

Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma

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To determine whether high-dose or prolonged inhaled steroid therapy for asthma increases a patient's risk of osteoporosis and fracture, we measured bone density in 26 men and 43 women (41 postmenopausal, all of whom had received supplemental estrogen therapy) after treatment with an inhaled steroid for 10.1 ± 5.5 years and oral prednisone for 10.7 ± 9.7 years (mean $\pm$ SD). Most had stopped receiving prednisone since commencing the inhaled steroid therapy. We found that bone densities (adjusted for age and sex to yield a z score) were lower in association with higher daily doses of inhaled steroid ($p = 0.013$ ANCOVA) and with the duration of past prednisone therapy ($p = 0.032$). Larger cumulative inhaled steroid doses were associated with higher bone densities ($p = 0.002$) and a reduction in the numbers of patients at risk of fracture. Bone density also increased with the amount of supplemental estrogen therapy ($p = 0.058$) and, at equivalent levels of inhaled and oral steroid use, women showed higher bone density z scores than did men. Women with a lifetime dose of inhaled steroid greater than 3 gm had normal bone density regardless of the amount of past or current prednisone use or the current dose of inhaled steroid. These data indicate that the daily dose, but not the duration, of inhaled steroid therapy may adversely affect bone density, and that estrogen therapy may offset this bone-depleting effect in postmenopausal women. (J ALLERGY CLIN IMMUNOL 1995;96:157-66.)

Key words: Asthma, glucocorticoids, inhaled steroids, budesonide, beclomethasone, steroid complications, bone densitometry, osteoporosis, vertebral fracture, estrogens

Inhaled steroid therapy is currently recommended for the treatment of moderate, or severe asthma.¹⁻⁸ Concerns persist, however, about the

Abbreviations used

ANCOVA:	Analysis of covariance
LBMD:	Lumbar bone mineral density (gm/cm ²)
LBMD-Z:	Lumbar bone mineral density z score
SD:	standard deviation

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safety of this therapy, particularly with respect to its possible effect on bone.⁹⁻¹¹

These concerns stem from the frequency with which osteoporosis is known to complicate the long-term use of oral steroids (estimated to be in some 30% to 50% of exposed patients¹²), coupled

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TABLE I. Patient characteristics at the time bone density was measured

	<i>n</i>	Mean $\pm$ SD	Range
Age (yr)	69	59.9 $\pm$ 13.3	
Male	26	58.5 $\pm$ 17.6	
Female	43	60.8 $\pm$ 9.6	
Menopausal status			
Pre	2		
Post	41		
Estrogen usage			
Current	23		
Previous	18		
Years of use	41	4.43 $\pm$ 7.28	
Activity score (1-10)	69	5.12 $\pm$ 2.12	
Prednisone			
Years of use*	69	10.7 $\pm$ 9.7	0-34
Current dose (mg/day)	69	3.0 $\pm$ 7.9	0-60
Inhaled steroid			
Years of use	69	10.1 $\pm$ 5.5	1-23
Current dose (mg/day)	69	1.3 $\pm$ 0.81	0-3.2
*Cumulative dose (gm)	69	3.1 $\pm$ 2.1	0.04-10.5
Intranasal steroid Users	30		

*Primary selection criteria for survey patients.

with the recent observation that inhaled steroid drugs may adversely affect various metabolic indices of bone turnover.¹³⁻²¹

It remains to be established whether these inhaled steroid-induced metabolic changes are clinically important. They might presage the development of osteoporosis and fracture after prolonged exposure to the drug, especially if high doses are given to growing children or to patients in whom additional risk factors for osteoporosis are present or develop (e.g., in the postmenopausal state). For these uncertainties to be resolved, the effect of inhaled steroid therapy on bone mass needs to be determined. Low bone mass is an important risk factor for the occurrence of osteoporotic fracture,²²⁻³² and bone mass is quantifiable in terms of bone mineral density. To date, cross-sectional surveys of bone density in patients treated with inhaled steroids have shown conflicting results.³³⁻³⁹ Where a significant reduction in bone density has been observed, the causal role of the inhaled steroid therapy remains unclear because of uncertainties about the documentation of the potentially confounding effects of past or current oral steroid treatment,^{34-36, 40} or because of the presence of nonsteroidal factors that also influence bone density (e.g., the postmenopausal state³⁵).

We examined these relationships in a cross-sectional survey of bone density in a group of

asthmatic adults. They were selected to facilitate comparisons between the effects of inhaled and oral steroid treatment on bone density over a wide range of exposure to each drug. The primary aims of the study were to determine whether the dose and duration of inhaled steroid therapy bear a discernible relationship to bone density, and to differentiate, if possible, between any effect of the inhaled steroid that might be observed and that due to the oral steroid therapy previously or currently used by most of these patients. Secondary aims included an assessment of the contributory effects of coexisting factors, such as age, sex, physical activity, the postmenopausal state, and the use of supplemental estrogen—each of which is known to influence bone density and the risk of fracture among steroid-dependent patients.

We also assessed the extent to which bone density correlated in these patients with nonosseous stigmata of chronic steroid excess and with the prevalence of vertebral fracture.

METHODS

The study was approved by the Review Board of the University of Western Ontario for health sciences research involving human subjects.

Patients

The 69 patients studied represented 15% of the total population of asthmatic patients attending this clinic for ambulatory care at the time the survey was done. There were no black, Asian, or Hispanic patients. They were older than our clinic population as a whole: 59.9 $\pm$ 13.3 vs 48.7 $\pm$ 17.75 years (mean $\pm$ SD, *n* = 453). Relevant demographic characteristics are summarized in Table I.

Measures of steroid use

Data on drug usage were collected by review of the clinical charts of the physician directly responsible for the long-term care of the patients (J.H.T.). These were supplemented by data from current symptom and drug-use diaries kept by 34 of the patients as part of a systematic surveillance of the safety of long-term inhaled steroid treatment. Clinic visits were scheduled twice yearly, or more frequently, for assessment and collection of the diary data.

The measures of oral and inhaled steroid usage derived from these records are listed in Table I. Inhaled steroid usage was quantified in terms of the current daily dose, duration of therapy, and cumulative lifetime dose. These factors could be accurately determined because inhaled steroid usage had been controlled solely by one physician (J.H.T.) throughout the entire period of inhaled steroid treatment for all the patients studied. Prednisone usage was quantified in terms of the current daily dose and years of treatment, both of which could be accurately determined. The cumulative prednisone dose

was not analyzed because it could not be reliably quantified for some members of the group, because their dosage had been adjusted by more than one physician during the period of follow-up in order to cope with exacerbations of asthma. Some additional nonsteroidal factors also present in these patients and known to influence bone density are listed in Table I. All but eight of the patients started receiving regular oral or inhaled steroid therapy after 30 years of age, by which time maximal bone mass is normally attained.

Every patient had used inhaled steroid therapy to treat asthma. The daily dosage of inhaled steroid was higher in these patients than in the inhaled steroid users of the clinic population as a whole: median doses 1.1 mg/day versus 0.79 mg/day, respectively. The drug was inhaled from a pressurized aerosol fitted with a spacer—in most cases, a 750 ml Nebuhaler (Astra Pharma Production AB, Södertälje, Sweden). No dry powder formulations were used. Patients were instructed, and then routinely monitored, to ensure inhalation commenced at residual volume, was sustained at an inspiratory flow of about 25 L/min., and was followed by a 5- to 10-second breath-hold. Patients were instructed to rinse the mouth and expectorate after completing each treatment. We have found this mode of administration to double the intrapulmonary delivery of inhaled budesonide in comparison with what can be achieved using the pressurized aerosol without a spacer and, in consequence, to slightly increase its systemic toxicity.⁴¹ The inhaled steroid drugs used included dexamethasone, beclomethasone, and budesonide, and most patients had used more than one of these. At the time bone density was measured, 49 were using budesonide, 15 beclomethasone, and five no inhaled steroid. Thirty patients used concurrent intranasal steroid spray as well, either seasonally or regularly (Table I).

Fifty-two of the patients had used regular daily or alternate-day doses of prednisone in the past or recently, for periods of at least 6 months at a time; 16 had used prednisone intermittently but never regularly; one had never been treated with prednisone. Of the 69 patients, 24 were still using prednisone at the time the bone density measurement was made.

Design

The study was a cross-sectional survey of a nonrandom sample of asthmatic adults at one point in time. Candidates were selected on the basis of their long-term exposure to inhaled and oral steroid drugs. A 3 × 3 table was constructed on the basis of low, medium, and high exposures to the two drugs, as quantified by their cumulative lifetime dose of inhaled steroid and years of prednisone therapy. Potential candidates were allocated among the nine cells of this cross-classification to achieve marginal ratios of approximately 7:3:7. When more than the required number of candidates were available in a particular cell, selection was made randomly. The joint stratification by the degree of exposure to both inhaled steroid and oral steroid was intended to ensure that these two factors were relatively indepen-

dent of one another statistically; thus making it feasible to estimate their separate effects on bone density.

The required sample size was estimated by determining the number of patients needed in the high- and low-exposure subgroups to detect a 20% difference in bone density with 90% power at the 0.05 significance level. This estimated sample size was then augmented by adding patients to the intermediate groups to conform as closely as possible with the predetermined 7:3:7 ratio.

Measurement of bone density

Bone density was measured once at the lumbar spine (L-2 to L-4) which is normally the area most sensitive to the effects of excess glucocorticoids. In 49 patients measurement was made by means of dual energy x-ray absorptiometry, using the Hologic QDR 1000 densitometer (Hologic Corp., Boston, Mass.). In 20 patients measurement was made by means of dual energy photon absorptiometry, using a Lunar DP3 densitometer (Lunar Corp., Madison, Wis.). The results were reported as absolute densities (in grams per square centimeter) and as *z* scores. The latter express the number of standard deviations (SD) by which the observed bone density (in grams per square centimeter) deviates above or below the predicted normal bone density for persons of the same age and sex. The *z* scores provide a basis for quantifying the risk of fracture,^{25, 26} since the lifetime risk of an osteoporotic fracture has been estimated to increase 1.5- to 3-fold for each SD decrease in bone density.^{23, 32, 42}

To adjust the data from the Lunar densitometer for compatibility with the data obtained from the Hologic densitometer, a regression equation was derived from pairs of measurements made on the same day by both instruments in 213 consecutive referrals to the Metabolic Bone Disease Clinic. The regression equation formula was: Hologic (in grams per square centimeter) = 0.825 · Lunar (in grams per square centimeter) – 0.018, with a standard error of estimate of 0.055 gm/cm² (*r* = 0.97). All Lunar data (in grams per square centimeter) were converted to Hologic-equivalent data (in grams per square centimeter), and then *z* scores were derived from the Hologic reference population data. Thus all *z* scores in this report are expressed in Hologic units.

Statistical methods

The individual effects of the amount of long-term exposure to inhaled steroid and to oral steroid and of the patient's sex on bone density were estimated by analysis of covariance (ANCOVA) (Statistical Analysis System/General Linear Model; SAS Institute, Cary, N.C.),⁴³ controlling for age, years of estrogen use, the patient's physical activity rating, and the current daily dose of inhaled steroid and oral steroid.

Nonsteroidal factors relating to bone density

A rating of the physical activity characteristic of each patient's lifestyle was made by the physician responsible

TABLE II. Bone density and prevalence of dorsolumbar fracture

Type of deformity	n	LBMD (gm/cm ²) Mean $\pm$ SD	p Value*	LBMD-Z Mean $\pm$ SD	p Value*
Wedge					
Yes	15	0.82 $\pm$ 0.23	0.10	-1.01 $\pm$ 1.72	0.34
No	48	0.90 $\pm$ 0.14		-0.57 $\pm$ 1.49	
Wedge plus biconcave					
Yes	7	0.71 $\pm$ 0.13	0.005	-1.48 $\pm$ 1.38	0.14
No	56	0.90 $\pm$ 0.16		-0.57 $\pm$ 1.54	

*P from unpaired *t* test.

for their long-term care (J.H.T.) using a 10-point ordinal scale. The distribution of these ratings was bell shaped, with a modal rating of 4, a mean of 5.1, and a range from 1 ("highly sedentary") to 9 ("frequent strenuous physical exercise"). Menopausal status and estrogen usage were determined by means of a patient questionnaire supplemented by chart review.

Radiographic survey for vertebral fracture

Lateral roentgenograms of the dorsolumbar spine were obtained in 63 patients, on or close to the day their bone density was measured. The films were reviewed en bloc by one examiner (R.G.H.). The statistical associations between fracture, on the one hand, and bone density and the various steroidal and nonsteroidal risk factors for osteoporosis, on the other, were analyzed by a combination of multiple regression and multiple logistic regression analysis.

Nonosseous effects of steroids

The presence or absence of nonosseous clinical stigmata of hypercortisonism was derived from chart reviews. Serum cortisol levels were assayed by standard laboratory methods on specimens secured at 8 AM (± 1.5 hours) on or close to the day bone density was measured.

RESULTS

The demographics of the survey group are summarized in Table I. The primary selection criteria (i.e., the duration of prednisone use and the cumulative lifetime dose of inhaled steroid) averaged 10.7 ± 9.7 years and 3.1 ± 2.1 gm, respectively (mean $\pm$ SD). Of the 69 patients, 41 were postmenopausal women, and all these had received supplemental estrogen therapy (Table I).

Nonosseous evidence of chronic hypercortisonism present in the survey group included weight gain ($n = 10$), moon face ($n = 11$), steroid purpura ($n = 17$), and hypertension ($n = 18$). Additionally, 12 of 62 had subnormal morning serum cortisol

levels at entry (<210 nmol/L), and 11 of 40 patients examined by means of slit lamp had posterior subcapsular cataracts.

Lumbar bone mineral density (LBMD) averaged 0.89 ± 0.13 gm/cm² (SD) in the men and 0.84 ± 0.20 in the women who participated in the survey. The respective *z* scores (LBMD-Z) were -1.35 ± 1.44 (SD) in the men and -0.70 ± 1.72 in the women.

Several nonosseous stigmata of chronic hypercortisonism correlated significantly with the presence of reduced bone density values. For example, serum cortisol suppression versus LBMD ($r = 0.378$, $p = 0.002$) or LBMD-Z ($r = 0.466$, $p = 0.0001$); and the presence of steroid purpura versus LBMD ($r = -0.322$, $p = 0.007$). In addition, low levels of LBMD correlated significantly with the presence of vertebral wedge fracture with biconcave deformity ($p = 0.005$, Table II).

The combined effects of the particular risk factors assessed explained 45% of the observed variability in LBMD-Z ($R^2 = 0.45$). The influence of each individual factor as determined by ANCOVA is shown in Table III. LBMD-Z decreased significantly in association with the duration of past oral steroid therapy ($p = 0.032$) and the current daily dose of inhaled steroid ($p = 0.013$). In contrast, the higher the cumulative lifetime dose of inhaled steroid, the higher the LBMD-Z value ($p = 0.002$). Higher LBMD-Z values also correlated with greater physical activity and age, each of which was statistically significant by ANCOVA, and with female sex and years of estrogen usage, which approximated significance (Table III). The current daily dose of prednisone did not correlate with LBMD-Z ($p = 0.94$). Co-treatment with intranasal steroid did not correlate with LBMD-Z ($p = 0.66$) or alter the associations shown in Table III.

The regression of LBMD-Z on the daily dose of inhaled steroid is illustrated in Fig. 1. On the average, LBMD-Z fell by 0.5 SD for each 1.0 mg increment in the daily dose of inhaled steroid. At a nominal dose of 1.0 mg/day, LBMD-Z was -0.50 with 95% confidence limits of -0.12 to -0.85 (mean $\pm$ 2 SEM).

The net effect of the cumulative dose of inhaled steroid on LBMD-Z and the risk of fracture is illustrated in Fig. 2. LBMD-Z was higher in patients with a greater lifetime exposure to inhaled steroid, as evidenced by a cumulative dose greater than 3 gm (the median of the group), than in patients who had had less exposure to inhaled steroid. The shift toward more normal values was more prominent in women. The percent of the group that had an LBMD-Z value indicating a substantial increase in the risk of fracture (i.e., equal to or lower than -2.0) was much lower among patients who had had a relatively high lifetime exposure to inhaled steroid than in those with a relatively low exposure (i.e., 5% vs 35% in women, and 12% vs 45% in men; Fig. 2). The larger the cumulative dose of inhaled steroid, the lower the prevalence of radiologically demonstrable wedge and biconcave vertebral deformities among these patients ($p = 0.02$; data not shown).

The relationship of the sex of the patient to the effect of different degrees of long-term exposure to inhaled and oral steroid on LBMD-Z is illustrated in Fig. 3. When compared at equivalent levels of exposure to inhaled and oral steroid, women consistently showed less deviation from normal than did men. In women with a cumulative dose of >3 gm inhaled steroid, mean LBMD-Z values were essentially normal: 0.005 and -0.001 , regardless of the amount of their past exposure to oral steroid. This was not the case for men with more than 10 years exposure to oral steroid. The daily dose of inhaled steroid currently used by these women, in whom a high lifetime exposure to inhaled steroid was coupled with a normal mean LBMD-Z, averaged 1.64 ± 0.68 mg/day.

DISCUSSION

To our knowledge, this is the largest group of asthmatic patients in whom the effects of high-dose or prolonged inhaled steroid therapy on bone density has been assessed, as well as the first study in which the effects of long-term inhaled and oral steroid therapy on bone density and clinical outcome (fracture) have been directly compared.

The observation of a significant association between the duration of oral steroid therapy and

TABLE III. Effects of steroidal and nonsteroidal factors on LBMD-Z

Change in LBMD-Z*		p Value from ANCOVA†
▼	Daily dose of inhaled steroid	0.013
▼	Years of prednisone	0.032
▲	Cumulative dose of inhaled steroid	0.002
▲	Age	0.005
▲	Physical activity	0.042
▲	Years of supplemental estrogen	0.058
▲	Female sex	0.062
►	Daily dose of prednisone	0.943

*Arrowheads signify a reduction (▼) or increase (▲) or no change (►) in LBMD-Z, relative to predicted normal z scores.

†Quantifies significance of effect of each variable on LBMD-Z, where the effects of the other seven variables shown were controlled in ANCOVA.

lower LBMD-Z values (Table III) accords with the findings of earlier investigators.^{44, 45} The absence of a discernible association between the daily dose of oral steroid and LBMD-Z presumably reflects the fact that most of the patients in our survey had stopped using prednisone before the time bone density was measured.

Effects of inhaled steroid on bone density

The contradictory associations between LBMD-Z and different measures of inhaled steroid usage that were observed in these patients (Table III) have not been reported previously. This paradox suggests the existence of two separate mechanisms by which inhaled steroid therapy may influence bone density: (1) a direct bone-depleting effect related to the current dose per day, and (2) an indirect effect that probably reflects the restitution of previously osteoporotic bone consequent to the withdrawal of prednisone after the commencement of inhaled steroid treatment.

The hypothesized *indirect* effect of inhaled steroid on bone is supported by the following evidence: (1) spontaneous bone restitution has been observed in some patients with osteoporosis caused by Cushing's syndrome after removal of the source of their excess glucocorticoid by surgical extirpation of a tumor or withdrawal from previously used prednisone⁴⁶⁻⁴⁹; (2) two thirds of our patient group had, in fact, withdrawn entirely from their previous prednisone therapy under the aegis

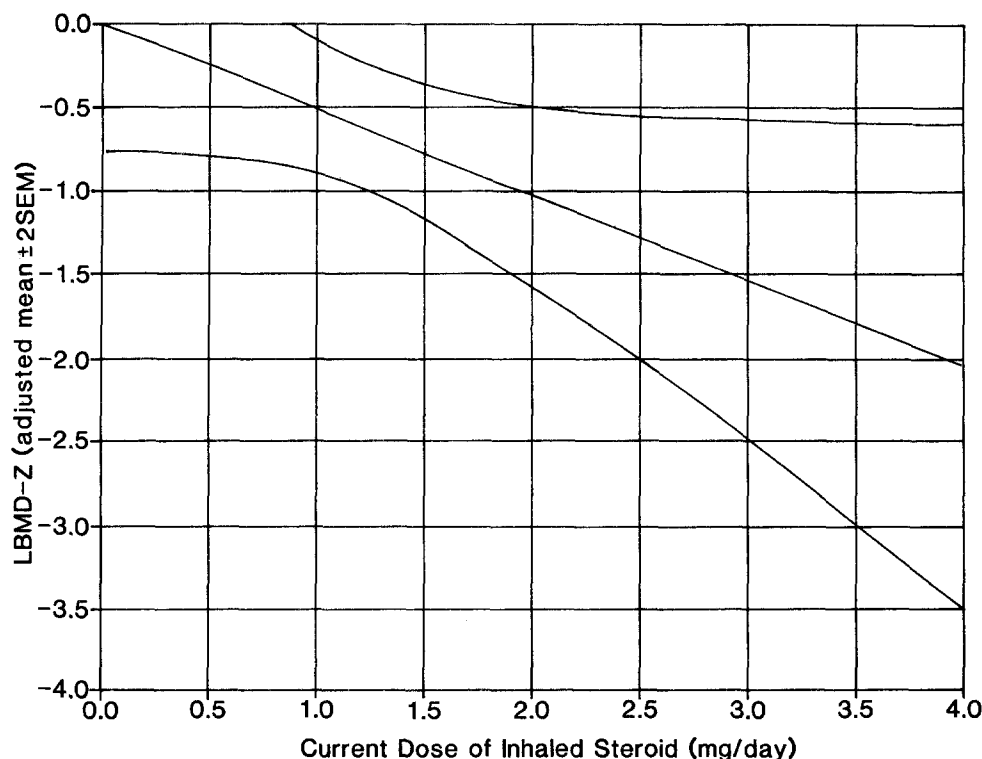


FIG. 1. Regression of LBMD-Z on the daily dose of inhaled steroid. Means shown are adjusted to control for the effects of age, sex, years of estrogen use, physical activity, the current daily dose of prednisone, years of prednisone usage, and the cumulative lifetime dose of inhaled steroid. LBMD-Z declined significantly on the daily dose of inhaled steroid ($p = 0.013$).

of inhaled steroid treatment, whereas the remainder used prednisone only at low dosage (mean, 7.5 mg/day); and (3) the adverse effects on bone metabolism known to be associated with the use of budesonide (the inhaled steroid drug used by most of these patients) have been shown to be much less than those of prednisone when the two drugs are compared at dose levels at which the inhaled steroid is equally or more effective than the oral steroid.¹⁴

Evidence in support of the hypothesized *direct* effect of inhaled steroid on bone includes the following: (1) inhaled steroid drugs have been shown to exert dose-dependent adverse effects on a number of metabolic indices that signify increased bone resorption or decreased bone formation,¹³⁻²¹ and (2) several cross-sectional surveys of asthmatic adults receiving inhaled steroid therapy have observed a reduction in bone mass in comparison with untreated subjects.^{34, 36}

The substantial unexplained variation in LBMD-Z observed in these patients (viz $R^2 = 0.45$), after controlling for the effects of the daily dose of inhaled steroid and the additional risk-factors analyzed, indicates a strong influence from

some unexplained factor or factors, possibly genetic, acting alone or possibly in conjunction with the daily dose of inhaled steroid as determinants of bone density.

Sex-related differences in bone density relative to inhaled steroid and oral steroid exposure

Among the women surveyed, those who had received a high cumulative lifetime dose of inhaled steroid conserved an LBMD-Z level that was essentially normal, regardless of the duration of their past oral steroid exposure or their current use of a relatively high daily dose of inhaled steroid of 1.64 ± 0.68 mg/day (mean $\pm$ SD, $n = 16$). This did not apply in the case of men who had had the same amount of long-term inhaled and oral steroid exposure (Fig. 3).

Of the 43 women surveyed, 41 had used estrogens after menopause. Furthermore, the duration of their estrogen usage correlated positively with higher LBMD-Z values ($p = 0.049$, Pearson correlation). This suggests that past and current estrogen use might account for the relatively high LBMD-Z values observed in the women surveyed.

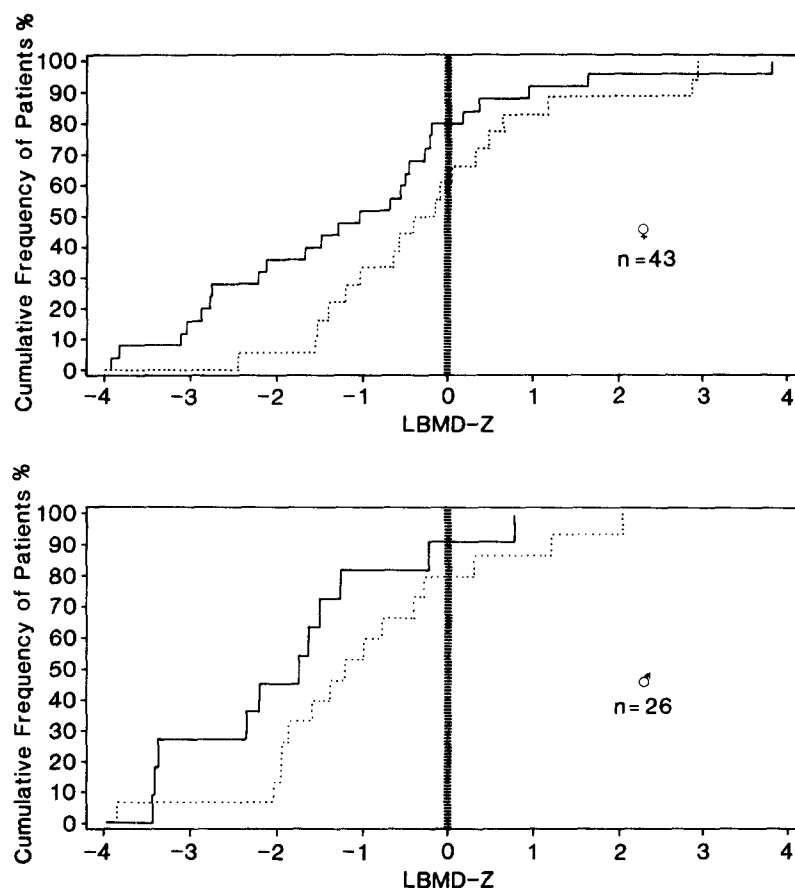


FIG. 2. Influence of the cumulative dose of inhaled steroid on the frequency distribution of LBMD-Z among women (above) and men (below), subdivided at the median cumulative dose of inhaled steroid: ≤ 3 gm (solid line) and > 3 gm (dotted line). A larger lifetime exposure to inhaled steroid was associated with more normal LBMD-Z values ($p = 0.002$) and a reduction in the number of patients at risk of fracture.

It further suggests that estrogens may have the capacity to mitigate glucocorticoid-induced osteoporosis as well as involutional osteoporosis, as postulated by some earlier investigators.^{50, 51}

Differences between drugs

These data do not provide a suitable basis for estimating the relative toxicity of one inhaled steroid versus another. However, the significant association between higher daily doses of inhaled steroid and lower LBMD-Z values that is documented in Table III remained significant ($p = 0.013$) when the analysis was limited to those patients who were taking budesonide at the time bone density was measured. In addition, the overall results of the ANCOVA in this subset of patients were identical with those shown in Table III. Thus budesonide—the least toxic of the three inhaled steroids to which our patients had been exposed—is not free from this adverse effect on

bone density, and it is reasonable to assume the association applies to inhaled steroid drugs in general.

Further studies

Prospective controlled studies are required to test the above mentioned hypotheses, that is, (1) the existence of two different mechanisms by which inhaled steroid therapy may influence bone density, one direct and the other indirect, and (2) the capacity of supplemental estrogen to prevent or correct glucocorticoid-induced osteoporosis in women.

Studies are also needed of adolescents and young adults up to 30 years of age to determine (1) the effect of inhaled steroid therapy on the maximum bone density achieved during their formative years, and (2) whether genetic factors that influence skeletal metabolism may interact with inhaled steroid therapy to reduce bone density and increase the risk of fracture in some persons.

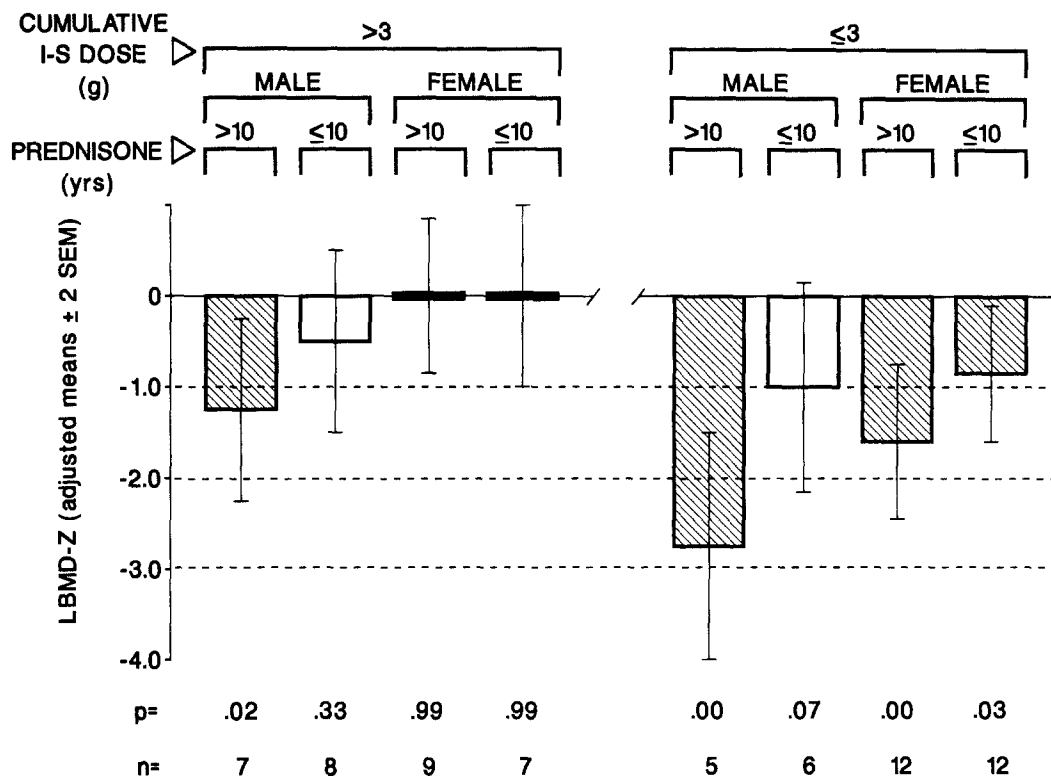


FIG. 3. Relationships between the sex of the patients and their long-term exposures to inhaled and oral steroids, as co-determinants of LBMD-Z. The group was subdivided at the median value for both years of prednisone use and the cumulative dose of inhaled steroid. Adjusted means $\pm$ 2 SEM are shown. Shaded bars indicate means significantly lower than normal. Women showed more normal LBMD-Z values than did men when subgroups with equivalent long-term exposures to inhaled and oral steroid were compared.

Clinical implications

These data indicate that the long-term use of inhaled steroid drugs is consistent with near normal or normal bone density and little or no increase in the risk of fracture (Fig. 3). They suggest that, in adults with prednisone-dependent asthma, long-term inhaled steroid therapy may lead to increases in bone density and a clinically important reduction in the risk of fracture (Fig. 2 and Tables II and III). They further suggest that these beneficial outcomes may accrue despite prolonged exposure to oral steroid in the past or the current use of relatively high daily doses of inhaled steroid, or both. Thus inhaled steroid is strongly favored over oral steroid therapy as the preventative treatment of choice in patients with moderate or severe chronic asthma.

The data also indicate that supplemental estrogen therapy may allow preservation of normal bone density in postmenopausal asthmatic women despite prolonged exposure to inhaled and oral steroid therapy (Fig. 3).

On the other hand, the evidence for a direct bone-depleting effect of the daily dose of inhaled steroid that is independent of past or current oral steroid usage (Table III and Fig. 1) is cautionary. As shown in Fig. 1, a dose of 2.0 mg inhaled steroid per day may be expected to reduce bone density by 1 SD, which implies that the lifetime risk of fracture resulting from osteoporosis would be increased about 1.5- to 3-fold.³² Doses of this order (≥ 2.0 mg/day) are required by only about 5% of adult patients attending our tertiary care clinic.⁵² In such patients co-treatment with nedocromil or theophylline (or both) may facilitate reduction of their daily dose of inhaled steroid.^{53, 54} In all cases the daily dose of inhaled steroid should be titrated individually and appropriate ancillary measures applied,^{55, 56} so as to minimize patients' overall exposure to both inhaled and oral steroid drugs.

Given the modest degree of bone loss that was observed in these patients treated with inhaled steroid for long periods, bone densitometry could reasonably be considered for assessment of frac-

ture risk, particularly in patients over 50 years of age and in postmenopausal women not receiving estrogen replacement therapy.

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