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An Instrument to Measure Skeletal Burden and Predict Functional Outcome in Fibrous Dysplasia of Bone

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ABSTRACT: An instrument to measure skeletal burden in fibrous dysplasia was developed. Biological and clinical relevance was shown by correlating skeletal burden scores with bone markers, quality of life, and ambulatory status. Childhood scores predict adult ambulatory status, and scores were unaffected when bone markers decreased with bisphosphonate treatment or aging.

Introduction: Fibrous dysplasia (FD) is a skeletal disease with a broad clinical expression. There is no objective method to assess the extent of skeletal involvement or predict outcome. We developed an instrument to measure skeletal burden that correlates with physical function, health-related quality of life (HRQL), and ambulatory status.
Materials and Methods: Seventy-nine patients with FD underwent bone scintigraphy. The skeletal burden score was derived from a weighted score based on the regional measurement using bone scintigraphy to estimate the amount of FD in anatomical segments. Six readers scored 20 scans twice to determine the inter- and intrareader agreement. To assess biological significance, scores were correlated with bone markers. To assess functional outcome, scores on the SF-36 (adults) or CHQ-PF50 (children) were correlated with skeletal burden scores. In a group of patients who had bone scans as children and adults ($n = 6$), the ability to predict ambulatory status was tested. Skeletal burden scores were assessed in patients before and after treatment with pamidronate ($n = 5$).
Results: The inter- and intrareader agreement of burden scores were $r = 0.96$, and 0.98, respectively ($p < 0.001$ for both). The scores correlated with markers of bone metabolism and HRQL (Spearman rho, 0.54–0.67 $p < 0.001$ and –0.43, $p = 0.001$, respectively). The mean score of patients who ambulated unassisted was significantly lower than those requiring assistance ($p < 0.001$ unassisted versus crutch and/or wheelchair). In unassisted ambulators, younger patients had higher scores, suggesting high childhood scores may predict adulthood impairment. In six patients with childhood and adulthood scans, childhood scores >30 predicted assisted ambulation in adulthood. There was a negative correlation between bone markers and age (Spearman rho, –0.42 to –0.70; $p < 0.001$), but not age and skeletal burden score. Pamidronate treatment decreased serum alkaline phosphatase but had no effect on the skeletal burden score.
Conclusions: This is a validated and reliable instrument for the measurement of skeletal burden of FD and is able to predict functional outcome.
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Key words: fibrous dysplasia, outcomes(s), instrument, disease burden, McCune-Albright syndrome, *GNAS*

INTRODUCTION

Fibrous dysplasia (FD) of bone is a skeletal disease in which normal bone and bone marrow are replaced by an abnormal fibro-osseous tissue, including an expanded population of osteogenic precursors.[1,2] Disease severity covers a broad spectrum. It can be limited to a single skeletal site (monostotic FD [MFD]), multiple sites (polyostotic FD [PFD]), or involve virtually the entire skeleton (panostotic FD).[3,4] The molecular etiology is somatic activating mutations in osteoprogenitor cells of the cAMP regulating protein $G_s\alpha$, which is coded for by the *GNAS* gene.[5–7] It is believed that the phenotype is explained by how early or

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late in development these mutations arise.[2] Mutations arising late in development may give rise to limited disease (MFD), and mutations arising early in development more extensive disease (PFD or panostotic disease). PFD is frequently associated with some combination of café-au-lait skin pigmentation, renal phosphate wasting,[8] and hyperfunctioning endocrinopathies, such as gonadotropin-independent precocious puberty, peripheral hyperthyroidism, and/or growth hormone excess.[9] When associated with these extraskeletal findings, it is known as McCune-Albright syndrome (MAS).[10–12]

The broad spectrum of disease expression, coupled with the lack of a method by which to quantify skeletal burden, makes it difficult to compare the results of studies of patients with FD. The rarity of the disease makes it difficult for most clinicians, who have seen few patients, to judge the relative disease severity. Our long-term observation of FD patients has suggested that children, who have significant skeletal disease at presentation are usually relatively functional, but often end up with significant functional impairment in adulthood. An objective measurement of the skeletal burden that predicts clinical outcome would be useful for prognostication. At present, there is no objective way to quantify the severity of skeletal disease (skeletal burden). In general, markers of bone metabolism correlate with disease activity, but these decrease with aging and in response to treatment with bisphosphonate medications.[9,13] Several studies have used a system developed by Feuillan to classify patients.[14] However, this system is relatively subjective, categorizes patients largely on a functional basis, and lacks validation.

Bone scintigraphy, using ^{99m}Tc-labeled bisphosphonate methylene diphosphonate (^{99m}Tc-MDP) is exquisitely sensitive for detecting FD lesions.[15] We took advantage of this point and used bone scintigraphy scans to detect lesions in this group of patients with FD. Using these scans, we developed and validated an instrument by which to quantify the amount of FD in each patient (skeletal burden score). To show that the skeletal burden scores were biologically and clinically meaningful, we correlated the scores with markers of bone metabolism, health-related quality of life (HRQL), and ambulatory status, and showed that high skeletal burden scores in young patients can predict functional outcome as adults. We showed that the skeletal burden score is unaffected by bisphosphonate treatment and aging, which are associated with a decreases in markers of bone metabolism.

MATERIALS AND METHODS

Patients

Seventy-nine patients were studied. All patients gave informed consent and were enrolled in an Institutional Review Board–approved study of patients with PFD/MAS at the NIH. The diagnosis of FD was established on clinical history, radiographic findings, and histopathological findings. When affected tissue was available, analysis of the *GNAS* gene for *R201* mutations was performed.[1] Forty-three of the patients (54%) had mutation testing performed. Fifty-three percent had *R201C* mutations, 42% had *R201H* mutations, and in 2%, no mutation was detected. All patients underwent an endocrine and metabolic evaluation to assess gonadal function, renal phosphate handling, thyroid function, and the growth hormone/insulin-like growth factor (IGF)-1 axis. The patients were studied as four groups. Group 1 consisted of 20 patients, who were used to assess inter- and intrareader agreement. These were the first 20 patients enrolled in the study that met the following criteria: a balance between males and females (10 males, 10 females), covered a broad age range (7–58 years), had not been treated with a bisphosphonate, and reflected the ratio of PFD to MAS patients in the larger study population (~1:4). Patients who were found to have poorly controlled endocrine diseases or untreated hypophosphatemia were excluded.

Group 2 was studied to show a relationship between skeletal burden score and markers of bone metabolism, HRQL, and ambulatory status. It consisted of the first 79 patients enrolled whose skeletal disease included involvement of the appendicular skeleton (i.e., those with only craniofacial FD were excluded). All patients completed the SF-36 (adults) or CHQ-PF50 (children). Patients were categorized as to their ambulation status: patients who ambulated without assistance most of the time were labeled "unassisted"; patients who used one or two crutches or a cane most of the time were categorized as "crutch"; and patients whose primary mode of ambulation was a wheelchair were categorized in the "wheelchair" group.

Group 3 was studied to show the ability to predict adult ambulatory status from childhood skeletal burden score. To be included, patients had to have had at least two bone scans: the first before the age of 12 and one after the age of 18. There were six patients that met this criterion. The first and the most recent bone scan were used for the analysis.

Group 4 was assessed to determine the effect of bisphosphonate treatment on skeletal burden score. This group consisted of five patients who had been treated with intravenous pamidronate at a minimum dose of 1 mg/kg/day for 3 days every 4 months for a minimum of 1 year, but no more than 3 years. Bone scintigraphy was performed before the initiation of treatment and after at least 1 year of treatment.

Several patients were in more than one group. None of the patients in group 1 had been treated with a bisphosphonate, and none of the patients had uncontrolled endocrine dysfunction or untreated hypophosphatemia. The demographics of the four groups are shown in Table 1.

Skeletal burden scoring instrument

All patients underwent ^{99}Tc-MDP bone scans using a standardized dosing and scanning protocol. The skeleton was subdivided into 11 discrete anatomic compartments (skull, right upper extremity, left upper extremity, right lower extremity, left lower extremity, spine, right ribs, left ribs, sternum, right pelvis, left pelvis; Fig. 1). The percent of each compartment that was involved with FD, as indicated by increased tracer uptake on bone scan, was estimated by the reader to be within the following ranges: 0%, 0–5%,

TABLE 1. PATIENT DEMOGRAPHICS

Group	n	Age		Male	Female	MAS	PFD
		Range	Median				
1. Validation	20	7–58	17	10	10	17	3
2. Ambulation	79	4–80	22	26	53	62	17
3. Ambulation prediction	6	4–10* 18–23†	8* 20†	0	6	6	0
4. Pamidronate	5	11–39	16	3	2	5	0

Group 1, inter- and intrareader reliability group; group 2, functional correlation group; group 3, ambulation prediction group (*childhood, †adulthood); group 4, pamidronate treatment group.

n = number of patients per group.

MAS, McCune-Albright syndrome; PFD, polyostotic fibrous dysplasia.

5–25%, 25–50%, and >50%. This nonlinear gradation with a maximum score of >50% was selected to minimize inter- and intrareader disagreement while maintaining physiologic/functional relevance. A difference of two grades would be unlikely (e.g., a score of 0–5% would be unlikely to be read as 25–50%). At the same time, maximum physiologic/functional effect is probably reached when >50% of a skeletal segment is involved with FD. This approach represents a modified amalgam of a number of approaches that have been used to quantify the degree of skeletal involvement in a number of diseases.[15–19]

The percent of the involved segment was multiplied by the percent of the total skeleton that the segment represents. The percent of the total skeleton of each compartment was derived from the literature (skull, 18.4%; right upper extremity, 9.5%; left upper extremity, 9.5%; right lower extremity, 21.0%; left lower extremity, 21.0%; spine, 8.3%; right ribs, 2.2%; left ribs, 2.2%; sternum, 0.3%; right pelvis, 3.7%; left pelvis, 3.7%).[20] For each skeletal compartment, the median of each estimated area was used in calculating the score as follows: 0 = 0%, 0–5 = 2.5%, 5–25 = 15%, 25–50 = 37.5%, and >50 = 75%. The skeletal burden score was derived from a formula that multiplied the median estimated percent area for each segment by a coefficient representing the percent of the total skeleton that that segment represents, yielding the following formula:

$$\text{Skeletal burden score} = (0.184 \times \text{skull area}) + 0.19 \times (\text{right upper extremity area} + \text{left upper extremity area})/2 + 0.42 \times (\text{right lower extremity area} + \text{left lower extremity area})/2 + 0.083 \times \text{spine area} + 0.044 \times (\text{right ribs area} + \text{left ribs area})/2 + 0.003 \times \text{sternum area} + 0.074 \times (\text{right pelvis area} + \text{left pelvis area})/2$$

For example, if the skull is scored as being 25–50% involved, that part of the equation was ($0.184 \times 0.375 = 0.69$). The range of possible scores is from 0 to 75.

Inter- and intrareader agreement

Inter- and intrareader agreement of the scoring instrument was determined by comparing the blinded readings of the same set 20 scans read twice (intrareader agreement) by six different readers (inter-reader agreement). The readers consisted of two nuclear medicine physicians (JCR and CCC), two endocrinologists (MTC and AG), and two research nurses (MHK and BB). There was a minimum of 1 week between an individual's first and second reading of a scan. Readers were unaware of the scores of the other readers, as well as the scores they assigned to a scan on the first scoring.

Markers of bone metabolism

Markers of bone metabolism are generally believed to correlate with and represent the degree of disease activity in FD. To assess whether the skeletal burden scores correlated with disease activity, the levels of the following markers of bone metabolism were assessed: alkaline phosphatase, bone-specific alkaline phosphatase, osteocalcin, pyridinium cross-links, deoxypyridinoline cross-links, and N-telopeptide. For serum measures (alkaline phosphatase, bone-specific alkaline phosphatase, and osteocalcin), serum was collected on 2 consecutive days at 8:00 a.m. after an overnight fast. The values were averaged. For urine measures (pyridinium cross-links, deoxypyridinoline cross-links, and N-telopeptide), two 24-h collections were averaged. All assays were standard commercially available assays, the specifics of which have been previously described.[8]

HRQL

HRQL was measured using the physical function domain of the SF-36 for adults and the CHQ-PF50 for children. The SF-36 and the CHQ-PF50 are widely used health status questionnaires.[21,22] These are short, multipurpose, validated, self-report health assessment tools composed of 36 (SF-36) or 50 (CHQ-PF50) questions that examine aspects of physical health. They are used in estimating the burden of different medical conditions, comparing health profiles, calculating treatment effects in clinical trials, and in monitoring health outcomes. Each domain is scored from 0 to 100, with a higher score correlating with better function. Norm-based methods are used to standardize scores using means, SD, and factor score coefficients for SF36 and CHQ-PF50 scales in the general U.S. population.[21,22]

Statistical analyses

Intrareader agreement was measured using the Pearson correlation coefficient, and inter-reader agreement was measured using the intraclass correlation coefficient. Spearman rho was used to measure the correlations among skeletal burden scores, markers of bone turnover, and age. Differences in skeletal burden scores among ambulation groups were compared using the Wilcoxon rank-sum test,

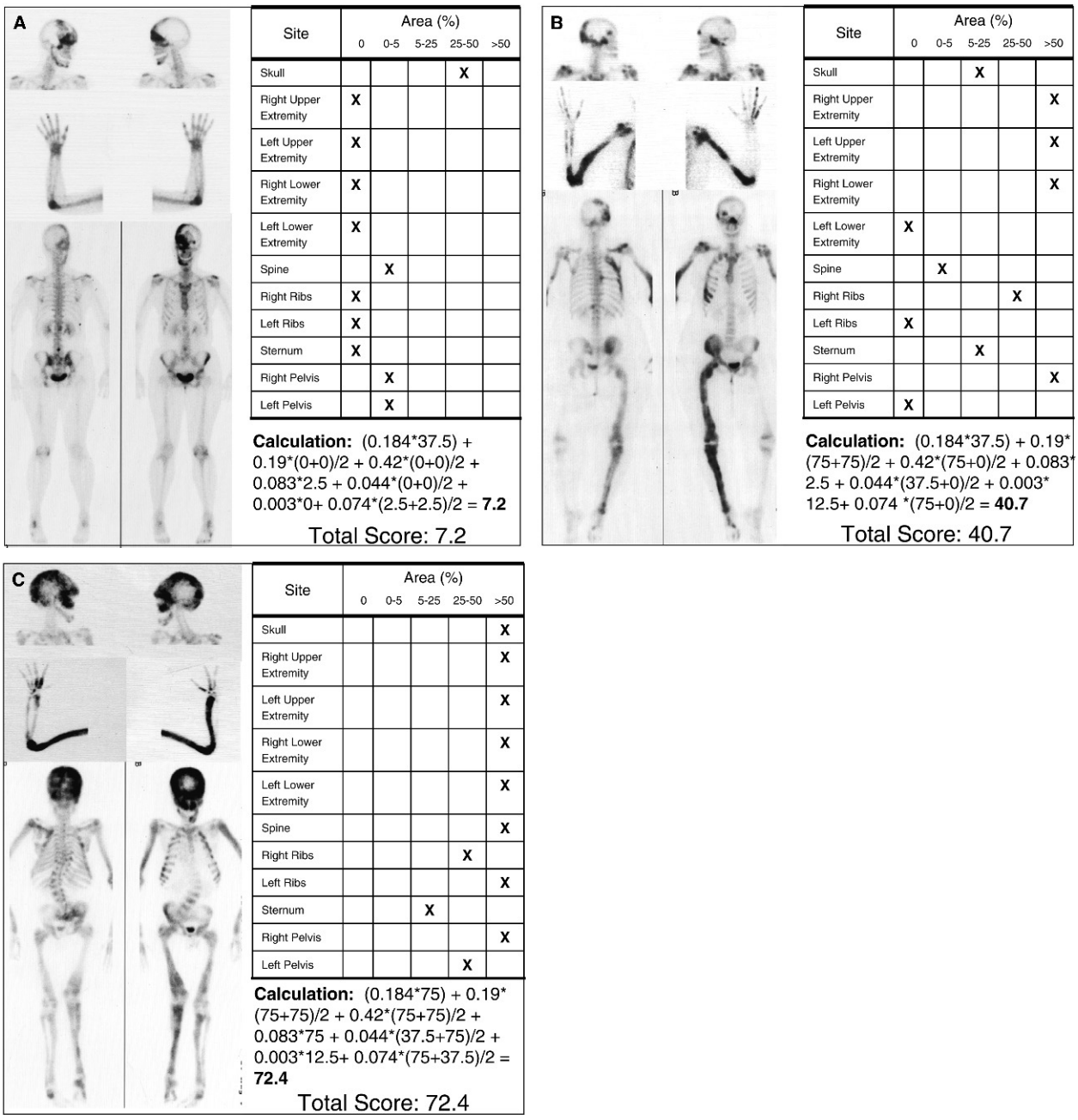

FIG. 1. Representative bone scans and skeletal burden scores. ^{99m}Tc-MDP bone scans from three patients with a spectrum of disease are shown together with the scoring form, and skeletal burden calculation. (A) Patient who ambulated without assistance. (B) Patient who ambulated with a crutch. (C) Patient that ambulated with wheelchair assistance.

and percent changes between before and after pamidronate treatment were compared using the Wilcoxon signed-ranks test; $p < 0.05$ was considered statistically significant. All analyses were performed using SAS (SAS Institute, Cary, NC, USA).

RESULTS

Skeletal disease burden scores and inter- and intrareader agreement

Typical bone scans with the accompanying scoring instrument and calculation, across a spectrum of disease severity (skeletal burden scores, 7.2–72.4), are shown in Figs. 1A–1C. The inter- and intrareader agreement on readings of 20 scans by six scorers, blinded to readings of the other scorers and their first scores, were $r = 0.96$, $p < 0.001$ and $r = 0.98$, $p < 0.001$, respectively.

Markers of bone metabolism

Figure 2 depicts the skeletal burden scores, levels of markers of bone metabolism, and the results of an analysis of the correlation between the two. The Spearman rho values were as follows: alkaline phosphatase (0.67), osteocal-

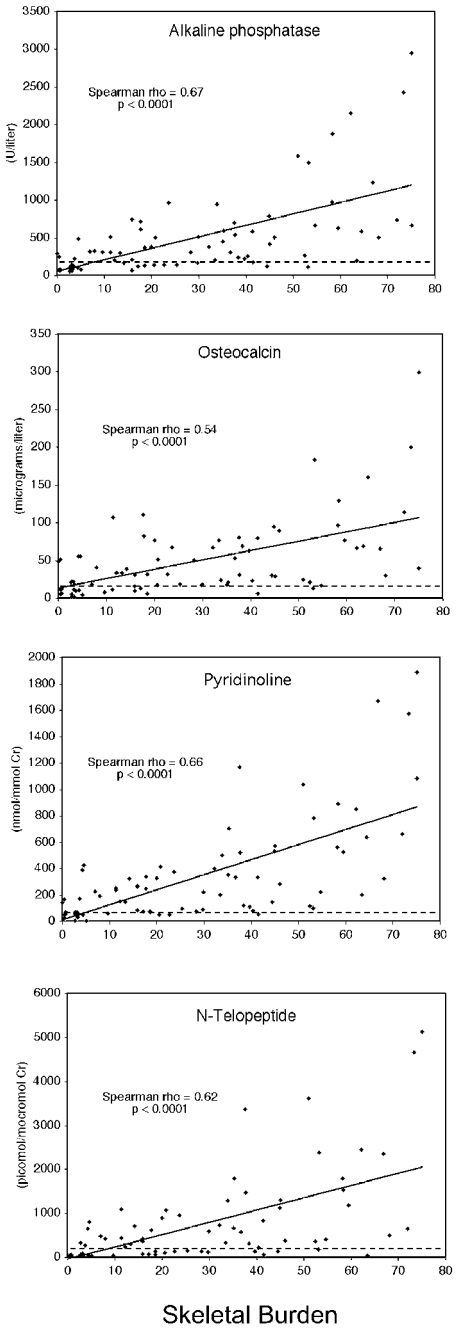

FIG. 2. Skeletal burden scores and markers of bone metabolism. The skeletal burden scores, markers of bone metabolism, and the results of correlation analyses for the 79 patients are shown. The transverse dashed lines in each panel represent the adult upper limit of the normal range.

cin (0.54), pyridinoline (0.66), and N-telopeptide (0.62). Not shown are bone-specific alkaline phosphatase (0.61) and deoxypyridinoline (0.65). For all markers, significance was $p < 0.001$. It is notable that the correlations on all markers are similar.

Functional relevance HRQL: There was a significant negative correlation between physical function and the skeletal burden score (Spearman rho = –0.43, $p = 0.001$; Fig. 3). This confirms that the greater the degree of skeletal involvement with FD, the greater the degree of impairment of physical function.

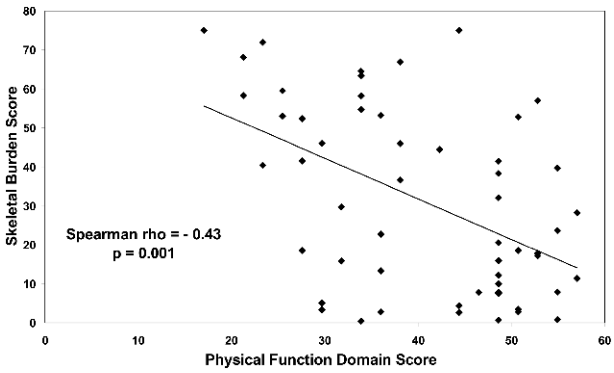

FIG. 3. Physical function and skeletal burden. The skeletal disease burden score, the score on the physical function domain of the SF-36 or the CHQ-PF50, and the correlation between the two are shown. The greater the skeletal burden of FD, the more impaired is physical function. The mean and SD for the U.S. population on both scales is 50 ± 10.

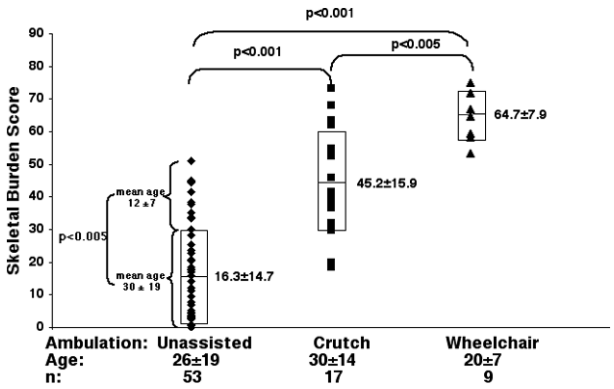

FIG. 4. Skeletal burden score according to ambulatory status. The skeletal burden score was determined in 79 patients with FD who had been categorized according to their ambulatory status. The mean score is indicated next to the shaded box, which represents 1 SD above and below the mean (crosshatch). The unassisted group was further divided into two subgroups: those with skeletal burden scores >1 SD and <1 SD above the mean. The subgroup with higher scores was significantly younger than those with lower scores. The crutch and wheelchair ambulators had significantly higher scores than patients who ambulated without assistance ($p < 0.001$), and the scores in the wheelchair group were significantly greater than in the crutch group ($p < 0.005$).

Ambulatory status: The skeletal burden score in a group of patients with FD who ambulated without assistance ($n = 53$) was 16.3 ± 14.7 (SD). In those who required the use of crutches ($n = 17$), the score was 45.2 ± 15.9, and in wheelchair-dependent ambulators ($n = 9$), the score was 64.7 ± 7.9. Scores in the groups requiring assistance were significantly higher than those in the unassisted group ($p < 0.001$), and the crutch group was significantly different from the wheelchair group ($p = 0.005$; Fig. 4). When the unassisted group was subdivided into two groups (scores >1 SD and <1 SD above the mean), the mean age of the group with higher scores was significantly less than that of the group with

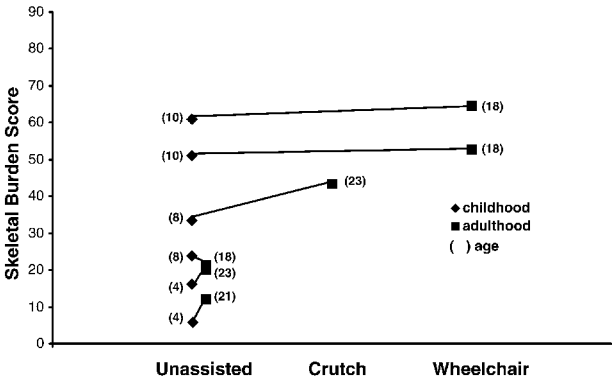

FIG. 5. Prediction of adulthood ambulatory status. The childhood and adulthood skeletal burden score and ambulatory status at the time of the bone scan in six patients are shown. The age at the time of the scan is indicated in parentheses next to the symbol. Each individual patient's set of childhood and adulthood scans is connected by a line. All patients ambulated without assistance as children, but those who had skeletal burden scores >30 ultimately required assistance with ambulation.

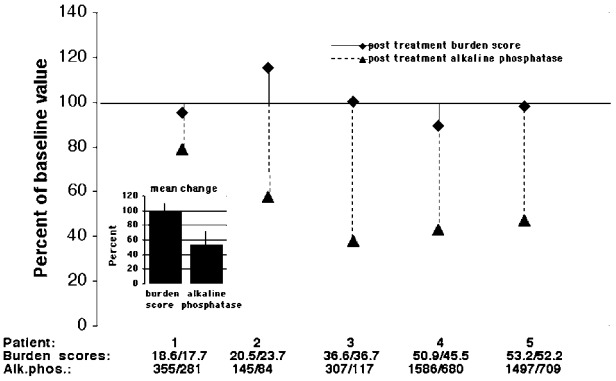

FIG. 6. Skeletal burden score and alkaline phosphatase in FD patients treated with pamidronate. The post-treatment skeletal burden scores and alkaline phosphatase levels (shown as percent of the pretreatment level) for five patients with FD treated with pamidronate (as detailed in the Materials and Methods section) are shown. The inset represents the mean percent changes and +1 SD for all five. For skeletal burden score, pre- versus post-treatment was $p = 0.63$ and for alkaline phosphatase was $p < 0.06$ (nonparametric test). The actual skeletal burden scores and alkaline phosphatase levels for each patient before and after treatment are indicated below the x axis. The skeletal burden score is unaffected by pamidronate treatment and does not vary with changes in serum alkaline phosphatase.

lower scores (12 ± 7 versus 30 ± 19; $p < 0.005$; Fig. 4). The majority of fractures in FD are completed by the age of 15 years.[23] The younger patients who ambulate without assistance have not yet completed this period, and thus, may have not yet incurred all of their fracture-related morbidity. It also suggests that the childhood skeletal burden score could be used to predict final ambulatory status. To test this, the childhood and adulthood ambulatory status in a group of six patients in whom childhood and adulthood skeletal burden scores were available were compared. In the children whose skeletal burden score was >30, final ambulatory status required assistance, even though none required assistance in childhood (Fig. 5).

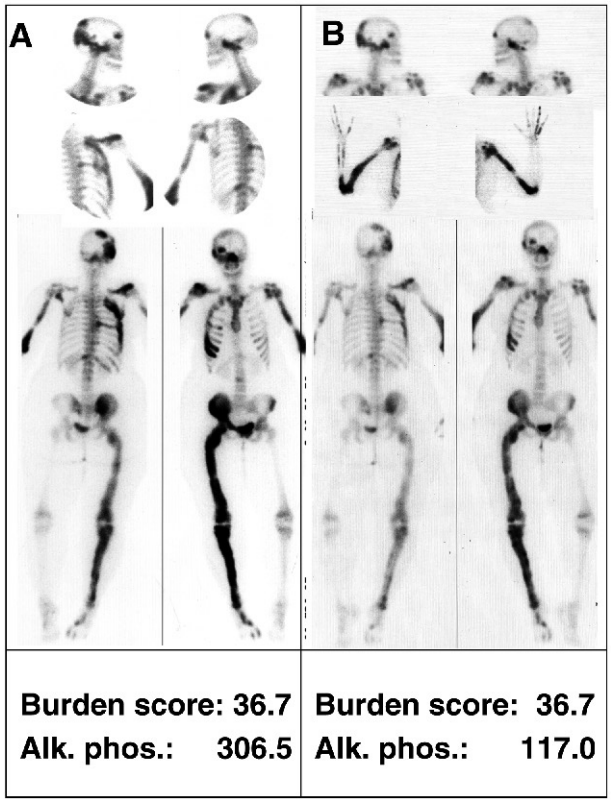

FIG. 7. Effect of pamidronate treatment. A representative set of pre- and post-treatment bone scans, skeletal burden scores, and alkaline phosphatase (alk. phos.) levels (A) before and (B) after pamidronate treatment in the same patient is shown. Note the significant change in alkaline phosphatase levels without changes in skeletal burden scores.

Pamidronate and age effect

In the group of patients who had been treated with the bisphosphonate pamidronate ($n = 5$), there was a decrease in the serum alkaline phosphatase in all subjects but no change in the skeletal burden score. The post-treatment alkaline phosphatase was 53.1% of the pretreatment score ($p = 0.06$), and the post-treatment bone scan score was 99.6% of the pretreatment score ($p = 0.63$; Fig. 6). A typical before and after bone scan and score are shown in Fig. 7. Similar patterns were seen for all the other markers of bone metabolism (data not shown). Furthermore, whereas a significant negative correlation could be shown between all six markers of bone metabolism and age (Spearman rho, –0.43 to –0.70; $p < 0.001$), there was not a significant correlation between the skeletal burden score and age (Spearman rho, –0.14; $p = 0.2$). Bisphosphonate treatment decreases markers of bone metabolism, but does not affect the skeletal burden score.

DISCUSSION

The tremendous variability in the degree of severity of FD has made it difficult to compare one patient or one

group of patients to another. Capitalizing on the fact that ^{99m}Tc-MDP bone scans are exquisitely sensitive at detecting the presence and extent of FD lesions, we used these scans to develop an instrument with which to measure the skeletal burden of FD. The instrument is simple and easy to use. It takes <5 minutes to score a scan and calculate the skeletal disease burden score. When the instrument is used by professionals with diverse backgrounds, there is a high degree of reader agreement.

Similar approaches have been developed using bone scintigraphy to measure skeletal burden for a number of diseases, including metastatic bone disease,[16,24] Paget's disease,[17] normal subjects,[18] and mixed metabolic bone diseases.[19] Some of these methods required calculations based on the counts generated and collected at the time of scanning. This is not useful for archived hardcopy scans, scans taken at different institutions, and scans performed under different conditions or with different counting technologies. Some techniques use subtraction of background activity from the activity of the diseased area with various imaging analysis technologies that can calculate intensities in regions of interest. All of these techniques are significantly more cumbersome, and none generated data of higher quality across such a broad spectrum of the amount of the skeleton susceptible to involvement as this instrument.

The scores generated with this instrument show biological significance by correlating with markers of bone metabolism. Correlations were equally strong for all markers of bone metabolism. Of note is the fact that the inexpensive marker, alkaline phosphatase, performed just as well as the significantly more expensive markers in correlating with the skeletal burden scores.

Whereas markers of bone metabolism may generally represent the activity of FD, there are circumstances in which the markers may change (the decrease in bone markers that occurs with age-related disease quiescence and bisphosphonate treatment). However, in both of these circumstances, the percentage of the skeleton involved with FD remains unchanged. Whereas markers may represent more subtle changes in cellular activity, they may not always accurately represent the "amount" of FD (skeletal burden). In this way, markers of bone metabolism and the skeletal burden score may yield complementary information. What occurs with bisphosphonate treatment and age highlights a phenomenon not normally observed: a divergence between markers of bone metabolism and the skeletal burden score. To some extent, this same divergence may also occur with aging in normal bone. In normal bone, markers of bone metabolism are higher in children, and this difference between young and old may be magnified in children with FD. This makes the use of markers of bone metabolism, as a sole measure of disease burden/activity, an unreliable measure for groups that include adults and children and/or patients that have been treated with bisphosphonates. For this reason, this scoring tool, which is unaffected by bisphosphonate treatment and aging, is of particular use. In this way, the bone scan and skeletal burden score serve as a "map" of the disease, a map that is established early and is unaffected by bisphosphonate treatment and aging.

Given that skeletal burden score reflects ambulatory status, this instrument may be useful in predicting functional outcome. This feature will be of particular use to clinicians caring for children with FD. The extent of skeletal involvement is established early in childhood at a time when, even with extensive disease, there is usually little functional impairment outside the perifracture period. With time, in children with extensive disease, there are likely to be multiple fractures and progressive deformity, which lead to significant functional impairment by adulthood. A high skeletal disease burden score in childhood (>30) may predict future functional impairment as an adult. This point is shown by the fact that patients who ambulated without assistance and who had high skeletal burden scores were younger than unassisted ambulators who had lower scores (Fig. 4) and the fact that there was a negative correlation with age and burden score in the unassisted ambulators. The mean skeletal burden scores of the patients in the unassisted (16.3), crutch (45.2), and wheelchair (64.7) groups can be used to roughly categorize patients as to having mild, moderate, or severe disease.

In conclusion, we have developed a simple and reliable instrument for the use of measuring skeletal burden in FD. It has both biological and functional significance and is unaffected by aging or bisphosphonate treatment. In addition, it is able to predict the final ambulatory status in young patients, and it is possible that this instrument could be applied to the assessment of other diseases in which there are variable amounts of skeletal involvement.

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