http://dx.doi.org/10.2106/JBJS.L.01596

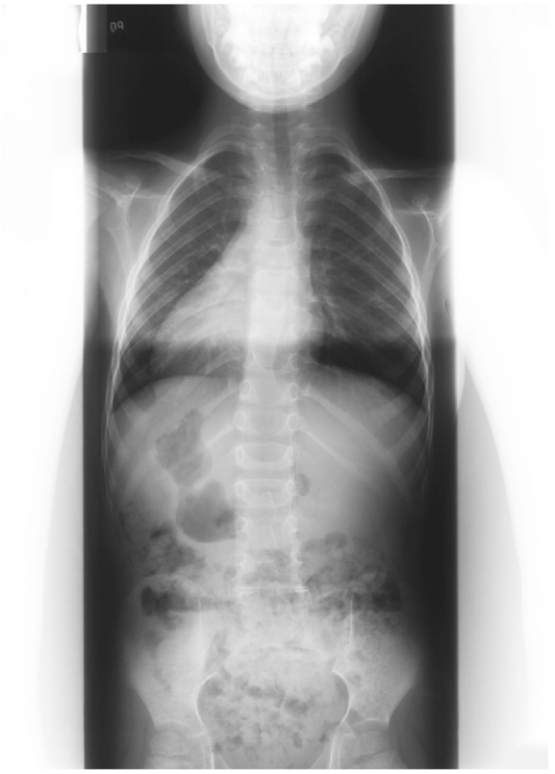

Fig. E-1A

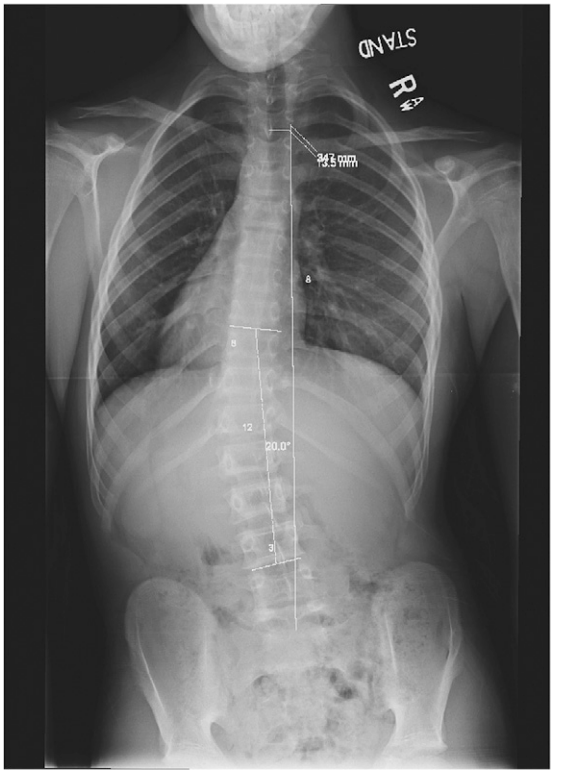

Fig. E-1B

Figs. E-1A and E-1B Patient with type-I osteogenesis imperfecta followed over eleven years. **Fig. E-1A** Curve onset at age five with a 4° lumbar levoscoliosis. **Fig. E-1B** The most recent follow-up radiograph, made when the patient was sixteen years of age, showing curve progression to 27° and the apex at the L1-L2 disc.

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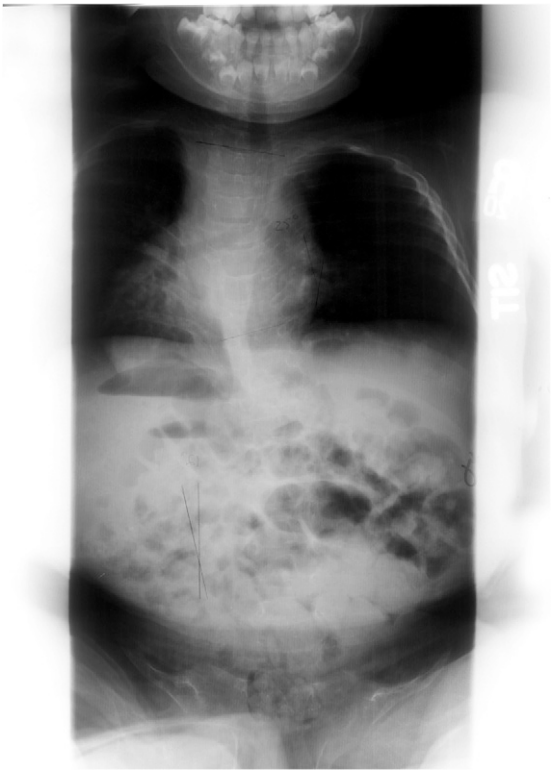

Fig. E-2A

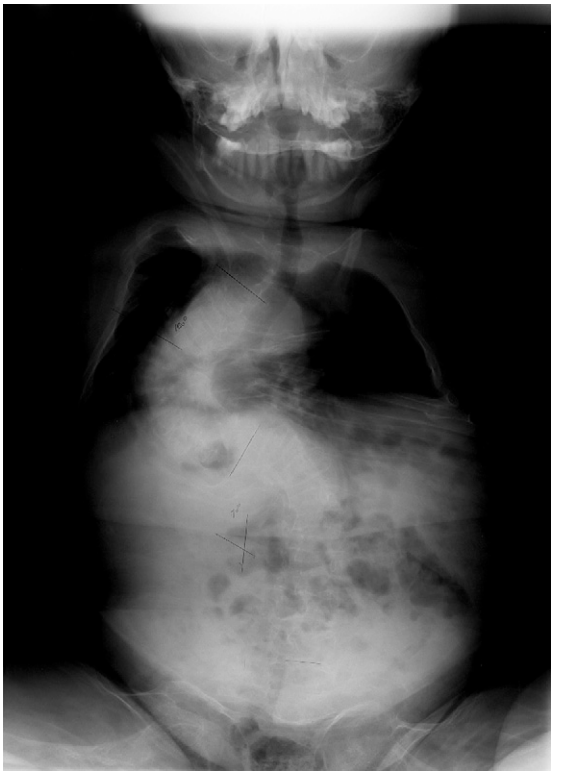

Fig. E-2B

Figs. E-2A and E-2B Patient with type-III osteogenesis imperfecta followed over twenty-one years. **Fig. E-2A** Radiograph made at the first visit, when the patient was three years of age, demonstrating a 25° thoracic levoscoliosis and a 16° thoracolumbar dextroscoliosis. **Fig. E-2B** The last follow-up radiograph, made when the patient was twenty-four years of age, showing a 116° thoracic levoscoliosis, with the apex at T6, and an 85° lower thoracic and upper lumbar dextroscoliosis, with the apex at L1.

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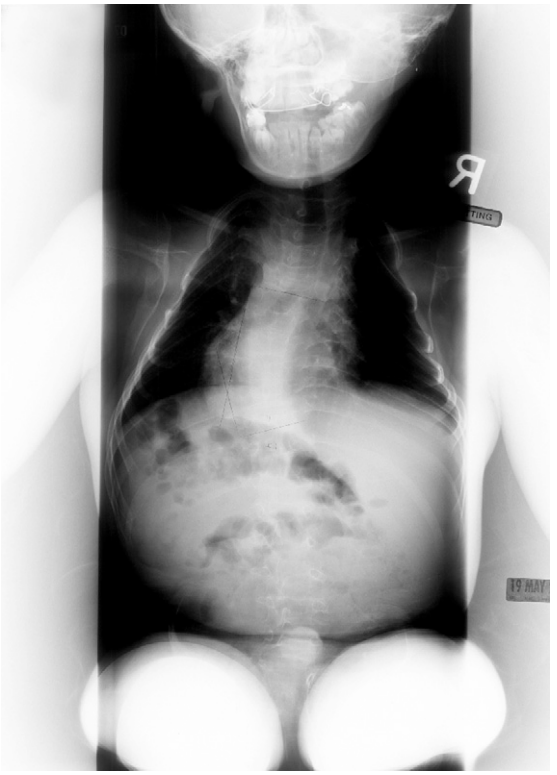

Fig. E-3A

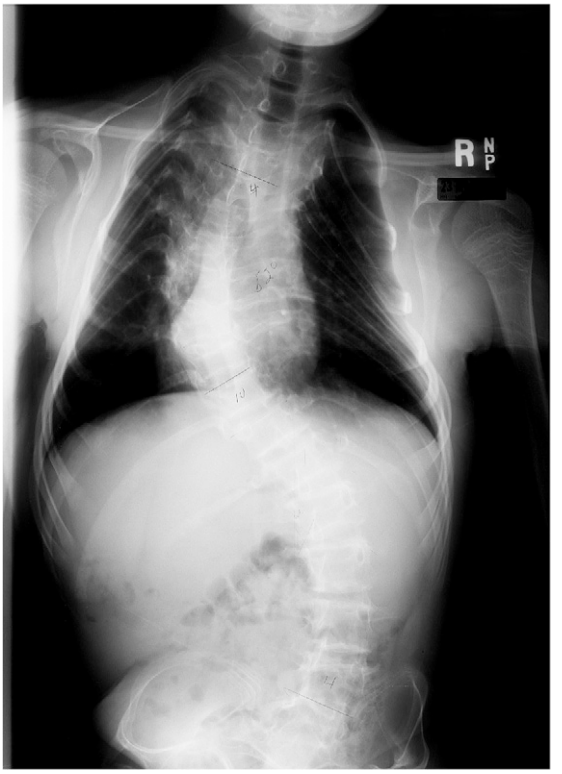

Fig. E-3B

Figs. E-3A and E-3B Patient with type-IV osteogenesis imperfecta followed over fifteen years. **Fig. E-3A** Radiograph made at the first visit, when the patient was ten years of age, demonstrating a 28° thoracic levoscoliosis. **Fig. E-3B** The last follow-up radiograph, made when the patient was twenty-five years of age, showing progression of a double curve to a 43° thoracic levoscoliosis and a 40° thoracolumbar dextroscoliosis.

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TABLE E-1 Demographic Data

Demographic Category	Type I	Type III	Type IV	Other Types (II, V, VIII)	Overall
Male *(no. [%])*	34 (55)	20 (36)	14 (44)	6 (75)	74 (47)
Female *(no. [%])*	28 (45)	35 (64)	18 (56)	2 (25)	83 (53)
Mean age at diagnosis of scoliosis *(yr)*	7.4	6.3	6.9	9.8	7
Mean duration of follow-up *(yr)*	8.8	8.5	6.6	3.8	8
Received pamidronate *(no.)*	14	19	10	0	43
Received alendronate *(no.)*	10	2	5	0	17

TABLE E-2 Bisphosphonate Treatment Among the Osteogenesis Imperfecta Types*

	No. of Patients			
Osteogenesis Imperfecta Type	No Treatment	Bisphosphonate Prior to Age Six Years	Bisphosphonate After Age Six Years	Total
I	24	4	16	44
III	18	7	10	35
IV	8	6	9	23
Total	50	17	35	102

*Eight children (four with type I four with type III) were excluded because of incomplete medication history.

TABLE E-3 Cobb Angle Progression Rates for Different Age and Osteogenesis Imperfecta Groups

Parameter	Age Group *(yr)*	Progression Rate *(deg/yr)*	95% Confidence Interval	P Value
Type I	0-5	0	−3.1-3.3	0.95
Type I	6-10	0	−2.4-1.1	0.46
Type I	11-15	3	1.2-4.9	<0.01
Type I	≥16	1	−0.1-2.5	0.08
Type III	0-5	4	1.7-7.0	<0.01
Type III	6-10	7	3.2-9.9	<0.01
Type III	11-15	8	5.1-10.0	<0.01
Type III	≥16	5	0.4-10.1	0.03
Type IV	0-5	4	−0.3-7.9	0.07
Type IV	6-10	3	1.6-4.1	<0.01
Type IV	11-15	6	1.7-9.9	0.01
Type IV	≥16	7	−2.1-15.7	0.14

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TABLE E-4 Regression Coefficients for Model (1): Analysis of Generalized Estimating Equations Parameter Estimates and Empirical Standard Error Estimates*

Parameter	Osteogenesis Imperfecta Type	Age at Which Bisphosphonates Initiated *(yr)*	Progression Rate *(deg/yr)*	Standard Error	95% Confidence Interval	Pr > |Z|
Intercept (β_0)	I		0.83	0.75	−0.63-2.29	0.2649
Type (β_1)	III		5.25	1.00	3.28-7.21	<0.0001
Type (β_2)	IV		2.68	3.12	−3.44-8.79	0.3904
Treatment (β_3)	I		1.41	1.09	−0.72-3.55	0.1931
Treatment (β_4)	II		0.89	0.91	−0.90-2.68	0.3295
Type treatment (β_5)	III	<6	−5.20	1.73	−8.58-−1.81	0.0026
Type treatment (β_6)	III	≥6	0.52	2.12	−3.63-4.67	0.8067
Type treatment (β_7)	IV	<6	−1.80	3.40	−8.46-4.86	0.5963
Type treatment (β_8)	IV	≥6	1.52	3.71	−5.76-8.81	0.6822

*We fitted a linear regression model for estimating Cobb angle progression rates separately for each osteogenesis imperfecta type and each bisphosphonate treatment. After identifying that predictors including age at diagnosis of the scoliosis, age group, and sex were not significant, the final model for the estimate of curve rate progression was:

$$E(r_{ij}|b_{ij1}, b_{ij2}, o_{i3}, o_{i4}) = \beta_0 + \beta_1 o_{i3} + \beta_2 o_{i4} + \beta_3 b_{ij1} + \beta_4 b_{ij2} + \beta_5 o_{i3} b_{ij1} + \beta_6 o_{i3} b_{ij2} + \beta_7 o_{i4} b_{ij1} + \beta_8 o_{i4} b_{ij2}$$

Where: r_{ij} = rate of curve progression for each participant *(i)* for visit *(j)*, β_0 = effect of osteogenesis imperfecta type I without history of bisphosphonate treatment, β_1 = effect of osteogenesis imperfecta type III, β_2 = effect of osteogenesis imperfecta type IV, β_3 = effect of starting bisphosphonate treatment prior to six years of age, β_4 = effect of starting bisphosphonate treatment after six years of age, β_5 through β_8 = interactions of osteogenesis imperfecta type by bisphosphonate treatment. Covariates: o_{i3} = osteogenesis imperfecta type III, o_{i4} = osteogenesis imperfecta type IV, b_{ij1} = starting bisphosphonate treatment prior to six years of age, b_{ij2} = starting bisphosphonate treatment after six years of age. To account for possible correlation of within-subject measurements, we used the generalized estimating equations with the identity link function and an exchangeable working correlation matrix. This generalized estimating equations modeling corresponds to the weighted least squares analysis with an assumed compound symmetry structure of the correlation matrix. The sandwich estimator was used to obtain consistent estimates of standard errors. The results of the generalized estimating model for progression rates are reported above. The effect of b_{ij1} (bisphosphonate treatment prior to six years of age) differed significantly between treatment groups, and the omnibus interaction test p value was 0.028. The table shows the regression coefficient estimates (effect on rate of progression) as well as p values describing their significance. Specifically the strongest effect of biphosphonate treatment was observed for patients with type-III osteogenesis imperfecta who started treatment before six years of age. The expected scoliosis progression rate is 0.83° per year for a patient with type-I osteogenesis imperfecta who does not receive biphosphonate and 6° (0.83 + 5.25) per year for a patient with type-III osteogenesis imperfecta who does not receive biphosphonate. If a patient with type-III osteogenesis imperfecta receives biphosphonate before the age of six years of age, then the expected progression rate is estimated to be 2.3° per year (0.83 + 5.25 + 1.42 − 5.20), which is substantially lower than 6° (p = 0.005). This is the only posttest that produced a significant p value. The effect of b_{ij1} was not significant for osteogenesis imperfecta types I and IV. The effect of b_{ij2} was not significant for any osteogenesis imperfecta group.