Multidisciplinary Treatment of Severe Osteogenesis Imperfecta: Functional Outcomes at Skeletal Maturity

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Abstract

Objective: To determine the functional outcomes associated with long-term multidisciplinary treatment, intravenous bisphosphonate treatment, orthopedic surgery, and rehabilitation in children with severe osteogenesis imperfecta (OI) (diagnosed clinically as OI types III or IV).

Design: Retrospective study where outcomes were measured prospectively.

Setting: Pediatric orthopedic hospital.

Participants: Adolescents (N = 41; age range, 15–21 y) with severe OI (OI type III: n = 17; OI type IV: n = 24) who had started therapy before the age of 6 years, had received treatment for at least 10 years, and had achieved final height.

Interventions: Intravenous bisphosphonate treatment, orthopedic surgery, and rehabilitation.

Main Outcome Measure: Pediatric Evaluation of Disability Inventory.

Results: At the time of the last available follow-up examination, none of the individuals diagnosed with OI type III (most severely affected group) was able to ambulate without ambulation aids, whereas 20 (83%) patients with OI type IV were able to ambulate without ambulation aids. Regarding self-care, we specifically assessed 8 skills that we deemed essential for living independently (grooming; dressing; toileting; bed, chair, toilet, tub, and car transfers). Only 6 (35%) of the youths with OI type III were able to complete all 8 items, whereas 23 (96%) individuals with OI type IV managed to perform all tasks. Teens with OI type III often needed assistance for the transfer to toilet, tub, and car and for personal hygiene and clothing management associated with toileting, usually because of limitations in upper-extremity function.

Conclusions: These observations suggest that further improvements in the functional status of the most severely affected children with OI are contingent on advances in the clinical management of upper-extremity issues.

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Osteogenesis imperfecta (OI) is a heritable connective tissue disorder that affects bone development and leads to bone fragility.1 Teeth (dentinogenesis imperfecta) and soft tissues (eg, discoloration of sclera, joint hyperlaxity) are also often involved. Bone fragility varies widely in severity, ranging from absence of symptoms to perinatal lethality. OI is typically inherited as an autosomal dominant trait and usually is caused by mutations in 1 of the 2 genes encoding collagen type I alpha chains, COL1A1 and COL1A2.1 The traditional clinical classification distinguishes 4 main types that differ in the severity of bone fragility. OI type I covers the mild end of the severity spectrum, OI type II represents the neonatal lethal form, OI type III is the most severe type of OI in survivors, and OI type IV is intermediate in severity between OI types I and III.2 Recently, new OI types have been proposed, but all of these are extremely rare.1

Even though there is no cure for the genetic defect causing OI, intravenous bisphosphonate therapy is widely used.3 Many observational studies in children with severe OI have found that during average follow-up periods of 2 to 4 years, this treatment is associated with increased bone mass, reshaping of compressed vertebral bodies, and decreased fracture rates.4-11 Nevertheless, the treatment of such patients therefore is not limited to pharmacologic approaches but often requires a multidisciplinary approach.12 Children with OI types III and IV frequently have

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long-bone deformities and therefore need corrective orthopedic interventions and rehabilitation services. The overall treatment goal for children with severe OI is to improve functional outcomes (eg, mobility, self-care) and thereby enable patients to live independently as adults.

It is not clear at present to what extent this goal is achieved with the currently available treatment approaches. We have previously reported that children with severe OI who had received 3 years of multidisciplinary therapy had better mobility than a historical control group of children that were matched for age and OI type. However, there is presently no information on the functional status at skeletal maturity in children with severe OI who started multidisciplinary treatment early. In the present study, we therefore assessed functional outcomes in children with severe OI who were at skeletal maturity after multidisciplinary treatment during the growing years.

Methods

Participants

The study population comprised adolescents with OI type III or IV who were followed at our institution. The diagnosis was based on clinical appearance according to the Silience et al classification, following an assessment by one of the authors (F.H.G. or F.R.). Data were obtained by retrospective chart review.

The following criteria were used to identify the study population: (1) multidisciplinary treatment was started before the age of 6 years; (2) the last available assessment of clinical outcomes occurred at least 10 years after the start of treatment; and (3) the patient had achieved final height. A total of 41 patients fulfilled the criteria. Data from these individuals were included in the cross-sectional analysis of results at the last follow-up. We identified a subgroup of 33 patients (OI type III: n = 13; OI type IV: n = 20) who had functional outcome data for at least 3 of the following chronologic age time points: 3, 6, 12, and 18 years. These data were included in the longitudinal analysis of the course during treatment follow-up. The study was approved by the Institutional Review Board of McGill University. Because this was a retrospective chart review, informed consent was not required.

Medical treatment

Intravenous bisphosphonate therapy consisted of infusions with pamidronate or zoledronate as previously described. The initial annual dose of pamidronate was 9mg/kg body weight (full-dose pamidronate). Zoledronate infusions were administered at an annual dose of 0.1mg/kg body weight (full-dose zoledronate). The annual doses of pamidronate and zoledronate were reduced to half of the full-dose schedules when the lumbar spine areal bone mineral density z scores exceeded −2. Infusion treatment was interrupted for at least 4 months after orthopedic interventions involving osteotomies to facilitate osteotomy healing. Bisphosphonate infusions were discontinued once longitudinal growth ceased.

Outcome measures

Functional outcomes were measured using the functional scores of the self-care and mobility domains of the Pediatric Evaluation of Disability Inventory (PEDI). The PEDI measures current functional performance. It was administered to patients from 6 months to 21 years of age. Children who used mobility aids were scored with these aids to provide the patient’s true performance within the environment. This assessment was performed by occupational therapists through a combination of parent interview and observation of the child’s performance. Each item was scored 0 or 1, indicating unable or able to perform the task, and a raw score was tabulated by summing up the number or items that could be performed. Raw scores were transformed into scaled scores, where 100 denotes full function and 0 denotes no function. Healthy children are expected to attain a scaled score of 100 by 7 years. The social function domain of PEDI was not tested because social

List of abbreviations:

OI osteogenesis imperfecta
PEDI Pediatric Evaluation of Disability Inventory
Table 1  Characteristics of the cross-sectional cohort at the last follow-up visit

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OI Type III</th>
<th>OI Type IV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (male/female)</td>
<td>17 (9/8)</td>
<td>24 (12/12)</td>
<td>.85</td>
</tr>
<tr>
<td>Start of treatment (y)</td>
<td>3.1±2.1</td>
<td>3.5±1.7</td>
<td>.51</td>
</tr>
<tr>
<td>Follow-up period (y)</td>
<td>14.7±2.2</td>
<td>14.8±1.6</td>
<td>.86</td>
</tr>
<tr>
<td>Age (y)</td>
<td>17.8±1.8</td>
<td>18.3±2.3</td>
<td>.46</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>114.4±11.8</td>
<td>163.4±15.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height (z score)</td>
<td>−7.2±1.6</td>
<td>−3.7±1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight (cm)</td>
<td>43.0±15.9</td>
<td>53.8±16.6</td>
<td>.04</td>
</tr>
<tr>
<td>Weight (z score)</td>
<td>−2.3±1.7</td>
<td>−1.1±1.3</td>
<td>.02</td>
</tr>
<tr>
<td>Lower-extremity segments rodded (n)</td>
<td>3.3±1.2</td>
<td>2.4±1.3</td>
<td>.04</td>
</tr>
<tr>
<td>Upper-extremity segments rodded (n)</td>
<td>0.9±1.0</td>
<td>0.2±0.6</td>
<td>.04</td>
</tr>
<tr>
<td>Spinal fusion</td>
<td>11 (65)</td>
<td>6 (25)</td>
<td>.01</td>
</tr>
<tr>
<td>Using power wheelchair</td>
<td>11 (65)</td>
<td>2 (8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ambulates without aids</td>
<td>0 (0)</td>
<td>20 (83)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bleck score</td>
<td>0.7</td>
<td>3.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PEDI mobility (score)</td>
<td>58±11</td>
<td>86±15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PEDI self-care (score)</td>
<td>87±13</td>
<td>99±5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NOTE. Results are given as mean ± SD, n (%), or as otherwise indicated.

and cognitive impairments were not expected in OI. A normative score from the raw score is also available for ages 6 months to 7.5 years.

Five mobility items (ability to transfer to chair, bed, toilet, tub/shower, and car) and 3 self-care items (grooming, dressing, and toileting) were analyzed separately because they were judged to be essential for independent living. The self-care skills are comprised of several subitems which were pooled into the 3 categories and then rated as acquired or not, based on the overall performance of the subitems.

Level of ambulation was measured by the therapist using the modified Bleck scale, a descriptor of ambulation consisting of a 5-point ordinal scale: 0 (nonambulator), 1 (therapeutic), 2 (household), 3 (limited community), and 4 (full community).17

Statistical analysis

Anthropometric measurements were converted to age- and sex-specific z scores based on reference data reported by the Centers for Disease Control and Prevention.18 Group differences in dichotomous variables were tested for significance using the chi-square test. Independent-sample t test or Mann-Whitney U test was used to compare mean values of continuous variables, as appropriate. The difference of the z-score results to 0 (ie, mean result expected in the general population) was tested for significance using the 1-sample t test. A 5% significance level was used throughout, and all tests were 2 sided. Calculations were performed using SPSS version 22.4

Results

Among the 41 patients (21 male, 20 female) included in the present study, 17 had a diagnosis of OI type III, and the other 24 patients were diagnosed with OI type IV (table 1). Sixteen patients had heterozygous mutations in COL1A1, 24 patients had heterozygous mutations in COL1A2, and 1 patient had a homozygous mutation in CRTAP. Patients had started multidisciplinary therapy between 6 weeks and 6 years of age and were between 15.0 and 21.6 years old at the time of the last follow-up evaluation. The average duration of the follow-up period was approximately 15 years.

The average height was very low in both diagnostic groups (see table 1). The number of limb segments that had undergone rodding surgery was higher in OI type III than in OI type IV at both the lower and the upper extremities. Nine of the 17 individuals with OI type III (53%) had had rodding of at least 1 upper-extremity segment, whereas only 2 of the 24 patients with OI type IV (8%) had undergone rodding at the upper extremities.

Cross-sectional evaluation at the last follow-up visit

None of the individuals diagnosed with OI type III was able to ambulate without ambulation aids (see table 1). All adolescents with OI type III used either a manual or power wheelchair on a daily basis; 16 (94%) used their wheelchair as the main mobility device, and 1 adolescent used both a walker and wheelchair. Correspondingly, 14 (82%) of the individuals with OI type III were either classified as therapeutic or nonambulators (fig 1). In contrast, most patients with OI type IV were able to ambulate without aids and were classified as either full or limited community ambulators.

The PEDI mobility scores reflected these observations (see table 1). More than a third of the individuals with OI type IV (9 of 24) successfully completed all 59 items, resulting in scaled scores of 100. Another 7 individuals with OI type IV (29%) had scores between 80 and 100, reflecting the need to use upper extremities during certain transfers, the need to use upper extremities on stairs, or an inability to manage uneven terrain. Three patients (13%) with OI type IV were therapeutic or nonambulators, primarily because of complications after surgery or fracture, and used a wheelchair as their main mobility. Twenty youths (83%) with OI type IV were community ambulators, with 4 of these individuals using ambulation aids outside the home for safety and endurance. In contrast, only 3 adolescents with OI type III (18%) could stand and take steps while transferring to a toilet or car. Three adolescents with OI type III (18%) walked for exercise 2 to 3 times per week.

Regarding self-care, only 5 of the 17 (19%) youths with OI type III achieved a scaled score of 100. Eight (47%) had scaled
scores >80, but 4 individuals with OI type III had markedly lower scaled scores (between 67 and 74) than others in this group. The reasons for the low scores in these 4 patients were nonunion of the humerus, severe bowing with shortening of all 4 upper-extremity segments, recessive form of OI with marked muscle weakness and deformities in the upper extremities, and major weight and pain issues. Figure 2 provides examples of upper-extremity issues in OI type III. In the OI type IV cohort, only 1 adolescent scored <100 for the self-care PEDI scaled score, and severe obesity was judged to be the reason.

Because this group of patients was on the threshold to adulthood, we specifically assessed their ability to live independently. The 8 essential skills for independent living derived from the PEDI items (grooming; dressing; toileting; bed, chair, toilet, tub, and car transfers) can be considered the criteria for the first phase of living independently. Mastering these skills means the adolescent with OI can embark on life away from home and without the assistance of a caregiver. Only 6 of the 17 (35%) youths with OI type III were able to complete all 8 tasks, whereas 23 of the 24 (96%) individuals in the OI type IV cohort achieved this goal (Fig 3). Teens with OI type III typically were able to perform the easier tasks (eg, moving from wheelchair to bed, doing grooming activities). Youths with OI type III were able to dress themselves; however, they often needed assistance for transfers to toilet, tub, and car and for toileting.

Longitudinal analyses

By the age of 12 years, most individuals with OI type IV achieved a score of 100 in the self-care domain; all were fully independent for self-care by 18 years (Fig 4). In most patients with OI type III, self-care scores were low, but the achievement of self-care skills continued gradually into adolescence, indicating that gains are possible past childhood. In fact, we observed that youths with OI type III sometimes developed the motivation to be independent in self-care only in adolescence.

Regarding mobility, children with OI type III tended to progress up to 6 years of age and then showed little gains. Eleven of 13 (85%) patients with OI type III with available data were able to achieve therapeutic ambulation by 6 years of age, but most did not maintain this skill, and at last follow-up only 6 (35%) had therapeutic ambulation or higher. In OI type IV, however, steady gains were noted during childhood, loss of function was noted around puberty in some individuals, and this was followed by recuperation of the upward trend.

Discussion

In the present study we assessed functional outcomes of youths with severe OI who were treated long-term with a multidisciplinary approach. We found that patients with OI type IV usually achieved independence in self-care activities and community ambulation and found a very functional level of general mobility, whereas individuals with OI type III had lower scores in both the mobility and self-care domains. Importantly, we observed that upper-extremity issues were the key limiting factors for achieving independence in toileting, the ability to perform complicated transfers, and therefore for independent living.

Fig 2  Examples of common upper-extremity issues in OI type III. Bowing translates into less range of motion, reach, and essentially shorter limbs. Joint deformities (eg, radial head dislocation) also result in decreased range of motion.

Fig 3  PEDI scores for transfer and self-care skills that are essential for living independently. Data obtained at the last evaluation. Abbreviations: OI-III, OI type III; OI-IV, OI type IV; Tx, transfer.
The OI type IV group attained independence in self-care; however, this was achieved later than is expected in the general population. This good outcome may reflect their lack of upper-extremity deformities. The 3 youths with OI type IV who used a wheelchair at the final follow-up had previously walked, but a major trauma or surgery in adolescence resulted in an inability to regain ambulation status. This observation suggests the importance of intensive rehabilitation and close follow-up to ensure ambulation is regained.

Children with OI type III were very short and had more upper-extremity deformities, and a high proportion underwent spinal fusion surgery. In OI type III, walking abilities were often not maintained past childhood. Perhaps the extreme short stature and the frequent need to use a wheelchair after fractures or surgery lead to the loss of therapeutic ambulation in late adolescence. However, the presence of therapeutic ambulation for even a limited period signals the potential for mobility. Promoting and maintaining some therapeutic ambulation and introducing transfer skills early is key for children with OI type III to achieve full independence in late adolescence.

Patients with OI type III had gains in self-care scores throughout adolescence, but this group usually still needed assistance for the complicated transfers to toilet, tub, and car. Engelbert et al.19 also found that many children with OI type III had high scores in the PEDI self-care domain, indicating high function in activities of daily living.

Despite relatively good self-care scores, only 35% of the adolescents with OI type III were able to perform the 8 skills that we deem essential for independent living. Our observations suggest that upper-extremity issues are often a limiting factor for the ability to live independently. Upper-extremity deformities that limit range of motion and upper-extremity fractures that contribute to muscle weakness play a significant role in the acquisition of independence in toileting and transferring to toilet, tub, and car. These findings support previous studies that upper-extremity deformity affects not only the performance of basic self-care tasks but markedly impacts mobility, transfers, and ambulation because children with severe OI use their upper extremities for these tasks.20 Although long-term intravenous bisphosphonate therapy has allowed early and successful lower-extremity surgery,15 the indications for upper-extremity surgery are still being developed.

Study limitations

The obvious limitation of this study is as a retrospective review the information extracted from the medical chart may be incomplete. However, the outcome measures were administered prospectively at regular intervals. Other limitations include the lack of a control group, which makes it difficult to conclude about overall therapeutic benefit. Also, the clinical diagnosis of OI type III or OI type IV is somewhat subjective.

Conclusions

We found that individuals with OI type IV receiving a long-term multidisciplinary treatment approach usually achieved community
ambulation and had excellent function in self-care and transfer skills, which is key to living independently. In contrast, none of the individuals with OI type III achieved independent ambulation, and upper-extremity issues limited their readiness to live independently. These observations suggest that further improvements in the functional status of the most severely affected individuals with OI are contingent on advances in the clinical management of upper-extremity issues.

Supplier

a. SPSS version 22 for Windows; SPSS.

Keywords

Mobility limitation; Osteogenesis imperfecta; Rehabilitation; Self care

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