

CLINICAL STUDIES

Osteopenia in Puerto Ricans with Crohn's Disease

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Background. Osteopenia has been reported in association to Inflammatory Bowel Disease, and in particular Crohn's disease. The use of corticosteroids, resection of the ileum, malabsorption, poor calcium intake, and the effect of inflammatory cytokines have all been considered as contributing factors. As Crohn's disease is more prevalent in young people, when peak bone mass is achieved, the presence of osteopenia is especially significant.

Objectives. The aim of this study was to evaluate the bone density of patients with Crohn's disease in the University of Puerto Rico IBD Clinic; to determine the prevalence of osteopenia in these patients and to correlate bone mineral density with risk factors for osteopenia.

Methods. Sixty-six patients, 30 males and 36 females were included. After informed consent, demographic, clinical and metabolic data was obtained. Serum albumin, calcium, inorganic phosphorus and alkaline phosphatase were measured. Body mass index (BMI)

was calculated. Bone density was determined by DEXA of the lumbar spine and femur and expressed as the Z score (standard deviations from normal correlated with sex and age). Severe osteopenia was a Z score ≥ -2 and osteopenia was $Z < -1.99$ or ≥ 1.01 . Results were expressed in means. Pearson correlation coefficient was used for quantitative variables and Pearson chi-square for categorical values.

Results. Osteopenia was present in the hip in 69% and in the lumbar spine in 68%. Most patients had received steroids; the difference between treated and not treated patients was not significant. Osteopenia did not correlate with ileal resection, gender, BMI, disease characteristics or biochemical parameters.

Conclusions. Low bone density was frequent in patients with Crohn's disease, but no specific risk factors could be identified. Bone density should be determined in patients with Crohn's disease in order to institute appropriate therapeutic measures.

Key words: Osteopenia, Crohn's disease

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract of unknown etiology with a diversity of clinical manifestations. The incidence of this disease in the United States is approximately 8 cases per 100,000, with a peak occurrence between the ages of 15 and 35. Most patients with Crohn's disease have a chronic intermittent course of remissions and exacerbations. Mortality rate increases with disease

duration and may range from 5% to 10%. In spite of this, therapy allows for a reasonably stable and productive life in most patients (1).

Because this disease is more frequent at the age when peak bone mass is achieved, any reduction in this mass would be more significant. Since most patients will have a near normal life expectancy, an early reduction in bone mass would place them at an increased risk for fractures at an earlier age than the normal population (2). Osteopenia has been frequently reported in association with Inflammatory Bowel Disease (IBD) (3,4). Patients with Crohn's disease have an increased prevalence of low bone density, ranging from 15% (5) to 41% (6). Osteoporosis is frequent in patients with Inflammatory Bowel Disease, mostly after small bowel resection (6,7). The prevalence of spinal trabecular and peripheral cortical osteoporosis has been reported as 16% and 24%

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respectively (6). Osteomalacia has been found more commonly than suspected without coexistent clinical or biochemical abnormalities (8,9). Newer radiographic techniques have helped us to recognize significant osteopenia in this group of patients in which metabolic bone disease is not clinically evident (3,10).

Most studies have reported that the majority of patients with Crohn's disease have low serum 25-OH vitamin D (9,11), in particular those with ileal resection (11,12). However, Hesson reported opposite results in a series of 35 patients (13). Patients with ileal resection for Crohn's disease have a prevalence of metabolic bone disease as high as 66% (9). Undernourished patients with this disease have a higher tendency towards reduced serum vitamin D levels, when compared to nourished patients (14).

Many factors seem to contribute to the metabolic bone disease observed in patients with Crohn's disease. These patients are commonly malnourished due to inadequate nutrient intake (15) and malabsorption (16). Nutrition status may directly affect bone mass, particularly if protein loss is present (17, 18). Another factor is decreased calcium intake due to dietary restriction and malabsorption of vitamin D due to decreased intestinal absorptive surface (19), or interruption of enterohepatic circulation of endogenous vitamin D due to ileal involvement (20,21). Reduced physical activity (19) and lack of adequate sun exposure (7) are other contributing factors. Parameters of disease activity have been found to correlate with decreased intestinal absorption of calcium (11,12), especially if associated with a protein losing enteropathy (23), but its relation to bone disease is controversial. A recent study of 108 patients with Crohn's disease demonstrated no correlation between disease activity and bone disease. Steroids, frequently used in the treatment of active Crohn's disease, have shown to cause osteoporosis (19,24). The use of cholestyramine, with its binding capacity of Vitamin D in the intestinal lumen, worsens bone metabolism further (25). Lastly, an important predisposing factor is estrogen deficiency in women (26) and male hypogonadism, commonly seen in states of chronic illness. Severe osteoporosis has been found in young amenorrheic women with IBD (6,25).

The aims of this study were to evaluate the bone density of patients with Crohn's disease, describe the prevalence of osteopenia in these patients and to correlate bone mineral density with risk factors for osteopenia.

Materials and Methods

Subjects. All consecutive patients with Crohn's disease in follow up at the University of Puerto Rico's IBD clinic

were prospectively included in the study. All patients had a diagnosis of Crohn's disease established on histological, endoscopic, radiological and clinical criteria. A total of 66 patients with Crohn's disease (30 male and 36 female) ranging in age from 22 to 63 years (mean, 36 years) were studied from March 1994 to October 1998. Patients were excluded from the study if they had a chronic disease that may affect the skeletal system (renal insufficiency, liver disease, diabetes mellitus, malnutrition, renal lithiasis, endocrinopathies or malabsorption of other etiology), chronic ingestion of drugs that may alter bone metabolism (anticonvulsants, thyroid or estrogen preparations, diuretics, cholestyramine), previous traumatic fractures, radiologic evidence of vertebral compression or scoliosis, alcoholism, drug abuse, were uncooperative or unable to comply with the protocol.

Clinical assessments. Each patient was evaluated in the clinic prior to consideration for inclusion in the study. After a history and physical examination, if the patient qualified, an informed consent was obtained and a Crohn's disease questionnaire was filled. The questionnaire included age, gender, extent of disease, related complications (abscess, fistula), onset, history of surgery and medical treatment. A metabolic questionnaire was also filled that included physical activity, menstrual history, habits, body mass index (BMI) and other systemic illnesses. Serum concentrations of albumin, calcium, inorganic phosphate and total alkaline phosphatase were measured by standard methods. A sample population was also tested for 25(OH) D, 1,25 (OH) 2D, osteocalcin and immunoreactive parathormone (iPTH). Body mass index, which is the height adjusted weight, was expressed in kilograms per square meter.

Bone mineral density. We studied bone mineral density in a series of patients with CD. Both spine and forearm bone mineral densities were measured so that trabecular and cortical mineralization could be assessed, as there are metabolic differences between these two. Bone mineral density was measured by Dual Energy X Ray Absorptiometry (DEXA) in the lumbar spine (second, third and fourth lumbar vertebrae) and the proximal left femur (femoral neck, trochanter and intertrochanter area were measured and an average for the hip was calculated). Bone mineral density results were expressed as the number of standard deviations from normal values correlated for sex and age (Z score). Severe osteopenia was defined as a Z score ≥ -2 SD, osteopenia as a Z score ≤ -1.99 or ≥ -1.01 , and normal as a Z score ≤ -1 .

Statistical analysis. Results were expressed as means. The Pearson correlation coefficient was used for quantitative variables and the Pearson chi-square test was used for categorical variables. A p value less than 0.05

was considered statistically significant. The study was approved by the Institutional Review Board of the Medical Sciences Campus of the University of Puerto Rico.

Results

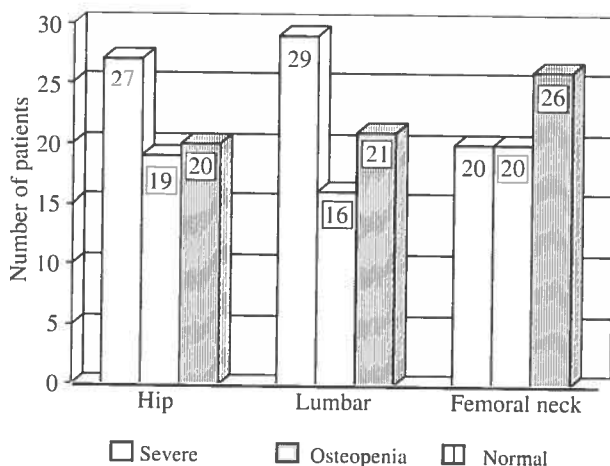
The age, sex, duration of disease, treatment, and surgery are summarized in Table 1. Ileocolitis was the most frequent presentation (42.4%). Osteopenia was present in the hip in 69%, in the lumbar spine in 68%, and in the

Table 1. Clinical Characteristics of 66 Patients with Crohn's Disease

Age (years)	36
Sex (M/F)	30/36
Duration of disease (years)	7.32
Site	
Ileum only	20 (30.3%)
Colon only	18 (27.3%)
Ileo-colon	28 (42.4%)
Previous bowel resection	35 (53%)
Previous or current oral steroids	49 (74.2%)

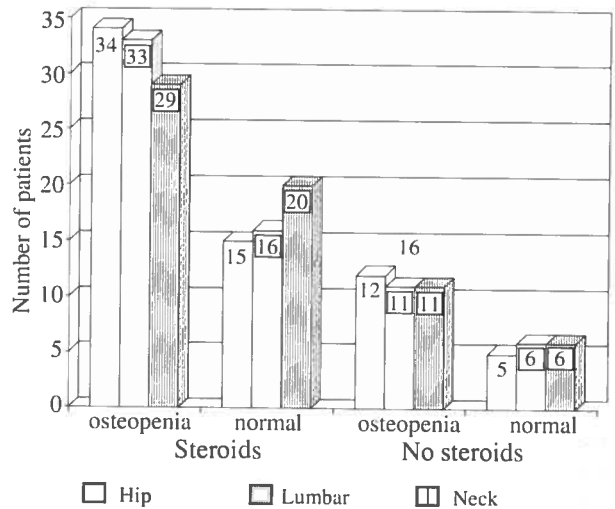
femoral neck in 60%. Severe osteopenia was greater in the lumbar area (43.3% or 29 patients) as compared to the hip (41.8% or 28 patients), spine (40.3% or 27 patients) and the femoral neck (31.3% or 21 patients), but the difference between the groups was not significant ($p=0.55$) (Figure 1). The majority of patients (49) were in treatment with steroids, alone or in combination with

Figure 1. Bone Mineral Density



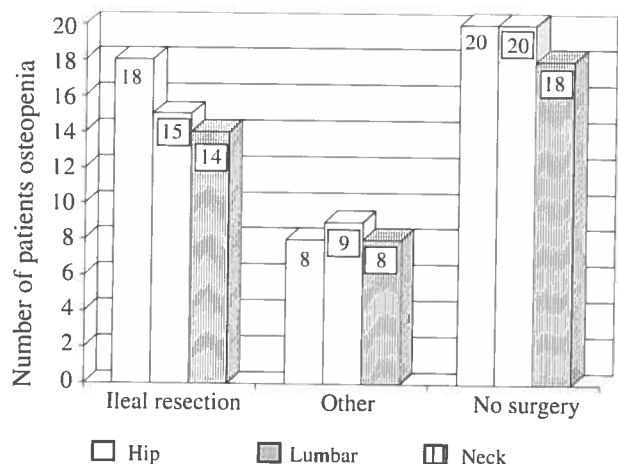
other medications for Crohn's disease. Osteopenia was more frequent in the group of patients that received steroids as compared to patients without steroid use (Figure 2), but the difference was not statistically

Figure 2. Osteopenia and Steroids



significant ($p>0.05$). Osteopenia and severe osteopenia were not significantly different in patients with an ileal resection as compared to patients with no surgery or other types of surgery (Figure 3). There was no significant sex difference in the prevalence of osteopenia or severity of Z scores ($p>0.2$). The grade of osteopenia did not correlate significantly with body mass index, duration of disease, disease location, extent of disease, treatment, surgery or any measured biochemical parameter ($p>0.05$).

Figure 3. Osteopenia and Surgery



Discussion

Our results show that low bone mass density (BMD) is a common complication in Puerto Ricans with Crohn's disease. Low BMD is a major clinical problem in Inflammatory Bowel Disease, especially in Crohn's disease, with a reported prevalence of 30%- 60 % in prospective and cross sectional studies (35). Osteopenia is an acknowledged risk factor for bone fractures in CD and can lead to serious morbidity. Assessing the bone density of patients with CD is important since preventive measures and newer therapeutic options with the potential to obviate this complication are becoming available.

Although the difference was not statistically significant, we found a larger number of patients with osteopenia among those using steroids as compared to those not using steroids. Corticosteroid use has been implicated as one of the mechanisms of osteopenia in CD and has been considered one of the major determinants of bone mass density in this disease (31), but the contribution of steroids to osteoporosis in CD is controversial. Pigot et al reported that loss of mineral density was more prominent in the proximal femur of patients receiving steroids (6). We found no difference in the degree of bone loss in any of the examined areas in patients with corticosteroid therapy. The lack of correlation between osteopenia and steroids in our study could be explained by the intermittent course of this treatment in these patients, a finding demonstrated by Pigot (6). Calculation of lifetime steroid dose is difficult because the treatment is usually intermittent, tapering and of varying duration and dose. Robinson et al estimated total lifetime dose of steroids from the records and information obtained from the patients and were unable to find any difference in bone mass density correlating with steroid use. (31). This suggests that there must be other factors that play a major role in the pathogenesis of osteoporosis in CD.

It has been suggested that disease activity has a greater role in diminished BMD in patients with CD (35). Inflammatory mediators released from the gut have a direct effect on bone turnover (31). The principal cytokines released by the inflammatory cells of the intestine in CD are tumor necrosis factor alpha (TNF- α), interferon gamma and interleukin 6. These cytokines, particularly TNF- α , disproportionately stimulate osteoclast activity, resulting in an imbalance in the regulation of bone metabolism (35).

The mechanism of reduced bone density seems to be due to increased bone resorption without a compensatory increase in bone formation, which differs from that found in other metabolic bone diseases (29). We analyzed bone turnover in a sample of patients with CD by measuring

osteocalcin (osteoblast activity) and iPTH (osteoclast activity), substances believed to be specifically related to the extent of bone formation and degradation. No correlation was found between the grade of osteopenia and these biochemical parameters.

It has been suggested that patients requiring surgery have more severe disease with a longer cumulative inflammatory effect (31). Robinson et al found a lower BMD in patients with intestinal resection, although the type of resection was not important (31). When we compared the degree of osteopenia with prior history of intestinal surgery considering ileal resection as one group, we did not find any difference between the groups, suggesting that surgery was not a determinant factor for osteopenia in our population.

Low bone mineral density is a predictor for an increased risk of bone fractures, thus placing patients with CD in this high risk group. Multiple factors seem to contribute to the osteopenia in these patients. Further studies are needed to establish the role of each of these factors in the individual patient and identify specific approaches to the treatment and prevention of this complication. Meanwhile, the physician taking care of patients with Crohn's disease should be aware of this possibility and take the necessary steps for early diagnosis and treatment.

Resumen

La osteopenia se ha asociado a Enfermedad Inflamatoria de Intestino (EII), y en particular a enfermedad de Crohn. Se han considerado el uso de corticoesteroides, resección de ileón, malabsorción, pobre ingesta de calcio, y el efecto de citocinas inflamatorias como factores contribuyentes a la osteopenia. Ya que la enfermedad de Crohn es más común en personas jóvenes, edad en que se logra la masa ósea máxima, la presencia de osteopenia tiene una significancia particular. Los propósitos de este estudio fueron evaluar la densidad ósea en pacientes de la Clínica de EII de la Universidad de Puerto Rico con enfermedad de Crohn; determinar la prevalencia de osteopenia en estos pacientes y correlacionar la densidad ósea con factores de riesgo para osteopenia. Sesenta y seis pacientes, 30 hombres y 36 mujeres, fueron incluidos. Luego de obtener consentimiento, se obtuvieron datos clínicos y metabólicos. Se midieron niveles séricos de albúmina, calcio, fósforo inorgánico y fosfatasa alcalina, y se calculó el índice de masa corporal. La densidad ósea se determinó por DEXA de la columna lumbar y el fémur y se expresó como puntuación Z (desviaciones estándar del normal correlacionadas con edad y sexo). Osteopenia severa se definió por una $Z \geq -2$ y osteopenia por $Z \leq -1.99$ ó ≥ 1.01 . Los resultados se expresaron en medianas. El

coeficiente de correlación de Pearson se usó para variables cuantitativas y la chi cuadrada de Pearson para variables categóricas. Se encontró osteopenia en la cadera en 69% y en la espina lumbar en 68%. La mayoría de los pacientes había recibido esteroides; la diferencia entre los tratados y los no tratados no fue significativa. La osteopenia no correlacionó con resección de ileón, sexo, índice de masa corporal, características de la enfermedad o parámetros bioquímicos. Se concluye que una disminución en la densidad ósea es frecuente en los pacientes con enfermedad de Crohn, aunque no se identificó un factor de riesgo en particular. La densidad ósea se debe determinar en todo paciente con la enfermedad de Crohn para poder instituir medidas terapéuticas apropiadas lo más temprano posible.

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