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Journal

Alimentary Pharmacology & Therapeutics, 10(5)

ISSN

0269-2813

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Publication Date

1996-10-01

DOI

10.1046/j.1365-2036.1996.63205000.x

Peer reviewed

Aliment Pharmacol Ther 1996; 10: 777–786.

A randomized, placebo-controlled trial of calcium supplementation for decreased bone density in corticosteroid-using patients with inflammatory bowel disease: a pilot study

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Accepted for publication 11 June 1996

SUMMARY

Background: Patients with inflammatory bowel disease (IBD) have a high prevalence of osteoporosis. A number of studies have found that corticosteroid use is associated with the development of osteoporosis in these patients. Calcium supplementation may be of benefit in corticosteroid-induced osteoporosis and calcium may be a nutrient that patients with IBD lack.
Aim: To test the benefit of calcium supplementation on bone density in a pilot study over a 1-year period, in a group of corticosteroid-using patients with IBD, in a randomized, double-blind, placebo-controlled treatment study.
Methods: Corticosteroid-using patients with IBD including males over the age of 18 years and premenopausal females, were randomized to receive either calcium carbonate 1000 mg plus vitamin D 250 IU (Oscal) or an identically matched placebo. Dual energy X-ray absorptiometry measurements of bone density were obtained at entry and at 1 year. At entry, and every 3 months thereafter, serum was collected for the measurement of haemoglobin, biochemistry and bone hormones. Simultaneously a 24-h urine collection was analysed for calcium excretion and creatinine clearance, and a 4-day food record was collected to document dietary calcium and vitamin D ingestion.
Results: We found a high prevalence of moderately severe decreased bone density in corticosteroid-using patients with IBD. The dose of prednisone in the year prior to study entry was inversely correlated with bone density at the hip ($R = -0.67$, $P = 0.004$). At study entry serum osteocalcin was inversely correlated with corticosteroid dose in the year prior to the study ($R = -0.64$, $P = 0.02$) and at study end, directly correlated with the percentage change in spine bone density ($R = 0.59$, $P = 0.01$). The dietary calcium intake of these patients was close to the current RDA (recommended daily intake) for premenopausal, post-adolescent adults. Calcium supplementation with small extra doses of vitamin D conferred no obvious benefit to bone density at the end of 1 year. There was no correlation between oral calcium ingestion and bone mass measurements. Both the treatment and placebo groups' bone density remained relatively stable at 1 year, suggesting that bone loss in corticosteroid-using patients may peak early into the use of the corticosteroids.
Conclusions: Calcium supplementation (1000 mg/day) conferred no significant benefit to bone density at 1 year in patients with corticosteroid-using IBD patients with osteoporosis. Future investigations should explore other therapeutic avenues that may have greater effects on increasing bone density in patients who already have considerable osteoporosis.

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INTRODUCTION

Patients with inflammatory bowel disease (IBD) have a high prevalence of diminished bone density.[1] Diminished bone density correlates with the development of fractures.[2] Thus, addressing the bone status of patients with IBD can have effects on their quality of life and potential morbidity. Some data suggest that newly diagnosed patients with IBD already have diminished bone density, implying an important role for the systemic disease process in bone homeostasis.[3] Others have found a high prevalence of diminished bone density in patients with long-standing disease.[1, 4–6] Our group and others,[1, 4, 6] have found that the main determinant of diminished bone density in patients with long-standing disease, is the use of corticosteroids.

Corticosteroid-induced bone disease is a well established condition. In 1976, Genant *et al.* suggested that IBD patients had undermineralized bones, and that corticosteroid use correlated with decreased bone mineralization in adolescents.[7] The rheumatology and pulmonary literature have highlighted the problems of corticosteroid-induced osteoporosis[8–11] and this issue has been increasingly addressed in IBD patients.[12] Corticosteroid therapy is often used as a primary treatment of IBD for prolonged periods. Therefore, osteoporosis can be a significant problem for a majority of patients with IBD. It has been estimated that $\approx 50\%$ of patients using long-term corticosteroids will experience fractures.[13]

Although considerable attention has been paid to the pathogenesis of corticosteroid-induced osteoporosis, and the correlation of osteoporosis with corticosteroid dosing schedules, bone hormone measurements and disease status, there are few data on how best to prevent or treat established corticosteroid-induced bone disease. Much of the approach to established corticosteroid-induced osteoporosis is extrapolated from other osteoporotic settings, particularly that of postmenopausal osteoporosis. For patients with IBD there are issues of dietary intake, bowel absorption and systemic inflammation that do not apply to the postmenopausal situation. Furthermore, the highest incidence of IBD is in the second and third decades during the period that peak bone mass is established, and therefore these patients require medical attention long before the natural process of bone involution begins. For these reasons, studies of therapy specific for the IBD population are imperative.

This report is the first randomized, double-blind, placebo-controlled study of an intervention aimed at reducing osteopenia in premenopausal corticosteroid-using patients with IBD. We chose a regimen of calcium supplementation (1000 mg/day). The active treatment also contained vitamin D (250 IU/day). The study design was mostly to determine the effects of calcium supplementation, so vitamin D doses were simply those that accompany many commercially available calcium compounds including the active drug in our study (Oscal). Calcium supplementation was chosen for a number of reasons: (a) the accumulating evidence in favour of the beneficial effects of calcium supplementation or high dietary calcium intake in maintaining bone mass throughout life, (b) data suggesting that calcium is beneficial specifically in corticosteroid-induced osteoporosis, (c) ease of administration and lack of significant toxicity, (d) calcium is a nutrient that patients with IBD may potentially lack, either because of dietary restrictions, or small bowel malabsorption, (e) there is general agreement that corticosteroids diminish intestinal calcium absorption and that corticosteroids can lead to hypercalcuria by interfering with renal calcium reabsorption, and (f) the lack of interference of this regimen with the myriad of potential medications that patients with IBD might use.

METHODS

Study design

This was a prospective, randomized, double-blind, placebo-controlled study. The study was approved by the UCLA Human Subjects Protection Committee.

Patients

Consecutive patients with ulcerative colitis and Crohn's disease (both males and females) from the UCLA Inflammatory Bowel Disease Centre were asked to participate. Study enrolment took place between March 1992 and August 1993, and patients were followed for 1 year. Informed consent was obtained. To be included, patients had to have been using corticosteroids for at least 3 of the prior 6 months. Exclusion criteria included: (i) age less than 18 years, (ii) postmenopausal women (natural or surgical), (iii) patients with known chronic liver disease (a known diagnosis or unexplained liver enzyme elevations), (iv) chronic renal insufficiency (serum creatinine > 1.5 mg/dL), (v) known primary hyper- or hypoparathyroidism, (vi) untreated thyroid disease, (vii)

deforming arthritis, (viii) Paget's disease of bone, (ix) concurrent dilantin or sex hormone therapy, and (x) patients who were bed or wheelchair bound.

Patient data

Data collected at enrolment included: (a) age, (b) sex, (c) disease diagnosis, (d) disease location, (e) disease duration, (f) current medications, (g) current and past corticosteroid use, (h) use of calcium and vitamin D supplements at the time of enrolment, (i) menstrual pattern, if female, (j) previous history of fractures and fracture type. Since there is an association between regular physical activity and bone mass,[14] we also asked patients if they participated in any regular activity or fitness programme (on their own or in a formal class) either (a) currently or (b) in the past 6 months. These questions have been validated as having a significant association with body mass index, HDL cholesterol and oxygen capacity[15] and therefore to some extent, physical fitness.

At study completion, the patients' disease state during the year of the study was documented. If patients had active disease for $>$ 3 months of the year they were considered to have had active disease for the year of the study. It was also determined if the patients were corticosteroid users during the year of the study. If corticosteroids were used for $>$ 3 months of the year of the study, they were considered to be 'users'.

Blood and urine evaluations

At enrolment, and at 3-month intervals, until study completion, blood was drawn between 08.00 h and 09.00 h for serum levels of haemoglobin, calcium, phosphate, magnesium, albumin, protein, alkaline phosphatase, 1,25-$(OH)_2$-vitamin D, 25-OH-vitamin D, parathyroid hormone (PTH), osteocalcin, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, bilirubin, and cholesterol. At the same time intervals, a 24-h urine was collected and assayed for urinary calcium and creatinine and a creatinine clearance corrected for body mass index was calculated. For each study visit and for visits between study intervals, patient compliance and side-effects from the study medication were reviewed (by the study nurse). Patients' heights and weights were also recorded.

Measurements of 1,25-$(OH)_2$-vitamin D and 25-OH-vitamin D were carried out using a radioreceptor assay obtained from calf thymus (Nichols Institute Diagnostics, San Juan Capistrano, CA). In our laboratory, the intra-assay coefficient of variation for serum 1,25-$(OH)_2$-vitamin D determinations is below 7% for values above 20 pg/mL and the inter-assay coefficient of variation is less than 6% for levels above 20 pg/mL. Serum immunoreactive PTH levels were measured using a two-site immunoradiometric assay (IRMA-PTH) for intact 1–84 PTH (Nichols Institute Diagnostics, San Juan Capistrano, CA). In our laboratory, the intra-assay coefficient of variation for this method has been consistently less than 3%, and the inter-assay coefficient of variation less than 6%. Osteocalcin was measured by radioimmunoassay using an antibody to human osteocalcin (Nichols Institute Diagnostics, San Juan Capistrano, CA). In our laboratory, the intra-assay coefficient of variation for osteocalcin determinations in serum is 5.8% and the inter-assay coefficient of variation is 7.5%. The bone hormone determinations were performed in batches over the course of the study.

Dietary calcium intake determination

At enrolment, the study nutritionist (S. G.) instructed the patients on the correct procedures for completing a 4-day food record. The nutritionist gathered information regarding patient height, weight, usual weight, vitamin/mineral supplement intake, usual dietary dairy sources, and activity level. The patient was provided with the forms for one food record. Once the food record was completed it was mailed to the nutritionist, and analysed using the NUTRITIONIST III/DINE nutrient analysis software program. The patient was contacted by telephone with the results of the initial food record analysis. The patient's calcium intake on the initial food record was used as the patient's goal for dietary calcium intake throughout the study.

At 3 month intervals, subsequent food records were mailed to the patient, 10 days prior to the designated completion date. Two days before the patient was to begin recording, the patient was contacted by telephone to remind them to keep the record, clarify instructions and answer any questions. Once the record was completed, the patient mailed the data to the nutritionist in a self-addressed, stamped envelope. Based on the data analysis, the patient was instructed to maintain a consistent calcium intake. For instance, if the nutritionist identified that in the 4-day food record calcium input had markedly increased, the patient was interviewed as to

whether or not that dietary intake was typical and was instructed to maintain a consistent calcium intake.

Bone mass determination

Dual energy X-ray absorptiometry (DXA) (Hologic Inc., Waltham, MA) was used to determine bone density and was performed at study enrolment and at 1 year. The equipment was calibrated daily using a phantom provided by the manufacturer and according to the manufacturer's recommendations. Measurements were taken at (a) the L2–L4 vertebra levels (to estimate predominantly trabecular bone mass), (b) total hip using measurements at the femoral neck, the greater trochanter and the intertrochanteric area (predominately to estimate cortical bone mass), (c) and at Ward's triangle (an area in the femoral neck that contains thin and loosely arranged trabeculae). *T* scores, which reflect the deviation from the mean at each site for sex matched controls were obtained. Measurements that were 1.0 standard deviation below the controls (*T* score < -1) were deemed mildly decreased bone density; 1.5 standard deviations below: moderately decreased bone mass; and 2.0 standard deviations below: severely decreased bone density.

Study medications

The randomization and dispensing of medications was carried out by a pharmacist at the UCLA Medical Center. Randomization was performed in blocks of four. The study medication was a tablet containing 500 mg elemental calcium (as calcium carbonate) and 125 IU vitamin D (Oscal). Both the study medication and an identical matching placebo tablet were provided by Marion Merrell Dow Inc. (Kansas City, MO). Patients were asked to take two tablets each morning, thus providing 1000 mg of elemental calcium and vitamin D 250 IU per day to those randomized to the active treatment arm.

Statistical analysis

For univariate analysis the difference between means was assessed using Student's *t*-test assuming unequal variances. The difference between proportions was assessed using χ^2 analysis. The Pearson correlation was used to determine correlations between variables. A *P*-value of < 0.05 was considered to be statistically significant.

RESULTS

Twenty-four patients were enrolled; seven did not complete the study. Of these seven patients, one withdrew because she was concerned that she was not receiving calcium supplementation, two withdrew because of lack of interest, two were lost to follow-up, and two were noncompliant. Four of these seven had been randomized to calcium supplementation. Withdrawals from the study occurred within 1 month of enrolment in three patients, after 3 months in two patients, after 6 months in one patient and after 9 months in one patient. The data were analysed for the 17 who completed the entire study, nine of whom were randomized to calcium supplementation. None of the 17 patients completing the study experienced any side-effects thought to be related to study medications.

Patient data at study entry

There were no significant differences in any of several patient characteristics between the two treatment groups at study entry (Table 1). There were 14 men. The three women all had regular menses for at least 1 year prior to study entry. Ten of the study patients had Crohn's disease. Of these 10, four had ileocolonic disease, three isolated ileal disease and three isolated colonic disease. Of the seven ulcerative colitis patients, four had left-sided colitis and three had pancolitis. The patients used an average of 12–14 mg/day of prednisone in the year prior to study entry (calcium group = 5071 mg, placebo group = 4514 mg) The average dietary calcium intake barely met the RDA (recommended daily intake) for premenopausal or post-adolescent adults (800 mg/day) (Table 2). The average daily dietary vitamin D intake was 3.2 μg (equivalent to 128 IU) (Table 2).

At study entry, the average bone density was between 1 and 2 standard deviations below the mean for sex matched controls' *T* scores at the spine, and between 2 and 3 standard deviations below the mean for sex matched controls' *T* scores at the hip and Ward's triangle in both groups. The *T* scores were negative in 16 of 17 patients at the spine, 15 of 17 patients at the hip, and 15 of 17 patients at Ward's triangle (Figure 1). The dose of prednisone used in the year prior to trial entry significantly inversely correlated with bone density at the hip ($R = -0.67$, $P = 0.004$), and at Ward's triangle ($R = -0.52$, $P = 0.04$) and did not show a significant correlation with bone density at the spine ($R = -0.26$, P

Table 1. Patient characteristics at enrolment

	Calcium ($n = 9$)	Placebo ($n = 8$)	P-value
Age (mean ± S.E.M., years)	35.3 ± 3.3	36.4 ± 5.8	0.88
Sex: Male/Female	9:0	5:3	0.17
Diagnosis: Crohn's disease/ulcerative colitis	7:2	3:5	0.23
Disease duration (mean years ± S.E.M.)	12.4 ± 2.3	8.6 ± 1.9	0.22
Steroid dose in 1 year prior to entry (mean, mg ± S.E.M.)	5071 ± 1098	4514 ± 843	0.69
Total years of steroid use	5.4 ± 2.0	2.5 ± 1.6	0.18
Medications at entry: 5-ASA/6-MP/nil*	5/3/3	6/4/1	
Exercise at entry: yes/no	4/5	4/4	

* 5-ASA drugs refers to any of salazopyrine, mesalamine, olsalazine; 6-MP refers to 6-mercaptopurine. Some patients used both a 5-ASA drug and 6-MP.

Table 2. Patient data during the study

	Calcium	Placebo	*P-value
Dietary calcium intake at entry (mean mg/day ± S.E.M.)	801 ± 86	677 ± 74	0.29
Average dietary calcium intake during the study (mean mg/day ± S.E.M.)	792 ± 81	752 ± 72	0.71
Mean spine T score at entry	−1.83 ± 0.28	−1.45 ± 0.41	0.46
Mean spine T score at study end	−1.53 ± 0.25	−1.36 ± 0.43	0.74
Mean percentage change in spine bone density (g/cm²)	3.38 ± 1.44	0.58 ± 1.35	0.18
Mean hip T score at entry	−2.12 ± 0.44	−2.29 ± 0.34	0.76
Mean hip T score at study end	−1.92 ± 0.38	−2.35 ± 0.35	0.42
Mean percentage change in hip bone density (g/cm²)	3.05 ± 2.4	−1.62 ± 1.24	0.11
Mean Ward's ΔT score at entry	−2.13 ± 0.39	−2.44 ± 0.24	0.5
Mean Ward's ΔT score at study end	−1.94 ± 0.34	−2.34 ± 0.24	0.35
Mean percentage change in Ward's Δ bone density (g/cm²)	2.42 ± 2.83	0.62 ± 1.91	0.61
Disease state during trial:			
active disease at some point/remission	4/5	4/4	
steroid use during trial: yes/no	4/5	5/3	

* P-values are for comparisons between the two groups. The P-values for comparisons within each group from study entry to study end were all > 0.05.

$= 0.33$). Neither total years of steroid use nor duration of disease was correlated significantly with bone density at any site.

Patient data during and at the close of the study

During the year of the trial, four patients in each group had active disease, and prednisone was used for at least 3 months by four patients in the calcium group and five patients in the placebo group. The bone density improved after 1 year at the spine, hip, and at Ward's triangle in the calcium group, but the changes were not statistically significant (Table 2). Bone density results were not statistically changed after 1 year in the placebo group (Table 2). There were no statistically significant changes in bone density between the calcium group and the placebo group for any site (spine, hip or Ward's triangle) at the end of the study. Two patients in the calcium group and three patients in the placebo group had non-statistically significant worsening in bone density at 1 year (Figure 1). There was no significant correlation between initial total corticosteroid dose or years of corticosteroid use at study entry and final bone density or ultimate percentage change in bone density for any of the three sites; nor was there a significant difference in

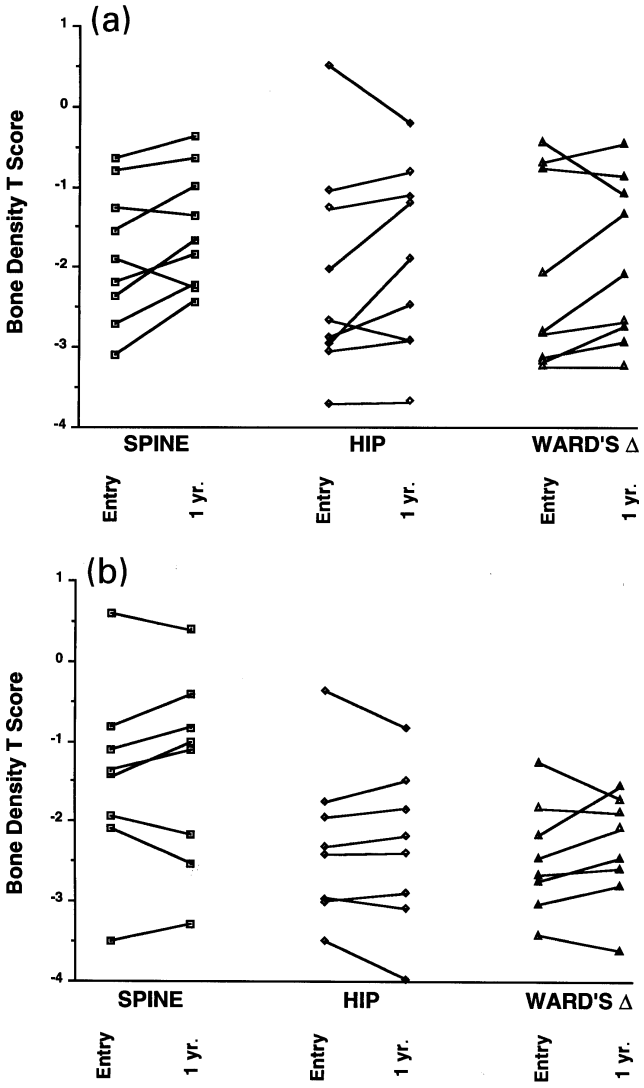

Figure 1. DXA *T* scores for spine, hip and Ward's Δ at study entry and at 1 year. (a) Calcium group, (b) placebo group.

ultimate bone density or percentage change in bone density at study end in users of corticosteroid during the study period compared with nonusers.

Dietary calcium intake was homogeneous throughout the study among individual patients and between groups. To further examine whether calcium intake might correlate with bone density measurements, we examined the relationship between total oral calcium intake and bone density outcome across all 17 patients, accounting for calcium supplementation in the treatment group by adding 1000 mg to the average dietary calcium intake for each treated subject. Using this approach there was no significant correlation between oral calcium intake in the entire study population and any of the bone density measurement sites. Similarly, dietary vitamin D intake was homogeneous throughout the study. There was no correlation between oral vitamin D ingestion among all 17 patients and bone density outcome (with the addition of 6.25 μg to the daily intake of the patients receiving supplements).

Laboratory measurements

There were no significant differences in any of the laboratory measurements between the two groups at enrolment or at study end. No subjects at enrolment had low levels of serum calcium or either of the vitamin D metabolites. 24-h urinary calcium and creatinine clearance levels were not significantly different at study end compared with study entry. Although there were no significant differences between patient groups in terms of serum 25-OH-vitamin D or 1,25-$(OH)_2$-vitamin D levels, the placebo group showed a decline from study entry to study end in serum 25-OH-vitamin D levels from 33 ± 5 ng/mL to 20 ± 3 ng/mL ($P = 0.04$) and of serum 1,25-$(OH)_2$-vitamin D from 59 ± 6 pg/mL to 42 ± 4 pg/mL ($P = 0.05$). In the calcium group, osteocalcin levels remained elevated compared with the placebo group at all measurement intervals (in the calcium group: 8.2 ± 1.9 ng/mL at study entry and 11.9 ± 1.7 ng/mL at sudy end, and in the placebo group: 4.9 ± 1.4 ng/mL at study entry and 7.9 ± 1.4 ng/mL at study end). There was a significant inverse correlation between osteocalcin levels from all 17 patients at study entry and the corticosteroid dose in the year prior to the study ($R = -0.64$, $P = 0.02$). At study end there was a significant correlation between osteocalcin levels and the percentage change in spine bone density ($R = 0.59$, $P = 0.01$). At study end there was also a significant correlation between the percentage change in spine bone density and the level of 1,25-$(OH)_2$-vitamin D ($R = 0.54$, $P = 0.02$). Parathyroid hormone levels at study end significantly correlated with percentage change in the bone density at the hip ($R = 0.54$, $P = 0.03$) and at Ward's triangle ($R = 0.54$, $P = 0.02$). There was no significant difference in bone hormone measurements at study end comparing those patients who used corticosteroids during the study with those who did not.

DISCUSSION

This is the first randomized controlled study for the treatment of osteoporosis in patients with IBD. This study reaffirmed the high prevalence of diminished bone

density in corticosteroid-using patients with IBD. However, the bone density remained relatively stable in the study population when followed-up at 1 year despite ongoing corticosteroid use by half the enrolees. This suggests that there is some initial period of chronic corticosteroid use at which bone density diminishes, followed by relative stabilization of bone density. A recent study suggested that decreased bone density was only seen in patients with Crohn's disease at initial presentation.[3] In that study, bone density did not further diminish at 1 year follow-up, despite 87% of patients using corticosteroids. Others have shown a diminishing bone density over time.[16–18] A longitudinal study in 54 patients with IBD revealed an average bone density loss of 3% at 1 year,[16] however, this group did not find a correlation of diminished bone density with total corticosteroid dose. This same group reported that over a mean follow up period of nearly 8 years, bone density decreased to a greater extent than that which was expected with ageing in women but not in men.[17]

In our study, 13 of the 17 enrolees who completed the study had entry bone density measurement *T* scores at the spine that were < -1, 15 enrolees < -1 at the hip and 14 enrolees < -1 at Ward's triangle. These figures are slightly higher than the prevalence of that degree of diminished bone density than we have reported previously.[1] Another recent cross-sectional study, including both newly diagnosed patients and those with chronic disease, revealed a higher prevalence of diminished bone density in corticosteroid-using patients (52%) compared with nonusers (28%).[4] A prevalence of severely diminished bone density (*Z* score < 2) has been described in $\approx$ 30% of Crohn's disease and in $\approx$ 15–30% of patients with ulcerative colitis.[1, 5, 6] All three of these studies found a significant correlation between corticosteroid use and degree of bone density loss. A critical difference between our study and those previously reported[3–6, 17, 18] is that our patient population excluded peri- or post-menopausal females, and females using sex hormone therapy. Unexpectedly, our data came to represent that of mostly a male corticosteroid-using IBD population.

These data highlight that clinicians should be addressing the potential effects of these drugs on bones early in their administration. An obvious treatment approach might be the use of oral calcium supplementation with or without concomitant vitamin D supplementation, particularly since it is generally accepted that corticosteroids can interfere with intestinal calcium absorption.[19–21] Furthermore, it has been suggested that the current recommended daily calcium intakes of 800 mg/day are low, and that patients 18–30 years old should receive 1200 mg/day. Patients from 30 years old until the menopause should receive 1000 mg/day.[22] It has been shown that for post-menopausal females, each 400 mg/day increase in dietary calcium was associated with a 1.1% increase in distal radius bone mass.[23] Others have also shown the beneficial effects of calcium supplementation in post-menopausal females.[24–26] In general, a consensus is emerging, including that reported in a meta-analysis of calcium supplementation studies, that calcium supplementation is important.[27] It has been shown that increasing dietary calcium positively affected vertebral bone mass in 25–35-year-old females, and that calcium intake during early adulthood affects premenopausal bone density.[28–30] In 11 patients with IBD (eight of whom were using corticosteroids) it has been shown that after 1 year total body calcium measurements were decreased by 6.5%.[31] In 13 corticosteroid-treated patients there was a suggestion that an additional 1 g/day of elemental calcium over 2 months might be beneficial to bones since it increased urinary hydroxyproline levels.[32]

One group of investigators suggested that vitamin D supplementation should be considered in IBD since there was a high prevalence of decreased bone density in patients with Crohn's disease and low serum 25-OH-vitamin D levels.[33] While some groups have shown a positive effect of vitamin D administration on bone density in rheumatological patients,[34,35] others have found no beneficial effect.[36–38] Furthermore, 1,25-$(OH)_2$-vitamin D administration is associated with hypercalcemia in up to 31% of patients.[36] Others have shown a relative intestinal resistance to the actions of 1,25-$(OH)_2$-vitamin D.[20] Most of these vitamin D supplement studies included some post-menopausal women, which may have confounded the results. In IBD, the only study testing vitamin D administration randomized 60 patients with Crohn's disease to either vitamin D 1000 IU/day or to no treatment and found that vitamin D therapy may have benefited patients on corticosteroids ($P = 0.05$).[39]

This study failed to show a benefit of calcium supplementation with large enough doses to bring patients well into the high range of daily requirements and greater, over a 1-year period, on spinal, hip, or Ward's triangle bone density in corticosteroid-using males and premenopausal females with long-standing disease. Furthermore, no significant correlation was found between

bone density and the entire groups' oral calcium intake. Because the sample size of this study was small, it is possible that a type II statistical error has been made. It is notable that on average, bone density improved at all sites in the calcium group while remaining stable in the placebo group. The numbers in these preliminary data indicate that 172 patients would be required to show an effect size of largest difference being $d = 0.6$, with an experiment-wise $\alpha = 0.05$, $\beta = 0.10$, two-tailed. Furthermore, this study has not addressed the potential benefit of calcium supplementation on patients initiating therapy with corticosteroids, nor has it addressed any possible advantages of calcium supplementation over a longer period (i.e. 2 years).

Although calcium supplementation did not significantly improve bone density in our study, these data should not be used to ignore calcium intake in this group of patients. Patients with IBD may limit their dairy intake because of lactose intolerance as in Crohn's disease[40] or perceived lactose intolerance in ulcerative colitis.[41] It is intuitive that calcium intake must be maintained at a level of at least that of the current RDA. For these patients who are relatively young and have not reached their peak bone density, the RDA should probably be closer to 1500 mg/day.[42] Our data show that patients with IBD are, on average, consistently ingesting just at or slightly below the currently recommended levels of 800 mg/day. It is possible that since their dietary calcium is low, 1000 mg/day supplementation may be insufficient to have achieved any real beneficial effects. A similar study might be undertaken with calcium supplements of 2000 mg/day.

Vitamin D metabolite and PTH levels were normal in this study population and there was only a significant change of vitamin D metabolites seen in the placebo group over the course of the study. The lower osteocalcin levels seen in those who used higher doses of corticosteroids is not surprising. The increased levels of osteocalcin in the calcium group may reflect a direct change secondary to calcium, or a secondary change from the vitamin D supplement. The increased osteocalcin levels significantly correlated with bone density of the spine at study end. It is possible that increased calcium ingestion may enhance osteocalcin secretion and therefore, osteoblast function. Others have speculated that lower osteocalcin levels seen in patients with newly diagnosed IBD were secondary to the higher corticosteroid doses used in the those patients and to the higher level of disease activity.[4] It was suggested that a low osteocalcin level was a risk factor for diminished bone density, and by implication the finding of a low level should heighten the clinician's investigation of the patients' bone density. It remains to be proved how best to use osteocalcin measures clinically. In general, measuring vitamin D metabolites, PTH levels or serum calcium, magnesium or phosphate levels provided little insight into the status of diminished bone mass in this group of patients, even at times when there were marked bone density abnormalities.

SUMMARY

We found a high prevalence of moderately severe decreased bone density in corticosteroid-using patients with IBD. This study was performed in males and menstruating females, eliminating any confounding of the postmenopausal state. The dietary calcium intake of these patients was close to the current RDA for premenopausal, post-adolescent adults. Calcium carbonate supplementation with small extra doses of vitamin D conferred no obvious benefit in bone mass at the end of 1 year. Both treatment and placebo groups' bone density remained relatively stable at 1 year, suggesting that bone loss in corticosteroid-using patients may peak early into the use of the corticosteroids. It is possible that our study sample size was too small to detect a benefit of calcium use; however, based on these pilot data future investigations should explore other therapeutic avenues that may have greater effects of increasing bone density in patients who already have considerable bone density loss.

ACKNOWLEDGEMENT

This study was supported in part by PHS Grant no. MO1 RR00865. Calcium and placebo pills were provided by Marion Merrell Dow Inc (Kansas City, MO).

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