated	+1.92% -7.78% +1.12% -6.30%
Lindsay, et al. (1978b)	14 controls; 15 treated 8 years; 14 treated, then treatment withdrawn	Clinical trial	8 years	Mean daily dose 27.6 mcg mestranol; 14 patients placebo; 14 patients 4 yrs. mestranol treatment then placebo 4 years; 15 patients received 8 years of mestranol treatment	Placebo group Estrogen group Estrogen, then withdrawal after 4 years	-11.9% -0.7% -10.070
Nachtigall, et al. (1979)	67 treated 62 controls	Clinical trial	10 years	Treated patients received CEE 2.5mg/day and 7 days each month medroxyprogesterone acetate 10mg.	<3 years from LMP: Estrogen-treated Placebo control >3 years from LMP: estrogen-treated placebo control	+8.67% ***-9.00%*** ***-0.5070*** -11.29%
Lindsay, et al. (1980)	42 control 58 treated	Clinical trial	Mean duration 9 years	Treated with mestranol mean daily dose 23.3mcg	Placebo: Metacarpal Radius Estrogen-treated: Metacarpal Radius	-10.4% -9.45% -1 .90% -2.1 5%

KEY: LMP = last menstrual period.

SOURCE: Office of Technology Assessment, 1995

who continued for a duration of at least 10 years. The mean duration of estrogen use among long-term estrogen users was 19.8 years. Controls were postmenopausal women who used estrogen for less than one year. There was a significant difference in mean spinal bone mineral density between long-term estrogen users (1.21 9 g/cm^2) and controls (1.092 g/cm^2), and this significant difference was retained after controlling for age and type of menopause.

In the only long-term prospective clinical trial of HRT and bone mineral density, 84 pairs of postmenopausal nursing home patients were randomly assigned to estrogen and progesterone or placebo (39). After 10 years, HRT-treated women had no significant decrease in bone mass. Women who began HRT within three years of menopause had a small **but** significant increase in bone mass after 1() years. Women assigned to placebo had a significant decrease in bone mass.

A number of studies have demonstrated that HRT is able to halt or possibly reverse bone loss even if it is started long after menopause (9,31, 32,35,41,43,45). Gains in bone mass of 5 to 10 percent or more have been found after initiation of HRT in the elderly. In a prospective study of 397 postmenopausal women between the ages of 51 and 80 years, Quigley found that estrogen replacement therapy reduced bone loss to about the same rate for estrogen users regardless of age (43).

Ettinger and Grady predicted that beginning therapy later in life may provide almost as much protection against osteoporotic fractures as starting at menopause (12). Ettinger and Grady used data on the effects of hormone replacement therapy on bone density, and the association of bone density to fracture risk to estimate and compare the expected benefits of three possible treatment scenarios: [1] 1) beginning therapy at menopause and continuing for the remainder of life; 2) beginning therapy at menopause and stopping at age 65; and 3) beginning therapy at 65 and continuing for the remainder of life (12). Their model included a number of key assumptions, based on their review of studies of the impact of hormonal replacement therapy in the elderly, including the assumption that bone mass would increase by 5 percent to 10 percent in the first two years after initiating therapy in the elderly. The investigators concluded that women who begin therapy at menopause and stop at age 65 have only a small (8 percent) increase in bone density at ages 75 to 85, the ages of highest hip fracture incidence, compared to never users, which translates into a 23-percent reduction in fracture incidence. Women who begin therapy at menopause and continue for the remainder of life were predicted to have the highest mean bone density at ages 75 to 85, about 22 percent higher than never users, and the greatest reduction in fracture incidence, a 73-percent reduction. But women who began HRT at age 65 had almost as great an increase in bone density, from 14 to 19 percent, and almost as great a reduction in fracture incidence, from 57 to 69 percent, as women who began HRT at menopause and continue for the rest of their lives.

Ettinger and Grady argued that starting hormone therapy later in life would halve the period of hormone exposure, reducing the potential risks of very long-term estrogen therapy (12).

There are several other reasons for beginning HRT in the elderly. Many of the early estimates of the rate of bone loss with aging were derived from cross-sectional studies, which may be biased if there are cohort effects. Recent prospective studies of bone loss with aging demonstrate that bone loss may accelerate with aging. Jones and colleagues reported on the rate of bone loss in 769 residents of Dubbo, Australia, aged 60 years and older, followed between January 1989 and June 1993. They found that bone loss at the hip was almost 1 percent per year in women, and about 0.8

[1] OTA's estimates of the impact of hormonal replacement therapy on fracture risk were calculated in a similar manner. See appendix D.

percent in men, and that bone loss increased with advancing age in both sexes (23).[2]

Recent data on the relation of bone mass to fracture risk in the elderly show that there continues to be a strong relationship of bone mass to hip fracture risk, even after age 80, so that therapies that slow bone loss will reduce fracture risk in this age group(3).

In addition, there is evidence from prospective studies that the rate of bone loss immediately after menopause may not be as great as previously thought, and the period of accelerated bone loss may not last as long as was predicted from cross-sectional studies (3). Finally, at age 65, densitometry can more precisely estimate the subsequent risk of hip fractures and target treatment more effectively (3).

There are, however, a number of reasons to question whether this type of model overestimates the number of fractures avoided by preserving bone mass in the elderly. Reports are inconclusive regarding how HRT initiated after substantial bone is lost affects fracture incidence (25). (See appendix B for discussion.)

In addition, progressive bone loss is associated with erosion and perforations in the trabecular structure, or struts, in cancellous bone (24,33). These perforations decrease the structural integrity of bone out of proportion to the amount of bone lost. Interventions such as estrogen that reduce bone resorption are at best capable of thickening the trabecular elements that remain, but are unlikely to be able to repair perforated trabeculae.

Finally, such a strategy would not be as effective in preventing wrist and vertebral fractures, which have a peak incidence earlier in menopause than hip fractures.[3]

After cessation of therapy, bone loss accelerates to a rate equivalent to that of untreated women at menopause (7,30,43). Thus, one would predict that the benefits of HRT on bone mineral density are maintained only so long as therapy is continued, and these benefits dissipate after cessation of therapy. Studies of bone mass in elderly women support this prediction. Felson and colleagues measured bone mass in 670 elderly women (mean age 76 years) in the Framingham study cohort to determine whether their bone mass was affected by earlier estrogen use (14). They found that, among the 212 women who had received estrogen therapy, only those who had taken estrogen for seven or more years had significantly higher bone mass than women who had not taken estrogen. The differences in bone mass between long-term users and nonusers was greatest among women under 75 years old (11.2 percent). Among long-term estrogen users 75 years old or older, bone density was only 3.2 percent higher than in women who had never taken estrogen around the time of menopause, and even those who had taken estrogen for 10 years had ceased therapy by the time they were 60 to 65 years old. Of the 24 women 75 years old or older who had taken estrogen therapy for at least seven years, only two had begun therapy at 60 years of age or later, and only three were still taking estrogen when their bone density was measured.

HRT has been found to reduce postmenopausal bone loss regardless of the route of administration (45,49,50). Lufkin and colleagues compared bone loss in 75 osteoporotic women randomly assigned to transdermal estrogen patches and progesterone tablets or to placebo patches and tablets (32). They found that bone mass was significantly greater in those who received the transdermal estrogen patch compared with those who received placebo. Those women receiving transdermal estrogen had a median annual increase in bone mass of 5.3 percent in the lumbar spine, compared to an increase of 0.2 percent for women receiving placebo. In a two-year clinical trial, Ribot and colleagues randomly assigned 94 postmenopausal women to a transdermal estrogen patch, a topically applied estrogen gel, or to a placebo (46). At the end of the

[2] They reported no significant bone loss at the spine, which was perhaps due to the presence of spinal arthritis (23).

3 Wrist fractures and vertebral fractures, however, cause relatively little morbidity compared with that incurred by hip fracture.

study, bone mineral density had increased significantly for the transdermal estrogen patch group and the percutaneous estrogen gel group, but not for the placebo group. There was no significant difference in the percent increase in bone density between the transdermal estrogen patch group and the percutaneous estrogen gel group.

The combination of estrogen and progestin, either given sequentially or as continuous combined therapy has been found as effective as estrogen alone in reducing postmenopausal bone loss (5,6,7,10,13,19,29,31,34,38,40,41 ,42,45,47,50).

In fact, a number of studies have demonstrated that progestins alone are effective in reducing bone loss in postmenopausal women (1,16,26, 29). Lindsay and colleagues demonstrated the ability of progestins to reduce bone loss in a clinical trial involving 30 postmenopausal women randomly assigned to the progestin gestranol, the estrogen mestranol, or placebo (29). Women treated with gestranol showed no significant change in bone mineral density after one year, and women treated with mestranol showed a nonsignificant increase in bone mineral density. Women assigned to placebo, however, showed a significant decline in bone mineral density after one year.

Abdalla and colleagues showed that progestin was able to increase bone mineral density in postmenopausal women in a cohort study of the progestin norethisterone versus placebo (l). Women assigned to norethisterone were referrals to a Glasgow, Scotland menopause clinic, and controls were patients chosen from placebo groups of other clinical trials matched to the treatment group for age, years since menopause, and initial bone mass. After two years, the bone mass of women assigned to norethisterone increased by 3.3 percent, whereas the bone mass of the matched controls declined by 5 percent. The difference in bone mass between the two groups after two years was statistically significant ($p < 0.002$).

Although progestins have been demonstrated to prevent bone loss in postmenopausal women, they do not appear to be as effective as estrogens in maintaining bone mass, especially mass of trabecular bone. Gallagher and colleagues randomly assigned 81 postmenopausal women to four groups: treatment with the progestin Provera R (medroxy - progesterone acetate), the estrogen Premarin (conjugated equine estrogen), Premarin plus Provera, or placebo (16). The group receiving Premarin plus Provera received half the dose of estrogen as the Premarin only group and half the dose of progestin as the Provera only group. After two years, bone mass of the spine (composed primarily of trabecular bone) was maintained in the Premarin group and the Premarin plus Provera group, but was lost in the Provera group and the placebo group. Bone density of the wrist (composed primarily of cortical bone) was lost in all four groups, but was least in the Premarin only, Provera only, and Premarin plus Provera groups, and was greatest in the placebo group. For both cortical bone and trabecular bone, Premarin alone was better able to maintain bone mass than Provera alone.

CONCLUSIONS

Controlled clinical trials have demonstrated that HRT is able to halt bone loss and perhaps increase bone mass in postmenopausal women. For this analysis, OTA has assumed as a base case that HRT maintains bone mass for as long as it is taken. There is less information about whether HRT is able to maintain bone mass over the long term. OTA also assumed that initiation of HRT at age 65 was able to maintain bone mass. Two recent reviews of studies of bone density have concluded that bone mass is lost in long-term HRT users, but at a rate that is one-half to one-third that of nonusers (3, 12). OTA assumed as a worst case that bone mass in HRT users is lost at half the rate of nonusers. Studies have demonstrated that bone loss is halted or reduced only as long as HRT is used. OTA assumed that, upon cessation of HRT use, bone mass is lost at a rate similar to the rate of bone loss at menopause.

Because there are relatively few data on the reduction of fracture in long-term estrogen users, OTA used data on the effects of HRT on bone density and the association of bone density on fracture risks to estimate the risks of hip fracture in HRT users at each age. This assumption is discussed in more detail in appendix D.

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