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Original Article

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Negative impact of Crohn's disease on bone mineral mass

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Abstract

Prolonged chronic inflammation and corticosteroid therapy increase the risk of osteoporosis in patients with Crohn's disease. It has been estimated that 30% of these patients, who take steroids for prolonged periods, will suffer a vertebral fracture. Patients with Crohn's disease are difficult to wean from corticosteroids and therefore are at risk of developing bone complications. The purpose of this cross-sectional study was to examine the relationship between cumulative steroid dose, duration of the disease and the development of osteopenia in patients with Crohn's disease. We studied 28 patients (17 men, 11 women) with Crohn's disease: eight had one or more bowel resections and all the women were premenopausal. Serum calcium, phosphate, total alkaline phosphatase, immunoreactive parathyroid hormone (iPTH), 25(OH)Vitamin D_3 and 1,25 $(OH)_2$ Vitamin D_3 were measured by autoanalyser methods or radioimmunoassay. Bone mineral density (BMD) was studied using dual energy X-ray bone absorptiometry of the lumbar spine (L2-L4) and the femoral neck. Of these 28 patients, 27 received an average of 17.3 ± 21.7 g (range 1 to 80) g of prednisone over a period of 4 to 216 months. Fourteen out of the 28 patients had mildly diminished bone density (z-score >-2.5 SD and < -1 SD) of the spine and 15/28 of the hip. We found a greater decrease in bone density (z-score < -2.5 SD) in 2 out of 28 patients at the spine and in 5 out of 28 at the femoral neck. Those in whom the duration of the disease was less than two years (12 patients) had significantly higher vertebral z-scores (-0.096 ± 0.91) than those who had the disease for over two years (-1.31 ± 2.37), ($p<0.05$). We found no significant correlation between lumbar spine and femoral neck z-scores and cumulative steroid therapy. Six out of 28 patients (four women and two men), of mean age 47.2±11.7, had one vertebral fracture. The mean cumulative dose of steroids (prednisone or budesonide) in patients with vertebral fractures was higher but not significantly different from that in patients without fractures -20.1±18.2 versus 14.1±11.2 g of prednisone, respectively ($p>0.05$). No correlation was found between various serum hormones and other biochemical parameters of bone turnover or bone density. We conclude that a large proportion of patients with Crohn's disease have reduced bone mineral density (58% at the spine and 75% at the femoral neck).The pathogenesis of bone loss is probably multifactorial. Although steroid therapy might be an important contributory factor, we were unable to find a significant correlation between it and bone loss. On the contrary, we observed that the duration of the disease makes a significant contribution to bone loss.

Keywords: Osteoporosis, Prevention, Bone Mineral Density, Bone Quality, D-Hormones

Introduction

Although musculoskeletal complications of Crohn's disease have been recognized for many years, their precise nature and incidence have not been studied exclusively[1]. Osteoporosis has been reported in 30 to 50% of patients with Crohn's disease and often it is a silent disease until a fracture occurs. The pathogenesis of osteoporosis associated with inflammatory intestinal bowel disease is multifactorial. Although many studies have noted that patients with Crohn's disease who use corticosteroids are at risk for the development of osteoporosis, the main cause of such osteopenia and/or osteoporosis remains unknown. Corticosteroid therapy likely plays an important role in some patients, while estrogen deficiency and amennorhea are major factors in women[2]. Other possible pathogenetic factors include calcium malabsorption, secondary hyperparathyroidism resulting from calcium and/or vitamin D deficiency and altered sex hormone status in men[3]. Thus, it is important to determine whether Crohn's disease has a direct bearing on whether

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these patients ultimately become osteopenic. It is also possible that over time, even in the absence of corticosteroid therapy, patients with Crohn's disease still might have diminished bone density secondary to chronic inflammation. Circulating cytokines i.e., interleukin-1, are known to have deleterious effects on bone formation[4]. This study was designed to determine the degree of decreased bone density in 28 patients with Crohn's disease, and to establish its relationship to various risk factors, such as clinical variables and laboratory findings.

Subjects and methods

We studied 28 consecutive patients with Crohn's disease (11 females, 17 males), ranging in age from 24 to 70 years (40.7±17.6 years). The diagnosis of Crohn's disease was based on histological, endoscopic, radiological and clinical criteria. Eight patients had undergone at least one intestinal resection. None of the women was pregnant or menopausal and none had known cholestasis, renal disease, hypogonadism, previous gastric surgery or parathyroid disorders. During the study, two patients had active Crohn's disease while all the others were in clinical remission.

The following parameters were recorded: history of bone fracture, contraceptive use, height, weight, body mass index (BMI), (weight/height) (kg/m^2) expressed in kilograms per square meter, the estimated duration of disease before diagnosis, age, sex, current medications, history of corticosteroid use, calcium and vitamin D intake. Cumulative lifetime steroid dose was expressed in grams of prednisone. At the time of enrollment, we measured hemoglobin, calcium, serum phosphate, serum alkaline phosphatase and serum levels of 25(OH) vitamin D_3, $1,25(OH)_2D_3$ (Incestar, Stillwater, MN) and parathyroid hormone (iPTH) (measured by immunoradiometric assay, IMMULITE analyzer). Blood samples were taken after an overnight fast.

Six patients used inhaled glucocorticoids, namely budesonide, to assist withdrawal from prednisone. A daily dose of 11.2 mg of oral prednisone is equivalent to 1.0 mg of inhaled budesonide. Twenty-five patients had taken calcium and vitamin D supplements during the study.

Bone mineral density (BMD) was assessed using dual energy X-ray absorptiometry (DEXA) (Lunar DPX-IQ, Lunar software version 1.32, Lunar Radiation, Madison, WI). The equipment is calibrated daily using a phantom provided by the manufacturer and following the manufacturer's recommendations. The data from normal controls, which is built into the system software, is provided by the manufacturer. A measurement was taken at a) the L2-L4 vertebrae, to estimate predominantly trabecular bone density and b) left femoral neck, to estimate predominantly cortical bone density. The results, z- scores, were expressed as the number of standard deviations above or below mean values of age- and sex-matched controls. Patients with z-scores between -1 and -1.5 were deemed to have mildly decreased bone density; between -1.5 and -2.5, moderately decreased bone density, and over -2.5 SD, were considered to have severely decreased bone density.

The first two groups are described as osteopenia, whereas the last is described as osteoporosis.

Vertebral crush fractures were assessed on lumbar spine and femoral neck views using standard X-ray examination.

Statistical analysis

The data for this study were analyzed using the SYSTAT software, version 7.0, 1998. Correlations between variables were tested by estimating the Pearson correlation matrices. Statistical significance of the correlations was evaluated based on the Bonferroni probability matrix. A correlation value was considered significant when the corresponding Bonferroni probability value was <0.05.

Results

Table 1 shows the demographic data and the mean values of the specific parameters in these 28 patients. Osteopenia of the spine was present in 19 of the 28 patients . In 12 of the 28, the z-score was between -1 and 1.5, and in 4, the z-score was between -1.5 and -2.5 SD. Regarding osteopenia of the hip, 8 out of 28 of the patients had a z-score between -1 and -1.5 SD and 7 had values between -1.5 and -2.5. A severe decrease in bone density (i.e., z-score <-2.5 SD) was found in 5/28 at the spine, and, in 10/28 at the hip. Among all of these patients, the overall z-score for spine and femoral neck was -0.81±1.61 and -2.11±1.51, respectively. Women had significantly higher lumbar spine z-scores than men (0.017±0.929 versus -1.189±2.112, $p<0.05$), and higher femoral neck z-scores than men (-0.583±0.899 versus -1.416±1.680, $p<0.05$), respectively. Regarding duration of the disease, the comparison between women and men did not show any significant difference (45.7±50.8 versus 52.9±49.6 months, respectively, p:NS).

Twelve patients with disease for less than two years had significantly higher lumbar spine z-scores than the 16 patients with disease for longer than two years (-0.096±0.91 versus -1.31±2.37, $p<0.05$). Femoral neck z-scores also differed significantly in patients with disease for less than 2 years compared with those with long-standing disease (>2 years) (-0.71±0.91 versus -1.91±1.89, $p<0.05$). A test of correlation between lumbar spine or femoral neck z-scores and cumulative steroid dose did not show any significant difference ($r = 0.274$, p = NS and $r = 0.006$, p = NS), respectively (Table 2). Average body mass index (mean ± SD) was 24.4±3.16 (range 17.8 – 29.3). Six out of 28 patients had one vertebral fracture. The lumbar spine z-score was significantly lower in patients who had fractures, compared with those who had no fractures (-1.960±2.476 versus -0.624±1.167, $p<0.05$). The cumulative steroid dose in those with vertebral fractures was higher but not significantly different from those without such fractures (20.1±18.2 versus 14.1±11.2, P=NS). Values (mean ±SD) of the main biochemical parameters are shown in Table 1. Urine concentration of calcium, phosphate and hydroxypro-

Sex (M/F)	17/11	Normal values
Age (mean years ± SD)	40.7 ± 17.6	
Duration of disease (months)	54.1 ± 56.3	
Corticosteroid cumulative dose (g)	17.2 ± 23.1	
Alkaline phosphatase (IU/L)	88.41 ± 23.21	30–115
25 (OH) – vitamin D (nmol/L)	56.9 ± 29.1	20–100
1,25 $(OH)_2$ vitamin D (pmol/L)	71 ± 13	37 – 119
iPTH (pg/ml)	4.2 ± 1.70	7 – 53
Serum Ca^{+2} (mmol/L)	2.19 ± 0.13	2.2 – 2.6
Serum P (mmol/L)	1.13 ± 0.18	0.8 – 1.45
Urinary calcium (mmol/L/day)	2.24 ± 1.11	<7.5
Urinary phosphate (mmol/L/day)	21 ± 13	<50
Urinary hydroxyproline (mmol/L/day)	163 ± 30	10 - 340
Daily calcium intake (mg)	1120 ± 311	
Daily caloric intake	2112 ± 304	
Z-score lumbar spine	-0.81 ± 1.61	
Z-score femoral neck	-2.11 ± 1.51	
BMI (kg/m^2)	24.4 ± 3.16	

Table 1. Characteristics of patients with Crohn's disease.

line was within normal limits (Table 1).

A correlation between biochemical markers of bone turnover: bone formation (serum alkaline phosphatase), bone resorption: (urinary excretion hydroxyproline) and cumulative steroid dose did not show any significant relationship ($r = 0.355$ p:NS, and $r = 0.279$ p:NS, respectively). None of these patients had levels of 25(OH) vitamin D_3 below the lower limit of the normal range (mean±SD) (56.9±29.1 nmol/L).

There was a significant positive correlation between the total caloric intake and daily calcium ($r = 0.98$, $p<0.005$).

Discussion

Although available data indicate that patients with Crohn's disease who take corticosteroids have osteopenia, many aspects of this relationship remain to be clarified [1,2,5].

In our study, 12 newly diagnosed patients (disease duration < 2 years) and one who had never received corticosteroids had reduced BMD (17% had lumbar spine z-score < -1.5 SD and 50% had femoral neck z-score <-1.5 SD). Although the WHO classification of osteoporosis is based on t-scores, we expressed the results based on z-scores as being more appropriate for this study. Expressing the results as z-scores provides an immediate comparison with age- and gender-matched controls. There was a significant difference in lumbar spine and femoral neck z-scores in those with Crohn's disease of less than and those with more than two years' duration ($p<0.05$), while we found no significant correlation between z-scores of lumbar spine and femoral neck and cumulative steroid dose (Table 2). In keeping with the findings of Ghosh et al. who studied 30 newly diagnosed patients, we also found that disease duration made a significant contribution to reduced BMD, but steroid treatment did not[6]. These findings raise the strong possibility that BMD is reduced (at least in part) in response to the intestinal inflammation itself. During the last two years, results of the latest research were added to those that already existed. New molecules such as RANK (Receptor Activator of Nuclear Factor Kappa B), RANKL (Rank ligand) and OPG (Osteoprotegerin), are cytokines that regulate osteoclastogenesis. RANK and its inhibitor OPG are decisive for the differentiation and osteoresorption functions of the osteoclasts. Concentration of OPG and RANKL is controlled by many osteotropic hormones and cytokines. Agents reducing OPG/RANKL ratio are steroids (enhance osteoclastogenesis by OPG inhibition that leads to increased osteoresorption), inflammatory cytokines such as IL-1, IL-4, IL-6, IL-11, TNF-alpha (stimulate osteoclastogenesis by induction of OPG expression) etc.[7-9].

We have assessed the effect of steroids by comparing the cumulative steroid dose, BMD, and bone formation parameters. In our group the mean cumulative steroid dose was 17.2±23.1 g. We noted a significant difference ($p<0.05$) between lumbar spine and femoral neck z-scores. However, we found no significant correlation between lumbar spine and femoral neck z-scores, and bone turnover markers (alkaline phosphatase, urinary OH-proline) and cumulative steroid dose. The relationship between severity of bone loss and cumulative steroid dose remains unclear. In an earlier study,

	Cumulative Steroid Dose	BMI	Disease Duration
Lumbar Spine	r=0.274	r=0.178	r=0.713
	p= NS	p= NS	p<0.05
Femoral Neck	r=0.006	r=0.148	r=0.736
	p=NS	p= NS	p<0.05

Table 2. Correlation between bone mineral density (BMD) measured at two levels and cumulative steroid dose, body mass index, and disease duration in 28 patients with Crohn's disease.

Reid et al. demonstrated a significantly greater bone loss in patients taking more than 12.5 mg prednisone daily, while later studies did not find a dose-response relationship[2,5,10]. Longitudinal studies in patients taking steroids for a long time have not shown any correlation between the rate of bone loss and the use of steroids[11]. Regarding Crohn's disease, total lifetime steroid dosage is an expression of disease activity and severity[12]. Therefore, one could argue that more severe disease may lead to more diminished bone density and that steroid use is simply a proxy measure of this. In addition, baseline concentrations or changes in bone formation markers have not been found to predict bone loss after corticosteroid treatment. In a recently published study, Cino et al. prospectively (over 2 years) investigated the effect of treatment with budesonide, prednisone and non-steroids on BMD in 138 patients with quiescent Crohn's disease[13]. These authors conclude that factors other than budesonide or prednisone contribute to bone loss in Crohn's disease, e.g., pro-inflammatory cytokines, increased osteoclastogenesis through activation of the PSS tumor necrosis factor receptor, the allele status of the interleukin-6, the IL-1ra gene, etc.[13-15]. Our findings agree with theirs.

Many studies suggest that reduced bone mineral density is a risk factor for fractures, which are the major clinical end point in these patients[3,14,16]. Twenty-one per cent of our patients (mean duration of Crohn's disease 26.4±41.7 months, mean cumulative steroid dose 20.1±18.2 g prednisone) had one vertebral fracture. In our patients with vertebral fracture, the cumulative steroid dose was higher, but not significantly different from that in patients without a fracture ($p>0.05$).

Low levels of circulating 25(OH) vitamin D_3 have been found in patients with Crohn's disease[16,17]. In contrast, others have reported normal levels of 25(OH) vitamin D_3 and 1,25 $(OH)_2$ vitamin D in these patients with Crohn's disease[17,18]. Also, normal vitamin D metabolite levels have been observed in patients with Crohn's disease even after small-bowel resection of an average of 105 cm and/or steroid use. In our study, vitamin D metabolites were within the normal range. It has been suggested that malabsorption, which may accompany small-bowel resection in patients with Crohn's disease, is an important determinant of bone loss[19]. Our findings do not support this theory because we found no difference between patients with and without small-bowel resection. In addition, calcium, phosphate and vitamin D metabolites were within normal limits in all patients. While no female patient was peri- or postmenopausal in our study, Clements et al. have suggested that sex hormone deficiency —a result of steroid treatment— makes an important contribution to low bone mineral density and that a reasonable therapeutic approach in patients with Crohn's disease receiving steroids is hormonal replacement therapy, calcium supplements and/or vitamin D metabolites[20].

The main limitation of this study is its retrospective design which makes cause-and-effect inferences impossible. Moreover, the small number of patients studied gives a lack of statistical power.

Conclusion

In this cross-sectional study we have shown that patients with Crohn's disease have a reduced bone mineral density (BMD), which is due not simply to steroids, but is significantly correlated with disease duration. Low BMD is a feature of the disease in newly diagnosed patients. Patients with vertebral fractures and low z-scores are more likely to have received relatively larger doses of steroids. Also, we recorded a noticeable difference in the significantly higher prevalence of reduced z-scores in the hip (femoral neck, cortical bone) than in vertebrae (L2-L4, trabecular bone). Because a low z-score predicts an increased risk for bone fracture, the increased prevalence of low mineral density among patients with Crohn's disease puts them at risk of fractures. Hence, one must provide early specific treatment, adequate nutritional support, caloric and dietary calcium intake to achieve proper and prompt control. The chronic inflammatory process and the nature of the disease itself are important with respect to loss of bone mineral density and need further exploration.

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