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## GROWTH IN OSTEOGENESIS IMPERFECTA

**HORACIO PLOTKIN, MD, FAAP**

*Departments of Pediatrics and Orthopedic Surgery  
University of Nebraska Medical Center  
and Children's Hospital  
Omaha, Nebraska*

### INTRODUCTION

Osteogenesis imperfecta (OI), or brittle bone disease, is a rare disorder with congenital bone fragility caused by mutations in the genes that codify for type I pro-collagen production in osteoblasts (*COL1A1* and *COL1A2*), located in chromosomes 7 and 17.<sup>1</sup> Numerous mutations have been described as causing the condition.<sup>2</sup> In the vast majority of cases, OI is inherited in a dominant fashion, or caused by a new mutation. The prevalence of OI is estimated to be 1 in 20 000 to 50 000 infants.<sup>3</sup>

Besides brittle bones, clinical characteristics and severity of OI are widely variable. There

may even be a different degree of severity in different members of the same family.<sup>4,5</sup> Clinical features that may be present include bone fragility, joint hyperlaxity, muscle weakness, chronic unremitting bone pain, and skull deformities (eg, posterior flattening) due to bone fragility in infants with severe OI. Fractures may still occur after puberty,<sup>6</sup> with bone fragility persisting throughout life. Individuals with mild forms of the disease may have normal stature with no deformities or fractures at all, and the condition would be diagnosed only when an x-ray is obtained for other reasons. People with severe OI may have extreme short stature and severe deformity of the long bones. Exercise tolerance and muscle strength are significantly reduced in patients with OI, even in the mild forms.<sup>7</sup>

Osteogenesis imperfecta can affect several organs and systems. For example, hearing loss may be present in about 50% of the

### From The Editor's Desk

Dear Colleague:

You may be aware that our former sponsor, Insmed, settled a patent infringement dispute and no longer promotes IGF-I/IGFBP-3 to patients with severe primary IGF-I deficiency or other short stature indications. Therefore, they no longer provide an educational grant to the GGH journal. Consequently, Pediatric Sunshine Academics, Inc., a 501(c)(3) non-profit organization, is funding the cost of this issue of GGH without prior anticipation or alternative funding sources available.

However, I am committed to seek new grants that will allow us to continue publishing this journal. I am grateful to the editorial board for their strong support; they have all pledged to contribute with their usual efforts and expertise while we seek more stable times. Since its inception 23 years ago, GGH has improved and expanded; it is held in high regard and enjoys over 11 000 subscribers. We all feel obliged not to let you down.

In order to forge ahead GGH will need the support of its readers while we elicit educational grants. You can help us during this transition by contributing to Pediatric Sunshine Academics, Inc. an organization whose mission is to support research and education in pediatric endocrinology and nutrition. Your fully tax deductible donation to **Pediatric Sunshine Academics, Inc., P. O. Box 3208, Tallahassee, FL 32315-3208**, either by check or online at [www.PedSacademics.org](http://www.PedSacademics.org) will be used entirely for the continued publication of GGH. Pediatric Sunshine Academics, Inc.'s federal EIN is 65-0854085.

On behalf of the editorial board, I thank you in advance for your donations and support. I will keep you apprised of our quest to elicit new grants and sponsorships for the continuation of the publication of GGH.

Fima Lifshitz, MD  
Editor-in-Chief

individuals with mild forms of OI after the third decade of life.<sup>8</sup> The incidence of congenital malformations of the heart in children with OI is probably similar to that of the normal population,<sup>9,10</sup> but respiratory complications secondary to kyphoscoliosis are common in individuals with severe OI.<sup>11</sup> Joint hyperlaxity is also a common occurrence in patients with OI,<sup>12</sup> and may lead to dislocation of hips and radial heads, sprains, and flat feet. Constipation and hernias are also a common complication of OI.<sup>13</sup> Dentinogenesis imperfecta (DI), caused by an abnormal dentin while enamel remains normal,<sup>14,15</sup> is prevalent in about 28% of OI patients.<sup>16</sup> Life expectancy in subjects with non-lethal OI appears to be the same as that in the normal population,<sup>17</sup> with the exception found in cases of very severe OI with respiratory or neurological complications.<sup>18</sup>

Histomorphometric analysis of the bone in patients with OI shows decreased trabecular bone volume, possibly secondary to the formation of fewer trabeculae, and to a lack of thickening of trabeculae with growth. There is evidence of defects in modeling of external bone size and shape, production of secondary trabeculae by endochondral ossification, and thickening of secondary trabeculae by remodeling.<sup>19</sup> Contrary to the common conception of attributing the defect in OI to the osteoclast, OI should be regarded as a disease of the osteoblast. Collagen plays an essential role in forming an interactive network between the cells by making extracellular matrix and noncollagenous proteins that lead to proper mineralization of the bone. When the fundamental structure of the collagen helix is disturbed by a mutation, a complex series of secondary changes to the bone develops, leading to increased bone fragility.

### **GROWTH IN CHILDREN WITH OI**

Severely affected patients may be short because of vertebral compression fractures, severe scoliosis, lower limb deformities, and disruption of growth plates.<sup>20</sup> However, growth can also be delayed in the absence of these abnormalities. The most commonly used classification divides OI into 4 types. Type I patients do not have bone deformities and may have normal height, but fractures may range from very few to dozens over a lifetime. Type II is the most severe, with patients usually not surviving the perinatal period. Patients with type III have a characteristic triangular face, very short stature, and severe bowing of long bones; they typically suffer many fractures throughout their life. Type IV is not clearly defined. Patients with this type of OI are generally short, although there is no consensus regarding the specific characteristics of this type. Other types have been described, but there is controversy because they actually represent syndromes resembling OI.<sup>1</sup> According to one study, during the first 10 years of life the number of fractures, extent of skeletal deformities, and growth retardation do not differ between OI types III and IV.<sup>10</sup> This is surprising, as individuals with type III OI usually have

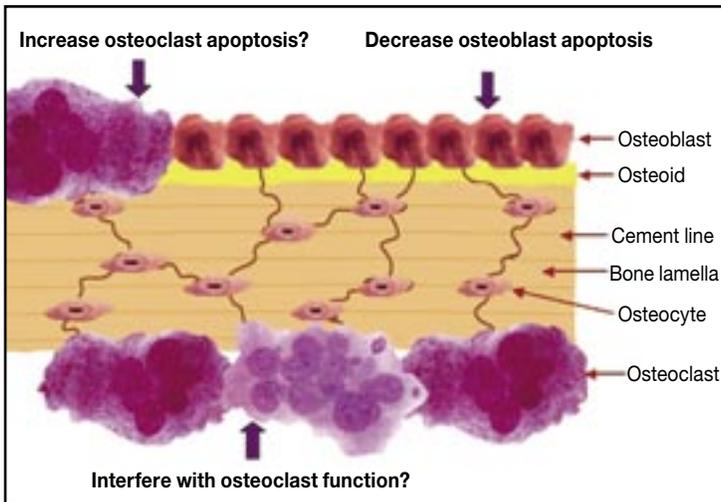
very short stature, whereas individuals with type IV OI may have mild-to-moderate short stature. Furthermore, according to some authors, individuals with type IV OI may have normal stature.<sup>21</sup> This highlights the inaccuracy of classifying this disease into 4 types.<sup>22</sup> I will, therefore, refer to OI “severity” throughout this article, instead of OI “type.”

The mean standing height of patients with OI is lower than that of their unaffected first degree family members, regardless of severity. Truncal height is reduced and head size increased in one third of the patients, more so in individuals with moderate or severe OI (Sillence’s types IV and III). During childhood, there appears to be no difference between the standing heights of girls and boys, but women had lower height z-scores than men. The reduction in arm span z-score generally follows the same pattern as for height: individuals with moderate or severe OI tend to have lower z-scores than individuals with mild OI. The arm span/height ratio appears to be increased in children with moderate or severe OI, but not in those with mild OI. Mean concentrations of insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 are generally normal, in the low range of age-specific reference values.<sup>10,21</sup> Growth hormone (GH) deficiency is very rare in patients with OI. In a group of 22 children tested by Marini et al,<sup>23</sup> none fulfilled the standard criteria for GH deficiency. A few children in that study had a blunted response to GH-releasing hormone or failed to double their serum IGF-I in a 5-day somatomedin generation test. However, there was no consistent relationship between those responses or between the responses and type of OI.

The etiology of the growth restriction in children with moderate and severe OI is not entirely clear. It has been suggested that it could be viewed as a self-protective mechanism: a given mechanical load creates smaller stresses in a short bone than in a long bone, thus a short bone will break less easily.<sup>24</sup> People with severe OI have a typical deformity of the growth cartilage, defined as “popcorn” appearance of the metaphysis. Microfractures of the growth cartilage may play a role in the growth problems experienced by these patients. There are no reports on the effects of puberty and hormonal changes on growth in children with OI.

### **USE OF BISPHOSPHONATES IN CHILDREN WITH OI**

Bisphosphonates are synthetic drugs with a chemical structure based on pyrophosphate,<sup>25</sup> and have been used to treat osteopenia of primary and secondary origin in both children and adults.<sup>26</sup> Effects on both osteoblasts<sup>27,28</sup> and osteoclasts<sup>29,30</sup> have been shown, although the mechanism through which bisphosphonates increase bone mineral density (BMD) is not clear (Figure 1). Likewise, effects of bisphosphonates on growth have been documented, but the mechanism of those effects has not been elucidated. There are differences



**Figure 1.** Possible mechanisms of action of bisphosphonates on bone.

among the bisphosphonates that may influence their mechanisms for binding and inhibiting bone crystal growth and dissolution. This may explain differences in potency among different bisphosphonates, such as the apparently more prolonged duration of action of alendronate and zoledronic acid, compared with the more readily reversible effects of risedronate.<sup>31</sup>

Different treatment protocols recommend the use of different bisphosphonates (ie, pamidronate, risedronate, alendronate, olpadronate, neridronate), and at different dose regimens for the pediatric population. For example, pamidronate doses range from 4.5 mg/kg/yr<sup>32,33</sup> (Tables 1 and 2) to 9 mg/kg/yr.<sup>34,35</sup> Children treated with high-dose pamidronate experience dramatic increase in BMD, with changes of as high as 200% per year.<sup>35,36</sup> Other positive effects observed include increase of the cortical width of the metacarpals, and increased vertebral height in previously fractured vertebrae. The incidence of fractures

decreases as well. Fracture healing does not appear to be impaired in patients with OI when compared to untreated OI patients.<sup>37,38</sup> There is a striking disappearance of bone pain and decreased fracture incidence noted with intravenous treatment. This may contribute to greater mobility,<sup>39,40</sup> an essential factor for the development of the skeletal system.<sup>41</sup> A lower fracture incidence, despite higher risk of injury due to increased mobility, suggests a direct effect of the therapy. These effects contribute to an improvement in the quality of life of patients with OI who are receiving treatment.

A side effect of high doses of pamidronate (9 mg/kg/yr) is retention of calcified cartilage within secondary spongiosa in children with OI.<sup>30</sup> Higher doses have caused osteopetrosis in a patient with no diagnosis.<sup>42</sup> Retention of calcified cartilage within secondary spongiosa is a hallmark of osteopetrosis, this suggests a dose-related effect of pamidronate. Studies using oral bisphosphonates for the treatment of OI (olpadronate,<sup>43</sup> alendronate) showed no differences between the drugs and placebo on functional outcome, anthropometrics, fracture incidence, or vertebral height, although it has been suggested that oral alendronate may improve quality of life in this group of patients.<sup>44</sup>

#### EFFECTS OF BISPHOSPHONATE TREATMENT ON GROWTH IN CHILDREN WITH OI

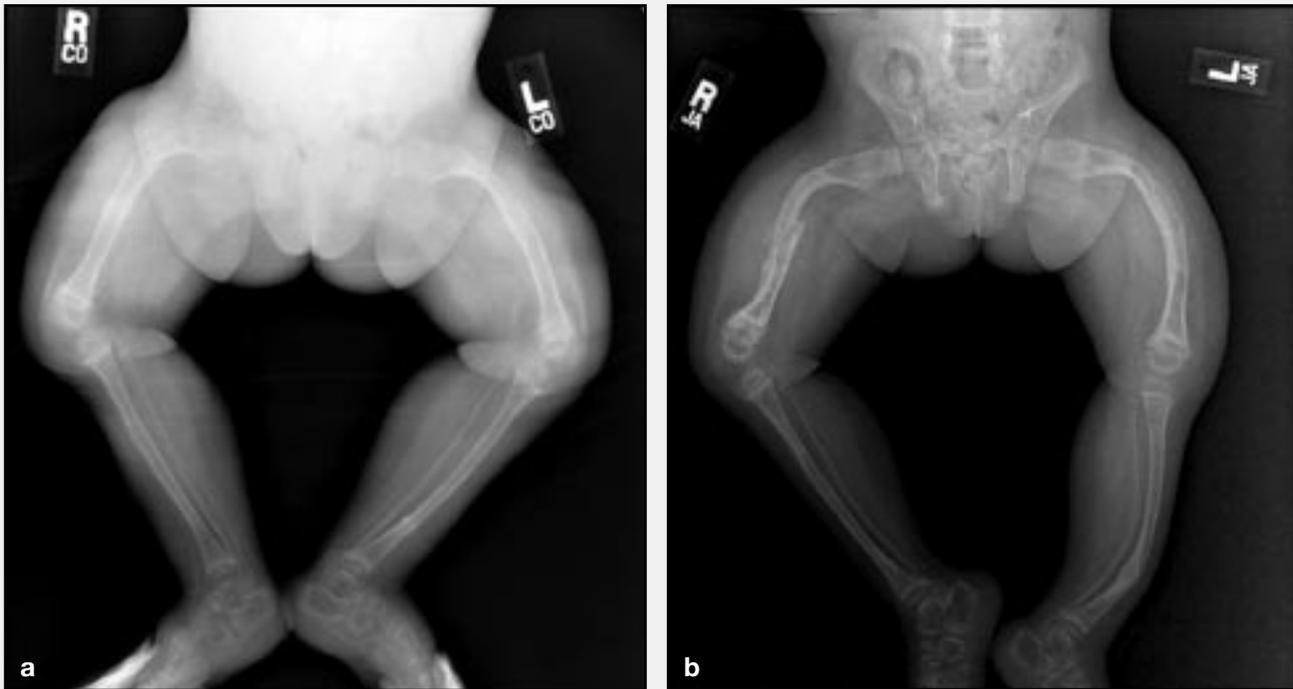
The effect of treatment with bisphosphonates on longitudinal bone growth in children has been a concern among clinicians.<sup>45</sup> Bone resorption is an essential part of the normal endochondral ossification process,<sup>46</sup> and of the bone modeling and remodeling process. Despite the fact that the mechanism of long bone growth relies upon clonal expansion and subsequent hypertrophy of chondrocytes, endochondral bone growth requires resorption of the septa of calcified cartilage at the chondro-osseous junction of the growth plate by chondroclasts, permitting vascular invasion of the hypertrophic cell lacunae.<sup>47</sup> Drugs interfering with this mechanism could potentially cause impairment of the bone elongation process. Bisphosphonates interfere with osteoclast function<sup>29</sup> or survival,<sup>48</sup> and could, therefore, have a deleterious effect on bone growth. This undesired effect has actually been shown in animal studies.<sup>49</sup> High doses of alendronate (>2.5 mg/kg/wk) inhibited long bone length in the OIM mice (a model of OI) through alteration of the growth plate and possibly reduced resorption at the chondro-osseous junction.<sup>50</sup> Furthermore, lower doses of alendronate do not appear to have a detrimental effect on growth in oim/oim mice,<sup>51</sup> suggesting another dose-related effect of bisphosphonates. On the other hand, bisphosphonates do not appear to be detrimental for growth in human subjects at the doses currently used (Figure 2).<sup>24,52-55</sup> Each time a patient receives a pamidronate infusion, a new sclerotic line appears in the

**Table 1. Protocol for administration of low-dose IV pamidronate treatment.**

Age group	Dose	Interval
<2.0 years	0.37 mg/kg/day for 2 days	2 months
2.0-3.0 years	0.56 mg/kg/day for 2 days	3 months
>3.0 years	0.75 mg/kg/day for 2 days	4 months

**Table 2. Suggested dilution and infusion rates for IV pamidronate treatment.**

mg of pamidronate	mL of normal saline	mL/hr
0-5	50	15
5.1-10	100	30
10.1-15	150	45
15.1-25	250	75
25.1-45	500	150



**Figure 2.** Lower limbs x-ray of a child with severe OI before (a) and after 12 months (b) of treatment with low-dose pamidronate (4.5 mg/kg/yr). Treatment was started at 18 months of age. Note longitudinal growth. Fractures do occur under treatment as evident in the panel on the right, but at much lower rate than before treatment.

metaphysis of long bones. The distance between these lines reflects longitudinal bone growth (Figure 3).

Pamidronate in high doses (9 mg/kg/yr) does not appear to negatively affect growth. Height z-score actually increased in a group of patients with OI who had started treatment before 3 years of age.<sup>35</sup> After one year of pamidronate therapy, height z-scores increased significantly in a group of children with severe OI and did not change in children with mild and moderate OI.<sup>24</sup> After 4 years of therapy with the same dose regimen of pamidronate, mean height z-scores increased significantly in children with moderate OI, whereas non-significant trends to increase were seen in patients with mild and severe OI.<sup>24</sup> Low doses of pamidronate appear to have a similar effect (data not published) (Figure 3).

Low doses of pamidronate elicited no short-term evidence of growth impairment in children with a variety of pathologies leading to osteoporosis, including OI. A median annualized change in height SDS of 0 (range, -0.4 to 0.5) was noted in that group.<sup>56</sup> As expected, growth changes are greater in children with milder OI than

in those with more severe forms of the condition when receiving therapy with alendronate or pamidronate.<sup>57</sup>

One study showed that patients treated with high doses of pamidronate (9 mg/kg/yr) had similar growth plate width but



**Figure 3.** Distal femur of a pediatric patient with OI receiving treatment with IV pamidronate. Note the sclerotic lines, each representing an infusion. The distance between lines reflects longitudinal bone growth in a 2-month period.

wider metaphyses when compared with untreated OI patients who were matched for OI type and age, despite the lack of detrimental effects of bisphosphonates on longitudinal growth,<sup>58</sup> suggesting an effect of the high dose on bone remodeling. A different study showed that metaphyseal modeling in the distal femur is constant in children on bisphosphonates—with slight variation between sexes—resulting in a similar shape of the distal femur throughout childhood when looking at the modeling process.<sup>59</sup> Noteworthy, the observed positive effect of pamidronate on bone growth does not appear to be secondary to acceleration of bone age.<sup>24</sup>

Infants with OI appear to grow better when treatment with neridronate is started soon after birth, rather than at 6 months of age.<sup>60</sup> Older children with OI receiving neridronate grew faster than controls in one study.<sup>61</sup> At the microscopic level, the size of iliac crest bone biopsies is not significantly different before or after treatment in children

with OI. Changes are seen in cortical width, which increased by about 90%. Cancellous bone volume increases by about 45% with treatment. This change is due to higher trabecular number, with no change in trabecular thickness.<sup>30</sup> Importantly, there is no evidence for a mineralization defect in children with OI treated with high doses of pamidronate.<sup>30</sup> Growth in children continues after treatment with pamidronate is stopped, and the newly-formed bone will be unprotected and prone to fractures (Figure 4).

### LONG-TERM EFFECTS OF BIPHOSPHONATES ON HEIGHT

In one study, mean height z-scores of subjects with all OI degrees of severity tended to increase after 4 years of pamidronate therapy when compared with baseline. However, the change in height z-scores was significant only for the group with moderate OI, but not for mild or severe OI.<sup>24</sup> It is of note that these comparisons were done against normal growth charts designed for healthy children. To more accurately assess the growth rate of children with OI undergoing treatment, the same group compared their growth with that of a group of children with OI who were not receiving treatment with bisphosphonates. In that study, each height measurement of patients was expressed as a percentage of the mean value expected for untreated OI patients. During 4 years of pamidronate therapy, height significantly increased above the values expected for untreated patients.<sup>24</sup>

### EFFECT OF PAMIDRONATE ON FINAL HEIGHT

There is very little information about final height in children with OI treated with bisphosphonates. There is the description of only 8 patients who attained final height while receiving treatment with pamidronate.<sup>24</sup> In this study, final height, expressed as a percentage of the expected height in untreated patients, was significantly higher than baseline height. This study suggests that an average gain of 7 cm in patients with mild OI, 12 cm



**Figure 4.** Long bones continue growing after treatment with bisphosphonates is stopped (arrow), causing susceptibility to fractures.

in patients with moderate OI, and 9 cm in patients with severe OI can be expected at 15 years of age. These results suggest that acceleration of growth is not just a transitory effect, but rather a lasting outcome on height in children with OI who are receiving pamidronate intravenously. As mentioned above, it is not entirely clear how pamidronate treatment might improve growth. Part of the effects of bisphosphonates on growth in children with moderate and severe OI could be due to prevention of long bone deformity and regeneration of vertebral fractures (Figure 5),<sup>35,62</sup> and to prevention of microfractures affecting growth cartilage.

### EFFECTS OF GROWTH HORMONE IN CHILDREN WITH OI

Growth hormone regulates post-natal bone growth; IGF-I mediates the growth-promoting action of GH, although it has been shown that

GH may have independent, direct effects on growth.<sup>63</sup> Also, IGF-I has mitogenic effects in dividing cells and is closely associated with growth, although plasma levels do not correlate with growth rates. It is known to

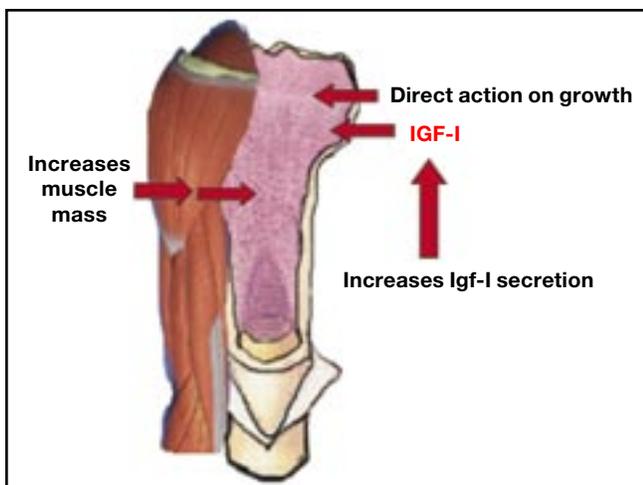


**Figure 5.** Lumbar spine x-ray of a child with severe OI before (a) and after 12 months (b) of treatment with low-dose pamidronate (4.5 mg/kg/yr). Treatment was started at 18 months of age. Note increased vertebral height with treatment.

increase 1- $\alpha$  hydroxylase in kidneys, with subsequent increased production of calcitriol (1,25 [OH]<sub>2</sub> vitamin D<sub>3</sub>). As calcitriol is the active form of vitamin D, IGF-I and GH treatment can make calcium more available for bone mineralization,<sup>64</sup> which could add to a possible beneficial effect in patients with OI. Inversely, it has been suggested that vitamin D, calcium, and protein supplements may elicit part of their effect on osteoporosis through increased IGF-I levels.<sup>65</sup>

IGF-I promotes longitudinal bone growth by 'insulin-like' anabolic actions which augment chondrocyte hypertrophy.<sup>66</sup> Chondrocyte differentiation, in turn, leads to cartilage expansion and linear growth. Furthermore, osteoblasts and pre-osteoblasts secrete IGF-I, and bone resorption causes release of stored IGF-I. This hormone appears to be a growth factor for osteoblasts. A homozygous molecular defect in the gene encoding IGF-I caused severe intrauterine growth failure, sensorineural deafness, and mild mental retardation in one individual.<sup>67</sup> Treatment with IGF-I improved linear growth and insulin sensitivity in that patient.<sup>68</sup> There is also some weak evidence that IGF-I has a role in declining BMD with aging. In patients with Laron syndrome, IGF-I treatment increases bone growth in the absence of GH.<sup>69</sup> Low IGF-I concentrations appear to be associated with low BMD in patients with cystic fibrosis.<sup>70</sup>

As discussed above, some children with OI have a blunted response to GH-releasing hormone or fail to double their serum IGF-I in a 5-day somatomedin generation test (13 of 22 had less than a 2-fold stimulation of somatomedin-C by GH).<sup>71</sup> There was no overlap between the group with blunted IGF-I response and the group with decreased GH-releasing hormone response, suggesting that there might be 2 different mechanisms of GH resistance in children with OI. GH is an anabolic hormone and, together with IGF-I, is a potent regulator of muscle mass. As such, there is potential for it to increase bone density. In the absence of trauma, muscles are responsible for the largest loads



**Figure 6.** Mechanisms for growth hormone stimulation of bone growth and increase of bone mineral density.

and the largest bone strains, and those strains help to control the biological mechanisms that determine whole-bone strength (Figure 6).<sup>72</sup>

There are no large controlled studies of GH treatment in children with OI. Furthermore, there are no data in the literature regarding final height in OI patients treated with GH. An increase of fracture rate during GH therapy has been reported in children with OI by different groups,<sup>73,74</sup> although another group did not find an increase in fracture rate in a small group of children with mild OI who were treated with GH for 1 year.<sup>75</sup> Extending treatment to 2 years did not change the fracture risk either.<sup>76</sup> Like all children who are initially started on GH, children with OI experience an initial acceleration of growth rate,<sup>64,77</sup> but a sustained effect has not been demonstrated. In one study, GH (0.1- 0.2 IU/kg/d for 6 days/wk) was administered for at least 1 year to children with OI of different severity,<sup>78</sup> about one-half of the treated OI children sustained a 50% or more increase in linear growth, compared to their baseline growth rate. It is of note that most responders (10 of 14) did not have a severe form of OI. Incidentally, only the linear growth responders had a significant decrease in long bone fractures. After 1 year of treatment, responders' iliac crest biopsy showed significant increases in cancellous bone volume, trabecular number, and bone formation rate, but no significant increase in cortical thickness. Histomorphometric parameters of bone resorption were not significantly changed in responders, whereas non-responders had an 80% increase in the percentage of bone surface covered by osteoclasts. The incidence of fractures was unchanged in non-responders. Bone formation parameters did not increase with treatment in this group. Although progression of scoliosis was unchanged compared with the National Institute of Child Health and Human Development (NICHD) OI population, data on individual cases are not offered in the report.

Recombinant human IGF-I, complexed with its predominant binding protein IGFBP-3 is currently being tested as a treatment for osteoporosis, alone or in combination with anti-resorptive drugs and GH.<sup>79</sup> There appears to be a correlation between the dose of GH (and the obtained IGF-I plasma levels) and the increase in bone turnover markers and/or BMD in adults,<sup>80</sup> although a different study found that 1 year of IGF-I treatment, at a dose sufficient to elevate circulating IGF-I to young normal values, was not an effective means to alter body composition or blood parameters, nor to improve bone density, strength, mood, or memory in older women.<sup>81</sup>

## CONCLUSION

Bisphosphonate treatment does not appear to have a detrimental effect on linear growth in children and adolescents with OI, regardless of the severity of the condition. Long-term bisphosphonate therapy in children with OI may be associated with a significant height gain, as compared with untreated OI patients with the same

disease severity. The use of GH in this population is still controversial. It has been suggested that GH treatment should probably not be used as a first-line therapy in OI.<sup>82</sup> Combined protocols administering both bisphosphonates and GH are warranted. Other therapeutic options currently used or in research for patients with osteoporosis (PTH, IGF-I, strontium, RANK ligand) may have a role in the treatment of OI in the future.

**Disclosures:** The author discloses no conflicts of interest. Pamidronate use for children with OI is off label.

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