

Antiresorptive therapy in asthmatic patients receiving high-dose inhaled steroids: A prospective study for 18 months

Wei Qing Wang, MB, Mary Sau Man Ip, MD, Kenneth Wau Tak Tsang, MD, and Karen Siu Ling Lam, MD *Hong Kong*

Background: Inhaled steroid therapy is an effective and well tolerated mode of therapy for asthma. Although systemic side-effects of inhaled steroids are much less common than those found with systemic steroids, the drugs may be absorbed through mucosal surfaces. Inhaled steroids have been reported to disturb normal bone metabolism, and they are associated with a decrease in bone mineral density.

Objective: We conducted this study to investigate bone density in asthmatic subjects receiving long-term high-dose inhaled steroids and the effects of supplementation with oral calcium with or without etidronate.

Methods: We evaluated thirty-eight Chinese subjects (24 men and 14 premenopausal women; 28 patients and 10 healthy control subjects) in this prospective study. Patients were randomized into three arms: those receiving no supplement, those receiving 1000 mg/day calcium supplement, and those receiving 400 mg/day cyclical sodium etidronate with 1000 mg/day calcium, respectively. The patients and control subjects were matched for age, sex, and dose of inhaled steroids. Bone density at lumbar spine and hip region was measured by dual energy x-ray absorptiometry with a densitometer at baseline and at 6, 12, and 18 months for the asthmatic groups and at baseline and at 12 and 18 months for the control group. Serum calcium, phosphate, alkaline phosphatase, osteocalcin, parathyroid hormone, 25-hydroxyvitamin D, and urinary hydroxyproline/creatinine were measured simultaneously to bone density assessments.

Results: There were 10 control subjects, 10 asthmatic subjects receiving no supplement, eight asthmatic subjects receiving calcium supplement, and 10 asthmatic subjects receiving calcium and etidronate therapy, respectively. The mean ($\pm$ SEM) dosages of beclomethasone or budesonide for the three groups of asthmatic subjects were 2.2 ± 0.3 , 2.0 ± 0.2 , and 2.0 ± 0.2 mg/day, respectively. Mean dietary calcium intake of the study subjects was 766 ± 39 mg/day. At baseline, bone mineral density of the spine in the group receiving no supplement was significantly lower than that found in the control group ($p < 0.05$). At 18 months, patients receiving no supplement had significantly greater bone loss at the lumbar spine than patients receiving etidronate plus calcium lactate-

gluconate (CaLG) or CaLG alone ($p < 0.05$). The increase in bone mineral density versus baseline observed in patients receiving CaLG with or without etidronate ($p < 0.05$) probably did not result from increased bone formation because serum osteocalcin levels showed a significant reduction in all three groups of patients ($p < 0.05$). An increase in mean serum calcium ($p < 0.05$) was seen in patients receiving CaLG with or without etidronate.

Conclusion: Our results suggest that long-term administration of high-dose inhaled steroid (>1.5 mg/day) induces bone loss that is preventable with calcium supplementation with or without cyclical etidronate. Long-term studies involving more patients should follow to confirm these preliminary findings. (*J Allergy Clin Immunol* 1998;101:445-50.)

Key words: Asthma, corticosteroid, bone mineral density, bone loss, etidronate

Inhaled corticosteroid therapy is an effective mode of treatment that reduces frequency and severity of acute exacerbation and lessens the need for systemic steroids in the treatment of asthma.^{1,2} Although the adverse systemic effects of inhaled steroid therapy are believed to be minimal, steroids are well absorbed across mucous membranes and may be absorbed in significant quantities in some patients. Moreover, they are usually used on a long-term basis. Because inhaled and oral steroids share the same cell surface receptors, they can have similar pharmacologic actions after systemic absorption, including suppression of adrenal function, inhibition of intestinal absorption of calcium and phosphate, increase in urinary calcium excretion, predisposition to secondary hyperparathyroidism, and inhibition of bone formation.³⁻⁶ High-dose budesonide (1.2 to 2.4 mg/day) reduces serum osteocalcin without affecting the morning urinary calcium or hydroxyproline output.⁵ Our group has recently shown in a retrospective study that a decrease in bone mineral density occurs in women who take moderate doses of inhaled beclomethasone or budesonide compared with normal subjects.⁷ Prophylactic measures to minimize steroid-induced osteopenia may therefore be indicated in patients receiving long-term inhaled steroid therapy. Calcium supplementation has been known to be beneficial in preventing osteoporosis induced by systemic steroid therapy,⁸ probably by reducing bone resorption.⁹ Cyclical use of etidronate, an antiresorptive agent that binds to hydroxyapatite crystals and depresses osteoclastic activities, has been shown to increase bone mass and decrease the fracture rate in

From the University Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong.

Supported by a grant from the Committee on Research and Conference Grants, and W. Q. Wang is the recipient of an Ivy Wu Fellowship of the Medical Faculty, The University of Hong Kong.

Received for publication July 22, 1997; revised Nov. 24, 1997; accepted for publication Nov. 25, 1997.

Reprint requests: Karen S. L. Lam, MD, FRCP, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong.

Copyright © 1998 by Mosby, Inc.

0091-6749/98 \$5.00 + 0 1/1/87936

TABLE I. Clinical characteristics and biochemical markers of bone turnover (mean $\pm$ SEM) in patients

	No supplement (n = 10)				Calcium (n = 8)			
	Baseline	6 months	12 months	18 months	Baseline	6 months	12 months	18 months
Age (yrs)	41 $\pm$ 1.9				40 $\pm$ 2.1			
BMI (kg/m ²)	23.4 $\pm$ 1.2				22.6 $\pm$ 1.1			
IS (mg/day)	2.2 $\pm$ 0.3				2.0 $\pm$ 0.2			
Sex (F/M)	4/6				2/6			
25-OHD (ng/ml)	25.7 $\pm$ 2.77	21.6 $\pm$ 2.91	23.5 $\pm$ 2.35	27.6 $\pm$ 2.35	30.7 $\pm$ 4.0	29.2 $\pm$ 3.32	29.7 $\pm$ 2.51	27.4 $\pm$ 3.02
OS (ng/mL)	2.50 $\pm$ 0.21	2.18 $\pm$ 0.13	1.99 $\pm$ 0.15	1.7 $\pm$ 0.26*	2.74 $\pm$ 0.31	1.97 $\pm$ 0.27*	2.14 $\pm$ 0.39*	1.87 $\pm$ 0.30*
ALP (U/L)	76.2 $\pm$ 5.8	75.0 $\pm$ 4.9	67.3 $\pm$ 6.7	65.0 $\pm$ 6.6	71.5 $\pm$ 3.3	65.3 $\pm$ 3.2	66.9 $\pm$ 4.3	72.8 $\pm$ 6.1
Ca (mmol/L)	2.35 $\pm$ 0.03	2.36 $\pm$ 0.03	2.38 $\pm$ 0.03	2.38 $\pm$ 0.03	2.30 $\pm$ 0.02	2.36 $\pm$ 0.05	2.38 $\pm$ 0.03*	2.38 $\pm$ 0.03*
Phos (mmol/L)	0.97 $\pm$ 0.04	0.96 $\pm$ 0.05	1.02 $\pm$ 0.05	1.07 $\pm$ 0.05	1.00 $\pm$ 0.06	0.95 $\pm$ 0.03	1.01 $\pm$ 0.04	1.00 $\pm$ 0.08
PTH (μ g/L)	35.1 $\pm$ 5.1	40.5 $\pm$ 5.1	22.7 $\pm$ 4.4	32.8 $\pm$ 9.1	23.0 $\pm$ 3.0	33.7 $\pm$ 5.8	30.2 $\pm$ 2.9	25.3 $\pm$ 5.6
OH-Pro/Cr (mmol/mmol)	0.015 $\pm$ 0.003	0.023 $\pm$ 0.006	0.018 $\pm$ 0.004	0.028 $\pm$ 0.004	0.023 $\pm$ 0.005	0.026 $\pm$ 0.009	0.026 $\pm$ 0.006	0.016 $\pm$ 0.003

BMI, Body mass index; IS, inhaled steroids; 25-OHD, 25 hydroxyvitamin D (N. 13-50 ng/ml); osteocalcin (N. 1.3-27.0 ng/ml); ALP, alkaline phosphatase (N. 49-138 U/L); Ca, calcium (N. 2.11-2.55 mmol/L); Phos, phosphate (N. 0.88-1.45 mmol/L); PTH, parathyroid hormone (N. 11-54 μ g/l); OH-Pro/Cr, hydroxyproline/creatinine (N. 13-50 μ g/ml).

* $p < 0.05$ versus baseline.

Abbreviations used

BMD:	Bone mineral density
CaLG:	Calcium lactate-gluconate
OH-Pro/Cr:	Hydroxyproline/creatinine

postmenopausal osteoporosis.¹⁰ There is also evidence that intermittent cyclical etidronate may prevent bone loss caused by systemic steroids.¹¹

This randomized, prospective longitudinal study was therefore performed to evaluate the effects of oral calcium lactate-gluconate (CaLG) supplementation with or without cyclical etidronate on bone mineral density (BMD) in asthmatic patients receiving long-term high-dose inhaled steroid (beclomethasone or budesonide) therapy.

METHODS

Subjects

Patients were recruited and followed up at the Asthma Clinic at the University of Hong Kong between May 1994 and May 1997. Inclusion criteria included Chinese ancestry, age 30 to 50 years, premenopausal status, and a history of inhaled beclomethasone dipropionate or budesonide (>1.5 mg/day) therapy for at least 12 months. Exclusion criteria included chronic systemic steroid use (defined as continuous administration of oral steroids for more than 1 month in the previous 12 months); more than four rescue courses of systemic steroids in the previous 12 months; use of systemic steroids within the previous 3 months; concurrent treatment with estrogen, calcitonin, phosphate, calcium, oral contraceptives, sodium fluoride, vitamin D, or any bisphosphonate during the past 12 months; use of thiazide diuretics during the previous 3 months; and presence of other major unstable systemic illnesses such as renal, liver, or thyroid diseases and known metabolic bone diseases. Control subjects consisted of Chinese graduate students or hospital staff with no known systemic disease who were taking no medication.

Study design

Asthmatic patients and control subjects matched for age, sex, and body mass index were followed up prospectively for 18 months. The BMD of lumbar spine and hip and biochemical markers of bone turnover (serum osteocalcin, alkaline phosphatase, parathyroid hormone, and urine hydroxyproline) were compared. Patients were grouped into triplets. Within each triplet, the patients with similar sex; age; body mass index; and daily inhaled steroid doses, preparations, and delivery systems were randomly assigned to 18 months without supplementation; calcium supplementation in the form of CaLG equivalent to a daily dose of 1000 mg of elemental calcium; or CaLG plus 400 mg daily cyclical etidronate for 14 days, followed by 1000 mg daily CaLG for 76 days. Calcium was not administered during etidronate treatment.

For each patient, the BMD, expressed as absolute densities (i.e., grams per square centimeters) of lumbar spine (L₂ to L₄) and hip (femoral neck, greater trochanter, and Ward's triangle), was measured at baseline and at 6, 12, and 18 months by using dual energy x-ray absorptiometry (Hologic QDR-2000; Hologic Incorp., Boston, Mass.). For the control subjects, measurement of BMD was done at baseline and at 12 and 18 months. The BMD levels of the control subjects were within normal limits (± 2 SD) for the Chinese population in Hong Kong (normal range data provided by Professor A. Kung, University Department of Medicine, The University of Hong Kong).

Blood and urine samples were collected for asthmatic subjects at baseline and at 6-, 12-, and 18-month visits and for normal subjects at baseline and at 12- and 18-month visits. After subjects refrained from heavy exertion and fasted for 12 hours overnight, blood and urine samples were taken between 9 and 10 AM. Biochemical analysis was performed immediately by the Clinical Biochemistry Department of the University of Hong Kong for alkaline phosphatase by using an established method of the Interfederation Clinical Chemistry (IFCC), for calcium by using the method of o-cresolphthalein complexone, for phosphate by using the method of Molybdate reaction, for parathyroid hormone by using a chemiluminescence method (Maglicite, Chiron-Corning), and for urinary creatinine by

Calcium + etidronate (n = 10)				
Baseline	6 months	12 months	18 months	
38 ± 2.6				
23.2 ± 1.3				
2.0 ± 0.2				
4/6				
29.69 ± 3.79	27.16 ± 4.88	32.60 ± 4.85	24.6 ± 5.4	
1.98 ± 0.30	1.30 ± 0.19*	1.47 ± 0.15	1.32 ± 0.23*	
64.3 ± 5.7	55.5 ± 3.4	56.8 ± 3.3	61.2 ± 4.7	
2.35 ± 0.03	2.30 ± 0.02	2.36 ± 0.03	2.40 ± 0.04*	
0.96 ± 0.04	0.98 ± 0.05	0.97 ± 0.04	1.09 ± 0.11	
33.7 ± 5.8	30.2 ± 2.9	27.2 ± 3.4	20.8 ± 7.1	
0.022 ± 0.005	0.022 ± 0.006	0.015 ± 0.002	0.015 ± 0.004	

using standard multi-channel computerized analysis. Serum for osteocalcin and 25-hydroxyvitamin D were stored at -70° C until measurement with radioimmunoassays (INCSTAR Corporation, Stillwater, Minn.). Urine for hydroxyproline was stored at -20° C until measurement with a colorimetric method.

Daily calcium intake was estimated by using questionnaires that assessed the frequency and quantity of food intake.¹² This study was approved by the local ethics committee (the University of Hong Kong) and patients were recruited with written informed consent.

Statistical analysis

Mann-Whitney U and Wilcoxon tests were performed for between-group (unpaired) and within-group (paired) comparison analysis, respectively. Nonparametric methods were used because of the small sample size in each experimental group. A *p* value less than 0.05 was regarded as significant.

RESULTS

Forty subjects were recruited (10 each of normal control subjects, patients without supplementation, patients with CaLG, and patients with CaLG plus etidronate). The results of two patients in the CaLG group were excluded from the analysis because the patients' body weight increased significantly within the study period.¹³ The clinical characteristics of the four groups of subjects are summarized in Tables I and II. The mean (± SEM) dosage of beclomethasone and budesonide in the three groups of patients did not change significantly during the study periods. For the CaLG only and CaLG plus etidronate groups, this was 2.0 ± 0.2 mg/day at baseline; for the group receiving no supplement, this was 2.2 ± 0.3 mg/day. All patients were followed up at 4- to 12-week intervals and were compliant (taking more than 90% of prescribed doses) with inhaled steroids and supplementation medications. Five of the 30 patients required rescue systemic steroids (reducing course of prednisolone) starting from 30 mg daily over 1 to 3 weeks (two patients in CaLG group, two patients in CaLG plus etidronate group, and one patient in group receiving no supplement) for exacerbation of asthma during the study period. BMD and biochemical assess-

TABLE II. Clinical characteristics and biochemical markers for bone turnover (mean ± SEM) in control subjects

	Baseline	12 months	18 months
Age (yrs)	40.1 ± 2.2		
BMI (kg/m ²)	22.2 ± 0.9		
Sex (F/M)	4/6		
25-OHD (ng/ml)	22.3 ± 2.5	23.9 ± 2.5	19.8 ± 2.1
OS (ng/ml)	2.59 ± 0.48	2.35 ± 0.40	2.41 ± 0.22
ALP (U/L)	57.3 ± 4.0	54.2 ± 5.7	54.9 ± 3.1
Ca (mmol/L)	2.33 ± 0.03	2.30 ± 0.02	2.25 ± 0.02
Phos (mmol/L)	0.98 ± 0.03	0.95 ± 0.03	1.00 ± 0.03
PTH (μg/l)	38.1 ± 8.8	35.4 ± 4.4	35.5 ± 4.9
OH-Pro/Cr (mmol/mmol)	0.011 ± 0.002	0.015 ± 0.002	0.017 ± 0.001

BMI, Body mass index; 25-OHD, 25 hydroxyvitamin D (normal, 13-50 ng/ml); OS, osteocalcin (normal, 1.3-27.0 ng/ml); ALP, alkaline phosphatase (normal, 49-138 U/L); Ca, calcium (normal, 2.11-2.55 mmol/L); Phos, phosphate (normal, 0.88-1.45 mmol/L); PTH, parathyroid hormone (normal, 11-54 μg/L); OH-Pro/Cr, hydroxyproline/creatinine (normal, 13-50 μg/ml).

ments were performed as scheduled irrespective of the timing of rescue systemic steroids. The mean dietary calcium intake of the subjects in this study was 766 ± 38.9 mg/day (± SEM).

At baseline, there was no significant difference in BMD between the group receiving no supplement and the two groups of patients receiving supplementation. However, compared with control subjects, patients receiving no supplement had a significantly lower BMD at the lumbar spine (*p* < 0.05; Table III). Although the increase in bone loss compared with control subjects was not statistically significant (Fig. 1), a downward trend in BMD was seen in all four regions studied in the group receiving no supplement. Compared with patients receiving CaLG or etidronate plus CaLG, the group receiving no supplement had significantly greater bone loss in the lumbar spine (Fig. 1, A) during the study period. On the other hand, when compared with their own baseline values, lumbar spine BMD showed a significant increase in patients receiving etidronate plus CaLG or CaLG alone (*p* < 0.05, Fig. 1, A). The increases in BMD at the greater trochanter (Fig. 1, B) and Ward's triangle (Fig. 1, C) were statistically significant in the CaLG group (*p* < 0.05) but not in the etidronate plus CaLG group.

Serum osteocalcin levels showed significant reductions during the study period in all three groups of patients (*p* < 0.05; Table I) but not in control subjects (Table II). There was no significant change in serum alkaline phosphatase or parathyroid hormone in any of the study groups (Tables I and II). No significant change in the ratio of hydroxyproline/creatinine (OH-Pro/Cr) was observed in the three groups, although at 18 months, the change versus baseline was positive for the group receiving no supplement but negative for the two groups receiving supplementation. Serum calcium concentra-

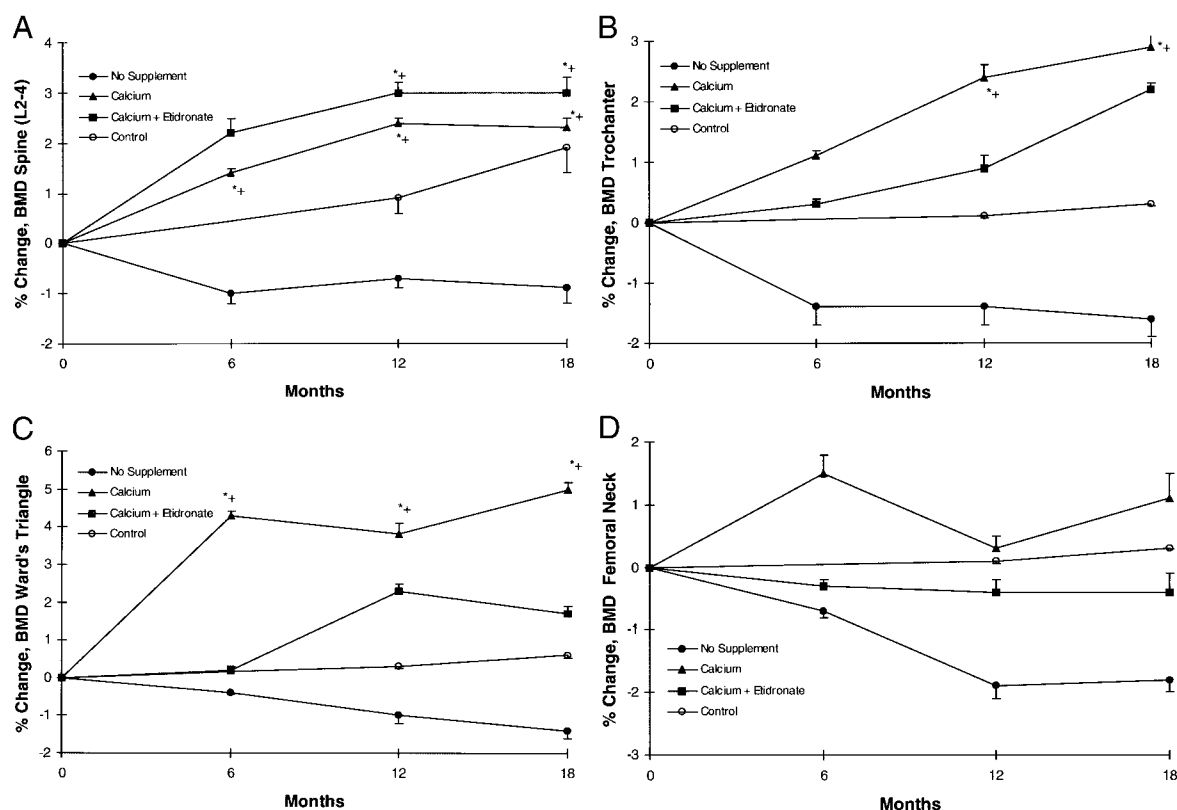


FIG. 1. Changes in regional BMD expressed as percent of baseline value at spine (A), greater trochanter (B), Ward's triangle (C), and neck (D) of femur in patients without supplement (filled circles), with calcium alone (filled triangles), with calcium plus etidronate (filled squares), or in normal control subjects (open circles). Values are mean $\pm$ SEM. * $p < 0.05$ versus comparable months of group receiving no supplement; + $p < 0.05$ versus baseline reading.

TABLE III. Baseline BMD (gm/cm²) of lumbar spine and hip (mean $\pm$ SEM)

	No supplement (n = 10)	Calcium (n = 8)	Calcium + etidronate (n = 10)	Normal control (n = 10)
Spine	0.894 $\pm$ 0.032	0.951 $\pm$ 0.064	0.981 $\pm$ 0.046	0.986 $\pm$ 0.019*
Femoral neck	0.737 $\pm$ 0.034	0.724 $\pm$ 0.030	0.790 $\pm$ 0.066	0.761 $\pm$ 0.024
Trochanter	0.621 $\pm$ 0.022	0.621 $\pm$ 0.030	0.682 $\pm$ 0.055	0.626 $\pm$ 0.030
Ward's triangle	0.572 $\pm$ 0.048	0.598 $\pm$ 0.040	0.658 $\pm$ 0.071	0.653 $\pm$ 0.028

* $p < 0.05$ versus group receiving no supplement.

tion was significantly increased versus baseline ($p < 0.05$; Table I) at 12 and 18 months in the CaLG group and at 18 months in the etidronate plus CaLG group. Vitamin D status, as reflected by serum 25-hydroxyvitamin D levels, was similar among the four groups of subjects throughout the study period.

DISCUSSION

Despite the small sample size and relatively short duration of follow-up, this 18-month prospective study has provided supporting evidence for the adverse effects of inhaled steroids on bone density, previously demonstrated in cross-sectional studies.^{7,14} It has also provided evidence that such effects may be amenable to preventive measures.

In agreement with published data on steroid-induced osteoporosis,¹⁵ the reduction in BMD in the patients receiving no supplement was most obvious in the spine, which consists predominantly of trabecular bone. The reduction of serum osteocalcin in these patients reflects on the suppressive effect of glucocorticoids on bone formation through the reduction in osteoblastic activity.^{4,16} It was not surprising that in these patients, who had received at least 1 year of inhaled steroid before the study, the increased bone loss versus control subjects over the 18-month study period failed to reach statistical significance because the effect of glucocorticoids on BMD has been shown to become less marked after the first 6 to 12 months of steroid therapy.¹⁵

At baseline, the group receiving no supplement had the lowest BMD at the spine, but the difference was statistically significant only when compared with control subjects. Although this group might have had a greater than expected decline in BMD before entry by chance and might therefore continue to exhibit a greater decline than the other groups during the study, this possibility was not supported because of the lack of a significantly different rate of bone loss from the control group, which had the highest spine BMD at baseline. The observed differences in the rate of bone loss between the group receiving no supplement and the groups receiving calcium supplementation were also in accordance with the reported beneficial effects of calcium supplementation in nonsteroid-treated postmenopausal women.¹⁷

It is well known that glucocorticoids decrease intestinal calcium absorption and increase urinary calcium excretion, predisposing to secondary hyperparathyroidism and enhanced bone resorption.^{5, 15} Calcium supplementation may therefore be beneficial in patients with steroid-induced osteoporosis by reducing bone resorption.⁹ A recent metaanalysis has shown that a daily calcium supplement of 1000 mg/day prevents annual bone loss of 1% in postmenopausal women.¹⁷ Vertebral bone density has been found to be 6.7% higher in young women consuming more than 800 mg/day calcium than in those consuming less.¹⁸ However, a ceiling effect is observed such that there is no additional benefit beyond 800 mg/day.^{17, 19} Because of the effect of glucocorticoids on calcium absorption and urinary loss, the calcium deficiency in the patients receiving inhaled steroids in this study was likely to be considerably greater than what their estimated dietary calcium intake would suggest. It was therefore not unexpected that calcium supplementation (1000 mg/day) was associated with increased BMD in the lumbar spine and hip. The changes in BMD in patients receiving etidronate were in agreement with previous reports on the antiresorptive effects of bisphosphonates, with the benefit being most obvious in trabecular bone.^{20, 21} The reduction in serum osteocalcin suggested that both calcium supplementation and cyclical etidronate work through a reduction in bone resorption, and hence reduced bone turnover, rather than an increase in bone formation. It was not possible, on the basis of the results of this small study of relatively short duration, to comment on the relative efficacy of cyclical etidronate plus calcium versus calcium supplementation alone in preventing osteoporosis in patients receiving inhaled steroids. However, the encouraging effects of calcium supplementation alone on BMD, together with its safety and low cost, suggest that it can serve as an economical and useful prophylactic agent to prevent bone loss in asthmatic patients receiving inhaled steroids.

Hydroxyproline excretion is considered to be a reflection of bone collagen turnover,²² and fasting OH-Pro/Cr is an indicator of bone resorption. A substantial increase in fasting urinary OH-Pro/Cr ratio occurs after 2 to 4

weeks of prednisolone treatment.²³ An increase of 46% in OH-Pro/Cr ratio has been reported in healthy men after 4 weeks of inhaled beclomethasone dipropionate therapy.²⁴ In adults, daily administration of 1000 mg of elemental calcium decreases the fasting urine OH-Pro/Cr ratio in glucocorticoid-treated patients.⁸ In this study, although the changes in OH-Pro/Cr ratio were not statistically significant, the directions of changes at 18 months in the three groups of patients were in accordance with the expected effects on bone resorption of glucocorticoid, calcium supplementation, and cyclical etidronate. More conclusive results may be obtained if newer, more sensitive bone resorption markers²⁵ (e.g., urinary oxyproline, deoxypyridenolone, or type 1 collagen cross-linked N-telopeptide) are measured instead.

In conclusion, this prospective study has provided the first piece of evidence for the beneficial effects of antiresorptive agents in preventing bone loss in asthmatic patients on long-term inhaled steroid therapy. Because of the small sample size in each experimental group, the likelihood of making a Type II statistical conclusion cannot be excluded. Further studies involving more patients and longer duration of follow-up should be done to confirm these important and clinically relevant findings.

We thank Mr. Stanley Yeung, Scientific Officer, University Department of Medicine for assistance in statistical analysis.

REFERENCE

1. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;148:S1-26.
2. Ernst P, Spitzer WO, Suissa S. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. *JAMA* 1992;268:3462-4.
3. Prah P. Adrenocortical suppression following treatment with beclomethasone and budesonide. *Clin Exp Allergy* 1991;21:145-6.
4. Puolijoki H, Liippo K, Herrala J, Salmi J, Tala E. Inhaled beclomethasone decreases serum osteocalcin in postmenopausal asthmatic women. *Bone* 1992;13:285-8.
5. Toogood JH, Jennings B, Hodsman AB, Baskerville J, Fraher LJ. Effects of dose and dosing schedule of inhaled budesonide on bone turnover. *J Allergy Clin Immunol* 1991;88:572-80.
6. Sorva R, Turpeinen M, Juntunen-Backman K, Karonen SL, Sorva A. Effects of inhaled budesonide on serum markers of bone metabolism in children with asthma. *J Allergy Clin Immunol* 1992;90:808-15.
7. Ip M, Lam KSL, Yam L, Kung AWC, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994;105:1722-7.
8. Reid IR, Ibbertson HK. Calcium supplements in the prevention of steroid induced osteoporosis. *Am J Clin Nutr* 1986;44:287-90.
9. Schwartz E, Panariello VA, Saeli J. Radioactive calcium kinetics during high calcium intake in osteoporosis. *J Clin Invest* 1965;44:1547-60.
10. Storm T, Thamsbory G, Steiniche T, Genant, Sorensen OL. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990;322:1265-71.
11. Mulder H, Struys A. Intermittent cyclical etidronate in the prevention of corticosteroid-induced bone loss. *Br J Rheumatol* 1994;33:348-50.
12. Pun KK, Chan LWL, Chung V, Wong FHW. Calcium and other dietary constituents in Hong Kong Chinese in relation to age and osteoporosis. *J Appl Nutrition* 1990;42:12-7.
13. Holbrook TL, Barrett-Connor E. The association of lifetime weight

- and weight control patients with bone mineral density in an adult community. *Bone Miner* 1993;20:141-9.
14. Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 1995; 96:571-9.
 15. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990;112:352-64.
 16. Pouw EM, Prummel MF, Oosting H, Carel MR, Endert E. Beclomethasone inhalation decreases serum osteocalcin concentration. *Br Med J* 1991;302:627-8.
 17. Cumming RG. Calcium intake and bone mass: a quantitative review of the evidence. *Calcif Tissue Int* 1990;47:194-201.
 18. Kanders B, Dempster DW, Lindsay R. Interaction of calcium nutrition and physical activity on bone mass in young women. *J Bone Miner Res* 1988;3:145-9.
 19. Heaney RP. Calcium bone health, and osteoporosis. *J Bone Miner Res* 1986;4:255-301.
 20. Harris ST, Watts NB, Jackson RD, Genant HK, Wasnich RD, Ross P, et al. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. *Am J Med* 1993;95:557-67.
 21. Liberman UA, Weiss S, Broll J, Minne HW, Quan H, Bell NH, et al. Effects of alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;333: 1437-43.
 22. Dull TA, Henneman PH. Urinary hydroxyproline as an index of collagen turnover in bone. *N Engl J Med* 1963;268:132-5.
 23. Morrison D, Ali NJ, Routledge PA, Capewell S. Bone turnover during short course prednisolone treatment in patients with chronic obstructive airways disease. *Thorax* 1992;47:418-20.
 24. Ali NJ, Capewell S, Ward MJ. Bone turnover during high dose inhaled corticosteroid treatment. *Thorax* 1991;46:160-4.
 25. Prummel MF, Wiersinga WM, Lips P, Sanders GTB, Sauerwein HSP. The course of biochemical parameters of bone turnover during treatment with corticosteroids. *J Clin Endocrinol Metab* 1991;72:382-6.

ON THE MOVE?

Send us your new address at least six weeks ahead

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.

JOURNAL TITLE:

Fill in the title of the journal here. _____

OLD ADDRESS:

Affix the address label from a recent issue of the journal here.

NEW ADDRESS:

Clearly print your new address here.

Name _____

Address _____

City/State/ZIP _____

COPY AND MAIL THIS FORM TO:

Periodical Subscription Services
Mosby, Inc.
11830 Westline Industrial Dr.
St. Louis, MO 63146-3318

OR FAX TO:

314-432-1158



OR PHONE:

1-800-453-4351
Outside the U.S., call
314-453-4351