

# Rapid Increase in Grip Force After Start of Pamidronate Therapy in Children and Adolescents With Severe Osteogenesis Imperfecta

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**ABSTRACT.** *Objective.* To examine changes in grip force during pamidronate therapy in children and adolescents with severe osteogenesis imperfecta (OI).

*Methods.* Maximal isometric grip force of the non-dominant hand was prospectively determined in 42 patients (age at the start of the study: 7.3–15.9 years; 18 girls) with severe forms of OI. Patients were treated with intravenous pamidronate infusions given in 4 monthly cycles, each cycle consisting of 3 infusions (1 mg pamidronate/kg body wt) on 3 successive days.

*Results.* At the start of pamidronate therapy, grip force was low compared with age-specific reference data (age z score mean  $\pm$  standard deviation:  $-2.7 \pm 2.1$ ) but was normal for weight (weight z score:  $-0.1 \pm 1.8$ ). Four months after the first pamidronate infusion cycle, grip force had increased significantly, whether related to age (age z score:  $-2.0 \pm 1.8$ ) or to weight (weight z score:  $0.6 \pm 1.5$ ). At 2 years after the start of therapy, grip force z scores were not significantly different from the 4-month results.

*Conclusions.* Maximal isometric grip force markedly increases after a single cycle of intravenous pamidronate in children with severe forms of OI, and this gain in grip force is maintained for at least 2 years. *Pediatrics* 2003;111:e601–e603. URL: <http://www.pediatrics.org/cgi/content/full/111/5/e601>; grip force, muscle force, osteogenesis imperfecta, pamidronate.

ABBREVIATION. OI, osteogenesis imperfecta.

Osteogenesis imperfecta (OI) is a congenital disorder characterized by low bone mass and increased bone fragility. Several different types are commonly distinguished on the basis of clinical features and disease severity.<sup>1–3</sup> Patients with OI type 1 usually have a mild phenotype with normal or near-normal height, whereas OI type 2 is usually lethal in the perinatal period. OI type 3, known as progressive deforming OI, is the most severe form in children who survive the neonatal period. Patients who have a moderate to severe form of the disease and do not fit one of the above descriptions are classified with OI type 4.

We and others have recently shown that cyclical intravenous administration of pamidronate has a

beneficial effect in children and adolescents with severe osteogenesis imperfecta.<sup>4,5</sup> Areal bone mineral density increased, fracture rates decreased, and mobility improved markedly. Many patients report having “increased stamina” and “more strength” shortly after treatment is started. This clinical observation suggests that increased muscle strength contributes to the improved functional status of these patients.

Muscle function in OI has received relatively little attention until now. The available evidence is mostly limited to the studies of Engelbert et al,<sup>6,7</sup> who used a semiquantitative score to determine muscle strength in a large group of children with OI. Muscle strength was judged to be normal in children with OI type 1 but low in OI types 3 and 4. However, no data are available on muscle strength during pamidronate treatment.

We therefore undertook a systematic study to verify objectively the subjective impression of increased muscle strength after the start of pamidronate therapy. Muscle strength was quantified by measuring maximal isometric grip force using a standard dynamometer.

## METHODS

### Study Participants

The study population comprised children and adolescents who had moderate to severe forms of OI (at least 3 fractures per year in the 2 years preceding the study) and received intravenous pamidronate therapy at the Shriners Hospital for Children (Montreal, Canada). After a baseline evaluation, all study participants were treated with cyclical pamidronate infusions, as described in detail before.<sup>4</sup> Briefly, pamidronate was given intravenously in 4-month cycles. Each cycle consisted of 3 infusions on 3 successive days at a dose of 1 mg/kg body weight. All evaluations reported here were performed at baseline and before each treatment cycle.

Grip force was measured in all patients who were older than 6 years, unless pain or recent fracture made the measurement impossible. Here we report on the longitudinal results of patients who have received pamidronate for least 2 years. Of the 63 patients eligible for the present study, 21 did not have grip force measurements in at least 1 of the 3 time points of this study. Thus, we report on results from those 42 patients (18 girls, 24 boys) who had complete data sets. Age at baseline ranged from 7.3 to 15.9 years. The diagnostic distribution of these patients was as follows: OI type 1, 9 patients; OI type 3, 9 patients; OI type 4, 15 patients; OI type 5, 5 patients; OI type 6, 2 patients; Cole-Carpenter syndrome, 1 patient; osteoporosis-pseudoglioma syndrome, 1 patient.

Limiting the analysis to patients with complete data sets might introduce some selection bias. To evaluate this possibility, we performed a second evaluation. This included all patients in whom baseline grip force data and at least 1 measurement at 4 months or at 2 years of treatment were available. The results at 4 months of therapy were carried forward to the 2-year time point

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when these data were missing. With this approach, 55 of the 63 eligible patients (26 girls, 29 boys; age at baseline: 7.3–15.9 years) could be included in the analysis.

Age- and gender-specific z scores for height and weight were calculated on the basis of the National Center for Health Statistics growth curves.<sup>8</sup> Functional motor ability was evaluated using the Pediatric Evaluation of Disability Inventory, a standardized assessment of functional capacities with a scale from 0 to 100.<sup>9</sup> Some clinical and densitometric results of a subset of these patients had been reported earlier.<sup>4</sup> Informed consent was obtained in each instance from the subject and/or a legal guardian, as appropriate. The study protocol was approved by the Ethics Committee of the Shriners Hospital.

### Grip Force Testing

Maximal isometric grip force of the nondominant hand was determined with a standard adjustable-handle Jamar dynamometer (Preston, Jackson, MI) as described previously.<sup>10</sup> Briefly, setting 2 of the dynamometer was used to ensure that the line of the subject's proximal interphalangeal joints rested on top of the adjustable handle. The maximal value of 3 trials was noted. We use the term "grip force" instead of the more widely used "grip strength" because "force" is a term that is clearly defined by physics, whereas "strength" is used inconsistently in the medical literature to denote a variety of different parameters, including force, torque, and power.

### Areal Bone Mineral Density

Areal bone mineral density in the anteroposterior direction was determined at the lumbar spine (L1–L4) using a Hologic QDR 2000W or 4500A device (Hologic Inc, Waltham, MA). Results were transformed to age-specific z scores using data provided by the densitometer manufacturer.

### Statistical Analyses

Z scores were calculated for various parameters using the following formula:  $z \text{ score} = [(\text{test result for a patient}) - (\text{expected mean in reference population})] / (\text{standard deviation in the reference population})$ . Age- and weight-dependent grip force z scores ( $z_{\text{age}}$  and  $z_{\text{weight}}$ ) and the expected rate of increase in healthy children were calculated using published reference material.<sup>10</sup>

Differences among OI types 1, 3, 4, and 5 were tested for significance using analysis of variance followed by *t* tests using Bonferroni's adjustment. Associations are given as Pearson correlation coefficients. All tests were 2-tailed, and throughout  $P < .05$  was considered significant. These calculations were performed using the SPSS software, version 9.0 for Windows (SPSS Inc, Chicago, IL).

## RESULTS

At the start of pamidronate therapy, height, weight, and areal bone mineral density of the lumbar spine were low for age in the entire patient population and in all subgroups (Table 1). Grip force was also decreased compared with age-specific reference

data (Fig 1) but was normal for weight (Table 1). OI types differed significantly in age-specific grip force z scores but not in weight-specific z scores (Table 1). A significant relationship was found between age-specific z scores for grip force and areal bone mineral density at the lumbar spine ( $r = 0.71$ ;  $P < .001$ ). This relationship remained significant after correction for weight ( $r = 0.58$ ;  $P < .001$ ).

Four months after the first pamidronate infusion cycle, grip force had increased by 18% (median, interquartile range: 8%–48%) in the entire group. In healthy children, the expected increase during a 4-month period is 5%. Consequently, grip force z score increased significantly in the patient population, whether related to age or to weight (Fig 2). At 2 years after the start of therapy, grip force z scores tended to be higher than at 4 months, but this difference did not achieve significance ( $P > .2$  each). The median mobility score (determined in 32 patients) increased ( $P = .001$ ) from 66 (interquartile range: 55–100) to 87 (interquartile range: 61–100) during the 2 years of therapy.

In the 55 patients who had at least 1 grip force measurement during treatment, grip force z scores increased significantly after the start of pamidronate therapy, both when related to age (by  $.85 \pm 1.30$ ;  $P < .001$ ) and to weight (by  $.67 \pm 1.26$ ;  $P < .001$ ). Thus, it is unlikely that selection bias affected the results in the group of patients with complete data at all 3 time points.

## DISCUSSION

The present results confirm that children and adolescents with severe forms of OI have lower grip force than healthy controls of the same age. The age-specific grip force z score was lowest in the most severely affected patients and thus could be regarded as an indicator of disease severity. In fact, a close correlation was found between the age-specific z scores for grip force and for areal bone mineral density of the lumbar spine, a widely used parameter of disease severity in OI.<sup>11,12</sup> The low muscle force in patients with OI may result from an intrinsic muscle defect or could be simply secondary to small body size. The second possibility is supported by the observation that grip force was normal when adjusted for body weight.

**TABLE 1.** Baseline Results in 42 Children and Adolescents (18 Girls) With Moderate to Severe OI

	All	OI 1	OI 3	OI 4	OI 5	P
<i>n</i>	42	9	9	15	5	
Age (y)	11.4 ± 2.6	9.9 ± 2.4	11.2 ± 2.7	11.8 ± 2.4	12.3 ± 2.9	.26
Height (z age)	-5.5 ± 3.6‡	-2.2 ± 1.4*	-10.3 ± 2.4‡	-5.1 ± 2.7‡	-3.8 ± 2.7*	<.001
Weight (z age)	-2.5 ± 2.1‡	-1.1 ± 1.8	-3.5 ± 1.8‡	-2.4 ± 2.0‡	-1.8 ± 2.3	.10
aBMD (z age)	-5.2 ± 1.3‡	-4.1 ± 0.8‡	-5.9 ± 1.0‡	-5.2 ± 1.2‡	-5.4 ± 1.6‡	.02
Grip force (z age)	-2.7 ± 2.1‡	-0.9 ± 1.1*	-4.6 ± 1.9‡	-2.2 ± 1.7‡	-2.8 ± 1.7*	<.001
Grip force (z weight)	-0.1 ± 1.8	0.4 ± 1.6	-1.0 ± 2.6	0.4 ± 1.4	-0.8 ± 1.6	.20

Results are also given for OI types 1, 3, 4 and 5. The other diagnostic categories (OI type 6, Cole-Carpenter syndrome, osteoporosis-pseudoglioma syndrome) were too rare for statistical analysis.

Values are mean ± standard deviation.

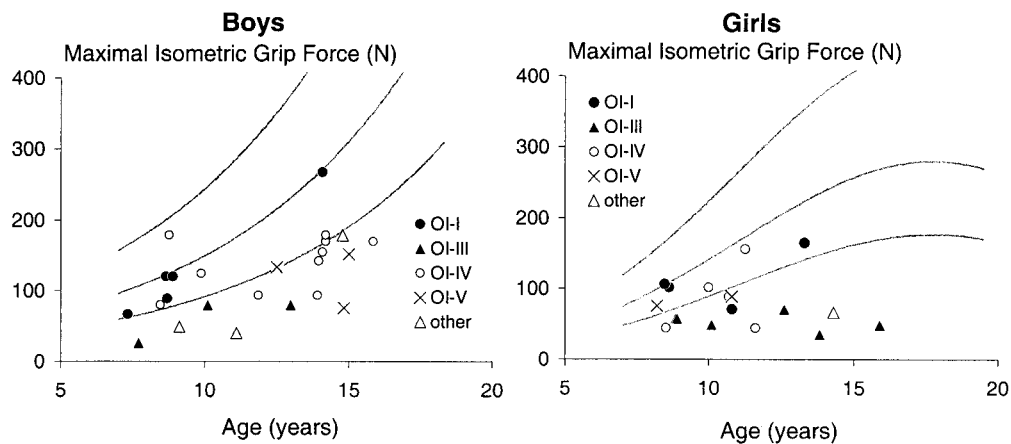
The P value indicates the significance of the difference between OI types 1, 3, 4, and 5 (analysis of variance).

Significant differences of the 2-score mean value from 0 are indicated by symbols.

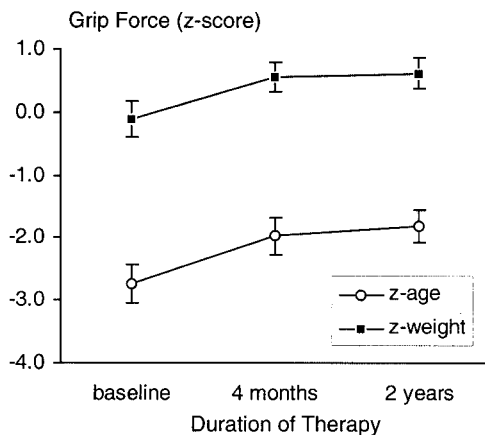
\*  $P < .05$ .

†  $P < .005$ .

‡  $P < .0005$ .



**Fig 1.** Grip force at the start of therapy. The lines represent the reference range. They indicate mean (middle line), 2 standard deviations above the mean (upper line), and 2 standard deviations below the mean (lower line) in healthy children and adolescents.



**Fig 2.** Grip force changes during therapy with pamidronate. Both age-dependent and weight-dependent z scores are indicated. Results at 4 months and 2 years are significantly different from baseline values ( $P < .001$  each).

Whatever the interpretation of the baseline results may be, we found a rapid increase in grip force within 4 months after a single pamidronate infusion cycle. It seems highly unlikely that this rapid increase reflects the natural evolution of grip force in OI. Indeed, inspection of the baseline results (Fig 1) and literature data rather suggests that grip force increases slowly or not at all in such patients. Thus, the increase in grip force after a single pamidronate cycle is most probably attributable to a direct or indirect drug effect. Improved muscle function may have contributed to increase mobility in these patients.

The present data shed no light on the mechanisms that lead to increased muscle force after the start of pamidronate therapy. A direct effect on muscle cells cannot be excluded. The drug enters the muscle, although the concentration in muscle tissue is very low.<sup>13</sup> It is also likely that the rapid disappearance of bone pain after the first pamidronate cycle contributes to improved performance in the grip force test.<sup>4</sup> This might explain why there was no additional increase in grip force z scores after the first 4 months of therapy.

## CONCLUSIONS

This study provides evidence that maximal isometric grip force markedly increases after a single cycle of intravenous pamidronate in children with severe forms of OI and that this gain in grip force is maintained for at least 2 years. The mechanism whereby pamidronate influences muscle force remains to be elucidated.

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