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BRIEF ARTICLE

Bones and Crohn's: No benefit of adding sodium fluoride or ibandronate to calcium and vitamin D

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Abstract

AIM: To compare the effect of calcium and cholecalciferol alone and along with additional sodium fluoride or ibandronate on bone mineral density (BMD) and fractures in patients with Crohn's disease (CD).

METHODS: Patients (n =148) with reduced BMD (T-score < -1) were randomized to receive cholecalciferol (1000 IU) and calcium citrate (800 mg) daily alone(group A, n = 32) or along with additional sodium fluoride (25 mg *bid*) (group B, n = 62) or additional ibandronate (1 mg iv/3-monthly) (group C, n = 54). Dual energy X-ray absorptiometry of the lumbar spine (L1-L4) and proximal right femur and X-rays of the spine were performed at baseline and after 1.0, 2.25 and 3.5 years. Fracture-assessment included visual reading of X-rays and quantitative morphometry of vertebral bodies (T4-L4).

RESULTS: One hundred and twenty three (83.1%) patients completed the first year for intention-to-treat (ITT) analysis. Ninety two (62.2%) patients completed the second year and 71 (47.8%) the third year available for per-protocol (PP) analysis. With a significant increase in T-score of the lumbar spine by +0.28 ± 0.35 [95% confidence interval (CI): 0.162-0.460, P < 0.01], +0.33 ± 0.49 (95% CI: 0.109-0.558, P < 0.01), +0.43 ± 0.47 (95% CI: 0.147-0.708, P < 0.01) in group A, +0.22 ± 0.33 (95% CI: 0.125-0.321, P < 0.01); +0.47 ± 0.60 (95% CI: 0.262-0.676, P < 0.01), +0.51 ± 0.44 (95% CI: 0.338-0.682, P < 0.01) in group B and +0.22 ± 0.38 (95% CI: 0.111-0.329, P < 0.01), +0.36 ± 0.53 (95% CI: 0.147-0.578, P < 0.01), +0.41 ± 0.48 (95% CI: 0.238-0.576, P < 0.01) in group C, respectively, during the 1.0, 2.25 and 3.5 year periods (PP analysis), no treatment regimen was superior in any in- or between-group analyses. In the ITT analysis, similar results in all in- and between-group analyses with a significant in-group but non-significant between-group increase in T-score of the lumbar spine by 0.38 ± 0.46 (group A, P < 0.01), 0.37 ± 0.50 (group B, P < 0.01) and 0.35 ± 0.49 (group C, P < 0.01) was observed. Follow-up in ITT analysis was still 2.65 years. One vertebral fracture in the sodium fluoride group was detected. Study medication was safe and well tolerated.

CONCLUSION: Additional sodium fluoride or ibandronate had no benefit over calcium and cholecalciferol alone in managing reduced BMD in CD.

Key words: Crohn's disease; Bone mineral density; Vertebral fracture; Cholecalciferol; Calcium; Ibandronate; Sodium fluoride

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INTRODUCTION

Inflammatory bowel disease (IBD) patients are at risk of reduced bone mineral density (BMD), especially in Crohn's disease (CD)[1-5]. Genetic, endocrine, metabolic and nutritional factors contribute to CD-associated osteoporosis, and inflammation *per se* may exert an important risk since inflammatory mediators such as the pro-inflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-1β or IL-6 and other TNF-related cytokines such as receptor activator of nuclear factor κB (RANK) and its ligand, RANKL or osteoprotegerin, are directly involved in the disease process[6-13].

The prevalence of a reduced BMD in IBD patients is up to 38% with some 15% suffering from osteoporosis[1-5,7]. Thus, of approximately 300 000 patients with IBD in Germany[14], up to 45 000 may have an increased fracture risk. The high prevalence of up to 21.7% in osteoporosis-related vertebral fractures is of clinical relevance[1,2,15-18].

Different strategies to improve BMD and to prevent osteoporosis-related fractures have been examined. Hormone replacement therapy (HRT) and bisphosphonates are established in postmenopausal osteoporosis and bisphosphonates in steroid-induced osteoporosis[19-21]. In particular, the efficacy of bisphosphonates has received special interest in large clinical trials[22-24]. Bisphosphonates have reduced the fracture risk considerably in patients with postmenopausal osteoporosis[25,26]. Sodium fluoride can also increase BMD but its efficacy in reducing fractures remains controversial[27-29].

To this day, few studies have evaluated the management of reduced BMD in IBD patients. Calcium and vitamin D administration can inhibit the rate of bone loss[30]. HRT is an effective treatment to prevent bone loss in postmenopausal women with CD[31]. In a previous study, we demonstrated the efficacy of sodium fluoride in increasing BMD in CD patients[32]. Other studies reported a significant increase in BMD with the administration of iv pamidronate (30 mg every 3 mo)[33], alendronate (10 mg/d)[34] or etidronate periodically (400 mg orally for 14 d)[35]. However, the primary end-point in all studies was BMD and only small cohorts with limited follow-up were investigated; the prevalence and incidence of vertebral fractures was not evaluated.

Our aim was to assess the effectiveness of cholecalciferol and calcium alone or with additional sodium fluoride or ibandronate in a larger CD patient population and longer follow-up period. The primary endpoint was to assess the efficacy of the 3 therapeutic approaches to improve BMD (in-group change). Secondary endpoints were to compare the 3 therapies for the best improvement in BMD (between-group change), fracture rate and safety.

MATERIALS AND METHODS

Patients

The 148 randomized outpatients had a diagnosis of CD based on histological, endoscopic, radiological or clinical criteria and a reduced BMD of the lumbar spine: T-score < -1, i.e. osteopenia according to World Health Organization (WHO) criteria as published in 1994[36]. Disease-related data on previous and current state of health were recorded using a standardized questionnaire throughout the study including adverse effects and serious adverse effects reporting. Disease activity was estimated using the CD activity index (CDAI)[37]. Cumulative lifetime steroid-dose was estimated and expressed in grams of prednisolone equivalent. Nutritional status was assessed by body mass index (BMI). Exclusion criteria included: age < 18 years, chronic renal insufficiency (creatinine > 1.5 mg/dL), known primary hypo- or hyperparathyroidism, untreated thyroid disease, and any known medication, e.g. previous treatment with either sodium fluoride or bisphosphonates, or a condition affecting BMD other than glucocorticoid therapy. None of the patients was pregnant and female patients planning pregnancy were excluded.

Ethics

The study was approved by the Ethics Committee of the University of Ulm/Germany, and conducted in accordance with the 1975 Helsinki Declaration, as revised in 1983. All participants gave written informed consent before inclusion.

Protocol, assignment and masking

Patients were randomized to treatment group A, B or C, taking study medication as follows: (1) 1000 IU cholecalciferol (Vigantoletten®, Merck, Darmstadt, Germany) and 800 mg calcium citrate (Calcitrat®, Merckle, Ulm, Germany) daily (group A); (2) additional 25 mg of slow-release sodium fluoride (Nafril®, Merckle, Ulm, Germany) *bid* (group B); and (3) additional ibandronate 1 mg iv 3-monthly (Bondronat®, Roche, Basle, Switzerland) (group C). A random 1:2 allocation sequence, basic cholecalciferol and calcium (A) and additional sodium fluoride or additional ibandronate (B or C), was computer-generated and the sequences were concealed until intervention was assigned. Baseline examination included dual energy X-ray absorptiometry (DXA) of the spine and femur and plain radiographic imaging of the thoracic and lumbar spine in 2 planes. Follow-up examinations were conducted at 3-mo intervals. In group B, sodium fluoride was taken daily for 12 mo, followed by a 3-mo fluoride-free period. The second and third 12-mo cycle started at month 15 and 30. Follow-up DXA and plain radiography of the spine were performed after 12, 27 and 42 mo, i.e. 1.0, 2.25 and 3.5 years. With the last patient in study in June 2005, this patient completed the 3.5-year study period in January 2009 (last patient out).

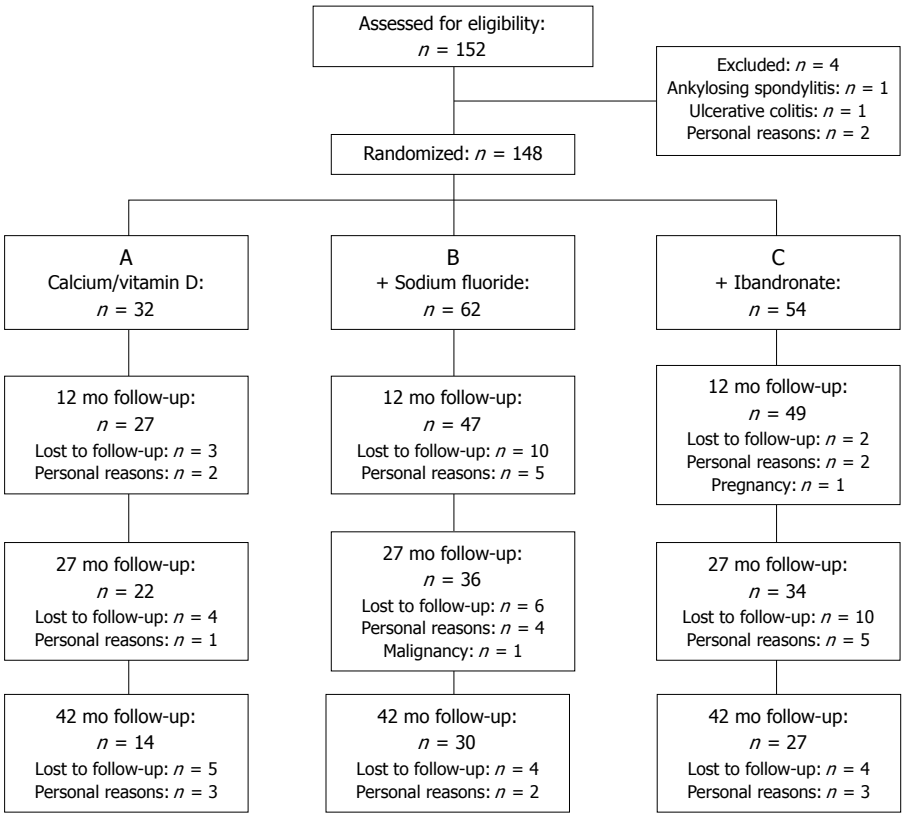

Figure 1 CONSORT diagram.

Bone densitometry

BMD of the spine (L1-L4) was assessed by DXA (Hologic QDR1000, Hologic Inc., Waltham/MA). At the proximal right femur, 4 sites (femoral neck, trochanter and intertrochanteric area, Ward's triangle) were measured; an average (total femur) was obtained from the first 3 sites. Average BMD values for L1-L4 and total femur were used for calculations. The manuacturer supplied the normal values. BMD was expressed as absolute values (g/cm^2) and as number of standard deviations from the peak bone mass of a young adult gender-matched reference population (T-score). According to the WHO recommendation for postmenopausal women as published in 1994, reduced BMD was defined as a T-score < -1.0[36]. Patients with e.g. major sclerosis of the aorta, osteophytes and scoliosis on X-rays precluding accurate measurements of lumbar BMD by DXA were excluded.

Quantitative morphometry

Morphometric methods have been developed for standardized assessment of vertebral deformities in studies of spinal osteoporosis[38]. The use of a fixed percentage reduction in vertebral height is the simplest and most practical method to study vertebral deformities[39]. In this study, visual reading of X-rays and the quantitative morphometry (QM) of the vertebral bodies were standardized according to criteria of the European Vertebral Osteoporosis Study[40]; only the threshold value was set from 25% to 20%. QM was performed using 6-point digitization to calculate the anterior (Ha), mid (Hm), and posterior (Hp) height of the vertebral bodies T4-L4 (Figure 1). A vertebra was classified deformed if at least one ratio (Ha/Hp, Hm/Hp, Hp/Hp-up and Hp/Hp-low) was below the threshold value. For every vertebra considered deformed quantitatively, a radiological differential diagnosis was performed for the etiology, distinguishing osteoporotic, degenerative, traumatic and other reasons. Differential diagnosis prevents overestimation of prevalent osteoporotic fractures due to deformations of other etiology, since 45.9% and 30.9% of spinal deformities in men and women are reported to be of non-osteoporotic origin[41].

Laboratory testing

A patient's hematocrit was determined for the calculation of the CDAI, and other inflammation-related parameters [leukocytes, platelets, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] were obtained. Regarding bone metabolism, we focused on calcium phosphate homeostasis and investigated calcium and phosphate as well as the 25(OH)- and 1,25(OH)$_2$-vitamin-D$_3$ serum levels and parathyroid hormone. All laboratory tests were performed in the DIN EN ISO 15189:2007 accredited "Zentrale Einrichtung Klinische Chemie" of the University Hospital of Ulm, Germany. Laboratory technology and standard values can be checked at http://www.uniklinik-ulm.de/index.php?id=1159.

Statistical analysis

Results are presented as mean ± SD. Qualitative variables were expressed as frequencies and percentage. The Mann-

Whitney rank sum test was used to test the effect of each therapy on BMD and biochemical markers after 12, 27 and 42 mo compared to baseline. The Student *t*-test for unpaired observations was used to compare between-group differences. Intention-to-treat (ITT) analysis was performed for all patients with at least one DXA during follow-up. Two-tailed tests for significance were used in the statistical analyses and $P \leqslant 0.05$ was considered significant. The Statistical Package SAS V6.11 was used for analysis.

RESULTS

Participant flow and follow-up

The CONSORT diagram shows the number of patients randomly assigned and receiving intended treatment, the patient flow through each year of the study, the number completing the study protocol, and the number analyzed for the primary outcome (Figure 1). One hundred and forty-eight patients with a T-score < -1.0 were ITT analysis, 92 (62.2%) completed the 27-mo and 71 (47.8%) the 42-mo study period and were available for per-protocol (PP) analysis. Reasons for withdrawal were failure to attend follow-up [48 patients (32.4%)] and personal reasons [27 patients (18.2%), withdrawal of written informed consent ($n = 7$), referred to primary care ($n = 10$), moving house ($n = 7$), unknown ($n = 3$)]. One patient was excluded due to a malignancy (testicular cancer), retrospectively present before randomization; he recovered completely.

Baseline characteristics

Baseline characteristics of the patients are given in Table 1. With a 1:2 random allocation to treatment groups, group A was smaller compared to group B or C. BMD was slightly but non significantly higher in group A. Patients in group A were a little younger than in group B ($P = 0.3$) and C ($P = 0.06$). No further differences in baseline characteristics were observed.

BMD of the spine, in-group change

In group A, BMD of the spine increased continually during the 1.0, 2.25 and 3.5-year study period (Table 2, Figure 2). In group B, lumbar BMD increased during the 1.0 and 2.25-year period, and in the third year, a further but non significant increase was observed (Table 2, Figure 2). In group C, BMD of the spine increased continually during the 1.0, 2.25 and 3.5-year period, again with the greatest increases in the first and second year (Table 2, Figure 2).

BMD of the spine, compared between-groups

Comparing the increase in lumbar spine BMD of the groups A, B and C at 1.0, 2.25 and 3.5 years, no group revealed superior results. There was no difference for group B receiving added sodium fluoride or for group C receiving added ibandronate in comparison with group A receiving only cholecalciferol and calcium citrate nor was there a significant difference in the comparison of groups B and C at any time in the 3.5-year study period (Table 2, Figure 2).

Table 1 Baseline characteristics (mean ± SD) *n* (%)

	Group A calcium/ vitamin D	Group $B_{0/1}$ + sodium fluoride	Group $C_{0/1}$ + ibandronate
No. of patients	32	62	54
Male/female	14/18	29/33	27/27
Age (yr)	33.8 ± 9.76	35.7 ± 12.8	36.8 ± 13.1
Duration of disease (yr)	7.4 ± 1.7	9.4 ± 2.1	8.1 ± 1.9
Smoking	13 (40.6)	23 (37.1)	19 (35.2)
Postmenopausal	0	2	1
Extent of disease			
Ileal disease	11 (34.4)	20 (32.3)	21 (38.9)
Colonic disease	5 (15.6)	8 (12.9)	7 (13)
Ileocolonic disease	16 (50.0)	34 (54.8)	26 (48.1)
Bowel resection			
No bowel resection	18 (56.2)	39 (62.9)	29 (53.7)
Ileal resection	8 (25.0)	12 (19.4)	14 (25.9)
Colonic resection	2 (6.2)	5 (8.1)	4 (7.4)
Ileocolonic resection	4 (12.6)	6 (9.7)	7 (13)
Patients with bowel resection during study	4	6	5
Use of corticosteroids			
No previous use	3 (9.4)	6 (9.7)	6 (11.1)
Cumulative dose < 10 g	22 (68.8)	36 (58.1)	34 (63)
Cumulative dose > 10 g	7 (21.8)	28 (32.2)	14 (25.9)
Body weight (kg)	69.4 ± 15.51	63.71 ± 11.9	64.8 ± 13.91
Body height (cm)	172 ± 7.63	170 ± 8.8	170 ± 9.0
BMI (kg/m^2)	23.54 ± 5.34	22.01 ± 3.6	22. 4 ± 3.92
CDAI	141.5 ± 100.96	145 ± 95.5	135.9 ± 85.03
T-score spine	-1.57 ± 0.31	-1.82 ± 0.75	-1.89 ± 0.71
BMD spine (g/cm^2)	0.90 ± 0.04	0.87 ± 0.09	0.85 ± 0.08
Pre-existing vertebral fractures[1]	6 (22.2) of patients with 10 fractures	9 (19.2) of patients with 18 fractures	14 (28.6) of patients with 28 fractures

[1]Intention to treat (ITT) analysis. BMI: Body mass index; CDAI: Crohn's disease activity index; BMD: Bone mineral density.

BMD of the femur, in-group change and compared between-groups

There was no significant change in femur BMD in any of the 3 groups during the entire follow-up period, and no significant differences between groups A, B and C at 1.0, 2.25 and 3.5-year follow-up in the change in femur BMD (data not shown).

BMD of the spine (ITT)

A pre-planned ITT analysis was performed. As in PP analysis, comparing the increase in BMD in in- and between-group A, B and C analysis, cholecalciferol and calcium alone did not perform any worse than with additional sodium fluoride or ibandronate, and no group revealed superior results (Table 3, Figure 3) Mean observation time in the ITT analysis was 2.65 years.

Prevalence and incidence of vertebral fractures

For assessment of prevalent fractures and fracture incidence, the ITT population was analyzed, i.e. 123 (83.1%) patients who completed at least the first 12-mo follow-up. The duration of follow-up did not differ significantly for the treatment groups A, B and C. At baseline, a total of 56 vertebral fractures was seen in 29 (23.6%) of 123 patients,

Table 2 Bone mineral density of spine and femur, in- and between-group change

Lumbar spine		Baseline	First year	Second year	Third year
Group A	*n* (%)	32	27 (84.4)	22 (68.6)	14 (43.8)
calcium/vitamin D	T-score	-1.57 ± 0.31	-1.32 ± 0.42[b]	-1.21 ± 0.49[b]	-1.18 ± 0.36[b]
	Δ T-score (95% CI)		+0.28 ± 0.35 (0.162–0.460)	+0.33 ± 0.49 (0.109-0.558)	+0.43 ± 0.47 (0.147–0.708)
	BMD	0.90 ± 0.04	0.92 ± 0.05	0.94 ± 0.05	0.94 ± 0.04
Group B	*n* (%)	62	47 (75.8)	36 (58.0)	30 (48.4)
+ sodium fluoride	T-score	-1.82 ± 0.75[h]	-1.60 ± 0.84[d]	-1.40 ± 1.01[d]	-1.37 ± 0.95[d]
	Δ T-score (95% CI)		+0.22 ± 0.33 (0.125–0.321)	+0.47 ± 0.60 (0.262–0.676)	+0.51 ± 0.44 (0.338–0.682)
	BMD	0.87 ± 0.08	0.88 ± 0.09	0.90 ± 0.11	0.91 ± 0.11
Group C	*n* (%)	54	49 (90.1)	34 (63.0)	27 (50)
+ ibandronate	T-score	-1.89 ± 0.71	-1.69 ± 0.78[e]	-1.61 ± 0.83[e]	-1.56 ± 0.78[f]
	Δ T-score (95% CI)		+0.22 ± 0.38 (0.111– 0.329)	+0.36 ± 0.53 (0.147–0.578)	+0.41 ± 0.48 (0.238–0.576)
	BMD	0.85 ± 0.08	0.87 ± 0.08	0.89 ± 0.08	0.90 ± 0.08
Total	*n* (%)	148	123 (83.1)	92 (62.2)	71 (47.8)

In-treatment group change, baseline to first, second and third year: Group A, [b]$P < 0.01$; group B, [d]$P < 0.01$; group C, [e]$P < 0.025$, [f]$P < 0.01$; Between-treatment groups: [h]$P < 0.01$, group A *vs* group C. BMD: Bone mineral density.

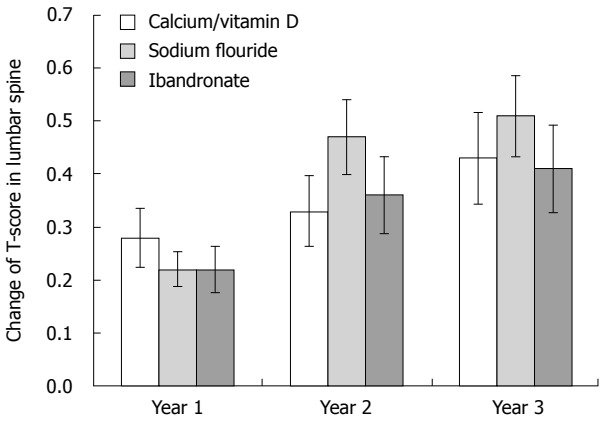

Figure 2 Change in T-score of the lumbar spine from baseline to first, second and third study year, during the 3.5-year long-term study in treatment groups A, B or C, in the per protocol population.

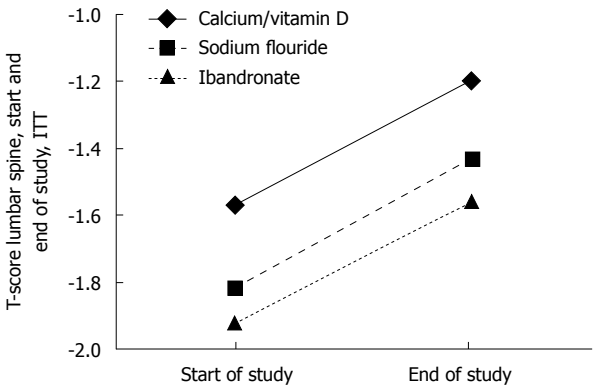

Figure 3 T-score of the lumbar spine from baseline to end of study depending in treatment groups A, B or C, in the intention to treat population. ITT: Intention-to-treat.

and one incident vertebral fracture in group B receiving sodium fluoride, but no other fractures, e.g. fractures of the hip or radius, was observed during the entire follow-up (Table 4).

Table 3 Bone mineral density of the lumbar spine, in- and between-group change (intention-to-treat)

Lumbar spine	Baseline	End of study	Δ
Group A (*n* = 27)			
T-score	-1.57 ± 0.31	-1.20 ± 0.46[b]	+0.38 ± 0.46
BMD	0.9 ± 0.04	0.94 ± 0.06	+0.04 ± 0.05
Follow-up (yr)		2.58 ± 1.0	
Group B (*n* = 47)			
T-score	-1.82 ± 0.40	-1.43 ± 0.62[b]	+0.37 ± 0.50
BMD	0.87 ± 0.05	0.91 ± 0.06	+0.04 ± 0.05
Follow-up (yr)		2.92 ± 0.89	
Group C (*n* = 49)			
T-score	-1.91 ± 0.40	-1.56 ± 0.56[b]	+0.35 ± 0.49
BMD	0.86 ± 0.04	0.90 ± 0.66	+0.04 ± 0.05
Follow-up (yr)		2.44 ± 1.17	

[b]$P < 0.01$. BMD: Bone mineral density.

Clinical course of the underlying CD and change in BMD

Seventy (57%) of the 123 patients who completed at least the first 12-mo study period were treated with systemic glucocorticoids at least once during the study, as reported in the standardized questionnaire completed at every follow-up examination at 3-mo intervals. Change in spine and femur BMD did not differ from the change observed in patients who had not received any systemic steroids (data not shown). While a slight increase in BMI and an improvement in CDAI was observed during the study period with no significant differences in and between the 3 treatment groups, the increase in BMI and the decrease in CDAI again did not correlate with the change in spine and femur BMD in all patients (data not shown).

Laboratory markers and change in BMD

No significant difference in inflammation parameters (leukocytes, platelets, ESR, CRP) were obtained in and between the groups A, B and C. Focusing on calcium-phosphate-homeostasis we investigated calcium and phosphate as well as the 25(OH)- and 1,25(OH)$_2$-vitamin-D$_3$ serum levels

Table 4 Prevalence and incidence of vertebral fractures

	All patients	Group A calcium/vitamin D	Group B + sodium fluoride	Group C + ibandronate
No. of patients	123	27	47	49
Patients with fractures, *n* (%)	29 (23.6)	6 (22.2)	9 (19.2)	14 (28.6)
No. of fractures	56	10	18	28
New fractures (*n*)	1	0	1	0
T-score lumbar spine	-1.80 ± 0.34	-1.57 ± 0.31	-1.82 ± 0.40	-1.91 ± 0.04
BMD lumbar spine (g/cm^2)	0.87 ± 0.05	0.90 ± 0.04	0.87 ± 0.05	-0.86 ± 0.04
Follow-up (yr)	2.65 ± 1.00	2.58 ± 1.00	2.92 ± 0.89	2.44 ± 1.17

BMD: Bone mineral density.

and parathyroid hormone. Only 25(OH)-vitamin-D$_3$ serum levels increased significantly in all 3 groups over time, but no change was seen in the other calcium phosphate homeostasis parameters investigated. No correlation of any serum levels of any parameter of calcium phosphate homeostasis with BMD or change in the BMD of the spine or femur could be observed (data not shown).

Adverse events

Adverse events (AEs) were reported in the standardized questionnaire used throughout the study at every 3-mo follow-up examination. AEs occurred in 35 patients (9 in group A; 14 in group B; 12 in group C). Most AEs were related to worsening of CD (28 patients), with 15 patients who had a bowel resection during study follow-up. One patient in the ibandronate group had to be withdrawn due to pregnancy (Figure 1). Study medication was generally well tolerated. Seven patients reported undigested calcium citrate and 2 undigested sodium fluoride pills in their feces. Six patients reported minor and completely reversible bone pain (< 2 h) or flu-like symptoms after intravenous infusion of ibandronate, manageable with acetaminophen if needed.

DISCUSSION

This is one of the most extended studies in the management of reduced BMD in CD. In our randomized study, we compared the effectiveness of cholecalciferol and calcium supplementation alone or along with additional sodium fluoride or additional ibandronate. More than 140 CD patients with reduced BMD (T-score < -1) were included in this study with a maximum follow-up of 3.5 years. In this young CD patient setting, increases in BMD were similar in all in- and between-treatment-group analyses, calcium and cholecalciferol supplementation not only prevented further bone loss but increased lumbar BMD and the effect was not increased further by addition of sodium fluoride or ibandronate. Regarding the prevention of fractures, the overall fracture rate in this study was too small to demonstrate between-group differences.

There were a number of limitations with the design of our study that could affect the interpretation of results. First, the study was not placebo-controlled nor blinded, and the dropout rate was high particularly after the first year. For ethical reasons we decided not to deny a basic therapeutic regimen with cholecalciferol and calcium to any patient with reduced BMD. Unfortunately, it is a flaw of the study design that there was therefore no placebo or simple observation arm. Also, by using a blinded study comparing an oral *vs* iv administrated study drug, a single tertiary outpatient clinic such as ours doing an investigator initiated trial as large as this would just be overworked. The dropout rate after the first year and only about 50% of patients completing the study reflects again the setting of our tertiary outpatient clinic where patients usually only show up if a primary or secondary health care center refer them for special reasons and problems. To manage this and to avoid misleading results we did the pre-planned ITT analysis, and found no difference in the results compared to PP analysis in- and between-group analyses and with a mean observation time of 2.65 years, which was still longer than any follow-up in the CD patient setting before.

Oral treatment of osteoporosis with bisphosphonates relies on compliance and the absorption is low, probably especially in CD patients. When we planned this study, ibandronate was the only bisphosphonate to be administered safely as an iv bolus injection, and therefore offered an interesting alternative suitable for outpatient treatment[42]. At that time, data of a study investigating 3-monthly iv injections of ibandronate in the treatment of postmenopausal osteoporosis were published, and treatment was reported to be safe and effective with a dose of 1 mg[43]. This is why we had a 1 mg ibandronate 3-monthly iv intervention arm in our study. A recent meta-analysis pooled data from 4 phase Ⅲ clinical trials to assess the relationship between ibandronate dose, changes in BMD, and rates of fractures. Lumbar spine BMD increased with increasing ibandronate dose and the incidence of fractures decreased as lumbar BMD increased. The pooled data pointed out the effectiveness of ibandronate to increase BMD and decrease fracture rate[44]. In our predominantly young CD patient setting, the increase in lumbar BMD with 1 mg 3-monthly iv dosing equaled the efficacy of ibandronate for the treatment of postmenopausal osteoporosis, and the overall increase in BMD in our CD patient setting was as good as with higher doses in postmenopausal osteoporosis[43,44].

When we planned this study, the discussion whether sodium fluoride can not only increase BMD but also prevent fractures was still open, and based on our pilot study we decided to have again a sodium fluoride intervention

arm. Here, the increase in lumbar BMD was somewhat less than in our pilot studies[32,45]. In both, serum fluoride at 0, 6 and 12 mo was in the effective range of 0.095-0.19 mg/L[46]. Nevertheless, the difference was most probably due to the lower sodium fluoride dose in the present study (50 mg *vs* 75 mg) which we chose based on an investigation using the same 50 mg dose and slow-release formula in postmenopausal women reporting an increase in BMD of 4%-5% per year[27]. There remains little information available on sodium fluoride and fracture rate and therefore the efficacy of sodium fluoride in preventing fractures remains controversial[27,28]. Nevertheless, Rubin has reported the efficacy of slow-release sodium fluoride in the prevention of vertebral fractures in postmenopausal osteoporosis[29]. In our study, only one incident vertebral fracture was diagnosed in the sodium fluoride group. With the scientific interest focused on bisphosphonates, this question will be left open and up to now, sodium fluoride is not approved for the treatment of osteoporosis, if any, in most countries..

To this day, some other studies have evaluated the management of osteoporosis in CD, most using bisphosphonates. The primary end-point in all these studies was BMD and none reported the prevalence and incidence of fractures. Haderslev *et al*[34] examined in a 12-mo double-blind, randomized, placebo-controlled trial the effect of 10 mg alendronate daily and reported a significant increase in lumbar BMD compared to placebo. Bartram *et al*[33]. reported an increase in BMD within 1 year with either a daily dose of 500 mg calcium and 400 IU vitamin D alone or with 3-monthly infusions of 30 mg pamidronate. The gain in BMD was a little more pronounced in the pamidronate group Siffledeen *et al*[35] reported a randomized trial of etidronate (400 mg orally) or not for 14 d and 500 mg calcium and 400 IU vitamin D for 76 d. This cycle was repeated 8 times. BMD significantly increased in both the etidronate- and the non-etidronate-treated groups.

Only a minority of recently diagnosed IBD patients had optimal serum 25-hydroxyvitamin-D_3 levels and serum 25-hydroxyvitamin-D_3 was positively correlated with baseline BMD of the lumbar spine, total hip, and total body, in a study by Leslie *et al*[13]. Therefore, optimization of vitamin D may play an important role in preventing IBD-related bone disease[13]. Vogelsang *et al*[30] prevented BMD loss in CD patients by long-term vitamin D supplementation. Increases in BMD were especially prevalent among patients who had normal serum levels of 25-hydroxyvitamin-D_3 (68%), whereas increases occurred in only 18% of patients with low serum levels of 25-hydroxyvitamin-D_3.

Our study in CD patients with reduced BMD (T-score < -1, i.e. osteopenia according to WHO criteria as published in 1994[36]) confirmed for the first time that the safe and well tolerated cholecalciferol and calcium supplementation alone not only prevented further bone loss but increased BMD of the lumbar spine for the better. Additional sodium fluoride or ibandronate had no benefit over cholecalciferol and calcium alone in managing reduced BMD. CD patients may take cholecalciferol and calcium first, and only add optional bisphosphonates, first and foremost in patients with reduced BMD and prevalent fractures, taking into account all the data on bisphosphonates and fracture rate in postmenopausal osteoporosis which we still do not have for CD. Our results support the common clinical practice reported with the implementation of the American College of Gastroenterology and American Gastroenterology Association osteoporosis screening guidelines in inflammatory bowel disease[47], with specific therapies based on DXA findings initiated in 69% of patients: oral calcium and vitamin D supplementation in 69% and bisphosphonates in 20%[48].

COMMENTS

Background

Reduced bone mineral density (BMD) commonly afflicts patients with Crohn's disease (CD). Many facts link the 2 states together. With reduced BMD, the fracture risk increases.

Research frontiers

In postmenopausal women, therapy for reduced BMD is well established, but not in CD. In postmenopausal women, the standard of care is bisphosphonates. In CD, this question is still open. In this study, the authors test the effectiveness and safety of basic cholecalciferol and calcium supplementation alone or along with oral sodium fluoride or intravenous ibandronate to improve BMD compared to baseline.

Innovations and breakthroughs

In this study, sodium fluoride or ibandronate had no added benefit over basic cholecalciferol and calcium supplementation alone in increasing BMD in patients with CD and reduced BMD at baseline. One vertebral fracture in the sodium fluoride group was not sufficient to suggest a difference between groups. The study medication was safe and well tolerated.

Applications

In CD patients with reduced BMD, cholecalciferol and calcium supplementation is common clinical practice. Our data support this approach to improve bone BMD in CD patients.

Peer review

This is an interesting paper for readers.

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