

Calcium potentiates the effect of estrogen and calcitonin on bone mass: review and analysis¹⁻³

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See corresponding editorial on page 5.

ABSTRACT We reviewed published clinical trials that measured bone mass of postmenopausal women from at least one skeletal site to evaluate whether calcium supplementation influenced the efficacy of estrogens and intranasal calcitonin on bone mass change. We compared results of the administration of oral estrogen or nasal calcitonin in conjunction with additional calcium intake either through diet or supplements compared with those of estrogen or calcitonin alone. Of the 31 published estrogen trials analyzed, 20 modified the diet or used a calcium supplement (total 1183 mg/d) and 11 did not (total 563 mg/d). The mean increase in bone mass of the lumbar spine when estrogen was given alone was 1.3%/y ($n = 5$) compared with 3.3%/y when estrogen was given in conjunction with calcium ($n = 14$; $P = 0.01$). The mean increase in bone mass of the femoral neck with estrogen alone ($n = 3$) was only 0.9%/y compared with 2.4%/y when calcium was given with estrogen ($n = 6$; $P = 0.04$). Similarly, forearm bone mass increased 0.4%/y with estrogen alone ($n = 7$) compared with 2.1%/y when estrogen was given with calcium ($n = 12$; $P = 0.04$). Similar results were found when weighted means were calculated. Of the seven published trials evaluating the effects of 200 IU nasal salmon calcitonin, six also used calcium supplements (total 1466 mg/d) whereas one used calcitonin alone (total 627 mg/d). Bone mass of the lumbar spine increased 2.1% with calcitonin plus calcium supplementation compared with -0.2%/y with calcitonin alone. These results suggest that a high calcium intake potentiates the positive effect of estrogen on bone mass at all skeletal sites and perhaps that of calcitonin on bone mass of the spine. *Am J Clin Nutr* 1998;67:18-24.

KEY WORDS Calcium, osteoporosis, estrogen, calcitonin, bone mass, postmenopausal women

INTRODUCTION

An adequate calcium intake has been shown to be beneficial to bone mass at all stages of life, but most societies have calcium intakes well below the recommended amounts. Increased calcium intake maximizes peak bone mass and reduces bone loss in premenopausal women (1-4). Furthermore, calcium supplementation reduces the rate of bone loss in postmenopausal women by $\approx 0.8\%/y$, a 40% decrease, when compared with untreated women (5, 6). Calcium's effects are generally significantly less

than those of standard antiresorptive therapy; therefore, calcium cannot replace antiresorptive therapy (7, 8). However, what is unknown is whether additional calcium can benefit bone mass when added to standard antiresorptive therapy.

The existing Food and Drug Administration-approved drugs used for treating osteoporosis are all agents that reduce bone turnover. After initiation of these treatments, bone resorption is rapidly reduced. Previously existing resorption sites (the remodeling spaces) need to be filled with new bone, which obviously requires calcium. Although estrogens may increase fractional gastrointestinal calcium absorption, a greater calcium supply may be needed to accomplish this temporarily increased demand. Furthermore, an increased calcium supply may act by a separate mechanism to increase bone mass, particularly at sites in which estrogen is less effective, such as the hip and forearm (9, 10).

Synergism between calcium and estrogen has been suggested. In an open study in which patients self-selected their medication, doses of estrogen thought to be suboptimal for preservation of bone mass (0.3 mg) when given in conjunction with a high calcium intake (1700 mg/d) were found to be equally effective as the higher standard estrogen dose (0.625 mg) (11). Furthermore, a recent study in Hong Kong found that the addition of calcium to estrogen led to a significant increase in bone mass of the femoral neck compared with estrogen alone (12).

Published clinical trials investigating the efficacy of antiresorptive treatments on bone mass have often involved dietary modifications in calcium (with or without the use of a supplement) in both the treatment and control groups. Therefore, the additional benefit, if any, of calcium with antiresorptive treatment on bone mass is not known. The following analyses were therefore performed to determine the possible additional benefit of an adequate calcium intake in conjunction with estrogen treatment for osteoporosis. Similar analyses were performed with

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calcitonin. Although a similar analysis was planned for bisphosphonate therapy studies, it was not possible because in all of the trials all patients received supplemental calcium.

METHODS

A search of the MEDLINE computer database using GRATEFUL MED software (National Library of Medicine, Bethesda, MD) from 1977 onward was conducted for the key words fracture, osteoporosis, or bone mass and both estrogen and calcitonin. The MEDLINE search resulted in 306 publications on estrogen and 191 on calcitonin. All studies concerning the treatment for osteoporosis due to secondary causes (eg, steroid-induced osteoporosis) were eliminated. The remaining collection of publications was restricted to clinical trials in postmenopausal women in which the measure of outcome was bone mass or bone mineral density. The analysis only included those studies in which the antiresorptive agents were given in a treatment dose that was at or above the current Food and Drug Administration-approved dose. The clinically relevant endpoint, fracture, was not chosen as the primary endpoint because of the lack of studies examining fracture occurrence.

For each study, the following information was abstracted: author and year of the publication, randomization status (yes or no), sample size, mean age of the study subjects, treatment details, amount of calcium intake, skeletal site of measurement and measurement technique, study length, mean effect of the treatment per year, and any relevant comments. In the event of multiple publications in which the length of follow-up of the same population varied, the publication based on the most person-years of follow-up was used in the analysis. The measurement of bone mass change was based on the percentage change regardless of which measurement technique was used; however, measurement techniques were limited to single-photon absorptiometry, dual-photon absorptiometry, or dual-energy X-ray absorptiometry. The bone mass of the lumbar spine was measured by dual-photon absorptiometry in 80% of the studies, of the femoral neck by dual-photon absorptiometry in two-thirds of the studies, and of the forearm by single-photon absorptiometry in 18 of 19 studies. When distal and proximal radius data were both reported, an average effect for the two sites was used.

For several studies that did not include data on calcium intake, the authors were questioned regarding the calcium intake of their study population. However, for three studies it was assumed that the study subjects had an intake of calcium equal to the mean for the nation in which the study took place [United States (13) and United Kingdom (National Dairy Council, unpublished observations, 1990)] and this information was used to estimate an average calcium intake.

The established minimal effective dose of estrogen is 0.625 mg conjugated equine estrogen or its equivalent of estradiol or estrone sulfate (14). The route of administration does not appear to affect the efficacy of estrogens for skeletal protection, and 50 μ g estraderm is effective in preventing bone loss (15–17). Furthermore, the addition of progestins does not appear to affect the efficacy of estrogens (17). Therefore, we included oral and transdermal estrogens (dose > 50 μ g) in the analysis. Of the trials used in this analysis, 25% used transdermal estrogen, 47% used conjugated equine estrogen, 22% used estradiol, and 6% used ethinyl estradiol. There are no available data on dose equiva-

lences among the different types of estrogen; thus, we analyzed results from all studies in which the dose of estrogen was above the minimal effective dose. A separate analysis was made after excluding data from studies in which "higher" doses of estrogen were used: > 0.625 mg conjugated equine estrogens (1 study); > 50 μ g transdermal estrogen (1 study); and > 0.5 mg micronized estradiol or > 25 μ g ethinyl estradiol (7 studies).

Data analysis

Most of the trials analyzed presented longitudinal bone mass measures as a percentage of bone loss or gain from study initiation. The actual rate of bone change (g/cm^2) over the length of the clinical trial was reported in some studies and for these studies results were converted to the percentage change in bone mass per year. The annual percentage difference in bone mass was determined between baseline and after treatment separately for the group that received estrogen plus calcium and for the group that received estrogen alone. One-tailed Student's *t* tests were used to test the hypothesis that calcium in conjunction with estrogen or calcitonin would lead to greater improvements in bone mass at each skeletal site as compared with estrogen or calcitonin alone. In addition, the weighted mean percentage changes in bone mass after each treatment were calculated on the basis of the sample size for each study.

RESULTS

Controlled trials of estrogen

Thirty-one clinical trials were identified in which estrogen therapy was investigated in postmenopausal women. Of these trials, 20 increased calcium intake by modifying the diet or by using a calcium supplement in addition to estrogen (Table 1) and 11 used estrogen alone (Table 2). In the 20 studies that modified calcium intake, the total calcium intake was 1183 mg/d as compared with an average intake of 563 mg/d in the studies in which estrogen was given without any additional calcium.

Mean baseline descriptive data for the women that were treated with estrogen alone (11 studies) compared with women that were treated with estrogen and calcium (20 studies) are shown in Table 3. The women who received estrogen and calcium were slightly older and had a greater number of years since menopause (6 compared with 3 y). The mean duration of the studies was 1.7 y in the calcium-supplemented group (range: 1–5 y) and 2.6 y (range: 1–9 y) in the group treated with estrogen alone. In the higher calcium intake group, there were six studies in which patients were not only older but osteoporotic at baseline; there were no osteoporotic patients in the lower calcium intake groups. Four of these six studies also used higher estrogen doses; therefore, it is impossible to determine whether the synergy between estrogen and calcium would be greater in an osteoporotic population.

The effects on bone mass of estrogen plus calcium compared with estrogen alone are shown in Figure 1. The mean (\pm SEM) estrogen-related increase in lumbar-spine bone mass was $3.3 \pm 0.62\%$ after calcium plus estrogen and $1.3 \pm 0.29\%$ after estrogen alone ($P = 0.01$). The weighted mean percentage changes in lumbar-spine bone mass were similar: 1.4% after estrogen alone compared with 2.5% after estrogen plus calcium. The average increment in femoral-neck bone mass as a result of estrogen

TABLE 1

Selected characteristics of controlled studies of the effect of estrogen treatment and high calcium intake on bone mass in postmenopausal women¹

Study	Randomization size	Sample	Mean age	Total calcium intake	Progesterone treatment	Skeletal site/scan	Mean effect of treatment		Study length	
							Treated	Placebo		
		<i>n</i>	<i>y</i>	<i>mg</i>			% <i>y</i>		<i>y</i>	
Aloia et al (8)	Yes	67	52	1700	No	0.625 mg CEE	LS/DPA	-0.23	-2.10	3
Aloia et al (8)	Yes	67	52	1700	No	0.625 mg CEE	FN/DPA	+0.10	-2.00	3
Aloia et al (8)	Yes	67	52	1700	No	0.625 mg CEE	FA/SPA	+0.54	-0.65	3
Adami et al (18)	Yes	34	49	1200	Yes	50 µg E	FA/DPA	+2.87	-2.33	1.5
Christiansen and Riis (19)	Yes	31	64	1000	Yes	2 mg E ₂	LS/DPA	+4.5	-2.9	1
Christiansen and Riis (19)	Yes	31	64	1000	Yes	2 mg E ₂	FA/SPA	+6.78	-0.16	1
Christiansen and Riis (20)	Yes	59	50	1000	Yes	2 mg E ₂	FA/SPA	0	-2.5	5
Evans and Davie (21)	No	96	58	1000	Yes	50 µg E	LS/DPA	+3.0		1
Evans and Davie (21)	No	96	58	1000	Yes	50 µg E	FN/DPA	+0.9		1
Ettinger et al (22)	Yes	32	53	1500	Yes	1.0 mg E ₂	LS/DPA	+3.0	-0.9	1.5
Ettinger et al (22)	Yes	32	53	1500	Yes	1.0 mg E ₂	FA/SPA	+0.2	-0.5	1.5
Haines et al (12)	Yes	42	43	1360	Yes	0.625 mg CEE	LS/DXA	-3.0		1
Haines et al (12)	Yes	42	43	1360	Yes	0.625 mg CEE	FN/DXA	+5.0		1
Horsman et al (23)	No	29	52	1550	No	25-50 EE	FA/SPA	+0.5	-2.5	2
Kohut and Birge (24)	No	24	66	1650	Yes	0.625 mg CEE	LS/DXA	+5.0	+0.7	1
Kohut and Birge (24)	No	24	66	1650	Yes	0.625 mg CEE	FN/DXA	+3.2	-1.3	1
Kohut and Birge (24)	No	24	66	1650	Yes	0.625 mg CEE	FA/DXA	-0.4	-2.1	1
Lindsay and Tohme (25)	Yes	40	62	1500	Yes	0.625 mg CEE	LS/DPA	+5.3	-4.0	2
Lindsay and Tohme (25)	Yes	40	62	1500	Yes	0.625 mg CEE	FN/DPA	+2.8	-2.4	2
Lufkin et al(15)	Yes	75	64	800	Yes	100 µg E	LS/DPA	+5.30	+0.20	1
Lufkin et al(15)	Yes	75	64	800	Yes	100 µg E	FN/DPA	+2.60	+1.40	1
Lufkin et al(15)	Yes	75	64	800	Yes	100 µg E	FA/SPA	+1.0	-2.60	1
Luciano et al (26)	Yes	20	55	1500	Yes	0.625 mg CEE	LS/DPA	+6.4		1
MacLennan et al (27)	Yes	27	53	1000	Yes	0.625 mg CEE	FA/SPA	+4.5		1
Meschia et al(28)	Yes	37	51	800	Yes	1.25mg CEE	LS/DPA	+3.2	-3.5	2
Resch et al (29)	Yes	18	62	1200	Yes	2 mg E ₂	FA/SPA	+8.0	0	1
Ribot et al (30)	No	40	52	900	Yes	1-2 mg E ₂	LS/DPA	+3.5	-2.4	2
Ribot et al (31)	No	44	51	900	Yes	50 µg E	LS/DPA	+2.7	-2.4	2
Riis et al (32)	Yes	43	51	1000	Yes	2 mg E ₂	FA/SPA	+0.45	-3.0	2
Riis et al (32)	Yes	43	51	1000	Yes	2 mg E ₂	LS/DPA	+2.7	-1.85	2
Steiniche et al (33)	Yes	28	66	1000	Yes	2 mg E ₂	LS/DPA	+5.6	-0.8	1
Webber et al (34)	No	56	55	1100	Yes	0.625 mg CEE	LS/DPA	+2.1	-0.6	2
Webber et al (34)	No	56	55	1100	Yes	0.625 mg CEE	FA/SPA	+0.73	-1.3	2

¹ LS, lumbar spine; FN, femoral neck; FA, forearm; EE, ethinyl estradiol; E₂, estradiol; CEE, conjugated equine estrogen; E, estraderm; DXA, dual-energy X-ray absorptiometry; DPA, dual-photon absorptiometry; SPA, single-photon absorptiometry.

therapy alone was only $0.9 \pm 0.2\%$ (calcium intake: 563 mg/d) as compared with an average increment of $2.4 \pm 0.7\%$ after estrogen plus calcium (calcium intake: 1183 mg/d). Results were similar for the weighted mean percentage changes in femoral-neck bone mass: 0.6% after estrogen alone compared with 2.1% after estrogen plus calcium. At the forearm site, bone mass increased $0.4 \pm 0.4\%$ (weighted mean: 0.5%) after estrogen alone compared with $2.1 \pm 0.8\%$ (weighted mean: 1.8%) after estrogen plus calcium.

When the studies were stratified by the duration of the study there were no differences in the results. When we looked at the results after removing data from studies that used higher estrogen doses, the results were similar, although the smaller sample sizes precluded statistical significance. The women in the studies were also separated into categories of early (<5 y) and late (>5 y) postmenopause. The combined effect of estrogen and calcium was slightly less in the younger patients; however, there was still a two- to three-fold greater effect as compared with estrogen alone.

Controlled trials of calcitonin

The recommended dose for salmon calcitonin is 200 IU/d as a single nasal administration, although higher doses may be required in the immediate postmenopausal period to prevent bone loss (42). Therefore, we have limited the analysis to those studies or subgroups of patients that were treated with ≥ 200 IU intranasal salmon calcitonin. This resulted in the review of seven studies (Table 4).

Of these seven trials, six used a calcium supplement in conjunction with calcitonin. The one study that used calcitonin alone only reported bone mass data for the spine and hip. Therefore, no forearm data were available to assess the effects of supplemental calcium plus calcitonin on bone mass. Furthermore, only one study in which calcitonin and calcium were given together presented hip bone mass data. Therefore, comparison of hip data was based on one study with calcitonin and calcium and another with calcitonin alone, and neither group was protected against bone loss. The lumbar spine analysis was based on six studies of calcitonin and calcium compared with one study with

TABLE 2

Selected characteristics of controlled studies of the effect of estrogen treatment and low calcium intake on bone mass in postmenopausal women¹

Study	Randomization	n	Mean age	Total calcium intake	Progesterone treatment	Skeletal site/scan	Mean effect of treatment		Study length	
							Treated	Placebo		
Writing group (17)	Yes	875	y	mg	Yes	0.625 mg CEE	LS/DXA	+1.4	-0.6	y
Writing group (17)	Yes	875	56	575	Yes	0.625 mg CEE	FN/DXA	+0.56	-0.56	3
Field et al (35)	Yes	71	48	700	No	50 µg E	LS/DPA	+0.40	-3.20	2
Field et al (35)	Yes	71	48	700	No	50 µg E	FA/SPA	-0.40	-2.45	2
Fioretti et al (36)	No	37	53	500	Yes	50 µg E	FA/DPA	+1.8	-3.61	2
Genant et al (37)	Yes	15	42	575	No	0.6 mg CEE	FA/SPA	-0.40	-3.12	2
Horsman et al (23)	No	30	53	700	No	25-50 µg EE	FA/SPA	+1.0	-2.5	2
Haines et al (12)	Yes	53	43	320	Yes	0.625 CEE	LS/DXA	+1.0	—	1
Haines et al (12)	Yes	53	43	320	Yes	0.625 CEE	FN/DXA	+1.25 ¹	—	1
Lindsay et al (39)	Yes	100	48	700	No	23.2 mg EE	FA/SPA	-0.2	-1.1	9
Palacios et al (39)	Yes	51	48	450	Yes	0.625 mg CEE	LS/DPA	+1.9	-4.5	2
Palacios et al (39)	Yes	51	48	450	Yes	1.5 mg E	LS/DPA	+2.3	—	2
Prince et al (40)	Yes	81	56	500	Yes	0.625 mg CEE	FA/SPA	+1.7	-2.5	2
Recker et al (41)	No	38	60	500	Yes	0.625 mg CEE	FA/SPA	-0.7	-2.9	2
Stevenson et al (16)	No	96	53	669	Yes	50 µg E	LS/DPA	+1.7	-1.3	1.5
Stevenson et al (16)	No	96	53	669	Yes	0.625 mg CEE	FN/DPA	+0.8	-1.8	1.5

¹ LS, lumbar spine; FN, femoral neck; FA, forearm; EE, ethinyl estradiol; CEE, conjugated equine estrogen; E, estraderm; DXA, dual-energy X-ray absorptiometry; DPA, dual-photon absorptiometry; SPA, single-photon absorptiometry.

calcitonin alone. The populations were similar with regard to age (55 compared with 59 y) and years since menopause (5 compared with 8 y).

The benefit of 200 IU nasal calcitonin in addition to calcium compared with calcitonin alone is illustrated in **Figure 2**. Bone mass of the spine increased by $2.1 \pm 1.0\%$ in patients with a total calcium intake of 1467 mg/d compared with a loss of 0.2% in the one population given calcitonin alone, in whom the calcium intake was 627 mg/d.

DISCUSSION

Standard treatment for postmenopausal osteoporosis usually includes calcium supplementation and exercise along with the prescription of antiresorptive drugs, including estrogen, calcitonin, and alendronate (49). Calcium itself may decrease bone turnover, and given alone leads to decreases in bone loss. The average effect of calcium was reported as a 0.8% decrease in bone loss each year in early postmenopausal women, given a mean rate of bone loss in untreated early postmenopausal women of 2%;

TABLE 3

Baseline descriptive data for postmenopausal women in controlled studies of estrogen treatment with and without additional calcium¹

	Estrogen alone (n = 11)	Estrogen + calcium (n = 20)
Age (y)	51 ± 1.5	55 ± 1.4 ²
Time since menopause (y)	3 ± 0.84	6 ± 1.2 ²
Calcium intake (mg)	589 ± 37	1183 ± 65
Study length (y)	2.6 ± 0.7	2.2 ± 0.2

¹ $\bar{x} \pm SE$.

² Significantly different from estrogen alone, $P < 0.001$.

this is equivalent to a 40% reduction in bone loss (5). A later report by Dawson-Hughes (6) indicated the preservation of bone mass by calcium alone was greatest in the hip and forearm. We have just completed an analysis of published clinical trials of calcium supplementation confirming that calcium supplementation generally decreases bone loss in the spine by 40% and minimizes bone loss in the forearm and femoral neck in postmenopausal women. The average annual increase in bone mass from hormone replacement therapy in the absence of calcium we reported here is 1.3% for the spine, 0.9% for the femoral neck, and 0.4% for the forearm. Therefore, the beneficial effect of estrogen and an adequate calcium intake appears greater than the sum of each effect alone: an increase of 2.4%/y in the femoral neck, 2.1%/y in the forearm, and 3.3%/y in the lumbar spine. Supportive of this con-

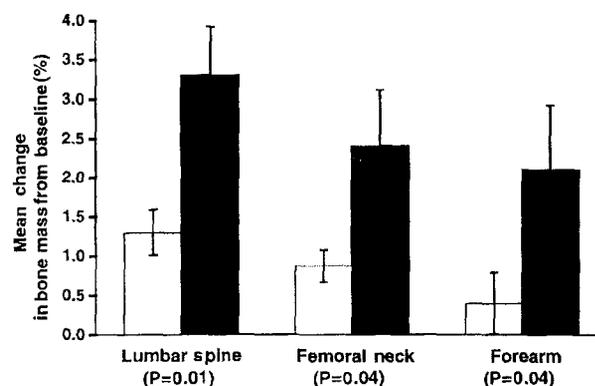


FIGURE 1. Mean (\pm SEM) annual percentage change in bone mass at the lumbar spine, femoral neck and forearm in postmenopausal women treated with estrogen alone (□; total average calcium intake: 563 mg/d) compared with women treated with estrogen and calcium (■; total average calcium intake: 1183 mg/d).

TABLE 4
Selected characteristics of controlled randomized studies of calcitonin treatment (200 IU) and bone mass in postmenopausal women¹

Study Reference	Sample size	Mean age	Total calcium intake	Skeletal site/scan	Mean effect of treatment/y		Study length
					Treated (200 IU)	Placebo	
	<i>n</i>	<i>y</i>	<i>mg/d</i>		<i>%/y</i>		<i>y</i>
Overgaard et al (42)	45	52	1500	LS/DXA	-0.3	-0.8	2
Overgaard et al (43)	81	70	1500	LS/DPA	+1.87	+0.8	2
Overgaard et al (43)	81	70	1500	FA/SPA	-0.45	-0.6	2
Overgaard et al (44)	37	65	1500	LS/DPA	+1.40	-0.7	1
Overgaard et al (44)	37	65	1500	FA/SPA	-0.10	-2.50	1
Reginster et al (45)	167	53	1300	LS/DPA	+1.1	-3.4	2
Thamsborg et al (46)	62	65	1500	LS/DPA	+1.25	+0.85	2
Thamsborg et al (46)	62	65	1500	FN/DPA	-1.1	+0.8	2
Thamsborg et al (46)	62	65	1500	FA/SPA	-0.6	-0.55	2
Thamsborg et al (47)	40	67	1500	LS/DPA	+7.1	+2.19	1
Thamsborg et al (47)	40	67	1500	FA/SPA	0.35	-1.38	1
Ellerington et al (48)	68	55	627	LS/DPA	-0.2	-1.2	2
Ellerington et al (48)	68	55	627	FN/DPA	-0.8	-1.1	2

¹ LS, lumbar spine; FN, femoral neck; FA, forearm; DXA, dual-energy X-ray absorptiometry; DPA, dual-photon absorptiometry; SPA, single-photon absorptiometry.

clusion are the studies by Ettinger et al (11) and Haines et al (12). Lower doses of estrogen (0.3 mg) when given in conjunction with a high calcium intake (1700 mg/d) were found to be as effective as a standard dose of 0.625 mg estrogen at both the spine (by quantitative computed tomography) and at the forearm (11). In a randomized trial from Hong Kong, the group that received calcium in addition to estrogen had a significant increase in bone mass of the femoral neck as compared with the group that received estrogen alone (12). Therefore, calcium supplementation appears to potentiate the benefit of estrogen therapy on bone mass at the lumbar spine, femoral neck, and forearm, even when standard doses of estrogen are given.

It is possible that higher doses of estrogen would be more effective, although published results indicate that there is no significant difference in effectiveness between 0.625 and 1.2 mg estrogen (14, 50). Furthermore, different types of estrogen could have different potencies. In this review, even when studies providing "higher" estrogen doses were eliminated from the analysis, similar results concerning the additional benefit of calcium to estrogen were found. The potential risks and cost of additional calcium through dietary changes or supplementation are considerably less than those of a higher dose of estrogen, and therefore, if the same effect can be achieved by the combination of 0.625 mg conjugated equine estrogen (or its equivalent) and calcium, it would clearly be preferable.

Calcitonin is a polypeptide hormone that decreases bone resorption and reduces bone loss. Like estrogens, calcitonin can cause a small increment in bone mass. Our data, albeit sparse, show that the bone-sparing benefit of calcitonin on the spine appears to be enhanced when there is an adequate intake of calcium, either through diet or supplements. Intranasal calcitonin in a population of postmenopausal women with a mean dietary calcium intake of 627 mg/d was only able to halt bone loss, however. When calcium intakes were almost 1500 mg/d there were gains in bone mass of $\approx 2.1\%/y$ in the spine. One explanation for the enhanced effect of calcitonin and calcium compared with calcitonin alone on lumbar spine bone mass may be that the dose for calcitonin is suboptimal at 200 IU.

The synergistic increments in bone mass we see between calcium and antiresorptive therapy may only be related to a transient remodeling effect such that increments in bone mass are simply the result of filling in of remodeling sites where resorption has already occurred. In this scenario, the effect of calcium in conjunction with estrogen may be a result of the combined effects of strong and weak antiresorptive agents (estrogen and calcium, respectively) effecting an overall more potent suppression of bone resorption. This would allow even more remodeling sites to fill in with new bone and result in a greater effect on bone mass. If this is the case, the effect might be more pronounced in the studies of shorter duration (< 1.5 y). This was not the case, however. Results of studies with long and short durations appeared similar, although there were only a few long-term (> 2 y) studies published. To exclude the possibility that the synergy we observed was due only to a transient remodeling imbalance would require studies of a longer duration than that of those that currently exist. In fact, even the long-term effects of hormone therapy alone on bone mass are unknown.

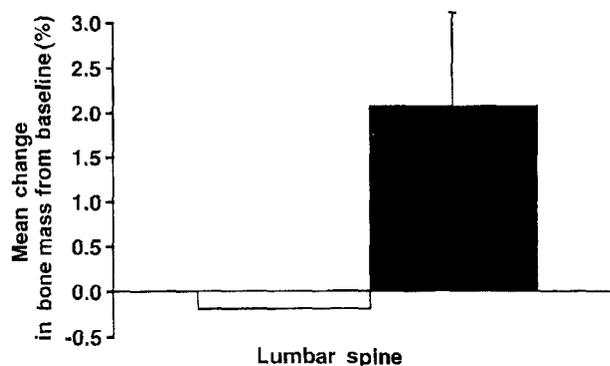


FIGURE 2 Mean (\pm SEM) annual percentage change in bone mass at the lumbar spine in postmenopausal women treated with calcitonin alone (\square ; total average calcium intake: 627 mg/d) compared with women treated with calcitonin and calcium (\blacksquare ; total average calcium intake: 1466 mg/d).

Several possible alternative explanations for the synergistic relation between estrogen and calcium can be offered. It is possible that the calcium supply is the limiting factor for patients receiving estrogen alone. The total skeleton, on average, contains ≈ 1000 g Ca. To increase this total-body bone mineral by 2% would require an excess calcium supply of 20 g, or 20 000 mg over a year. This means that ≥ 55 mg elemental Ca/d would have to be bioavailable to the skeleton, even assuming total skeletal efficiency. Because average fractional gastrointestinal calcium absorption is only $\approx 20\%$, this would require an additional intake of ≥ 275 mg elemental Ca/d. In fact, the net absorption from an increment in intake approximates 10%, therefore leading to a requirement of an additional 550 mg elemental Ca/d. This quantity of calcium is not available given the average unsupplemented calcium consumption, which may not even be enough to maintain bone mass, let alone increase it.

Another possible theoretical mechanism of the added effect of an additional calcium supply superimposed on an estrogen effect is that it could allow an increase in the mineral deposition density of newly formed or perhaps even previously formed bone. In this scenario, the size of newly formed bone packets or wall width would not be increased, but each packet would be hyper-mineralized. This would result in an increase in apparent bone mass and possibly an increase in bone strength. Regulation of the mineralization process is poorly understood, but the major substrate for the process could conceivably be one of the regulatory constituents.

In conclusion, there appears to be a synergistic relation between a high calcium intake and estrogen and calcitonin treatment for osteoporosis, with the greatest effect predominantly at the cortical sites, such as the femoral neck and forearm. These data need to be confirmed in the large, prospective clinical trials currently underway (such as the Women's Health Initiative, National Institutes of Health, Bethesda, MD). In addition, the optimal calcium intake (mg/d) in conjunction with antiresorptive therapy is unknown although the benefit we showed was for calcium intakes of ≈ 1200 mg/d. An increasing calcium intake throughout the life span can benefit the skeleton, and, even in combination with antiresorptive treatment, calcium supplementation has a significant positive benefit to the skeleton. 

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