

Scoliosis in Fibrous Dysplasia/McCune-Albright Syndrome: Factors Associated With Curve Progression and Effects of Bisphosphonates

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ABSTRACT

Scoliosis is a complication of fibrous dysplasia/McCune-Albright syndrome (FD/MAS); however, risk factors and long-term outcomes are unknown. Bisphosphonates are commonly used; however, it is unknown whether their use decrease the risk of progressive scoliosis. Clinical data from the National Institutes of Health (NIH) cohort study was reviewed. Cobb angles were measured, and variables associated with scoliosis progression were identified. Of 138 subjects with available radiographs, 84 (61%) had scoliosis, including 55 (65%) classified as mild (Cobb angle >10 to ≤ 30 degrees), 11 (13%) as moderate (>30 to ≤ 45 degrees), and 18 (22%) as severe (>45 degrees). Total skeletal disease burden was highly associated with scoliosis severity ($p < 0.0001$). Endocrinopathies associated with scoliosis included fibroblast growth factor 23 (FGF23)-mediated hypophosphatemia ($p < 0.001$) and hyperthyroidism ($p < 0.001$). Bone turnover markers, including osteocalcin and NTX-telopeptides, were associated with severe scoliosis ($p < 0.01$). Associations were identified between Cobb angle and functional metrics, including leg length discrepancy ($p < 0.01$), hip range of motion ($p < 0.05$), and strength of the gluteus medius and maximus ($p < 0.01$). Longitudinal analyses were conducted in 69 subjects who had serial radiographs over a median 4.9-year period (range, 0.9 to 14.7 years). Twenty-two subjects were treated with bisphosphonates; there was no difference in Cobb angle progression compared to untreated subjects (0.10 versus 0.53 degrees/year, $p = 0.36$). Longitudinal data was available for 10 of 12 subjects treated with spinal fusion; one had instrumentation failure, but in nine subjects Cobb angles were stable with 6.1 years of follow-up (range, 0.9 to 14.7 years). Two fatalities from scoliosis-associated restrictive lung disease occurred in subjects managed non-operatively. Scoliosis occurs frequently in patients with polyostotic FD, and may be potentially fatal. The primary risk factor for progressive scoliosis is total skeletal disease burden. Treatable features that contribute to scoliosis progression include leg length discrepancy, FGF23-mediated hypophosphatemia, and hyperthyroidism. Current data do not support routine use of bisphosphonates to prevent progression of spinal curvature. Spinal fusion is frequently effective in providing long-term stability, and may be lifesaving. Published 2018. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS: ANTIRESORPTIVES; THERAPEUTICS; IMPLANTS; ORTHOPAEDICS; PRIMARY TUMORS OF BONE AND CARTILAGE; CANCER

Introduction

Fibrous dysplasia (FD) is a mosaic disorder arising from somatic activating mutations in $G\alpha_s$, resulting in the replacement of bone and marrow with fibro-osseous tissue.^(1,2) Discrete, expansile bone lesions lead to fractures, deformity,

functional impairment, and pain.⁽³⁾ FD can involve one bone (monostotic) or multiple bones (polyostotic), and can affect any part or combination of the skeleton.⁽³⁾ FD may occur in isolation, or in association with café au lait skin macules and hyperfunctioning endocrinopathies, including hyperthyroidism, precocious puberty, growth hormone excess, hypercortisolism, and fibroblast growth factor 23 (FGF23)-mediated

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hypophosphatemia. The combination of FD and one or more extraskeletal features is termed McCune-Albright syndrome (MAS).^(3,4)

Scoliosis is common in FD/MAS, and when severe can result in significant morbidity, including pain, functional impairment, and respiratory compromise.^(5,6) Risk factors for the development and progression of scoliosis in FD have not been determined, and long-term clinical outcomes are unknown. Bisphosphonates have been advocated as a potential treatment to decrease bone turnover and pain in FD patients^(7,8); however, there is little data associating bisphosphonate treatment with skeletal outcomes such as progression of scoliosis.

The purpose of this investigation was to define the spectrum and natural history of scoliosis in a large cohort of patients with FD/MAS, to identify clinical factors that contribute to progressive scoliosis, and to evaluate the effect of bisphosphonate treatment on the rate of scoliosis progression.

Subjects and Methods

Subjects

Subjects were evaluated at the National Institutes of Health (NIH) Clinical Center as part of a longstanding cohort study in FD/MAS (<http://clinicaltrials.gov/show/NCT00001727>). The study was approved by the Institutional Review Board of the National Institute of Dental and Craniofacial Research (NIDCR), and all subjects gave informed consent/assent. The diagnosis of FD/MAS was established on clinical grounds with molecular diagnosis as needed, according to previously reported guidelines.⁽³⁾ Spinal radiographs were obtained in subjects with significant involvement of the axial skeleton as assessed on bone scan, or those in whom scoliosis was suspected based on physical examination. All subjects with spinal radiographs available for Cobb angle measurement were included in the analyses.

Radiographic evaluation

Cobb angles were measured using a digital picture archiving and communication system (PACS) platform by a single reader (SHT). When multiple curves were present, the largest angle was utilized. Scoliosis severity was categorized into three groups: mild (>10 to ≤30 degrees), moderate (>30 to ≤45 degrees), and severe (>45 degrees).

The skeletal disease burden score (SDBS) is a quantitative measure of total skeletal FD involvement validated to predict clinical outcomes.⁽⁹⁾ SDBS was determined for all subjects from ⁹⁹Tc- methylene diphosphonate bone scintigraphy using previously reported methodology.⁽⁹⁾ These bone scans were also evaluated to identify FD in the cervical, thoracic, and lumbar spine.

Functional metrics

Subjects underwent physiatric evaluation, including assessment of leg length, hip range of motion, and muscle strength based on manual muscle testing. Age- and sex-adjusted Z-scores were determined for range of motion based upon previously established normative data.⁽¹⁰⁾

Bisphosphonate treatment

Information was collected regarding bisphosphonate treatment, including formulation, dose, and dates administered.

Statistical analysis

Statistical analyses performed with GraphPad Prism (version 7.01; GraphPad Software, Inc., La Jolla, CA, USA) included Fisher exact tests, chi-square analyses, Mann-Whitney tests, Kruskal-Wallis tests, linear regressions, and Spearman correlations as appropriate. SPSS (version 23; IBM Corp., Armonk, NY, USA) was used to perform multiple linear regression analysis. Mediation analyses between variables was performed using Baron and Kenny's joint significance test.⁽¹¹⁾ Statistical significance was predetermined for *p* values <0.05. Numerically continuous variables are reported as median (interquartile range [IQR]; range).

Results

Subject characteristics

Of 198 total subjects in the NIH FD/MAS cohort, 138 had spinal radiographs available for Cobb angle measurement, and 84 (61%) of these subjects had some degree of scoliosis. Fifty-five subjects (65%) were classified as having mild scoliosis (>10 to ≤30 degrees), 11 subjects (13%) as moderate (>30 to ≤45 degrees), and 18 subjects (22%) as severe (>45 degrees). The primary curve was thoracolumbar in 39 subjects (46%), thoracic in 31 subjects (37%), lumbar in nine subjects (11%), and cervicothoracic in five subjects (6%). Curves were C-shaped in 34 subjects (40%), and S-shaped in 50 subjects (60%).

Subject characteristics are included in Table 1. There was no significant difference in the prevalence of scoliosis between male and female subjects. Subjects with scoliosis were younger than those without scoliosis (*p* = 0.03); however, there were no significant differences in age between scoliosis severity groups. A total of 106 subjects (77%) had at least one MAS-associated endocrinopathy. Of these, hypophosphatemia and hyperthyroidism were significantly associated with increased scoliosis severity (*p* < 0.001).

Radiographic evaluation

Skeletal disease burden score (SDBS) was significantly associated with severity of scoliosis (*p* < 0.0001, Table 1). When evaluating Cobb angle as a continuous variable, a significant positive association was identified between scoliosis severity and SDBS (*R*² = 0.34, *p* < 0.0001, Fig. 1A). Spinal FD was highly significantly associated with both the presence of scoliosis (*p* < 0.0001), and with scoliosis severity (*p* < 0.0001). Of 60 total subjects with an SDBS ≥35 (indicating that ≥50% of the total skeleton is involved with FD), 50 (83%) had FD involving the spine, and 10 (17%) had no spinal FD involvement. All subjects with an SDBS ≥35 had severe scoliosis.

Leg length discrepancy and functional metrics

For all groups with scoliosis (mild, moderate, and severe), there was a significant discrepancy in leg lengths when compared to subjects without scoliosis (*p* < 0.05, Table 1). When analyzing Cobb angle as a continuous variable, a significant positive regression was observed with leg length discrepancy (*R*² = 0.08, *p* < 0.01, Fig. 1B).

Negative associations were found between Cobb angle and manual muscle testing at the level of the hips bilaterally in both the gluteus medius and maximus (left gluteus medius: *R* = -0.34, *p* = 0.0006; right gluteus medius: *R* = -0.41, *p* < 0.0001; left gluteus maximus: *R* = -0.29, *p* = 0.0039; right gluteus maximus: *R* = -0.03, *p* = 0.002). There was no significant correlation

Table 1. Subject Characteristics

Characteristic	No scoliosis (n = 54)	Mild scoliosis (>10 to ≤30 degrees) (n = 55)	Moderate scoliosis (>30 to ≤45 degrees) (n = 11)	Severe scoliosis (>45 degrees) (n = 18)	p
Age at last follow-up (years), median (range)	14 (2–53) ^{bcd}	22 (3–80) ^a	28 (10–59) ^a	22.5 (3–50) ^a	0.03
Male, n (%)	26 (48)	25 (45)	3 (27)	6 (33)	NS
Endocrinopathies, n (%)					
Precocious puberty	28 (52)	25 (45) ^c	9 (82) ^b	13 (72)	0.06
Hyperthyroidism	11 (20) ^d	17 (31) ^d	5 (45)	14 (78) ^{ab}	<0.0001
Hypophosphatemia	6 (11) ^{bd}	17 (31) ^{ad}	4 (36)	11 (61) ^{ab}	0.0004
Growth hormone excess	11 (20)	12 (22)	4 (36)	6 (33)	NS
Hypercortisolism	4 (7)	1 (2)	0 (0)	6 (33)	N/A
Skeletal disease burden score, median (range)	12.2 (0.4–29.8) ^{bd}	34.6 (15.5–44.8) ^{ad}	40.2 (11.3–63.7)	64.4 (45.7–73.2) ^{ab}	<0.0001
Leg length discrepancy (cm), median (range)	0.5 (0.0–1.0) ^{bd}	1.5 (0.5–2.5) ^a	1.3 (1.0–3.0) ^a	2.0 (1.0–3.5) ^a	0.0002
Bone turnover markers, median (range)					
Alkaline phosphatase (U/L)	303 (164–422) ^d	351 (193–613) ^d	521 (233–883)	663 (481.5–1356) ^{ab}	0.0001
Osteocalcin (ng/mL)	100 (43–164) ^d	104 (47–184) ^d	96 (77–180)	229 (123–330) ^{ab}	0.0027
NTX-telopeptide (nmol/mmol)	495 (147–893) ^d	413 (119–1043) ^d	661 (270–1347)	1225 (885–3463) ^{ab}	0.0008

Values of *p* represent the overall significance of difference between scoliosis types as calculated by ANOVA or chi-square analyses.

NS = not significant, N/A = non-applicable.

^aSignificant difference from normal.

^bSignificant difference from mild.

^cSignificant difference from moderate.

^dSignificant difference from severe.

between iliopsoas strength and Cobb angle (left: $R = -0.17$, $p = 0.09$; right: $R = -0.14$, $p = 0.18$).

Negative correlations were observed between Cobb angle and hip range of motion Z-scores bilaterally with flexion (left: $R = -0.34$, $p = 0.0007$; right: $R = -0.38$, $p < 0.0001$), extension (left: $R = -0.38$, $p < 0.0001$; right: $R = -0.22$, $p = 0.03$), internal rotation (left: $R = -0.23$, $p = 0.02$; right: $R = -0.32$, $p = 0.001$), and abduction (left: $R = -0.33$, $p = 0.001$; right: $R = -0.38$, $p = 0.0001$). Insignificant correlation was observed in hip external rotation (left: $R = -0.05$, $p = 0.59$; right: $R = 0.02$, $p = 0.86$).

Impaired ambulation was defined as the regular use of assistive ambulation devices (cane, crutches, walker, and/or wheelchair). The presence of impaired ambulation was highly associated with scoliosis ($p = 0.0009$).

Bone turnover markers

Serum bone turnover markers included alkaline phosphatase and osteocalcin, reflecting bone formation, and N-terminal telopeptides, reflecting bone resorption. By categorical analysis, bone turnover markers correlated only with severe scoliosis ($p < 0.001$, Table 1). Linear regression analysis of Cobb angle as a continuous variable was positively associated with bone turnover markers (alkaline phosphatase $R^2 = 0.074$, $p = 0.0001$, osteocalcin $R^2 = 0.086$, $p = 0.0007$, and N-terminal telopeptides $R^2 = 0.093$, $p = 0.0003$) (Fig. 1C, D).

Spinal fusion procedures

Twelve subjects underwent posterior spinal arthrodesis. Procedures were performed outside of NIH between 1978 to 2011.

Instrumentation systems included Luque rods alone (1/12), Moss-Miami (1/12), Wisconsin segmental with Luque and Harrington rods (1/12), Unit rods (1/12), Zimmer rods (1/12), and dual rods with pedicle screws and hooks (1/12). Two subjects had anterior spinal decompression procedures performed prior to posterior fusions, one utilized Harm's interbody cages. Fusion was performed from as superiorly as T₁ to as inferiorly as the pelvis. Postoperative complications included one case of right upper lobar atelectasis, one case of pneumonia, and one case of retained surgical sponge requiring retrieval.

Only one case of instrumentation failure was reported. This patient was implanted with dual rods with pedicle screws, and hooks from T₃ to L₄. Three months postoperatively an upper claw and upgoing hook had loosened and were no longer stable. The patient developed pain at the location of the unstable instrumentation, after which the instrumentation was removed.

Longitudinal analyses

Sixty-nine subjects (50% of the cohort) had serial films available for longitudinal analysis of scoliosis progression. The median length of time between the initial and most recent radiograph was 4.9 years (IQR, 6.5 years; range, 0.9 to 14.7 years).

Bisphosphonate treatment

Twenty-two subjects were treated with bisphosphonates during the longitudinal observation period. Subjects were treated on clinical grounds, primarily outside of NIH by local clinicians. Regimens were therefore individualized and varied for each

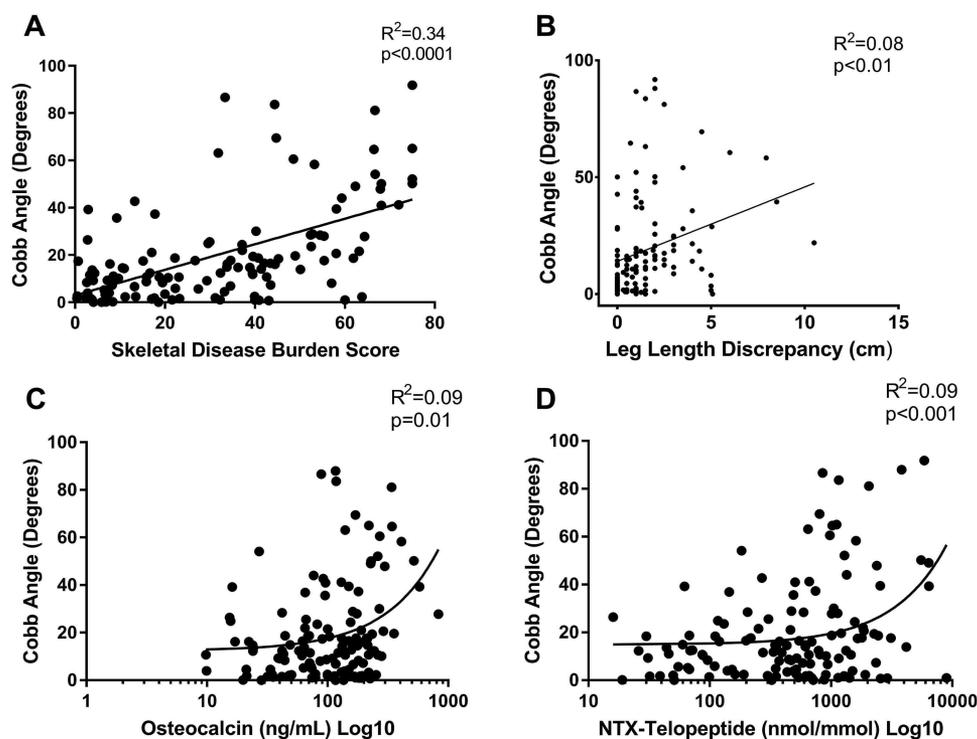


Fig. 1. Clinical and biochemical factors associated with scoliosis severity. (A) Skeletal disease burden score, a quantitative measure of overall fibrous dysplasia burden (see Collins and colleagues⁽⁹⁾). (B) Leg length discrepancy. (C) Osteocalcin, a bone formation marker. (D) NTX (a bone resorption marker) were all significantly associated with the severity of scoliosis, as measured by Cobb angle. NTX = N-terminal telopeptide.

patient. Although some subjects received fixed dosing intervals, others were infused at variable intervals, as needed to control bone pain. Table 2 shows the cumulative dose of bisphosphonates received for each subject during the observation period.

Thirty-one subjects in the longitudinal cohort never received bisphosphonates. Seven subjects received bisphosphonates prior to but not during the observation period, and were eliminated from the analyses. One bisphosphonate-treated subject was eliminated from the analyses because the dosing regimen could not be verified. For subjects treated with spinal fusion, only preoperative serial films were included in the analyses. Eight subjects were eliminated from the analyses because they did not have preoperative serial films available for review.

There was no significant difference in the change/year in Cobb angle for the 22 bisphosphonate-treated subjects compared to the 31 subjects who never received bisphosphonates: median (IQR; range) 0.10 degrees/year (IQR, 1.83 degrees; range, -14.90 to 5.67 degrees) versus 0.53 degrees/year (IQR, 2.17 degrees; range, -3.53 to 22.31 degrees) ($p = 0.36$) (Fig. 2A). No significant differences in clinical features were identified between the groups of bisphosphonate-treated and untreated subjects, including age (22 years [IQR, 29 years; range, 6 to 75 years] versus 16 [IQR, 12 years; range, 2 to 58 years]; $p = 0.09$), length of follow-up (4.9 years [IQR, 6.6 years; range, 0.9 to 13.5 years] versus 4.6 years [IQR, 6.5 years; range, 0.9 to 13.8 years]; $p = 0.93$), baseline Cobb angle (15.82 degrees [IQR, 27.42 degrees; range, 0 to 63.87 degrees] versus 12.16 degrees [IQR, 19.62 degrees; range, 0 to 66.15 degrees]; $p = 0.31$), SDBS (46.1 [IQR, 45.5; range, 7.8 to 68.1] versus 33.3 [IQR, 32.6; range, 2.4 to 68.1]; $p = 0.06$), and leg length

discrepancy (1.3 cm [IQR, 2.9 cm; range, 0 to 8.5 cm] versus 1.0 [IQR, 2.08 cm; range, 0 to 10.5 cm]; $p = 0.63$). There were no significant differences in the prevalence of MAS-associated endocrinopathies between groups (data not shown).

Surgical management

Longitudinal data was available for 10 of the 12 subjects treated with spinal fusion. Therefore, in the cohort of subjects evaluated longitudinally, 59 (86%) were managed non-operatively, while 10 (14%) underwent spinal fusion. The median follow-up for non-operative subjects was 4.3 years (IQR, 6.5 years; range, 0.9 to 13.8 years), and 6.1 years (IQR, 7.9 years; range, 0.9 to 14.7 years) for those treated with spinal fusion ($p = 0.05$). The median change/year in Cobb angle in the non-operative group was 0.59 degrees/year (IQR, 1.9 degrees/year; range, -14.9 to 22.3 degrees/year), whereas there was essentially no progression in the operative group (-0.25 degrees/year [IQR, 1.4 degrees/year; range, -14.3 to 1.78 degrees/year]; $p = 0.03$) (Fig 2B). For the purposes of the analyses, clinically significant progression was defined as an increase in Cobb angle of >10 degrees. Eighteen of the 59 non-operative subjects (31%) had clinically significant progression, with a median change in Cobb angle of 18.3 degrees (range, 10.7 to 66.9 degrees). Within the non-operative group, subjects with clinically significant progression had a significantly greater median SDBS compared to non-progressors (44.6 [IQR, 33.9; range, 29.4 to 63.4] versus 31.2 [IQR, 32.3; range, 10.7 to 43.0]; $p = 0.02$). Only one of the 10 operative subjects with serial films met criteria for clinically significant progression (10.5 degrees). Representative radiographs for non-operative and operative subjects are shown in Figs. 3A-D and 4A-C.

Table 2. Characteristics of Subjects Treated With Bisphosphonates

Sex/age (years)	Observation and treatment period (years)	Cumulative bisphosphonate dose
F/39	13.3	Zoledronate 40 mg
M/16	5.4	Zoledronate 48 mg
M/17	9.0	Zoledronate 84 mg
M/14	8.8	Zoledronate 28 mg
F/22	2.5	Zoledronate 4 mg
M/32	9.8	Pamidronate 150 mg, zoledronate 53 mg
F/28	2.5	Zoledronate 5 mg
M/44	13.3	Zoledronate 18 mg
F/41	4.9	Risedronate 10,950 mg
F/32	2.0	Alendronate 14,600 mg
M/14	3.0	Alendronate 14,600 mg
M/8	8.3	Pamidronate 160 mg
M/36	13.5	Alendronate 29,200 mg
F/4	2.7	Pamidronate 360 mg
M/9	3.1	Alendronate 7,300 mg
M/49	1.0	Alendronate 3,640 mg
F/7	6.2	Pamidronate 240 mg
M/8	6.4	Pamidronate 75 mg, zoledronate 2 mg
M/9	1.0	Pamidronate 40 mg, zoledronate 2 mg
F/3	4.3	Pamidronate 100 mg
M/17	1.2	Zoledronate 10 mg
F/12	2.0	Zoledronate 20 mg

F = female; M = male.

Fatalities

Two fatalities occurred from scoliosis-associated complications of restrictive lung disease in subjects with progressive scoliosis. Both subjects were managed non-operatively. A 19-year-old woman expired from multi-organ failure and disseminated intravascular coagulation due to pneumonia. Her Cobb angle at the time of death was 91.8 degrees. A 41-year-old man succumbed to respiratory failure and acidosis, with a Cobb angle of 121.4 degrees at time of death.

Multiple linear regression analyses

Multiple linear regression analyses were conducted to identify potential relationships between the clinical variables associated with scoliosis. After controlling for demographics (age and sex), SDBS remained significantly associated with Cobb angle ($p = 0.03$). When additional variables (including MAS endocrinopathies, leg length discrepancy, and bone turnover markers) were incorporated into a statistical model that controlled for both demographics and SDBS, no statistically significant associations with Cobb angle were identified (see Supplementary Table 1). Based on our observations that these variables may be clinically relevant, we tested for the possibility that the effects of these variables were mediated through the effects of SDBS using the Baron and Kenny's joint significance test (see Supplementary Fig. 1). The results of these analyses showed that relationships between the following variables and Cobb angle were fully mediated by SDBS: leg length discrepancy, alkaline phosphatase, osteocalcin, N-terminal telopeptide, and hypophosphatemia. Additionally, the relationships between Cobb angle and the location of FD in the spine (cervical, thoracic, lumbar), and hyperthyroidism were partially mediated by SDBS.

Discussion

Findings from this large series show that scoliosis occurs frequently in patients with polyostotic FD, and in severe cases may be progressive and potentially lethal. Total skeletal FD involvement was highly correlated not only with the presence and severity of scoliosis, but also with the likelihood of scoliosis progression. This highlights that staging of total disease burden with skeletal imaging (such as scintigraphy) is an important component of evaluation in FD that may inform the risk of developing future complications. Serum bone turnover markers were an additional marker of disease activity that correlated with severe scoliosis; these should be considered as an adjunct to clinical and radiographic assessment.

Statistical analyses indicated that skeletal disease burden was the only significant variable predicting scoliosis progression. However, mediation analyses showed that additional clinical variables may affect scoliosis through their relationship with disease burden. This suggests that these variables are clinically relevant if they are considered in the context of an individual's overall FD burden, and are likely to have a greater impact in

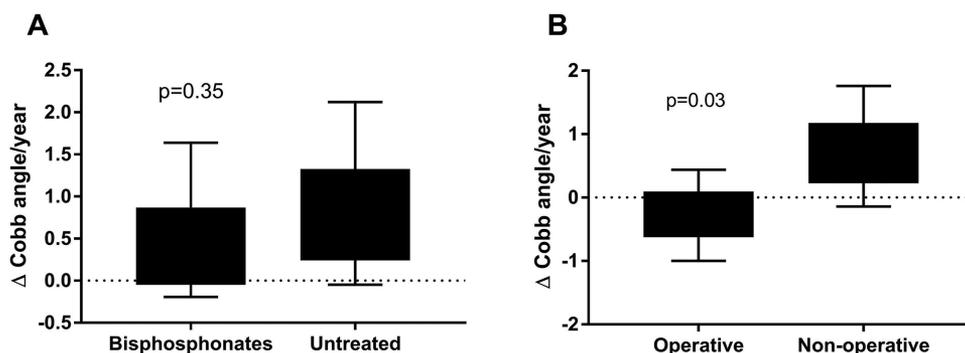


Fig. 2. Progression of scoliosis. (A) Change per year in Cobb angle in subjects treated and not treated with bisphosphonates. (B) Change per year in Cobb angle for subjects managed non-operatively and with spinal fusion. Boxes show median values, and whiskers show interquartile range.

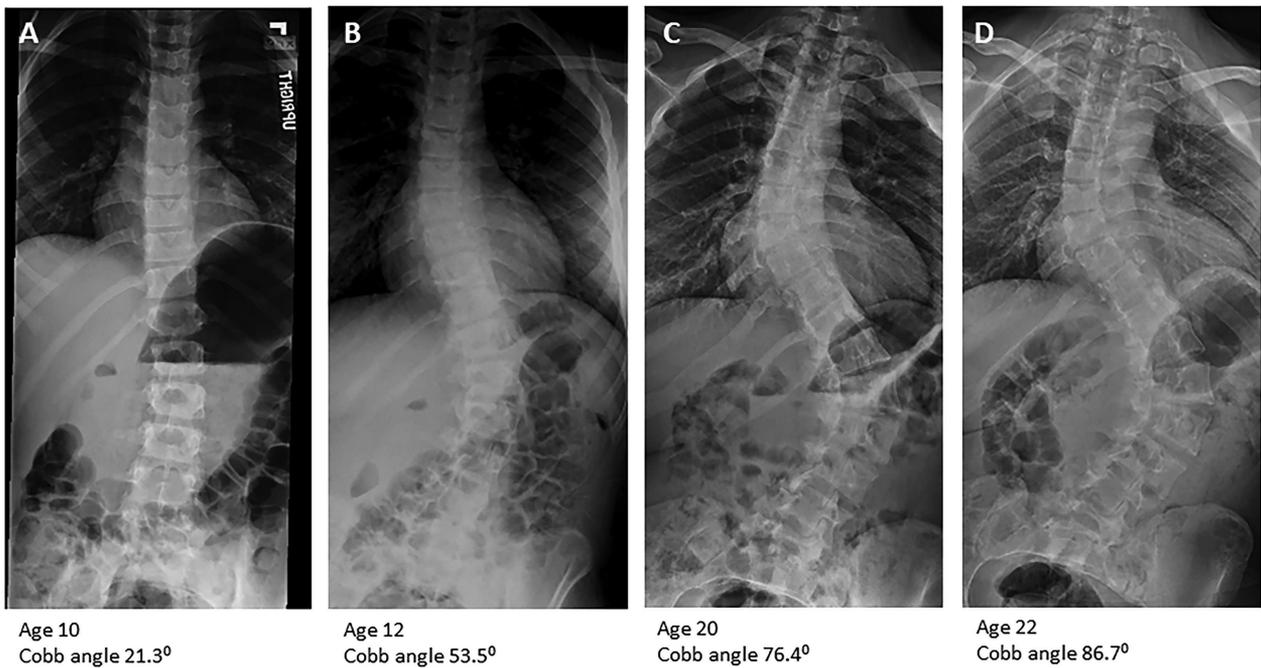


Fig. 3. Serial radiographs demonstrating progressive scoliosis in a subject managed non-operatively. (A) Scoliosis is mild at age 10 years, with a Cobb angle of 21.3 degrees. (B) By age 12 years, Cobb angle has progressed to 53.5 degrees. (C) Further progression of scoliosis, with a Cobb angle of 76.4 degrees at age 20 years. (D) By age 22 years, scoliosis is increasingly severe, with a Cobb angle of 86.7 degrees.

patients who have greater amounts of skeletal disease. Leg length discrepancy was one such variable that indirectly impacted Cobb angle, likely through its effects on spinal alignment.⁽¹²⁾ Leg length discrepancies are common in FD due

to mosaic involvement of the lower limbs. FD lesion growth tends to expand limb length, whereas fractures and deformities decrease limb length, resulting in complex and dynamic malalignment. Impairments in hip mobility and pelvic girdle

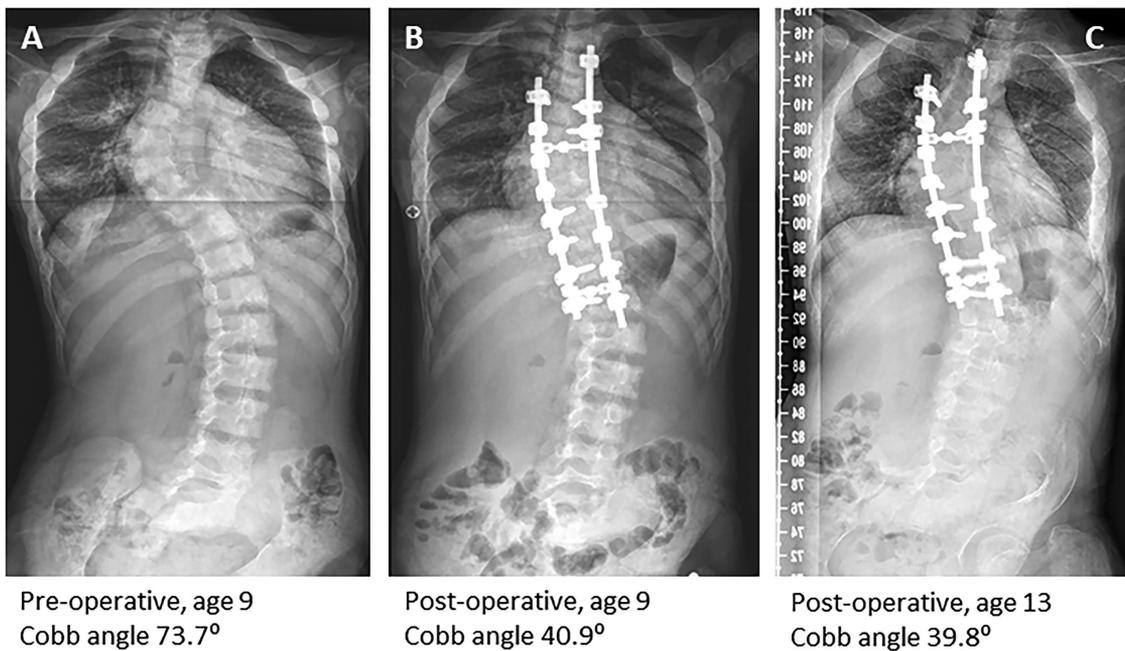


Fig. 4. Stable scoliosis in a subject managed operatively. (A) Preoperative radiograph from a 9-year-old girl with severe progressive scoliosis and a thoracic curve of 73.7 degrees. (B) Shortly following posterior spinal fusion with placement of pedicle screws, dual rods, and crosslinks, the thoracic curve has improved to 40.9 degrees. (C) 3.5 years postoperatively, the now 13-year-old girl has a stable Cobb angle of 39.8 degrees.

strength demonstrate that functional deficits contribute to clinical disease. Similar to other forms of scoliosis, it is unclear whether these muscular impairments directly impact spinal curvature, or arise as secondary effects.⁽¹³⁾ However, skeletal disease burden was highly associated with scoliosis even in subjects without spinal FD, suggesting a potential causative role for functional deficits. Of note, leg length discrepancy has been independently associated with decreased hip strength, range-of-motion, and gait efficiency in patients with FD.⁽¹⁴⁾ These findings highlight the critical importance of monitoring for and treating leg length discrepancies as part of routine care. Our current practice includes functional evaluation at least yearly for all patients with FD involving the spine or lower extremities, and more frequently for patients experiencing complications that may alter gait dynamics, such as fractures and surgeries. Management is targeted at correcting pelvic obliquity to balance the forces influencing spinal alignment, with a current threshold for intervention of 0.3 cm (1/8 inch). Conservative management, through introduction of lifts and other orthotic devices, is recommended in combination with targeted physical therapy. Surgical treatments such as epiphysiodesis should be undertaken cautiously given the multiple dynamic factors that may affect leg length discrepancies in FD, which may limit the long-term success of this approach.

Additional features associated with scoliosis included the MAS-associated endocrinopathies FGF23-mediated hypophosphatemia and hyperthyroidism. Hypophosphatemia has previously been associated with increased fractures in patients with FD,⁽¹⁵⁾ and this study is the first to demonstrate an association with bony deformities. Taken together, these findings demonstrate the critical importance of ongoing monitoring of phosphorus levels in patients with FD. Treatment should be initiated in patients who have serum phosphorus levels below the normal range for age, regardless of symptoms, with the goal of preventing skeletal complications. This study is the first to associate MAS-associated hyperthyroidism with negative skeletal outcomes in FD. This is consistent with the known detrimental effects of excess thyroid hormone on bone metabolism,^(16,17) and supports an aggressive approach to managing endocrinopathies in patients with MAS.

This study extends the clinical spectrum of FD with the first reported fatalities from progressive scoliosis. The lack of fatalities in subjects managed operatively supports that spinal fusion may be lifesaving in this population.

Bisphosphonate treatment was not associated with decreased progression of spinal curvature in longitudinal analyses. Bisphosphonates are frequently prescribed in patients with FD; however, data linking treatment with skeletal outcomes are lacking. Previous studies have reported reductions in bone turnover, but inconsistent effects on pain and radiographic appearance of FD lesions.^(7,18,19) A placebo-controlled trial of alendronate demonstrated improvements in resorption markers and bone density, but no effects on pain.⁽²⁰⁾ This study is the first to evaluate the effects of bisphosphonates on FD deformity. Interpretation of these findings is limited by the retrospective nature of the study design, which resulted in significant variability in bisphosphonate dosing. Although a variety of formulations and regimens were used, most subjects received a relatively high cumulative exposure. Although the study cohort was large, given the rarity of FD/MAS, it is possible that a larger population may be required to detect therapeutic effects of bisphosphonates. Prospective controlled studies with consistent treatment

regimens are needed to definitively determine the role of bisphosphonate therapy in preventing skeletal deformity in FD.

Strengths of this study include extensive follow-up and detailed subject phenotyping that allowed for investigation of associations between scoliosis and specific clinical features. This is the largest series of patients studied to date. Despite the considerable morbidity associated with scoliosis in FD, the current literature on this topic is extremely limited, and findings from this series have the potential to directly impact care for patients. Limitations include the retrospective nature of the study. Because subjects were seen at a tertiary referral center, the cohort may be biased toward more severely affected patients. This may limit the generalizability of the results; however, it also enables the identification of risk factors associated with scoliosis development and progression. In particular, findings from this study may overestimate the prevalence of scoliosis in FD/MAS, because patients with milder forms of the disease may not have been sufficiently represented. This is the largest series to include long-term outcomes from spinal fusion procedures in patients with FD. Somewhat surprisingly, given the generally poor durability of orthopedic operations in FD,^(21,22) this study shows that surgical management of scoliosis in FD can be safe and have durable efficacy. However, because of the variety of instrumentation and techniques, these findings are unable to inform specific surgical approaches.

Scoliosis occurs frequently in patients with polyostotic FD, and clinical monitoring as part of a multidisciplinary team should be part of routine care. The primary risk factor for progressive scoliosis in FD is total skeletal disease burden. Treatable features that contribute to scoliosis progression include leg length discrepancy, pelvic girdle weakness, FGF23-mediated hypophosphatemia, and hyperthyroidism. Clinical care for patients with FD should involve systematic evaluation and treatment of these features, which may impact long-term skeletal outcomes. The current data does not support routine use of bisphosphonates to prevent progression of spinal curvature. Spinal fusion is frequently effective in providing long-term stability, and may be potentially lifesaving.

Disclosures

The authors report no disclosures.

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content: RS, SP, LCG, MTC, and AMB. Approving final version of manuscript: JAB, SHT, KT, LK, LCG, SP, RS, MTC, and AMB. AMB takes responsibility for the integrity of the data analysis.

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