ORIGINAL ARTICLE

# Treatment of bone loss in osteopenic patients with Crohn's disease: a double-blind, randomised trial of oral risedronate 35 mg once weekly or placebo, concomitant with calcium and vitamin D supplementation

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## ABSTRACT

**Objective** Osteoporosis and fractures are frequently encountered in patients with Crohn's disease. In order to prevent fractures, treatment with bone protecting drugs appears warranted early in the course of bone disease when bone loss is not yet prominent. We therefore aimed to demonstrate a beneficial effect on bone density of the bisphosphonate risedronate in osteopenic Crohn's disease patients.

**Methods** This double-blind, placebo-controlled randomised trial of risedronate with calcium and vitamin D supplementation was performed in osteopenic Crohn's disease patients. Patients were treated for 2 years with follow-up after 3 and after every 6 months. Disease characteristics and activity and bone turnover markers were assessed at all visits; dual x-ray absorptiometry was performed at baseline, 12 and 24 months; radiographs of the spine at baseline and 24 months.

**Results** Of 132 consenting patients, 131 were randomised (67 placebo and 64 risedronate). Patient characteristics were similar in both groups, although the risedronate group was slightly heavier (body mass index 24.3 vs 23.0 kg/m$^2$). Bone mineral density at lumbar spine increased 0.04 g/cm$^2$ on average in the risedronate group versus 0.01 g/cm$^2$ in the placebo group (p=0.007). The mean increase in total hip bone mineral density was 0.03 versus 0.01 g/cm$^2$, respectively (p=0.071). Fracture prevalence and incidence were similar. Change of T-scores and concentrations of bone turnover markers were consistent with a beneficial effect of risedronate when compared with placebo. The effect of risedronate was primarily demonstrated in the first 12 months of treatment. No serious unexpected suspected adverse events were observed.

**Conclusions** A 24-month treatment course with risedronate 35 mg once weekly, concomitant with calcium and vitamin D supplementation, in osteopenic Crohn's disease patients improved bone density at lumbar spine.

NTR 163 Dutch Trial Register.

## Significance of this study

### What is already known on this subject?

- Bone loss is a feature of Crohn's disease, leading to osteoporosis and bone fractures, occurring also at a relatively young age.
- Treatment of Crohn's disease-associated bone loss is primarily based on findings in senile osteoporosis.
- Bisphosphonates are beneficial in treating (senile) osteoporosis.

### What are new findings?

- Early treatment of osteopenia in Crohn's disease patients improves bone density.
- Medical treatment with 35 mg risedronate orally, once weekly, has a more beneficial effect on bone density in osteopenic Crohn's disease patients than supplementation of calcium and vitamin D alone.
- Treatment effects of risedronate were mainly observed in the first 12 months of treatment in this 24-month randomised trial.

### How might it impact on clinical practice in the foreseeable future?

- Early treatment of decreased bone mineral density (thus, osteopenia) in relatively young Crohn's disease patients by risedronate once weekly improves bone density, which may decrease the incidence of osteoporosis-associated bone fractures occurring at a more mature age, a hypothesis to be substantiated by formal study.

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## INTRODUCTION

Crohn's disease (CD) is associated with a decreased bone mineral density (BMD) and causes bone loss,

osteoporosis and fractures.[1–4] In CD, the prevalence of osteopenia (−2.5 <T-score <−1) has been reported to be as high as 50% in specific subpopulations, and osteoporosis (T-score ≤−2.5) is encountered in up to 30% of patients.[5] A number of longitudinal studies concerning BMD in IBD patients have confirmed these results; however, a significant heterogeneity in the rate of bone loss has been observed. Overall, incidence and prevalence of low bone mass are high in IBD, as has been documented in the Netherlands as well.[6] Importantly, this bone loss is associated with an increased fracture rate in IBD patients, necessitating preventative therapeutic strategies.[1 3 7–9]

Risk factors for decreased bone mass in general comprise genetic factors leading to low peak bone mass, low body mass index (BMI), hypogonadism, other hormonal factors, immobility and smoking habits. In IBD, additional factors are considered to contribute to excessive bone loss including malabsorption and vitamin D deficiency, (terminal) ileum resection, disturbances of calcium homeostasis, drug use, in particular glucocorticoids, but most of all, ongoing chronic (intestinal) inflammation.[4 10–12]

The pathogenesis of bone loss and subsequent osteoporosis in patients with CD is complex and differs from decreased bone mass as a result of the ageing process.[4 5 10] This has recently been underlined by description of the histomorphometric characteristics of patients with quiescent CD in which reduction in bone mass due to trabecular thinning and reduced bone formation (as a consequence of reduced osteocyte viability) were specific for CD-associated bone loss.[13]

Early interventions to treat active CD and preventative treatment strategies to reduce excessive bone loss might prevent long term consequences of bone loss, including fractures. Risedronate, a bisphosphonate, improves bone quantity and quality in osteoporosis. To date, risedronate is globally approved in the treatment of postmenopausal osteoporosis to reduce the risk of fractures and in osteoporosis in men at high risk of fractures. We conducted a double-blind, randomised trial to assess the effects of early therapeutic intervention to protect bone mass by means of early treatment with risedronate in CD patients at risk, defined as CD patients with osteopenia in this study.

## METHODS

### Patients

A multicentre, prospective, double-blind, placebo-controlled trial was conducted in eight large IBD referral centres in The Netherlands. Eligible patients were recruited from these hospitals comprising of seven out of the eight Dutch academic medical centres, joined together in a national consortium for IBD research, the Initiative on Crohn and Colitis, and one large regional referral hospital (Medical Spectrum Twente, Enschede).

Patients provided written informed consent before any study procedure was conducted. They were included if they had established quiescent CD by standard clinical, histological, and endoscopic criteria and osteopenia. Osteopenia was defined as per usual WHO criteria, that is, a T-score value between −1.0 and −2.5 as assessed by standard dual x-ray absorptiometry (DXA) from lumbar spine or total hip.[14] Disease activity was assessed by Crohn's Disease Activity Index (CDAI) and C reactive protein (CRP) concentration. A CDAI <220 and CRP <10 mg/L were considered to represent quiescent CD.

Patients were between 18 and 70 years of age. No glucocorticoid therapy (more than 7.5 mg prednisolone-equivalent daily) was allowed in the 3 months prior to screening or during the screening phase, and use of bisphosphonates was disallowed for 12 months prior to study. In addition, patients with malabsorptive syndromes and patients with documented diseases with an impact on bone metabolism or medication specifically aimed to improve bone metabolism were excluded. Vitamin D deficiency was an exclusion criterion and therefore serum 25-hydroxyvitamin D concentration had to be above 25 nmol/L. Pregnancy or wish to become pregnant was an exclusion criterion.

Disease and patient characteristics to be recorded comprised sex, age, BMI, years after diagnosis of CD, localisation of CD, (immunosuppressive) medication use and surgical history with respect to CD.

Study variables included BMD, bone serum markers and radiographs of the spine.

### Bone mineral density

Bone density was assessed by means of standard DXA by a Hologic device (models Delphi A, Discovery A, Discovery Ci, and QDR 4500A; Hologic Benelux BV, Almere, The Netherlands) in all centres but one in which another device was used (Lunar Prodigy, General Electric Healthcare Company, The Netherlands);[14 15] device-specific reference values (including corresponding T-scores) were used. All centres performed daily calibration according to local protocol and manufacturer's instruction. At the end of the study, a phantom measurement (European Spine Phantom, QRM-ES, Möhrendorf, Germany) was performed in all centres to allow for statistical analysis with adjustment for inter-centre differences in measurement of outcome. BMD was measured at lumbar spine (L1–4) and at the hip of the non-dominant side. At baseline, duplicate measurements were performed from which the mean was considered to be the correct value. BMD was expressed as T-score and in g/cm$^2$.

### Serum bone turnover markers

Specific serum bone turnover markers comprised the bone formation marker N-terminal propeptide of procollagen type 1 (P1NP; radioimmunoassay, Orion Diagnostica, Espoo, Finland) and the bone resorption marker C-terminal cross-linked telopeptide of collagen type 1 (CTx; immunoassay, Roche Diagnostics, Basel, Switzerland). The intra-assay and inter-assay coefficient of variation of the P1NP assay were 4% and 8%, respectively, and of the CTx assay 1.7% and 4.7%, respectively.

### Radiographs of spine

Standardised anterior–posterior and lateral radiographs of thoracic and lumbar spine were obtained. All radiographs were semiquantitatively and centrally scored for the presence of vertebral fractures by three dedicated investigators (VKD, AEO, PL). When height loss of the vertebral body was 20% or more anteriorly, in the middle or posteriorly, it was considered a vertebral fracture. A height loss of 20%–25% was scored 'mild' (grade 1), 25%–40% was scored 'moderate' (grade 2) and a height loss of >40% was scored 'severe' (grade 3).

### Study design and follow-up

At screening, medical history, physical examination, CD activity scores (CDAI and CRP), DXA in duplo, standard haematological and biochemical parameters and a pregnancy test, if applicable, were obtained. At baseline, disease activity and concomitant medication were documented again and serum markers for bone metabolism were drawn. Spine radiographs were performed.

Patients had a follow-up visit at month 3, 6, 12, 18 and 24, during which medical history, disease activity, concomitant

medication (including drugs necessary for the treatment of (flares of) CD, as per physician's discretion), adverse events, standard safety laboratory measurements and markers of bone metabolism were collected. DXA was performed at 12 and 24 months of follow-up. Spine radiographs were made again after 24 months.

### Randomisation and treatment

According to study design, treatment with risedronate or placebo was started after baseline measurements in patients who met all inclusion criteria. The digital randomisation procedure was performed by the central pharmacist (P Bet, VU University medical centre, Amsterdam). Study treatment was dispensed in lots of four blinded drug packages per hospital. Patients received either 35 mg risedronate (Actonel) once per week or placebo once per week. Both groups received a supplement containing calcium and vitamin D (1000 mg and 800 IU, respectively, Calci-Chew D3) daily at night-time and not together with the study drug. In case of intolerance for Calci-Chew D3, substitutes containing 1000 mg calcium and 400–800 IU vitamin D were prescribed. Treatment was continued for 24 months.

### Outcome variables

The primary outcome of the study was the change in BMD and T-score at lumbar spine and/or total hip derived from DXA after 24 months treatment with risedronate compared with placebo. Additionally, changes in markers of bone metabolism and number of vertebral fractures were documented. CD activity and safety of drug administration were monitored by clinical scores (CDAI, CRP) and routine clinical, haematological and biochemical parameters.

### Study conduct

The study was performed according to the guidelines of Good Clinical Practice and monitored by an external, non-participating, research organisation (Denys Research Consultants, Wetteren, Belgium). The study was centrally approved by the Medical Ethical Committee of the Academic Medical Centre, Amsterdam (subsequently followed by approval of all local MECs) and registered as NTR 163 Dutch Trial Register.

### Sample size calculation

Assuming an SD in T-score at lumbar spine or total hip of 4.7%, 57 patients in each group would allow detection of a statistically significant difference between the two treatments of 2.5% in lumbar spine or total hip T-score, with a type I error of 5% (2-sided) and a type II error of 20% (power 80%). Including approximately a 10% drop out, 65 patients per study arm were anticipated to be needed.

### Statistical analysis and preparation of article

Analysis of the primary outcome was performed on all patients who were allocated for drug use, defined as the intention to treat population. In case of missing DXA measurement at 24 months, baseline DXA scores were imputed, being the most stringent imputation method. The safety population was defined as all subjects exposed to study treatment, regardless of the amount of treatment administered. In the event of subjects having received treatments that differed from those assigned according to the randomisation schedule, then the safety analyses were conducted according to the treatment received rather than according to the randomisation groups.

Box and Whisker plots were used to assess normality of all outcome variables at baseline, and at months 3, 6, 12, 18 and 24. Comparisons between the two groups with regard to the study outcomes were performed by the two sample independent t test (normal outcomes) or Mann–Whitney test (skewed outcomes) in case of continuous outcomes and by the $\chi^2$ test in case of categorical outcomes. Longitudinal measurements of DXA values, CDAI scores, CRP values and serum values between the two groups were analysed by a mixed model with fixed effects for group, time and their two-way interaction and a random intercept for subjects. The analysis of DXA measurements was adjusted for age (fixed effect), BMI (fixed effect), sex (fixed effect) and study centre (random effect). Only patients with complete measurements were analysed; however, in case of missing serum values at month 12, the measurement at month 6 was put forward, as was done with lacking values at month 24, in which case observations of month 18 were put forward.

Statistical analyses were performed using SPSS (V.20, IBM Corp., Armonk, New York, USA). A p value $<0.05$ was considered to indicate statistical significance, and a p value $<0.1$ a statistical trend.

## RESULTS

A total of 132 patients provided informed consent; as one subject withdrew informed consent before randomisation, 131 patients were analysed. Of these 131, 67 received placebo and 64 risedronate (see figure 1).

Patient characteristics are depicted in table 1. There were no clinically significant differences between the two treatment groups, although the risedronate group had a slightly higher BMI (24.3 vs 23.0 kg/m$^2$). The main results of change in BMD from baseline to month 24 are shown in table 2. The mean BMD of lumbar spine of patients receiving risedronate increased by 0.04 g/cm$^2$, which was statistically significantly more than the mean change of BMD in patients receiving placebo ($p=0.007$). Also, the increase of the T-score of the lumbar spine was higher in the risedronate than in the placebo group ($p=0.007$). The increase of total hip BMD did not differ between the two groups, although a statistical trend was observed for BMD in favour of the treatment group.

These results were adjusted for age, sex, study centre and BMI, and statistical findings remained consistent (see table 2); likewise, no interaction between the main outcome and age could be demonstrated ($p=0.661$ for lumbar T-score).

Standardised phantom measurements, performed following inclusion of all patients according to protocol, ranged from 0.913 to 1.030. These inter-hospital differences were applied to adjust and recalculate bone mass values which did not change the conclusions of statistical analyses.

Complete DXA measurements were available for 118 patients (see figure 1). A total of 14 patients were excluded from analysis because of withdrawal of consent (n=6), non-compliance to data acquirement according to the study protocol (n=5), adverse reaction to immune suppressants (n=2) and vitamin D deficiency (n=1). Per protocol analyses were done in the remaining 118 patients. The median CDAI score was 88 (IQR 38.5–137.5) at baseline in the placebo group, and 75 (IQR 42.8–126.3) in the risedronate group. At month 24, this was 82 (IQR 34–127.5) in the placebo group versus 67 (IQR 34.0–112.0) in the risedronate group. The median CRP value did not change over time. For the placebo group, the median CRP was 3.0 mg/mL (IQR 1.4–7.0) at baseline and 3.0 mg/mL (IQR 2.0–7.1) at the end of study, and in between ranged from 3.0 to 4.0 mg/mL. Median CRP values were 4.4 mg/mL (IQR 2.5–7.1) and 4.5 (IQR 2.5–7.0) at baseline and at the end of study for the risedronate group, and in between ranged from 4.0 to 5.0 mg/mL. All these values were consistent with CD in

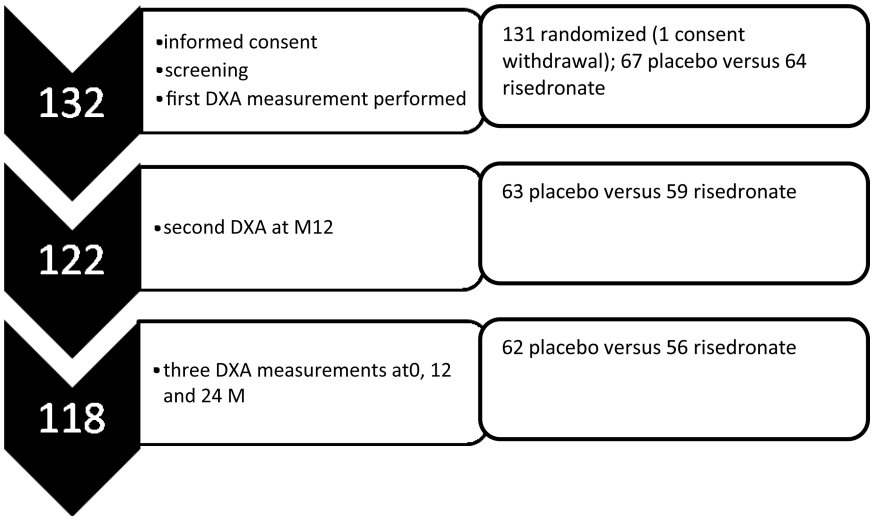


**Figure 1** Flowchart patients. Patients with all dual x-ray absorptiometry measurements were analysed in this study (n=118).

remission and differences between placebo and risedronate groups were not significant. CDAI above 220 points or CRP above 20 mg/mL, variables indicative of disease activity, were observed at various evaluation time points, but in maximal five subjects per group per evaluation moment, comprising finally 21 out of 118 patients of the total population, when taking all study observations into account.

A total of 19 vertebral fractures were observed in 17 of the 131 participants at baseline, of which two fractures in two patients were lost during follow-up. In the remaining completely analysed 118 patients, 17 fractures in 15 patients at baseline were mild, grade 1 fractures, in 11 patients in the thoracic and in four patients in the lumbar spine. After 2 years follow-up, one new grade 1 fracture was observed in a patient using placebo. In three out of 118 patients, a grade 1 fracture increased to a grade 2 fracture, all in the thoracic spine.

**Table 1** Patient characteristics at baseline

| | All patients (n=131) | Placebo (n=67) | Risedronate (n=64) | p Value |
|---|---|---|---|---|
| Age in years, mean (SD) | 42 (13) | 42 (13) | 43 (13) | 0.73 |
| BMI, mean (SD) | 23.6 (3.2) | 23.0 (2.8) | 24.3 (3.4) | 0.02 |
| Duration of CD, median (IQR) | 11 (6–18) | 10 (6–17) | 12 (6–21) | 0.51 |
| Sex | | | | |
| Male | 60 (46%) | 29 (43%) | 31 (48%) | 0.60 |
| Female | 71 (54%) | 38 (57%) | 33 (52%) | |
| Localisation | | | | |
| Ileum (L1) | 29 (22%) | 17 (25%) | 12 (19%) | 0.63 |
| Colon (L2) | 31 (24%) | 13 (19%) | 18 (28%) | |
| Ileocolonic (L3) | 69 (53%) | 36 (54%) | 33 (52%) | |
| Proximal (L4) | 2 (2%) | 1 (1%) | 1 (2%) | |
| Drugs | | | | |
| None | 2 (2%) | 1 (1%) | 1 (2%) | 0.71 |
| Corticosteroids* | 20 (15%) | 8 (12%) | 12 (19%) | |
| Immunosuppressives | 72 (55%) | 32 (48%) | 40 (63%) | |
| Anti-TNF-α therapy | 13 (22%) | 7 (10%) | 6 (9%) | |
| Miscellaneous, IBD | 92 (98%) | 46 (69%) | 46 (72%) | |
| Non-IBD medication | 86 (66%) | 48 (72%) | 38 (59%) | |
| Medical | | | | |
| None | 8 (6%) | 5 (7%) | 3 (5%) | 0.43 |
| History | | | | |
| IBD-related surgery | 82 (63%) | 40 (60%) | 42 (66%) | |
| IBD-associated arthropathy | 3 (2%) | 0 (0%) | 3 (5%) | |
| Perianal disease ±local surgery | 36 (27%) | 18 (27%) | 18 (28%) | |

Numbers expressed in n and %.
*At baseline, two patients used low dose prednisolone for CD, two for rheumatoid arthritis and all others used budesonide. During the course of study, eight prednisolone induction courses were initiated and tapered for CD exacerbation, four patients received prednisolone for rheumatoid indications, and one patient each for pulmonary disease, allergy, dermatological findings and multiple sclerosis, respectively. Sixteen patients received anti-TNF-α therapy during study. All patients were equally distributed over the two study groups (p=0.54).
BMI, body mass index; CD, Crohn's disease.

**Table 2** Change in DXA bone mineral density (BMD) and T-score in all ITT patients

| | Placebo N = 67 | Risedronate N = 64 | p Value* | Adjusted† p value |
|---|---|---|---|---|
| Lumbar spine | | | | |
| BMD in g/cm$^2$ | | | | |
| Baseline | 0.95 (0.11) | 0.94 (0.11) | | |
| 24 months | 0.96 (0.12) | 0.98 (0.10) | 0.007 | 0.013 |
| T-score | | | | |
| Baseline | −1.26 (0.78) | −1.30 (0.61) | | |
| 24 months | −1.17 (0.94) | −1.02 (0.75) | 0.007 | 0.003 |
| Z-score | | | | |
| Baseline | −0.83 (0.81) | −0.91 (0.68) | | |
| 24 months | −0.72 (0.95) | −0.61 (0.79) | 0.005 | 0.001 |
| Total hip | | | | |
| BMD in g/cm$^2$ | | | | |
| Baseline | 0.81 (0.11) | 0.81 (0.09) | | |
| 24 months | 0.82 (0.08) | 0.84 (0.11) | 0.071 | 0.094 |
| T-score | | | | |
| Baseline | −1.21 (0.51) | −1.22 (0.63) | | |
| 24 months | −1.16 (0.54) | −1.07 (0.70) | 0.192 | 0.228 |
| Z-score | | | | |
| Baseline | −0.80 (0.60) | −0.83 (0.71) | | |
| 24 months | −0.74 (0.60) | −0.67 (0.77) | 0.091 | 0.110 |

Numbers expressed as mean and SD.
*p Value for the comparison of the change in DXA from baseline to 24 months between the placebo and risedronate groups.
†p Value for the corrected model for age, sex, centre and BMI.
BMI, body mass index; DXA, dual x-ray absorptiometry; ITT, intention to treat.

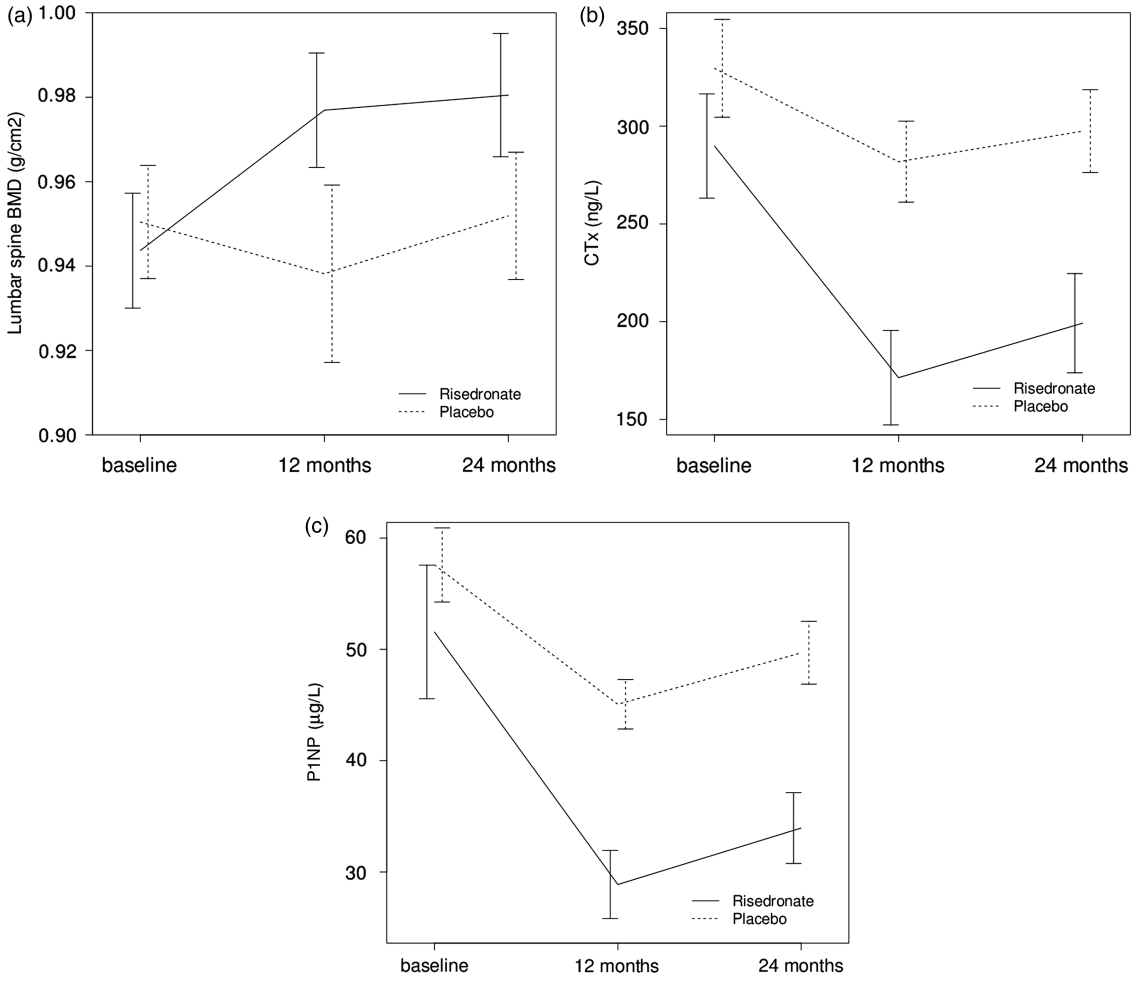


**Figure 2** Mean values of lumbar dual x-ray absorptiometry in g/cm$^2$ (A), serum concentration of bone resorption marker C-terminal cross-linked telopeptide of collagen type, CTx, in ng/L (B), and of bone formation marker N-terminal propeptide of procollagen type 1, P1NP, in µg/L (C) at baseline, after 12 and 24 months, with SEM between bars. The solid line represents the risedronate group, and the dashed line the placebo group.

Distribution of prevalent fractures between the placebo and the risedronate groups was similar (p=0.78 at baseline and p=1.00 after 24 months).

Serum bone formation and resorption markers (P1NP and CTx, respectively) values were maximal at baseline, decreased in the first 12 months of follow-up and slightly increased again towards the end of the study after 24 months, for both variables (figure 2). p Values are depicted in table 3.

No statistically significant association among serum markers of bone metabolism, CDAI or CRP and bone density was observed.

In total, 34 severe adverse advents (SAE) were observed in 24 patients, being surgical procedures (n=13, 10 CD-related), gastroenteritis with or without dehydration (n=5), vascular events (in four patients), carcinoma (in two patients) and miscellaneous (mainly hospital admissions for general reasons such as exacerbation of dyspnoea, dehydration, allergic reaction, retained video capsule and kidney stones). None of these SAEs was considered to be associated with participation in this study or use of the prescribed study medication. Relevant changes of any laboratory value indicative for AE were not observed.

## DISCUSSION

This double-blind, placebo-controlled study demonstrated an increase of lumbar spine bone density in osteopenic patients with quiescent CD while treated with the bisphosphonate risedronate 35 mg once weekly with concomitantly calcium and vitamin D; a statistical trend of bone density improvement was seen at the total hip. One new grade 1 fracture was observed during the study, and three existing grade 1 fractures aggravated

**Table 3** Change in serum bone turnover markers in all ITT patients: the specific bone resorption marker C-terminal cross-linked telopeptide of collagen type (CTx) and the bone formation marker N-terminal propeptide of procollagen type 1 (P1NP)

| | Placebo, n=62 | Risedronate, n=56 | p Value* |
|---|---|---|---|
| CTx | | | |
| Baseline | 329.6 (166.0) | 289.8 (170.7) | NS |
| 12 months | 281.8 (139.1) | 171.3 (149.0) | 0.001 |
| 24 months | 297.4 (142.1) | 199.2 (156.4) | 0.004 |
| P1NP | | | |
| Baseline | 57.6 (22.1) | 51.6 (38.4) | NS |
| 12 months | 45.1 (14.9) | 28.9 (19.1) | <0.001 |
| 24 months | 49.7 (18.9) | 33.9 (19.6) | <0.001 |

Numbers expressed as mean and SD.
*p Value for the comparison of the CTx or P1NP values between the placebo and risedronate groups at 12 or 24 months.
ITT, intention to treat.

to a grade 2 fracture, but the study was not statistically powered to detect differences in fracture rate between placebo and risedronate use.

Risedronate treatment was well tolerated, not influencing disease activity, and its use was not associated with severe adverse events.

The beneficial therapeutic effect of risedronate was substantiated by a decrease in bone turnover markers, that is, the bone formation marker P1NP and the bone resorption marker CTx, consistent with the known pharmacological effects of bisphosphonates.[16] The established pharmacodynamic effects in this population showed that risedronate had adequate bioavailability in terms of obtained pharmacological efficacy, even in CD patients.

Peak bone mass may be reduced in CD (occurring at young age), whereas increased bone loss is to be anticipated during periods of chronic active or relapsing disease. This contributes to an increased risk of osteopenic or osteoporotic bone, usually at a younger age, and may partly explain the reported increase in fractures in IBD patients.[4 10] Several studies have shown that bisphosphonates, primarily by intravenous administration, are effective in the treatment of bone loss of CD patients, although not all were performed in a randomised, placebo-controlled and double-blind fashion.[17–23] Study populations differed substantially in age, sex, disease activity, and therapeutic effects on trabecular or cortical bone. In a number of studies, evaluating the effect of oral administration of bisphosphonates on BMD in various small cohorts of IBD patients, comparable results were observed.[24–28] Analogous findings in a similarly designed study were reported by Soo *et al*,[28] but the outcome was not statistically significant, probably due to the small number of included patients. Notably, the decrease of bone turnover markers, which can be ascribed to the pharmacodynamic effect of risedronate, and an effect which may be primarily observed in the first period of treatment, underscores the role of bisphosphonates and not of the dietary calcium and vitamin D supplements in our study.[29] Increase of BMD was yet shown when only calcium and vitamin D were supplemented in a selected cohort of CD patients with a low bone mass from one of the participating study centres.[30] This was, however, a minor increase over years (0.43% and 0.76% in total hip and lumbar spine, respectively), and less than the reported effects of risedronate use in the current study.[30] This also holds true for the potential beneficial effect of anti-TNF-α therapy on bone density, an effect that is known to induce different changes of serum bone markers.[31] In this study, patients using or initiating anti-TNF-α therapy were equally distributed between the risedronate and the placebo groups (table 1).

In a subpopulation of this study, bone biopsies were obtained to analyse specific characteristics of CD-induced changes in bone architecture. These comprised reduction in bone mass due to trabecular thinning and reduced bone formation.[13] Subsequent experiments showed that bone cells from patients with CD had a reduced growth potential and an impeded maturation, and increased potential to generate osteoclasts from peripheral blood.[32 33] These mechanisms probably contribute to the pathogenesis of CD-induced bone loss and differ from osteoporosis due to ageing. Nevertheless, bisphosphonates, a well-established therapy for age-induced osteoporosis in women, proved to successfully increase bone density in CD-associated osteopenia.[17–23]

In this trial, in a well-documented, osteopenic CD population, the beneficial effect of therapy was shown in particular at the lumbar spine, whereas the total hip findings showed a statistical trend of improvement, probably because lumbar spine changes due to medical treatment may be detected earlier and more reliably.[34] Additionally, concurrent with the improvement of BMD, we showed a change in pharmacodynamic variables consistent with the specific effects of bisphosphonates (decrease of serum bone turnover markers P1NP and CTx), excluding confounding effects of calcium and vitamin D supplementation or treatment of CD, for example, by means of infliximab. The results of this study corroborate the concept that early bone protective treatment in osteopenic CD patients may prevent fractures and associated complications at later age.[3 10] Considering the established increased risk of fractures in CD patients, the current study results support more frequent and early use of risedronate in CD patients with an increased risk of metabolic bone disease and fractures, in this study identified as CD patients having osteopenia. As such, this preventive strategy may be recommended in particular risk groups, such as CD patients suffering from chronic active disease, those with chronic or high cumulative dose of glucocorticoids, a family history of osteoporotic fractures, and those with a low BMI.

This double-blind study showed a beneficial effect of risedronate in osteopenic CD patients as assessed by DXA. Quality of bone, assessed by bone histomorphometry, could only be assessed in a relatively small subgroup.[13] We did not measure risedronate concentrations in serum to ascertain treatment compliance, but calculated the number of tablets returned to the investigators at follow-up visits. This holds true for calcium and vitamin D supplements as well, although, due to randomisation, no skewing in compliance between the two groups was to be expected. The positive effect of risedronate on BMD provides additional proof for adequate intake and absorption of this bisphosphonate in our patients with IBD.

In conclusion, we demonstrated that risedronate 35 mg once weekly with concomitant calcium and vitamin D supplementation improved BMD in an osteopenic CD population.

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# Treatment of bone loss in osteopenic patients with Crohn's disease: a double-blind, randomised trial of oral risedronate 35 mg once weekly or placebo, concomitant with calcium and vitamin D supplementation

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