



Effects of Inhaled Glucocorticoids on Bone Density in Premenopausal Women

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EFFECTS OF INHALED GLUCOCORTICOIDS ON BONE DENSITY
IN PREMENOPAUSAL WOMENELLIOT ISRAEL, M.D., TARUNA R. BANERJEE, M.P.H., GARRETT M. FITZMAURICE, Sc.D., TANIA V. KOTLOV, M.S.,
KAREN LAHIVE, M.D., AND MERYL S. LEBOFF, M.D.**ABSTRACT**

Background Inhaled glucocorticoids are the most commonly used medications for the long-term treatment of patients with asthma. Whether long-term therapy with inhaled glucocorticoids reduces bone mass, as oral glucocorticoid therapy does, is controversial. In a three-year prospective study, we examined the relation between the dose of inhaled glucocorticoids and the rate of bone loss in premenopausal women with asthma.

Methods We studied 109 premenopausal women, 18 to 45 years of age, who had asthma and no known conditions that cause bone loss and who were treated with inhaled triamcinolone acetonide (100 μ g per puff). We measured bone density by dual-photon absorptiometry at base line, at six months, and at one, two, and three years. Serum osteocalcin and parathyroid hormone and urinary *N*-telopeptide, cortisol, and calcium excretion were measured serially. We measured inhaled glucocorticoid use by means of monthly diaries, supported by the use of an automated actuator-monitoring device.

Results Inhaled glucocorticoid therapy was associated with a dose-related decline in bone density at both the total hip and the trochanter of 0.00044 g per square centimeter per puff per year of treatment ($P=0.01$ and $P=0.005$, respectively). No dose-related effect was noted at the femoral neck or the spine. Even after the exclusion of all women who received oral or parenteral glucocorticoids at any time during the study, there was still an association between the decline in bone density and the number of puffs per year of use. Serum and urinary markers of bone turnover or adrenal function did not predict the degree of bone loss.

Conclusions Inhaled glucocorticoids lead to a dose-related loss of bone at the hip in premenopausal women. (N Engl J Med 2001;345:941-7.)

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INHALED glucocorticoids are now advocated for the treatment of many patients with asthma.^{1,2} Although it is known that oral glucocorticoid therapy accelerates bone loss, and fractures may occur in 30 to 50 percent of patients,^{3,4} it is not clear whether inhaled glucocorticoids accelerate bone loss. The results of prospective and cross-sectional studies of the effects of inhaled glucocorticoids on bone have been inconsistent,⁵⁻¹⁵ in that inhaled glucocorticoids have been associated with decreases in bone density in some studies and no change in bone density in others. Prospective studies have usually been small or of short duration, have relied on retrospective

data, or have not independently verified the doses of inhaled glucocorticoid taken by participants. Their results may also have been confounded by the intermittent use of oral glucocorticoid therapy, the lack of appropriate controls, superimposed menopausal bone loss, and differences among participants in the severity of asthma that may affect physical activity.

Osteoporosis and the fractures that may result from it are a major public health problem that predominantly affects women.¹⁶ To determine the safety of inhaled glucocorticoids in relation to bone, we conducted a prospective cohort study of premenopausal women with asthma. We used only one inhaled glucocorticoid formulation and carefully monitored inhaled glucocorticoid therapy in order to examine the association between the dose of the inhaled glucocorticoid and changes in bone density.

METHODS**Patients and Study Design**

Between October 1994 and February 1999, we conducted a prospective cohort study of premenopausal women with asthma. To assemble the cohort, we recruited three groups of women: those not taking inhaled glucocorticoids; those taking four to eight puffs per day of inhaled glucocorticoids; and those taking more than eight puffs per day of inhaled glucocorticoids.

The women were recruited through advertisements, direct mailings, and physicians' offices at the Harvard Community Health Plan, Brigham and Women's Hospital, Beth Israel Hospital, and the Massachusetts Institute of Technology Medical Plan, all in the greater Boston area. The study was approved by committees for the protection of human subjects at all the participating institutions, and written informed consent was obtained from all the women.

We enrolled 109 women who had received a diagnosis of asthma from a physician, who were between 18 and 45 years old, and who had had 10 or more menstrual periods during the preceding year. Women with a history of a disease affecting bone turnover, women who were taking any drugs known to influence bone metabolism, and women who had smoked within the preceding year were excluded, as were women with abnormal serum thyrotropin concentrations, low 25-hydroxyvitamin D concentrations, high serum parathyroid hormone concentrations, high serum follicle-stimulating hormone concentrations, 24-hour urinary calcium excretion of more than 250 mg (6.2 mmol), or low bone density (*z* score, -2 or less), unless approved by a physician, and those who did not return for a postscreening visit. We also excluded women who had received more than two short courses (lasting two weeks or less) of oral

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or parenteral glucocorticoids in the preceding year or any oral or parenteral glucocorticoids in the preceding three months. Women taking an oral contraceptive were not excluded.

The women included in the inhaled-glucocorticoid group had been prescribed inhaled glucocorticoids in a dose of four or more puffs per day and had received the same dose for at least six weeks. These women were subdivided into those taking four to eight puffs per day and those taking more than eight puffs per day. The women who were classified as not being treated with inhaled glucocorticoids had not received these drugs for at least six months. All women who were receiving glucocorticoids other than triamcinolone acetonide (100 µg per puff; Azmacort, Rhone-Poulenc Rorer, Collegeville, Pa.) were switched on a puff-for-puff basis to triamcinolone acetonide, which was supplied by the manufacturer. To decrease the need for any oral glucocorticoid therapy during the study, women who had received oral or parenteral glucocorticoid therapy in the preceding year had their dose of inhaled glucocorticoids increased by two puffs per day. All changes were made with the permission of each woman's primary care physician.

At base line, we confirmed each woman's history of asthma, performed spirometry, and measured the bone density of the total hip, trochanter, femoral neck, and lumbar spine. Serum calcium, osteocalcin, and cortisol; second-morning urinary *N*-telopeptide; and 24-hour urinary excretion of free cortisol and calcium were measured. Physical activity was assessed by a validated questionnaire.¹⁷ On the basis of the results of a dietary questionnaire,¹⁸ we supplemented the calcium intake of women with an intake of less than 1000 mg per day with calcium citrate (Citracal, Mission Pharmacal, San Antonio, Tex.) and the vitamin D intake of those not taking at least 400 IU of vitamin D with a daily multivitamin containing this amount of vitamin D (Compete, Mission Pharmacal).

At subsequent visits at six months and one, two, and three years, we reviewed and updated the information on medication use, as well as information about diet and activities; measured bone density; and repeated the measurements of serum parathyroid hormone, calcium, cortisol, follicle-stimulating hormone, and osteocalcin and urinary *N*-telopeptide, calcium, and cortisol excretion. We tracked inhaled-glucocorticoid use and the use of concomitant medications by means of monthly calendars that women mailed to the center. In order to encourage the keeping of accurate diary records, all women using inhaled glucocorticoids were issued a Chronolog moni-

toring device (Medtrac Technologies, Lakewood, Colo.), which electronically recorded all actuations of the glucocorticoid inhaler. Data from the device were reviewed with the women at the follow-up visits. In addition, empty canisters were mailed back to the center to be replaced by new canisters, and the returned canisters were weighed as another verification of medication use.

A total of 159 women were screened, and 109 were enrolled. Data for the 109 women from the time of enrollment to the time of the predetermined exclusionary events were included in the analyses (Table 1).

Laboratory Studies

Bone density was measured by dual-photon absorptiometry (QDR-2000, Hologic, Waltham, Mass.) in a single laboratory, and the results were interpreted by one investigator unaware of the dose of inhaled glucocorticoid. The coefficients of variation for the measurements of bone density in the spine, femoral neck, and trochanter in premenopausal women on different days were 0.68 percent, 0.99 percent, and 1.12 percent, respectively.¹⁹

Urinary excretion of *N*-telopeptide, calcium, and cortisol was measured by standard methods. Serum osteocalcin was measured by means of an immunoradiometric assay. Lung function was measured by spirometry (Jones Satellite Spirometer, Jones Medical Instruments, Oak Brook, Ill.).

Statistical Analysis

Initially, the change in bone density from visit to visit was analyzed as a continuous variable during the interval between visits and calculated as a function of the average of each woman's daily dose of the inhaled glucocorticoid in puffs (100 µg per puff). To account for the unequal length of the intervals between visits, these changes were subsequently expressed in terms of changes in bone density per year.

To account for the correlation among repeated measures in the same woman, we assumed an unstructured variance-covariance matrix (i.e., variances and correlations were not assumed to be constant over time). The regression parameters were estimated with the Proc Mixed program of the SAS software package (version 8.2, SAS Institute, Cary, N.C.). Additional analyses were performed with adjustment for all a priori confounders and all covariates that were found to be associated with the dose of inhaled glucocorticoids, including

TABLE 1. EXCLUSIONARY EVENTS DURING FOLLOW-UP.*

EVENT	WOMEN TAKING NO INHALED GLUCOCORTICOID (N=28)	WOMEN TAKING 4-8 PUFFS/DAY (N=39)	WOMEN TAKING >8 PUFFS/DAY (N=42)
	number		
More than 30 days of oral or parenteral glucocorticoid therapy	0	1	5
Bone loss†	0	0	1
Change of drug or cessation of glucocorticoid therapy	0	5	3
Started inhaled glucocorticoid therapy	5	0	0
Exclusionary medical condition developed	0	2	1
Onset of menopause	0	1	3
Hypercalciuria‡	0	1	0
Withdrawal or loss to follow-up	3	3	2

*Data for these women up to the visit before the predesignated exclusionary event were included in the analyses.

†Bone loss was defined by a loss of more than 6 percent per year in the lumbar spine and more than 8 percent per year in the hip.

‡Hypercalciuria was defined as urinary calcium excretion of more than 4 mg per kilogram of body weight per 24 hours.

age, the use of oral contraceptives, the use of oral glucocorticoids, and the use of topical nasal glucocorticoid preparations. Finally, in separate analyses, the changes in bone density were evaluated in relation to the serum measurements of calcium, cortisol, osteocalcin, and parathyroid hormone and the urinary measurements of *N*-telopeptide, calcium, and cortisol at different time points.

We compared the data from the actuation monitor and the information about doses reported in the diaries in a random sample of 33 of the women (30 percent). The intraclass correlation coefficient was calculated to determine the association between the two separate methods of reporting doses.

RESULTS

The characteristics of the 109 women enrolled in the study, categorized according to their use of inhaled glucocorticoids at base line, are shown in Table 2. The women in the high-dose group (more than eight puffs per day) were slightly older than those in the other two groups. A higher percentage of women who were using inhaled glucocorticoids at entry had used oral glucocorticoids in the past and were currently using top-

TABLE 2. BASE-LINE CHARACTERISTICS ACCORDING TO THE DOSE OF INHALED GLUCOCORTICOIDS AT BASE LINE.*

CHARACTERISTIC	WOMEN TAKING NO INHALED GLUCOCORTICOIDS (N=28)	WOMEN TAKING 4-8 PUFFS/DAY (N=39)	WOMEN TAKING >8 PUFFS/DAY (N=42)
Age (yr)†	34±7	33±8	37±7
Weight (lb)‡	140±20	139±29	154±40
Height (ft)§	5.4±0.2	5.4±0.2	5.4±0.2
Calcium intake (mg)	838±268	789±348	940±355
Serum 25-hydroxyvitamin D (ng/ml)	26±7	28±9	25±10
FEV ₁ (% predicted)	88.1±20.9	96.0±16.1	86.7±19.8
Physical-activity score¶	98±54	65±62	55±71
Smoking history (pack-years)	4±6	2±4	2±5
Current use of oral contraceptives (%)	25±44	33±48	19±40
History of oral glucocorticoid therapy (%)	36±49	76±43	79±42
Current or past use of topical inhaled glucocorticoids (%)	14±36	62±49	62±49
Daily dose of inhaled glucocorticoids (puffs)	—	7.3±1.2	14.6±4.7
Bone-density z score**			
Total hip	0.14±0.80	-0.06±0.85	-0.18±0.90
Trochanter	0.16±0.98	0.05±0.87	-0.13±0.90
Femoral neck	0.30±0.99	0.14±0.87	-0.22±1.03
Lumbar spine	0.21±0.83	0.04±1.10	0.09±1.11
Bone density (g/cm ²)			
Total hip	0.95±0.10	0.90±0.10	0.91±0.13
Trochanter	0.71±0.10	0.70±0.09	0.68±0.10
Femoral neck	0.86±0.12	0.84±0.10	0.80±0.13
Lumbar spine	1.05±0.10	1.01±0.08	1.03±0.12
Serum parathyroid hormone (pg/ml)††	29±2	30±11	33±13
Urinary calcium excretion (mg/24 hr)‡‡	137±83	142±63	158±93
Urinary <i>N</i> -telopeptide (nmol of bone collagen equivalents/mmol of creatinine)	41±32	45±48	39±28
Serum osteocalcin (ng/ml)§§	8±4	8±4	7±4
Urinary cortisol (μg/24 hr)¶¶	50±18	49±26	41±18

*Plus-minus values are means ±SD. FEV₁ denotes forced expiratory volume in one second.

†P<0.05 for the comparison among the three groups.

‡To convert values to kilograms, multiply by 0.45.

§To convert values to meters, multiply by 0.3.

¶The physical-activity score, expressed as metabolic hours per week, is a combined measurement of physical activities related to sports, employment, and household activities.

||P<0.01 for the comparison among the three groups.

**The z score is the number of standard deviations above or below the mean for age-matched normal women.

††To convert values to picomoles per liter, multiply by 0.106.

‡‡To convert values to millimoles per liter, multiply by 0.25.

§§To convert values to nanomoles per liter, multiply by 0.172.

¶¶To convert values to micromoles per 24 hours, multiply by 2.759.

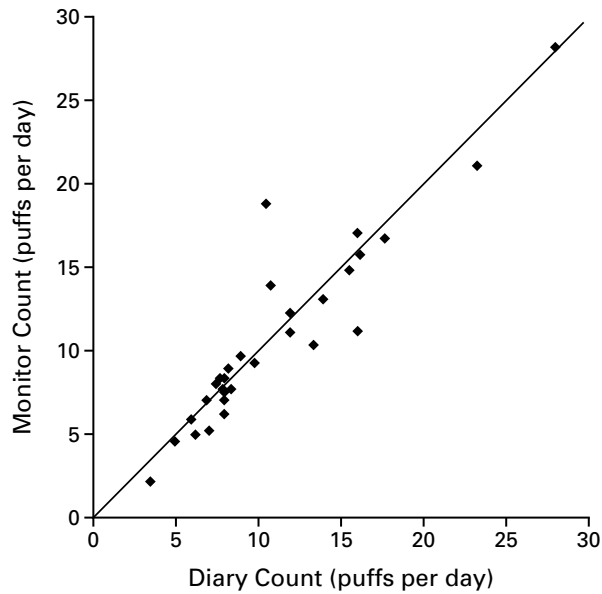


Figure 1. Relation between the Average Number of Puffs of Inhaled Glucocorticoid per Day as Recorded in the Women's Diaries and the Average Number as Recorded by the Actuation-Monitor Device in 33 Women. The intraclass correlation coefficient was 0.92. The diagonal line represents the line of identity.

ical inhaled glucocorticoid preparations. There were no significant differences in the forced expiratory volume in one second (FEV₁), the level of physical activity, calcium intake, oral-contraceptive use, or bone-density or biochemical values among the three groups.

We compared the number of puffs per day as calculated from the diary records with the number of actuations of the inhaler as recorded by the actuation monitor among 33 of the women. During the study, the maximal use of inhaled glucocorticoids during any period was 28 puffs per day. There was a direct linear correlation between the two values for the amount used (Fig. 1). The intraclass correlation coefficient was 0.92, indicating that the dose reported on the monthly questionnaires was very similar to the dose recorded by the actuation monitor.

There was a negative linear association between the average number of puffs per day of the inhaled glucocorticoid and the yearly change in bone density at both the total hip and the trochanter (P=0.01 and P=0.005, respectively) (Table 3 and Fig. 2). Each additional daily puff of the inhaled glucocorticoid was associated with a decline in bone density of 0.00044 g per square centimeter per year at both sites, but there was no significant association with the degree of decline at the femoral neck and spine (−0.00005 and −0.00008 g per square centimeter per year per puff, respectively [P=0.85 and P=0.68, respectively]).

Twenty-four percent of the women in the study used oral or parenteral glucocorticoids at a level below the threshold for exclusion (at least 30 days of use

TABLE 3. MEAN YEARLY CHANGE IN BONE DENSITY ASSOCIATED WITH INHALED GLUCOCORTICOID THERAPY.*

SITE	ALL WOMEN (N=109)				WOMEN WHO RECEIVED NO ORAL OR PARENTERAL GLUCOCORTICOID THERAPY (N=83)			
	UNADJUSTED YEARLY CHANGE (g/cm ² /puff)	P VALUE	ADJUSTED YEARLY CHANGE (g/cm ² /puff)†	P VALUE	UNADJUSTED YEARLY CHANGE (g/cm ² /puff)	P VALUE	ADJUSTED YEARLY CHANGE (g/cm ² /puff)‡	P VALUE
Total hip	−0.00044±0.00017	0.01	−0.00048±0.00018	0.008	−0.00041±0.00019	0.03	−0.00041±0.00020	0.047
Trochanter	−0.00044±0.00016	0.005	−0.00042±0.00017	0.01	−0.00048±0.00019	0.01	−0.00047±0.00019	0.02
Femoral neck	−0.00005±0.00028	0.85	−0.00017±0.00028	0.54	0.00015±0.00030	0.61	0.00015±0.00031	0.63
Spine (L1–L4)	−0.00008±0.00019	0.68	0.00012±0.00018	0.51	0.00001±0.00020	0.95	0.00015±0.00019	0.41

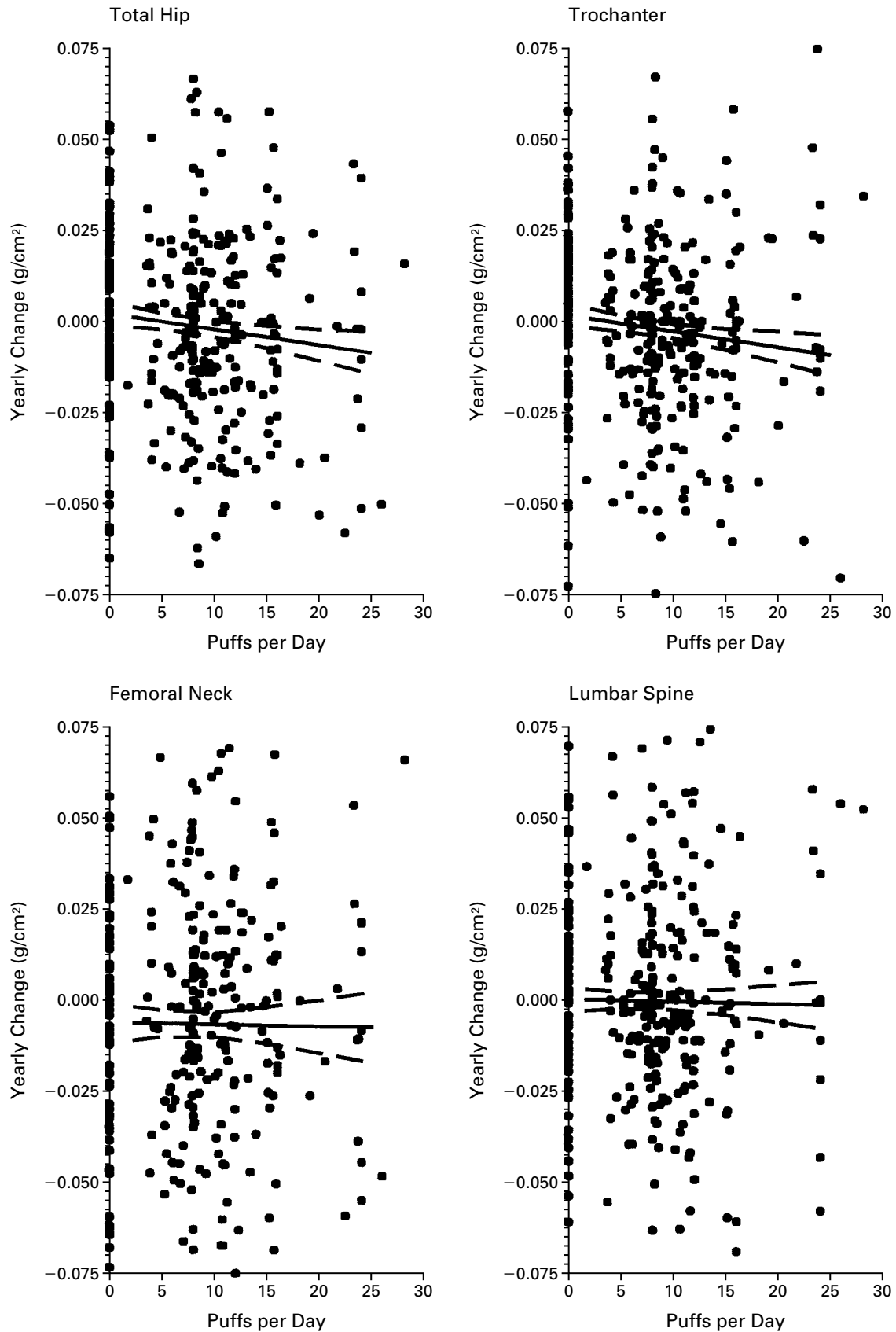
*Plus-minus values are means ±SE. P values are for the test of whether the change in bone density differs from zero.

†The results have been adjusted for age, the use of inhaled and oral glucocorticoids, and the use of oral contraceptives.

‡The results have been adjusted for age, the use of inhaled glucocorticoids, and the use of oral contraceptives.

Figure 2 (facing page). Change in Bone Density per Year in Relation to the Average Number of Daily Puffs of Inhaled Glucocorticoid from Diary Cards during the Intervals between Visits.

Values are shown for the total hip, trochanter, femoral neck, and lumbar spine (L1 through L4). For both the total hip and the trochanter, the rate of decline in bone density was 0.00044 g per square centimeter per year for each additional daily puff of inhaled glucocorticoid (P=0.01 and P=0.005, respectively). The solid line in each panel represents the mean yearly change in bone density. The dashed lines indicate the 95 percent confidence interval for the mean.



during the 3-year study). When we adjusted our analysis of all the women for this use of oral or parenteral glucocorticoids, for the concurrent use of topical nasal glucocorticoids, and for age and oral-contraceptive use, we still found an association between the decline in bone density at the total hip and trochanter and the average number of puffs per day of inhaled glucocorticoids (Table 3).

When all women who received oral or parenteral glucocorticoid therapy at any time during the study were excluded from the analysis, the inverse association between bone density and the dose of inhaled glucocorticoids persisted both before and after adjustment for other possible confounders (Table 3). Even when we excluded these women and adjusted for age and the use of nasal glucocorticoids and oral contraceptives, each additional puff of inhaled glucocorticoid was still associated with an additional decline in the bone density of the total hip and trochanter of 0.00041 and 0.00047 g per square centimeter per year, respectively ($P=0.047$ and $P=0.02$, respectively).

The urinary *N*-telopeptide, calcium, and cortisol values and the serum osteocalcin, calcium, cortisol, and parathyroid hormone values were not associated with the dose of inhaled glucocorticoids. Furthermore, these urinary and serum measurements and the changes in these values were not consistently correlated with the declines in bone density.

DISCUSSION

In this study of premenopausal women with asthma, we found a direct relation between a higher dose of inhaled glucocorticoids and small yearly decreases in the bone density of the total hip and the trochanter. Furthermore, this adverse effect on bone density was evident even among women who did not receive any oral or parenteral glucocorticoid therapy during the study, thus eliminating any possible confounding effect of these forms of glucocorticoid therapy.

These findings have potentially important clinical implications because consensus reports recommend the increased use of inhaled glucocorticoids in the treatment of asthma.^{1,2} In accordance with these recommendations, a woman with asthma who was treated with the equivalent of 1200 μg of inhaled glucocorticoids (six puffs of triamcinolone acetonide twice daily) beginning at 30 years of age and who entered menopause at 50 years of age would have a predicted bone mass at the trochanter that was 0.106 g per square centimeter less than that of an untreated woman of similar age. This degree of bone loss has been associated with a risk of hip fracture more than twice that among normal women 65 years of age or older.²⁰ The actual risk of fracture may be even greater in women with glucocorticoid-induced osteopenia than in those with naturally occurring osteopenia.²¹ Moreover, continued inhaled-glucocorticoid therapy could further increase the risk of fracture over time.

Our study design allowed us to avoid many of the limitations of previous studies. Our three groups were well matched in terms of FEV₁ and physical-activity scores. We supplemented dietary calcium and vitamin D intake as necessary and standardized the inhaled-glucocorticoid product. In addition, our prospective design allowed us to assess glucocorticoid exposure with a high degree of accuracy.

Several limitations of our study need to be considered. We restricted the study to a single inhaled glucocorticoid — triamcinolone acetonide. The use of a single glucocorticoid allowed us to define glucocorticoid exposure precisely, which was necessary because we expected the changes to be small. However, different inhaled-glucocorticoid preparations and delivery systems might have varying effects on bone. Nonetheless, since all the currently available inhaled glucocorticoids have dose-related systemic effects,^{22,23} it is likely that any of them would have a dose-related effect on bone. In fact, using data from a recent cross-sectional study in which patients used three other inhaled glucocorticoids (but not triamcinolone acetonide), we calculated that the decline in bone density at the trochanter per 100 μg of inhaled glucocorticoid per year (0.00040 to 0.00050 g per square centimeter) was strikingly similar in magnitude to the decline we found in our prospective study.¹⁵

Finally, differences among women in the severity of asthma may influence the rate of bone loss because of the effects of such differences on the extent of physical activity. However, in this study, the pulmonary function and physical-activity scores of the women treated with inhaled glucocorticoids were equivalent to or better than those of the women who did not take inhaled glucocorticoids.

Among the women in this study, bone density declined in the hip but not in the spine or femoral neck, suggesting that inhaled glucocorticoids affect different regions of the skeleton differently.^{24,25} Furthermore, there was wide variation in the rates of decline in bone density, just as there is in patients treated with oral glucocorticoids.⁴ In an attempt to find an easier way to predict the effect that an inhaled glucocorticoid might have on bone in a particular person, we sought a relation between bone loss and biochemical markers of bone homeostasis or of systemic absorption of the inhaled glucocorticoid (e.g., urinary cortisol excretion). None of the markers we measured predicted or was correlated with bone loss.

Inhaled glucocorticoids remain among the most effective and safest medications for the treatment of asthma. The availability of both inhalers that deliver a larger amount of inhaled glucocorticoid per puff and inhaled glucocorticoids of higher potency than those that have previously been available allows patients to receive much higher doses than they could receive in the past. We found a dose-related negative effect of inhaled glucocorticoids on bone density even among

women who did not receive oral or parenteral glucocorticoid therapy and who had adequate intake of calcium and vitamin D. Although the precise risk of bone loss associated with different inhaled-glucocorticoid preparations and different delivery systems may vary, our data suggest that, when used to treat asthma, inhaled glucocorticoids should be used at the lowest dose necessary to achieve control of the symptoms. Since serum and urinary markers did not predict the extent of bone loss, patients using high doses of inhaled glucocorticoids may benefit from periodic assessment of bone density and, when necessary, prophylactic measures to protect the skeleton.

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