ORIGINAL ARTICLE

Longitudinal study of bone mineral density in children after a diagnosis of Crohn’s disease

Suivi longitudinal de la densité minérale osseuse depuis le diagnostic dans la maladie de Crohn de l’enfant

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Available online 23 August 2010

Summary
Aim. — The purpose of this study was to measure the bone mineral density (BMD) of children with Crohn’s disease (CD) and to prospectively assess its evolution.

Patients and methods. — A total of 27 children (20 boys, seven girls), aged 12.1 ± 2.5 years, were recruited at the time of CD diagnosis. Dual-energy X-ray absorptiometry (DEXA) was used to measure BMD, expressed as Z scores for chronological age (BMD/CA) and bone age (BMD/BA).

One year later, BMD was measured again to identify any correlations with disease activity [group A (active disease) vs group R (remission)].

Results. — BMD/CA and BMD/BA were negatively correlated with delay in diagnosis (P < 0.0001 and P < 0.05, respectively). BMD/CA was less than −2 standard deviation (SD) in nine patients and BMD/BA was less than −2 SD in four patients. At the follow-up, the increase in BMD was smaller in group A (n = 14), whether expressed as absolute values (−0.002 vs 0.040 g/cm² per year; P < 0.024) or as percentages (−0.2 vs 6.6%; P < 0.041); changes in BMD/CA (−0.5 vs −0.1 SD/year) and BMD/BA (−0.3 vs 0 SD/year) did not differ.

Conclusion. — Diagnostic delay greatly affects BMD in children with CD even prior to corticosteroid therapy. The risk of low BMD increases with persistent CD activity, although the risk is reduced in association with bone maturation delay.

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Introduction

The pediatric population accounts for approximately 7% of Crohn’s disease (CD) patients in the Brittany registry [1].
The majority of those affected are adolescents or preadolescents in the process of acquiring their peak bone mass, a major determinant of their later potential for osteoporosis. CD-induced osteoporosis is defined as osteoporosis with decreased bone mass, low-level bone remodeling, and an altered microstructure in both cortical and trabecular bone [2]. Different techniques are available to measure bone mineral density (BMD), including standard X-rays, ultrasonography and quantitative computed tomography (CT). However, dual-energy X-ray absorptiometry (DEXA), which can be applied via several different techniques, is the most commonly used because it is readily available, precise, rapid and reproducible, and requires minimal radiation exposure [3,4]. A recent publication evaluating the practices of 166 pediatric gastroenterologists in the United States, Canada, Western Europe and Israel found that BMD was determined in around 45% of children with CD [5]. Osteopenia and osteoporosis— which arise through a still undefined, but multifactorial, mechanism— are common, but often underestimated, complications of CD. Given the diversity of measurement methods and the lack of consensus over the definition of osteopenia in CD (in certain studies, a BMD of measurement methods is not used for the analysis because of the difficulty in collecting reliable cumulative data. All children were given oral vitamin D supplementation (100,000 IU/3 months), and their dietary calcium intake was also evaluated.

**Statistical analysis**

SPSS 15.0 software for Windows was used for the statistical analyses. Spearman’s coefficient of correlation was used to quantify the association between BMD (CA and BA) and quantitative variables. The non-parametric Mann—Whitney test was used to compare BMD (CA and BA) with qualitative variables, and Fisher’s exact test was used to search for correlations between qualitative variables. Wilcoxon’s test was used for the prospective follow-up, an assessment 1 year after CD diagnosis was targeted. Variables recorded included clinical data (time between the two BMD measurements, gains in weight and height expressed in SD, increases in BMI expressed in percentiles, growth rate, summary of treatments received and disease activity) and radiographic data (gain in bone age, BMD (absolute value and percentage), and BMD/CA and BMD/BA expressed in SD). As no clinical score has been validated to classify disease activity over a 1-year period in the pediatric population, the present study patients were assigned to one of three categories, depending on their overall disease activity as assessed over the study period using the Harvey—Bradshaw (HB) index score [19]. Patients in remission at all visits during the year following diagnosis and initiation of treatment were scored as ‘0’ (HB score < 5 at all visits), while the score assigned was ‘1’ if the child had experienced a period of disease activity (at least one HB score ≥ 5). Chronically active disease (HB score ≥ 5 at all visits) was scored as a ‘2’. Treatments given during the follow-up period were recorded, and included nutritional treatment (continuous or discontinuous enteral nutrition), corticosteroid therapy and azathioprine. When a prescription was available, the number of months of treatment during the year was noted. For corticosteroids, the cumulative dose was not used for the analysis because of the difficulty in collecting reliable cumulative data. All children were given oral vitamin D supplementation (100,000 IU/3 months), and their dietary calcium intake was also evaluated.
Table 1: Clinical, biological, endoscopic, histological and radiological data in the study population at the time of Crohn’s disease diagnosis (n = 27).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Patients (boys/girls)</td>
<td>27 (20/7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.1 ± 2.5 (12.5; 7.2–15.9)</td>
</tr>
<tr>
<td>Delay to diagnosis (years)</td>
<td>1.1 ± 1.3 (0.5; 0.1–6.5)</td>
</tr>
<tr>
<td>Body weight (SD)</td>
<td>−0.4 ± 0.9 (−0.3; −2.2–1.3)</td>
</tr>
<tr>
<td>Height (SD)</td>
<td>0 ± 1.1 (0.2; −2.8–2.2)</td>
</tr>
<tr>
<td>Growth rate (SD)</td>
<td>−3.0 ± 2.0 (−3.3; −6.0–1.5)</td>
</tr>
<tr>
<td>Growth rate by bone age (SD)</td>
<td>−2.5 ± 2.4 (−2.8; −6.0–3.0)</td>
</tr>
<tr>
<td>Body mass index (percentiles)</td>
<td>27.7 ± 20.5 (30.0; 1.0–80.0)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.1 ± 1.1 (11.1; 8.4–13.6)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>34.8 ± 27.3 (29.0; 3.5–114.0)</td>
</tr>
<tr>
<td>Localizations and histology</td>
<td></td>
</tr>
<tr>
<td>Small bowel and colon [n (%)]</td>
<td>16 (59.3%)</td>
</tr>
<tr>
<td>Small bowel only [n (%)]</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Colon only [n (%)]</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Anoperineal involvement [n (%)]</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Extradigestive involvement [n (%)]</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Giant-cell epithelioid granuloma [n (%)]</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>Radiological variables</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis to X-ray workup (months)</td>
<td>0.8 ± 0.8 (0.0–3.0)</td>
</tr>
<tr>
<td>Bone age (years)</td>
<td>11.7 ± 2.5 (11.5; 8.0–18.0)</td>
</tr>
<tr>
<td>Retardation in bone age (years)</td>
<td>−0.5 ± 1.3 (−0.3; −3.0–3.2)</td>
</tr>
<tr>
<td>Bone mineral density, absolute value (g/cm²)</td>
<td>0.645 ± 0.1 (0.6; 0.5–0.9)</td>
</tr>
<tr>
<td>Bone mineral density/CAa (SD)</td>
<td>−1.7 ± 0.8 (−1.6; −3.2–0.3)</td>
</tr>
<tr>
<td>Bone mineral density/BAb (SD)</td>
<td>−1.4 ± 0.7 (−1.4; −2.6–0.6)</td>
</tr>
</tbody>
</table>

Data are expressed as means ± standard deviation (median; range).

a Z score for chronological age (CA).

b Z score for bone age (BA).

Results

During the study period, 87 patients were managed for CD at the Rennes University Hospital, and 27 of these patients met the inclusion criteria for the present study. A total of 54 children were excluded from the analysis because of long (> 3 months) delays between CD diagnosis and the first assessment of BMD; these long delays were generally due to the fact that the diagnosis had been established in another institution before referral to the specialized pediatric unit. A further six children were excluded because corticosteroid therapy had been started before the first assessment of BMD. None of the patients had active disease other than CD, and none were receiving treatment unrelated to their CD. The data collected at the time of diagnosis in the 27 recruited children are presented in Table 1. Between the time of diagnosis and the first BMD, 20 patients were given aminosalicylates only (74%), three received budesonide alone (11%) and four had no treatment (15%).

Data from the bone workups at diagnosis are also shown in Table 1. Bone age was less than −1 SD in nine (33%) children. The BMD/CA and BMD/BA scores gave different assessments of osteopenia and osteoporosis. The Z score was greater or equal to −1 SD for both BMD/CA and BMD/BA in seven patients. Using the BMD/CA, 11 patients exhibited osteopenia and nine showed osteoporosis. With the BMD/BA, 17 exhibited osteopenia and three had osteoporosis.

Three quantitative variables (weight in SD, height in SD, delay to diagnosis) were significantly correlated with BMD at the time of diagnosis (Table 2). There was a negative correlation between BMD (both CA and BA) and delay to diagnosis (P = 0.0001 and P = 0.026, respectively; Figs. 1 and 2). However, no correlations were found between BMD and the other variables studied (growth rate, BMI, bone age, gender, disease localization, biochemistry, histology and treatment).

Changes in clinical and radiographic findings during the year-long follow-up are presented in Table 3. Of the 27 patients included at the time of CD diagnosis,
Table 2  Correlation test results (Spearman’s) for bone mineral density (BMD) and diagnostic delay, and weight and height at the time of diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>BMD/CA&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th>BMD/BA&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>&lt;i&gt;P&lt;/i&gt;</td>
<td>Correlation coefficient</td>
</tr>
<tr>
<td>Diagnostic delay</td>
<td>−0.636</td>
<td>0.0001</td>
<td>−0.427</td>
</tr>
<tr>
<td>Weight (SD)</td>
<td>0.421</td>
<td>0.029</td>
<td>0.456</td>
</tr>
<tr>
<td>Height (SD)</td>
<td>0.597</td>
<td>0.001</td>
<td>0.493</td>
</tr>
</tbody>
</table>

<sup>a</sup>  Z score for chronological age (CA).

<sup>b</sup>  Z score for bone age (BA).

Figure 1  Correlation between bone mineral density by chronological age (BMD/CA) and the time of diagnosis and diagnostic delay.

Figure 2  Correlation between bone mineral density by bone age (BMD/BA) and the time of diagnosis and diagnostic delay.

Table 3  Changes in clinical and radiological data in the study population (n = 22) between baseline bone mineral density (BMD1) and the 1-year follow-up (BMD2).

<table>
<thead>
<tr>
<th>Clinical data</th>
<th></th>
<th>22 (16/6)</th>
<th>1.34 ± 0.5 (1.2; 0.8–2.3)</th>
<th>0.1 ± 0.3 (0.1; −0.7–1.2)</th>
<th>0 ± 0.5 (0; −1.1–1.5)</th>
<th>−0.2 ± 2.2 (−0.1; −5.0–3.0)</th>
<th>10.4 ± 21.9 (2.6; −20.3–65.4)</th>
<th>0.8 ± 0.7 (0.9; 0–2.6)</th>
<th>+4.4 ± 11.8 (1.9; −14.9–47.7)</th>
<th>−0.3 ± 0.5 (−0.3; −1.5–0.4)</th>
<th>−0.2 ± 0.5 (−0.21; −1.1–0.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (boys/girls) (n)</td>
<td>Time between assessments (years)</td>
<td>Gain in weight (SD/year)</td>
<td>Gain in height (SD/year)</td>
<td>Growth rate by chronological age (SD)</td>
<td>Growth rate by bone age (SD)</td>
<td>Gain in BMD (percentiles/year)</td>
<td>Disease activity level:</td>
<td>0 (remission; n)</td>
<td>8</td>
<td>Gain in BMD (%/year)</td>
<td>Gain in BMD/CA&lt;sup&gt;a&lt;/sup&gt; (SD/year)</td>
</tr>
<tr>
<td></td>
<td>1.34 ± 0.5 (1.2; 0.8–2.3)</td>
<td>0.1 ± 0.3 (0.1; −0.7–1.2)</td>
<td>0 ± 0.5 (0; −1.1–1.5)</td>
<td>−0.2 ± 2.2 (−0.1; −5.0–3.0)</td>
<td>−0.2 ± 2.2 (0.5; −6.0–3.5)</td>
<td>10.4 ± 21.9 (2.6; −20.3–65.4)</td>
<td>Disease activity level:</td>
<td>0 (remission; n)</td>
<td>8</td>
<td>Gain in BMD (%/year)</td>
<td>Gain in BMD/CA&lt;sup&gt;a&lt;/sup&gt; (SD/year)</td>
</tr>
<tr>
<td></td>
<td>0.1 ± 0.3 (0.1; −0.7–1.2)</td>
<td>0 ± 0.5 (0; −1.1–1.5)</td>
<td>−0.2 ± 2.2 (−0.1; −5.0–3.0)</td>
<td>−0.2 ± 2.2 (0.5; −6.0–3.5)</td>
<td>10.4 ± 21.9 (2.6; −20.3–65.4)</td>
<td>Result are expressed as means ± standard deviation (median, range).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>  Z score for chronological age (CA).

<sup>b</sup>  Z score for bone age (BA).
Table 4 Increases in bone age and bone mineral density (BMD), according to chronological age (CA) and bone age (BA), in children with active disease (group A) and in remission (group R).

<table>
<thead>
<tr>
<th>Gain</th>
<th>Group A (n = 14)</th>
<th>Group R (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone age (years/year)</td>
<td>+0.8 (0—2.6)</td>
<td>+0.9 (0—1.5)</td>
<td>NS</td>
</tr>
<tr>
<td>BMD (g/cm²/year)</td>
<td>−0.002 (−0.088—0.093)</td>
<td>+0.040 (0.001—0.264)</td>
<td>0.024</td>
</tr>
<tr>
<td>BMD (%/year)</td>
<td>−0.2 (−14.9—14.2)</td>
<td>+6.6 (0.1—47.7)</td>
<td>0.041</td>
</tr>
<tr>
<td>BMD/CA (SD/year)</td>
<td>−0.5 (−1.5—0.4)</td>
<td>−0.1 (−0.4—0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>BMD/BA (SD/year)</td>
<td>−0.3 (−1.1—0.9)</td>
<td>0.0 (−0.6—0.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as medians (minimum—maximum). NS: not significant.

Second-assessment data were available for 22 (follow-up was < 1 year for one patient, and four others were lost to follow-up). Regarding therapeutic regimens, eight patients were given prednisone for a median duration of 6.4 months/year (range: 1.4—10.3 months), five received enteral nutrition for a median 2.6 months/year (range: 1.2—10.8 months) and 11 took azathioprine for a median 10.8 months/year (range: 1.2—12 months). At the second assessment, BMD/CA revealed osteopenia in 13 patients and osteoporosis in eight. However, after correction for bone age, nine children had osteopenia and eight still had osteoporosis.

There was a positive correlation between increases in BMD (both CA and BA) and weight and height (P < 0.05) at the second assessment. However, no correlations were found with growth rate, BMI, bone age, gender, disease localization, CRP, presence of granuloma or treatment.

Variations in age, BMD as a percentage, and BMD/CA and BMD/BA between the two assessments are presented in Table 4 as a function of disease activity (adjusted for 1 year). During the follow-up, the increase in BMD was significantly less in patients with active disease (group A). In the 14 children in this group, there was a fall in the absolute value of BMD in eight, whereas none of the eight children in remission (group R) exhibited any decline in absolute BMD values (57.1 vs 0%, respectively; P = 0.018, Fisher’s exact test). Individual variations in BMD/CA and BMD/BA are shown in Figs. 3 and 4.

Multivariate analyses using the variables of age, gender, disease localization, disease activity and treatments received failed to identify any variable that significantly correlated with a gain in either BMD/CA or BMD/BA between the two assessments.

Discussion

Osteoporosis has recently been recognized as a consequence of inflammatory bowel disease and, in particular, CD. Sev-
eral risk factors increase susceptibility to a decreased BMD, including inflammation, malnutrition, deficit in lean body mass [20], hypogonadism, reduced physical activity and glucocorticoids. Such a decrease may be especially significant if it occurs when bone mass is being acquired [21]. Given the lack of a precise definition, it is difficult to obtain exact figures for the prevalences of osteopenia and osteoporosis in the pediatric population [22], particularly when different techniques and measuring devices are used. One of the obstacles for the present study was the lack of a reference standard for French children. For this reason, an ethnically similar reference population was used instead. The present study was also designed so that the recruited children served as their own controls during the prospective follow-up. Furthermore, as this was an open study, the choice of treatment was a potential influence on the slow gains in bone age and bone density. However, in light of the reported incidence of osteoporosis in CD, it was considered unethical to propose a blinded long-term follow-up.

The present study showed that delayed diagnosis was one of the major factors affecting BMD, and it persisted even after adjusting for retarded bone maturation and before administration of corticosteroid therapy. This finding highlights the importance of early CD diagnosis and management. The age at the time of diagnosis in our series was similar to those of earlier reports, with the majority of patients diagnosed after the age of 10 years and mostly during puberty. As in other pediatric series, disease localization (small bowel or colon) was not a factor influencing BMD [13,14]. The predominant finding from the anthropometric data at the time of diagnosis was the inflection of the growth curves, as illustrated by the mean growth rate of $-3$ SD ($-2.5$ SD for bone age) for a nearly normal mean height. This demonstrates the importance of analyzing the dynamics of growth curves. According to Kanof et al. [23], slow growth is observed in 88% of patients at diagnosis, and a decline in growth rate is expected in 45% before the onset of other symptoms. Slow growth may be the earliest symptom of CD, and several mechanisms may be involved, including the inflammatory process [24].

Some studies have demonstrated reduced BMD in children at the time of CD diagnosis [6,13,16] or during the disease course [6,14,15,25–30]. Sylvester et al. and Dubner et al. [6,7,20] have reported on the only other longitudinal studies of BMD from the time of CD diagnosis. The present study found osteoporosis in 33% of the patients at diagnosis and in 36% at the second assessment. Corrected for bone age, these proportions were 11% at diagnosis and 36% at the second assessment. These findings are in agreement with the data in the literature. In their study, Harpavat et al. [13] evaluated BMD according to bone age at CD diagnosis in 18 patients who had not received corticosteroids before the assessment: 11% had a Z score $<-2$ SD. In their population of children with CD, Herzog et al. [14] defined osteoporosis as a Z score $<-2$ SD and found a prevalence of 44%. After correcting this figure for bone age, the prevalence fell to 26%. Sylvester et al. [6] found osteoporosis (by bone age) in 12% of their patients (7/58) at diagnosis and also at 2 years of follow-up. In their longitudinal 2-year study, the Z score for bone mineral content, adjusted for age and height, improved from $-1$ to $-0.5$ SD, and they also found a correlation between lean body mass and bone mineral content [20]. Dubner et al. [7] used a different measuring method (evaluating tibia bone volume by CT), but came to the same conclusion of deficient BMD at diagnosis, which persisted at the 1-year follow-up. Our present results confirm that osteoporosis is present at the time of CD diagnosis before treatment could have any impact and, also, that this deficit persists despite adequate disease management. However, it is not uncommon to observe slow or retarded growth and maturation processes (puberty, bone) in the pediatric population, making it difficult to interpret BMD values without taking into account bone maturation. The risk is overestimation of the true deficiency in BMD. For this reason, it is essential to assess BMD in terms of a Z score for bone age rather than chronological age [3,6,12–15,31], and to monitor its time course using the same corrected procedure.

In certain studies of pediatric populations, the loss of bone mass described in CD was attributed to the undesirable effects of corticosteroid therapy [25,26,28,29], although other, more recent, studies have not found such an association [6,7,13,14,16,27]. In our present study, corticosteroid therapy was not a risk factor. Indeed, although corticosteroids have a demonstrated deleterious action on bone metabolism in children and adolescents, in the specific context of chronic inflammatory disease, several factors that play a role in bone mineralization are, as yet, still unknown. Chronic inflammation is a major determinant of bone demineralization, and the intestinal mucosa in patients with CD is the site of enhanced production of proinflammatory cytokines (interleukin-1β, interleukin-6, tumor necrosis factor-α) that stimulate osteoclastic activity [32]. Corticosteroids have a powerful anti-inflammatory effect and, despite their deleterious effect on bone, can impede the deleterious effect of cytokines on bone mineralization [33] and could even be considered, in certain situations, to have bone-sparing effects. As corticosteroids are often prescribed in situations involving severe inflammation, it is inadvisable to attempt to choose between steroids or the inflammatory syndrome as the cause of bone demineralization. The only way to distinguish the relative roles of inflammation and corticosteroid therapy in bone demineralization would be via a longitudinal study using a blinded protocol and inclusion at diagnosis of a large number of patients.

In addition, no validated index of annual disease-activity levels is available for the pediatric population and, so far, the data collected on the association between disease activity and BMD changes have been contradictory. Most studies in the literature have assessed the influence of disease activity based on scores generally used to assess flare-ups (as done here using the HB score) and have failed to demonstrate any such association [6,28,34], except for Semeao et al. [29], who used different indicators of disease severity (number and duration of hospital stays). In the present study, it was found that the persistence of active disease increases the risk of poor bone mineralization. The results also show that all children in remission at the second assessment had an increase in BMD, whereas half the children treated for relapse showed decreased bone mass, independent of the treatment received. All of the present results are in agreement with a better gain in BMD in group R than in group A, although the only significant finding was the increase in absolute BMD value. Certainly, however, sam-
ple size was a limiting factor in our analyses. Nevertheless, however the change in BMD is expressed, the gain in absolute values observed in children in remission, and independent of treatment, is a favorable finding.

In the present study, as in others, the use of immunosuppressants did not correlate with any effect on bone mineralization [35]. One study in pediatric patients described enteral nutrition as a factor related to decreased BMD and also concluded that this was an indirect marker of disease activity. That study, however, was not a longitudinal analysis [29].

**Conclusion**

The most important element in the regulation of osteogenesis in CD appears to be the severity of the disease itself. For this reason, the main target for limiting bone complications in CD, besides early diagnosis, is early sustained remission. Thus, in addition to careful surveillance of growth curves, pediatric gastroenterologists should focus on regular measurements of BMD, with correction for bone age, to identify patients at risk of bone complications and, consequently, to initiate preventative and curative measures as early as possible. Further studies should also be undertaken to follow larger cohorts of patients over several years to assess the relative impacts of nutritional factors, bone age, therapeutic interventions and disease activity on the development of bone mass.

**Conflict of interest**

The authors have no conflict of interest for this article.

**References**


