Cyclic Oral Phosphate and Etidronate Increase Femoral and Lumbar Bone Mineral Density and Reduce Lumbar Spine Fracture Rate Over Three Years

Edward B. Silberstein and Walter Schnur

Division of Nuclear Medicine, The Jewish Hospital of Cincinnati and E. L. Saenger Radioisotope Laboratory, University of Cincinnati Medical Center, Cincinnati, Ohio

We have performed a study of the safety and efficacy of cyclic sequential oral phosphate, diphosphonate and calcium carbonate. Forty-two postmenopausal women with osteoporosis diagnosed by dual-photon absorptiometry were treated with a sequential cyclic regimen of oral phosphate for 3 days, etidronate for 2 wk, and then a calcium salt for 12 wk. This was repeated cyclically for 3 yr. They were rescanned after every two 101-day cycles. A control group of 20 patient receiving only the calcium salt was matched for age, time since menopause, race and sex. The group treated with cyclic phosphate, etidronate, and calcium regimen had 80% fewer fractures than the control group over 3 yr of follow-up. Significant response in halting bone mineral loss and increasing bone mineral density was seen in none of the controls but in 90% of treated patients' lumbar spine and 70%–80% of the three regions of the femoral neck examined.

J Nucl Med 1992; 33:1–5

Osteoporosis is a disease characterized by the loss of bone mineral and has a high prevalence in postmenopausal white and Oriental females. The attendent morbidity and mortality and medical expenses related to this disorder are well documented (*1*).

Osteoporosis has been categorized into two forms by the Mayo Clinic group, one with its onset in the perimenopausal period, and the other in an older age group (*2*). The form beginning at menopause has been successfully prevented with estrogen and progestagen, although the effectiveness of hormone therapy on the older age group is less certain. Unopposed estrogenic therapy raises the risk of endometrial carcinoma (*3*) (and possibly breast carcinoma), although it decreases the probability of cardiovascular disease. When estrogen and progestagen are sequentially given, the risk of endometrial carcinoma is reduced but the benefits to the cardiovascular system appear to be lost (*4*). In either case, many older women find recurrent hormone-induced vaginal bleeding and other symptoms unpleasant and have great concern about the risk of not only endometrial but also breast cancer, especially in susceptible populations with a family history. There has therefore been great interest in nonhormonal approaches to treatment of osteoporosis, including calcium, vitamin D, fluorides, anabolic steroids, and calcitonin.

We have performed a study of the safety and efficacy of cyclic sequential oral phosphate, diphosphonate and calcium carbonate, a modification of the approach first suggested by Frost in which the bone multicellular unit is first activated, then osteoclast bone absorption depressed, followed by a free period for bone formation without resorption, and repetition of this regimen (activate, depress, free, repeat or ADFR) (*5*). We have hypothesized that the ADFR approach can stabilize or increase bone mineral density and hence reduce fracture incidence in the postmenopausal female.

MATERIALS AND METHODS

Patients

Forty-two osteopenic white post-menopausal patients in a solo family practice of one of us (W.S.) volunteered to participate in this study. The protocol was approved by the Institutional Review Boards of The Jewish Hospital of Cincinnati and the University of Cincinnati. None had a history of an osseous disorder. Abnormally low bone mineral density (in excess of 2 s.d. below the mean of a range of young normals established by the Mayo Clinic for the Lunar Corporation) was the criterion for inclusion in the study, as determined by bone mineral dual-photon densitometry of the lumbar spine and proximal femur. The patients were drawn from a larger group of 66 osteoporotic women, but 24 did not complete the study. The reasons for withdrawal were treatment with another modality (n = 6), moving from the Cincinnati area

Received Mar. 20, 1991; revision accepted Jul. 11, 1991.
For reprints contact: Edward B. Silberstein, MD, Mail Location 577, University of Cincinnati Medical Center, Cincinnati, OH 45267.

(n = 2), forgetting to take the medication (n = 6), death from intercurrent cancer (n = 2), phosphate-induced abdominal bloating or diarrhea and nausea (n = 3), rash from Didronel (n = 1), or lost to follow-up (n = 4). There was no difference in the years post-menopause, mean age, or bone mineral density (BMD) between the patients who completed 3 yr of the study and those who withdrew. All patients were white and were screened with a thorough history and physical examination and a battery of 11 laboratory tests to exclude other causes of osteopenia, including diabetes, renal osteodystrophy, thyrotoxicosis, hyperparathyroidism, vitamin D deficiency, hypercortisolism and myeloma. None had ever taken estrogen, glucocorticoids, androgens or other steroids, heparin, phenytoin, thiazide, fluoride, diphosphonate, or calcitonin. All had used prior calcium supplements in a dose of 1.0–1.5 g.

Controls

A control group of postmenopausal osteoporotic white women (n = 20) identical to the treatment group in Northern European site of origin, neighborhood of Cincinnati resided in, dietary habits, exercise level, and smoking history was retrospectively obtained from the population of all white, female patients referred for diagnosis of osteoporosis to the Division of Nuclear Medicine of The Jewish Hospital who had a low BMD, were on no therapy for osteoporosis except calcium, and had no other disorder causing osteopenia. Only 20 fulfilled all these criteria. They did not differ from the study group prior to therapy in mean age, time since menopause, racial, socioeconomic characteristics (e.g. zip code distribution), diet or BMD at any site (Tables 1 and 2) and were therefore designated as appropriately matched controls. All controls had at least two BMD measurements (12 had three or four) over the 3-yr period. The data from controls and patients were read blindly. Six patients were eliminated as controls because careful and continued follow-up revealed intermittent use of vitamin D or estrogen.

Treatment

The cyclic regimen was as follows:

1. The patients were given 1 g of phosphate as the sodium and potassium acid salt t.i.d. with food for only the first 3 days of the cycle (K-Phos Neutral, Beach Pharmaceuticals, Tampa, Fl). This theoretically activates a basic multicellular unit for bone formation.
2. Following these 3 days of theoretical "activation" of the bone mineral unit, phosphate was stopped and osteoclastic activity was depressed by oral etidronate disodium (10 mg/kg for 14 days for the first four cycles. In subsequent cycles, to reduce the possible risk of drug-induced osteomalacia, this was reduced to 5 mg/kg) also for 14 days per cycle (Didronel, Norwich Eaton Pharmaceuticals, Norwich, NY). No food was eaten for 2 hr before or after the etidronate dose.

TABLE 1
Demography of Study Population

Characteristics	ADFR	Control	p Value
Age (yr)	61.3 ± 11.0	61.6 ± 5.9	>0.05
Time since menopause (yr)	14.7 ± 7.7	11.3 ± 5.6	>0.05
Number	42	14	

TABLE 2
Pretreatment (BMD in g/cm^2 ± 1 s.d.)

Site	ADFR group	Control	p Value
Lumbar spine	1.04 ± 0.10	0.98 ± 0.14	>0.05
Femoral neck	0.76 ± 0.14	0.73 ± 0.10	>0.05
Ward's triangle	0.61 ± 0.14	0.57 ± 0.10	>0.05
Greater trochanter	0.64 ± 0.10	0.61 ± 0.10	>0.05

3. After a total of 17 days, both medications were stopped and the patients were given calcium carbonate (Os-Cal, Marion Merrell Dow, Inc., Kansas City, MO) orally (500 mg b.i.d.) for 12 wk, the "free" period. Daily calcium consumption from dietary sources was recorded but no dietary changes were made. The calcium carbonate was always stopped before the next sequence of phosphate and diphosphonate was repeated so that calcium and a phosphate compound were never given simultaneously. This regimen has been called coherence therapy or ADFR.

Bone Mineral Density Measurement

To measure and follow the degree of osteopenia, dual-photon absorptiometry (DPA) was performed prior to therapy and after every two cycles throughout the 12-cycle study period. The sites measured were lumbar spine, femoral neck, Ward's triangle and greater trochanter. Thoracic spine BMD was not measured since this option was not available in our hardware and software. A Lunar DPA-3 absorptiometer (Lunar Corp, Madison, WI) was employed using a ^{153}Gd source which was changed within 12 mo to avoid artifacts from source strength alterations (*6*). Our DPA has an in vitro precision of 1% and in vivo precision of 2.8% for the lumbar spine, femoral neck, Ward's triangle and the greater trochanter. This stability of precision persisted over three years of the study. An algorithm supplied by the manufacturer was employed which did not yield artifactual BMD results when the ^{153}Gd source was changed.

Fractures were defined as a decrease in lumbar vertebral height of 20% or more as imaged on the ^{153}Gd (DPA) transmission scan. To determine the precision of our measuring technique, four phantom vertebrae were scanned in water 10 times and the mean height of these was found to have a standard deviation of less than 0.8 mm, coefficient of variation 6%. Since all vertebral compression changes were found on a set of ten matching DPA scans where lumbar skeletal radiographs were also obtained, further x-rays were felt to yield only excess cost and radiation. Spondylotic lumbar vertebrae were excluded from analysis when: the superior and/or inferior margins of the vertebra could not be reproducibly distinguished by the edge detection algorithm of the DPA; vertebral anatomy was clearly distorted (as by scoliosis) on the scan; or when irregular areas of increased density throughout the vertebrae indicated significant reactive cortical bone formation (Fig. 1). Each unfractured vertebra of nonspondylotic patients (n = 27) and controls (n = 12) was then measured over time to look for fracture. All vertebral height measurements were made without knowledge of the status of the patient as belonging to the treated or control group.

We measured BMD so that compressed vertebrae were excluded from analysis of the integral of lumbar BMD from the first to fourth lumbar vertebrae. All measurements were done with reference to the previous area of interest on a given patient.

We have observed in unpublished data and others have also

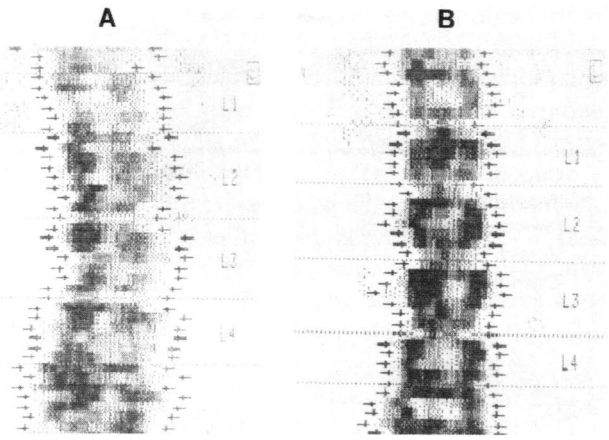

FIGURE 1. Dual-photon absorptiometry scans of the lumbar spine. (A) Spondylotic spine excluded from quantitative analysis and (B) spine within normal limits.

documented that spondylosis and other relevant radiologic changes can be well visualized with DPA (*7*). Therefore we did not require lumbar spine radiographs of our patients, thus markedly reducing radiation dose (to 10 mrad per measurement) and cost.

Statistics

Groups were compared employing Student's unpaired t-test (two-sided). Changes in bone mineral density were examined using a two-tailed sign test and regression analysis. A "significant" change was assessed as occurring when it exceeded the 95% confidence limits of bone mineral density measurements regressed on time. We employed a statistical model for the regression analysis which assumes that the rate of change is constant over time, that every patient is affected in the same way with respect to instrument precision, and that the DPA had no drift and was stable over the measurement period (as our quality control indicated) (*8,9*). Appropriate 95% confidence limits for variations in DPA precision, number of measurements over time, and different time intervals between measurements have also been published by the Mayo Clinic group (*8,9*). Differences in BMD over time in excess of 95% confidence limits as calculated by the Mayo group were called "significant."

Other Measurements

The patients' heights and weights were recorded every 6 mo. Weight changes of ±10% can alter BMD measurements using the DPA algorithm and any patient with such a weight change would have been excluded from analysis.

Serum calcium, phosphate, parathormone, calcitonin and vitamin D were also monitored after every two cycles, with phlebotomy performed just after completion of the 12-wk cycle of calcium carbonate and before oral phosphate was administered.

RESULTS

Changes in Bone Mineral Density

Tables 3 and 4 demonstrate that at the end of 3 yr, 25 of 27 patients responded to ADFR with increasing or stable BMD in the lumbar spine. The gain in responder BMD occurred largely within the first year, with stabilization thereafter, but with no continued increase in BMD. The response rate was lower in the femoral neck at 75%, while it was 69% in the Ward's triangle and 78% in the greater trochanter. These responses were all significant by 3 yr. In fact, three of the four sites measured have a statistically significant change with $p < 0.05$ within 1 yr, with only Ward's triangle taking a longer period of time. None of the controls had an increase in BMD over the 3 yr while taking only a calcium salt, with a range of loss in the controls of 0.05–0.07 g/cm^2 over this time. These losses are significantly different ($p = 0.01$) from the responders to ADFR treatment but not different from the patients who lost BMD and were classified as nonresponders. Response was independent of age at treatment and time since menopause. There were 83% fewer lumbar vertebral fractures in the ADFR treated group than in the control group ($p < 0.01$) (Table 5). Neither group had spontaneous painful lumbar fracture or suffered a fracture of the femoral head or neck during the study.

Side Effects

There were three cases of transient nausea during phosphate therapy in the 42 cases. One patient who was allergic to the starch excipient of calcium carbonate was given calcium gluconate. No other clinical side effects were noted.

Chemical Changes

Table 6 tabulates chemical changes in calcium, phosphate, parathyroid hormone, vitamin D, and calcitonin

TABLE 3
Response to ADFR Therapy

	ADFR group (n = 42)				Control group			
Site	Increase	Stable	Decrease	Total	Increase	Stable	Decrease	Total
Lumbar spine	24	1	2	27*	0	0	12	12†
Femoral neck	28	4	10	42	0	0	14	14
Ward's triangle	21	9	12	42	0	0	14	14
Greater trochanter	24	6	12	42	0	0	14	14

* Fifteen with spondylosis could not be precisely quantitated.
† Two with spondylosis could not be precisely quantitated.

TABLE 4
Responders/(Nonresponders) by Increase/(Decrease) in BMD (%) over Three Years*

Site	Response	Lumbar Spine 0–1 yr	0–2 yr	0–3 yr
Lumbar spine	Yes	6.6 ± 4.2	6.9 ± 4.1	6.5 ± 3.3
	No†	(2.3)	(1.7)	(3.2)
Femoral neck	Yes	4.8 ± 4.3	7.3 ± 6.1	6.8 ± 5.9
	No	(3.9 ± 2.5)	(4.6 ± 1.9)	(4.5 ± 1.7)
Ward's triangle	Yes	7.9 ± 6.4	6.8 ± 6.4	7.3 ± 4.7
	No	(5.5 ± 4.6)	(5.9 ± 2.7)	(7.5 ± 3.0)
Greater trochanter	Yes	8.6 ± 5.1	8.5 ± 6.4	8.4 ± 6.8
	No	(4.7 ± 5.6)	(5.0 ± 4.4)	(5.4 ± 3.6)

* Only five patients failed to respond in at least one site.
† Too few to calculate s.d.

(SmithKline Clinical Laboratories) in the patients who received ADFR. The blood tests were all obtained at the end of every second 12-wk calcium carbonate cycle. The most striking alteration was a decrease in parathyroid hormone in 38 of the 42 patients, although the levels remained within normal limits. There occurred a concurrent rise in serum phosphate, significant by the sign test at the 0.05 level. No other laboratory tests were significantly altered. In six of six randomly selected treated patients, serum parathyroid hormone was documented to increase by at least 30% after three days of oral phosphate therapy.

DISCUSSION

Bone mineral density may increase without a change in the fracture rate as has been recently demonstrated with fluoride therapy (*10*). Therefore, we believe that the 83% reduction in lumbar vertebral fracture rate, defined as a 20% reduction in height employing DPA, was an extremely important finding. DPA was found to have excellent precision in our study, and in the hands of others has reflected skeletal radiographic changes quite accurately (*7*). Skeletal radiography also gives considerably higher marrow doses to patients than the 10 mrad per study from DPA.

TABLE 5
Lumbar Vertebral Fracture Incidence (>20% Height Decrease)

	Number of vertebrae at risk	Time interval (yr) 0–1	1–2	2–3	Total fractures
Controls	56	6	1	2	9 (16.1%)*
ADFR treatment	108†	1	0	2	3 (2.8%)*

* $p < 0.01$.
† Twenty-seven spines evaluable (four lumbar vertebrae).

TABLE 6
Changes in Biochemical Parameters After Three Years in ADFR Recipients

Serum test	Rise	No change	Decrease	p Value
Calcium	11	28	3	>0.05
Phosphate	19	18	5	0.05
Parathormone	3	1	38	<0.01
Vitamin D	7	19	16	>0.05
Calcitonin	3	30	9	>0.05

The reduction in fracture rate in our study was seen within the first year, unlike the data recently published by Storm et al. (*11*), but the overall reduction is comparable. Diphosphonates have a long biologic half-life and it is not surprising that those early effects were seen. In both our study and that of Storm et al., the rate of new vertebral fracture is reduced to a greater extent than that recently published from seven collaborating centers by Watts et al. (*12*). Both of these recent publications used skeletal radiographs to assess lumbar fracture. Watts et al. defined lumbar fracture as a reduction of 20% or more in the anterior, middle or posterior height with reduction of 10% or more in the area of a recently unfractured vertebra (*12*) and Storm et al. called lumbar fracture at least a 20%–25% reduction in anterior, middle or posterior height, with reduction in area of approximately 10%–20% (*11*). The similarity of our results to those of the two recently published studies (*11,12*) further indicate the validity of our use of DPA alone to assess fracture, although our data set differs in some areas from these. The study of Storm et al. did not examine the proximal femur while ours did. Watts et al. found a significant increase in only one proximal femur site (greater trochanter but not Ward's triangle or femoral neck) in patients receiving etidronate alone, while the group given phosphate and etidronate, a regimen similar to ours, had no femoral BMD changes after 2 yr. With our approach, giving phosphate and etidronate, the proximal femur did respond in all sites measured at 3 yr. Both of the two recent studies (*11,12*) employed intermittent cyclic etidronate. The use of oral phosphate was studied in randomized fashion by the seven center group (*12*), which found that the combination appeared to result in no additional benefit beyond that from etidronate alone.

However, our study at 3 yr does show an increase in BMD at all three sites measured in the proximal femur. Thus, the question of the value of oral phosphate as well as our use of an increased dose of etidronate in just the first year as part of ADFR treatment must remain open at this time, since we have found it efficacious. Our ADFR cycle of 101 days (repeated 12 times) differs slightly from that of Storm et al. (10 cycles of 105 days) (*11*). The Watts et al. cycle was 91 days repeated only eight times (*12*).

Not all of our patients were responders. The following

parameters at initiation of therapy were not predictive of response: age; years since menopause; presence or absence of cardiovascular disease; serum calcium, alkaline phosphatase, phosphate, vitamin D, thyroxine, parathormone, calcitonin, cortisol, serum protein electrophoresis, creatinine, glucose; or initial BMD.

Clinical side effects were not significant. Parathyroid hormone was found to be lower after 3 yr of ADFR than at the initiation of treatment presumably from the mild suppressive effect of oral calcium, with a resultant mild increase in serum phosphate levels at the end of the cycle. However, these serum levels always remained within normal limits even though the changes were statistically significant (Table 6).

Response of our patients was not unlike that from prior studies of calcitonin and etidronate as antiresorptive agents (*13–15*), where an early increase in BMD did not continue at the same rate but stabilized at a higher plateau. This could be due to a decrease in bone remodeling with filling in of resorption cavities. Also, with a decrease in resorption there is, of necessity, a decrease in the rate of bone turnover, which would lead to an increase in the mean age of bone. Since older bone is more heavily mineralized, BMD could initially increase (*16*).

Other studies involving cyclic etidronate have shown an increase (*11,12,17*) or stability (*18*) in BMD, but our study is unique in providing positive results in both lumbar spine and hip lasting over 3 yr of treatment.

Our therapeutic approach differed from those of Storm et al. (*11*) and Watts et al. (*12*) in employing 10 mg/kg etidronate in the first four cycles and then 5 mg/kg. This may be the explanation for our uniquely better results in improving or stabilizing hip BMD.

We have not yet determined if the nonresponders to ADFR may have early osteomalacia. Vitamin D levels in these patients were normal and they will be followed closely with bone biopsy as necessary.

Pacifici et al. (*19*) reported that intermittent ADFR therapy did not prevent the loss of vertebral bone, although radial bone was stable over 2 yr. One gram of calcium was given by this group on the days when phosphate and diphosphonate were ingested. Their methodology, unlike that of Storm et al., who also gave calcium throughout the therapy cycle, does not include instructions to separate ingestion of calcium and the other two drugs by a number of hours. Since calcium inhibits the absorption of etidronate (*20*), a positive effect of ADFR under these circumstances would not be expected.

Storm et al. performed bone histomorphometry and found that etidronate-treated patients had no increase in the mean volume of trabecular bone or any accumulation of unmineralized bone (*11*). Perhaps low doses of etidronate contribute to trabecular strength when resorption is inhibited and osteoblasts can lay down new lamellar bone.

In conclusion, we have shown that the ADFR regimen is efficacious and safe over a 3-yr period in partially reversing lumbar and femoral BMD losses and in reducing lumbar fracture incidence. The ADFR regimen, with oral phosphate and etridronate followed by calcium carbonate, is easy to administer. There are none of the unpleasant or potentially carcinogenic side effects of hormonal therapy. No injections or nasal sprays are required as with calcitonin. Clearly, further studies are required to determine the long-term efficacy of ADFR therapy; to ascertain whether osteomalacia eventually results because of the long biologic half-time of etidronate in bone, since etridronate may interfere with osteoid calcification; and whether administration of ADFR therapy at the time of menopause can prevent the high rate of bone mineral loss occurring at that time.

ACKNOWLEDGMENTS

We are indebted to Ms. Robin Hilton for skilled secretarial assistance. This study was funded by The Jewish Hospital Research Council of The Jewish Hospital of Cincinnati.

REFERENCES

1. Lindsay R. Osteoporosis. *Clin Ger Med* 1988;4:411–430.
2. Riggs BL, Melton LJ III. Involutional osteoporosis. *N Engl J Med* 1986;314:1676–1686.
3. Lufkin EG, Carpenter PC, Orz SJ, et al. Estrogen replacement therapy. *Mayo Clin Proc* 1988;63:453–460.
4. Beaglehole R. Oestrogen and cardiovascular disease. *Br Med J* 1988;297:571–572.
5. Frost HM. Treatment of osteoporoses by manipulation of coherent bone cell populations. *Clin Orthop Rel Res* 1979;143:227–243.
6. DaCosta MA, Luckey MM, Meier DE, et al. Effect of source strength and attenuation on dual-photon absorptiometry. *J Nucl Med* 1989;30:1875–1881.
7. Hopkins A, Zylstro S, Hreshchyshyn MM, et al. Normal and abnormal features of the lumbar spine observed in dual-photon absorptiometry scans. *Clin Nuc Med* 1989;14:410–414.
8. Wahner HW. Can the rate of bone loss be measured with repeated bone mineral measurements. In: Dequeker J, Geusens P, Wahner HW, eds. *Bone mineral measurements by photon absorptiometry.* Leuven, Belgium: Leuven University Press; 1988:301–304.
9. Wahner HW. Assessment of bone loss with repeated bone mineral measurements: application to measurements on the individual patient. *Nuc Compact* 1987;18:7–10.
10. Riggs BL, Hodgson SE, O'Fallon WM, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990;322:802–809.
11. Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl Med* 1990;322:1265–1271.
12. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990;323:73–79.
13. Gruber HE, Ivey JL, Baylink DJ, et al. Long-term calcitonin therapy in postmenopausal osteoporosis. *Metabolism* 1984;33:295–303.