

## Physical Training in Children with Osteogenesis Imperfecta

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**Objective** To study the effects of a physical training program on exercise capacity, muscle force, and subjective fatigue levels in patients with mild to moderate forms of osteogenesis imperfecta (OI).

**Study design** Thirty-four children with OI type I or IV were randomly assigned to either a 12-week graded exercise program or care as usual for 3 months. Exercise capacity and muscle force were studied; subjective fatigue, perceived competence, and health-related quality of life were secondary outcomes. All outcomes were measured at baseline (T = 0), after intervention (T = 1), and after 6 and 9 months (T = 2 and T = 3, respectively).

**Results** After intervention (T = 1), peak oxygen consumption ( $\dot{V}O_{2peak}$ ), relative  $\dot{V}O_{2peak}$  ( $\dot{V}O_{2peak/kg}$ ), maximal working capacity ( $W_{max}$ ), and muscle force were significantly improved (17%, 18%, 10%, and 12%, respectively) compared with control values. Subjective fatigue decreased borderline statistically significantly. Follow-up at T = 2 showed a significant decrease of the improvements measured at T = 1 of  $\dot{V}O_{2peak}$ , but  $\dot{V}O_{2peak/kg}$ ,  $W_{max}$ , and subjective fatigue showed no significant difference. At T = 3, we found a further decrease of the gained improvements.

**Conclusion** A supervised training program can improve aerobic capacity and muscle force and reduces levels of subjective fatigue in children with OI type I and IV in a safe and effective manner. (*J Pediatr* 2007;xx:xxx)

Osteogenesis imperfecta (OI) is a congenital connective tissue disorder characterized by increased bone fragility and osteopenia. The biochemical basis in most cases involves a quantitative abnormality, qualitative abnormality, or both in the biosynthesis of type I collagen, the principle organic component of the skeleton.<sup>1</sup> Severity varies in a wide range, reaching from intrauterine fractures and perinatal lethality to very mild forms with incidental fractures.<sup>2</sup> Although children with mild and moderate forms of OI are in general walkers (varying from household to community walkers<sup>3</sup>), fatigue, diminished exercise capacity, and exercise intolerance is frequently reported to limit these patients in their activities of daily living.<sup>4</sup>

Takken et al<sup>5</sup> studied cardiopulmonary function in 17 children with OI type I. They found that heart and lung abnormalities in rest were absent. However, they also reported that exercise capacity and muscle force were significantly reduced compared with those of their healthy peers,<sup>5</sup> whereas complaints of fatigue were related to proximal muscle weakness and a reduced peak oxygen consumption ( $\dot{V}O_{2peak}$ ). It was unclear whether the reduced  $\dot{V}O_{2peak}$  and muscle force were a consequence of a hypoactive lifestyle or a specific consequence of the impaired muscle collagen synthesis. Takken et al suggested that a physical intervention study in patients with OI might improve exercise capacity and muscle force.<sup>5</sup> In other chronic conditions in childhood such as cystic fibrosis<sup>6</sup> and leukemia,<sup>7</sup> exercise interventions have been reported to be beneficial in improving muscle force, exercise tolerance, and activities in daily living.

To our knowledge, physical intervention studies have not been performed in children with OI. Exercise might have no effect on the disease itself; but possibly may improve the level of activities of daily living, self-esteem, and fitness in many of these children. Therefore, we designed a randomized controlled trial to study the effects of a

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AT	Anaerobic threshold	OI	Osteogenesis imperfecta
CBSK	Self-perception Profile for Children	RER	Respiratory exchange ratio
CHQ	Child Health Questionnaire	$\dot{V}O_{2peak}$	Peak oxygen consumption
CIS-20	Checklist Individual Strength-20	$\dot{V}O_{2peak/kg}$	Relative $\dot{V}O_{2peak}$
CPET	Cardio-pulmonary exercise test	$W_{max}$	Maximal working capacity
HRQoL	Health-related quality of life		

physical training program on exercise capacity, muscle force, and subjective fatigue in patients with the mild to moderate forms of OI.

## METHODS

### Design and Participants

Medical histories of children with skeletal dysplasias were obtained from the patient records of our hospital. The most widely used classification of OI is by Sillence et al and distinguishes 4 clinical types.<sup>8</sup> Recently, this classification was expanded into 7 types.<sup>9</sup> The type of OI was diagnosed by a clinical geneticist in our hospital on the basis of the clinical features and a collagen biopsy of the patients. OI type I includes patients with mild disease and absence of major bone deformities, with typical vertebral fractures leading to mild scoliosis. Patients with OI type IV have mild to moderate bone deformities and variable short stature. Children were eligible for inclusion when they had documented OI type I or IV, were between 8 and 18 years old, had no fractures in the last 3 months before start of the study, and were at least household walkers according to the modified Bleck scale.<sup>10</sup> Forty children met our inclusion criteria (Figure; available at [www.jpeds.com](http://www.jpeds.com)) and were invited to participate. Of these children, 1 child could not take part because of a fracture of the patella just before the start of the study. The parents of 2 children refused to participate for personal reasons, and the parents of 3 other children refused for logistical reasons. The remaining 34 children (12 boys and 22 girls) were enrolled in the study. Twenty-seven children had OI type I, and 7 children had OI type IV. Randomization was performed with a list of computer-generated numbers by an offsite data manager. Participants were randomly assigned to 1 of 2 groups (intervention and control) stratified for age, sex, and bisphosphonates usage by using a block randomization procedure. In general, according to our hospital protocol, patients with OI were treated with medication (bisphosphonates [Olpadronate] at a dose of 10 mg/m<sup>2</sup> daily) when bone mineral density as measured with the DEXA Z-score was < -1.5 (measured at the lumbar spinal cord [L1-L4]) and platyspondyly or biconcave endplates are present. After randomization, and before the start of the intervention, 1 patient withdrew from the study because personal reasons (Figure). The observers (R.E./T.T.) who assessed outcome variables were blinded to treatment allocation and were highly experienced in their assessments. Treatment allocation and the observers were kept blinded until the evaluation of the results. The study protocol was approved by the medical-ethics committee of the University Medical Center Utrecht, the Netherlands. Informed consent was obtained from the parents, from the children when they were older than 12 years of age, or both.

### Exercise Training Program

Patients allocated to the intervention group received a graded exercise program consisting of 12 weeks (30 sessions) aimed at improvement of exercise capacity and muscle force,

whereas patients in the control group only received usual care. Patients allocated to the intervention group were instructed to attend exercise sessions twice a week held at a local physical therapy practice for 12 weeks consecutively and to perform home-based exercises once a week, starting after the sixth week of the intervention. The exercise sessions were supervised by local pediatric physical therapists, trained in our hospital to warrant the uniformity of the training program.

The 45-minute sessions included a 10-minute warm-up period. Ten minutes of aerobic training (on the basis of an intensity ranging from 60%-80% of their baseline peak heart rate) were followed by 15 minutes of free play and muscle training, and thereafter another 10 minutes of aerobic training were performed. The session ended with 10 minutes of cool-down exercises. The strength training consisted of exercises without heavy weights; the children learned the proper strength-training techniques and only used light weights as heavy as a maximum of 1 kg. This was performed to ensure a minimal risk of fracture. Attendance records were kept by the pediatric physical therapists. Patients in the intervention group maintained activity records for the home exercise sessions. Children (in both the intervention and control groups) were examined 4 times at our hospital in 9 months of follow-up (baseline [start of the intervention]: T = 0), after intervention (3 months follow-up: T = 1), and 6 months (T = 2) and 9 months (T = 3) after the start of the study. We primarily studied the exercise capacity and muscle force; secondary outcomes were subjective fatigue, perceived competence and health-related quality of life (HRQoL).

### Clinical Characteristics

Weight (kg), arm span (cm), height (cm), and sitting height (cm) were determined by using an electronic scale and a stadiometer. Subcutaneous fat distribution was measured from skin fold measurement by using Harpenden skin fold calipers. The measurements were taken at 7 sites (bilaterally), at the triceps, biceps, subscapular, supra-iliacal, mid-abdominal, medial calf, and thigh, in accordance with the American College of Sports Medicine guidelines,<sup>11</sup> and the sum of the 7 skin folds were used as an index for body fat.<sup>12</sup> Body mass index was calculated as body weight (kg)/height (m)<sup>2</sup>.

The fracture history (total number of fractures), presence of bowing of the long bones of the lower extremities and the presence of intramedullary rodding, presence of scoliosis (Cobbs angle >10 degrees), bone mineral density (with DEXA presented in Z-scores), and use of medication (Olpadronate, dose of 10 mg/m<sup>2</sup> daily) are described in the results section, presented in Table I, or both.

### Cardio-Pulmonary Exercise Test

Patients performed a cardio-pulmonary exercise test (CPET) by using an electronically braked cycle ergometer (Lode Corival, Lode BV, Groningen, the Netherlands). The test started with 1 minute of unloaded cycling before the application of resistance to the ergometer. After this minute,

**Table I. Clinical characteristics of the intervention group and the control group at baseline (T = 0)**

Variables	Intervention group (n = 16)			Control group (n = 17)		
	Mean	SD	Range	Mean	SD	Range
Age (years)	12.3	3.3	7.9-17.8	13.2	3.6	8.3-18.6
Weight (kg)	41.9	13.8	21.2-71.1	43.8	15.4	23.2-77.9
Height (cm)	150	20.0	120-180	150	20.0	120-170
BMI (kgm <sup>-2</sup> )	19.0	3.3	15.1-24.4	20.5	5.5	14.4-31.4
Σ7SF (mm)	335.0	113.2	162.4-522.6	359.6	130.0	193.8-568.6
Sitting height (cm)	76.5	6.9	66.0-92.0	77.1	7.9	64.0-88.0
Arm span (cm)	147.3	19.8	103.0-183.0	150.6	18.8	125.0-184.0
DEXA L1-L4 (Z-score)	-1.7	1.1	-3.1-1.0	-1.6	1.1	-4.8-0.0
Fracture history	5.1	1.5	3.0-8.0	5.1	4.3	3.0-21.0
Bowing		38%			41%	
Scoliosis		13%			35%	
Male:female ratio		6:10			5:12	
Bisphosphonates: yes/no		8:8			9:8	

BMI, Body mass index; Σ7SF, sum of 7 skinfolds; DEXA, dual X-ray absorptiometry; L1-L4, lumbar spine, vertebra 1 to 4.

workload was increased with a constant increment of 15 or 20 W every minute according to the Godfrey protocol.<sup>13</sup> This protocol continued until the patient stopped because of voluntary exhaustion, despite strong verbal encouragement of the test-leader. The highest achieved workload ( $W_{max}$ ) was recorded. During the CPET, subjects breathed through a face-mask (Hans Rudolph, Kansas City, MO) connected to a calibrated respiratory gas analysis system (Cortex Metamax B<sup>3</sup>, Cortex Medical, Leipzig, Germany). Expired gas was passed through a flowmeter (Triple V volume transducer), an oxygen (O<sub>2</sub>) analyzer, and a carbon dioxide (CO<sub>2</sub>) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation ( $\dot{V}_E$ ), oxygen uptake ( $\dot{V}O_2$ ), carbon dioxide output ( $\dot{V}CO_2$ ), and the respiratory exchange ratio (RER;  $\dot{V}CO_2/\dot{V}O_2$ ) from conventional equations. The oxygen uptake eliciting the ventilatory anaerobic threshold (AT) was determined by using the criteria of an increase in both the ventilatory equivalent of oxygen ( $\dot{V}_E/\dot{V}O_2$ ) and end-tidal pressure of oxygen (PETO<sub>2</sub>) with no increase in the ventilatory equivalent of carbon dioxide ( $\dot{V}_E/\dot{V}CO_2$ ).<sup>14</sup>

Heart rate was measured continuously during the maximal exercise test by using a heart rate monitor (Polar, Kempele, Finland). Maximal effort occurred when 1 of the 2 criteria were met: heart rate >180 beats per minute or RER >1.0. Peak oxygen consumption ( $\dot{V}O_{2peak}$ ) was taken as the average value for the last 30 seconds during the maximal exercise test. Relative  $\dot{V}O_{2peak}$  was calculated as absolute  $\dot{V}O_{2peak}$  divided by body mass.

### Muscle Force

Muscle force was measured with a hand-held dynamometer (Citec dynamometer CT 3001, C.I.T. Technics, Groningen, the Netherlands) in 4 muscle groups (shoulder abductors, grip force, hip flexors, and dorsiflexors of the ankle joint). Maximum muscle force was tested with the “break” method, in which the examiner gradually overcomes the mus-

cle force of the patient and stops at the moment the extremity gives way. The tests were performed according to the Backman protocol.<sup>15</sup> Grip force was measured with the “make” method, in which the dynamometer was gripped as hard as possible for 3 seconds without pressing the instrument against the body and without touching the elbow to the body. Every muscle group was measured 3 times, and the highest score was recorded.

### Fatigue

Fatigue was measured with the subscale subjective fatigue of the self-report questionnaire Checklist Individual Strength-20 (CIS-20).<sup>16,17</sup> The CIS-20 asks about fatigue in the 2 weeks before the assessment. There are 4 respective subscales, fatigue, concentration, motivation, and physical activity, consisting of items scored on a 7-point Likert scale. A high total score indicated a high level of subjective fatigue and concentration problems and a low level of motivation and physical activity. The questionnaire has good reliability and discriminative validity.<sup>17</sup>

### Perceived Competence

The translated version of the Self-perception Profile for Children<sup>18</sup> (CBSK) was used to measure perceived competence.<sup>19</sup> The translated version has been cross-culturally validated for Dutch children.<sup>20</sup> The test consists of 36 items, formulated as opposite pairs. Each answer was scored between 1 (most competent) and 4 (least competent). There are 6 subscales: scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct, and global self-worth.

### Health-Related Quality of Life

The Child Health Questionnaire Parent-Form 50 (CHQ) is a proxy report of assessing HRQoL.<sup>21</sup> A Dutch translation of the CHQ was used in this study,<sup>22</sup> and was

**Table II.**  $\dot{V}O_{2peak}$ ,  $\dot{V}O_{2peak/kg}$ , and muscle strength during the intervention and follow-up

	Intervention group Mean (SD)	Control group Mean (SD)	Mean group difference (95% CI)	Mean group difference (95% CI) adjusted for baseline (T = 0) measurements
$\dot{V}O_{2peak}$ (L/min)				
T = 0	1.25 (0.4)	1.50 (0.6)	0.25 (-0.1; 0.6)	
T = 1	1.49 (0.4)	1.54 (0.6)	0.05 (-0.3; 0.4)	<b>-0.19 (-0.3--0.1)</b>
T = 2	1.41 (0.4)	1.59 (0.6)	0.18 (-0.2; 0.5)	-0.06 (-0.2-0.1)
T = 3	1.42 (0.4)	1.64 (0.7)	0.21 (-0.2; 0.6)	-0.05 (-0.2-0.1)
$\dot{V}O_{2peak/kg}$ (mL/kg/min)				
T = 0	30.9 (5.8)	35.6 (10.4)	4.7 (-1.3; 10.7)	
T = 1	36.4 (6.4)	35.5 (10.2)	-0.9 (-7.0; 5.3)	<b>-5.1 (-8.0--2.2)</b>
T = 2	33.8 (6.8)	36.3 (11.1)	2.5 (-4.2; 9.1)	-1.6 (-6.0-2.9)
T = 3	33.7 (9.3)	37.1 (12.0)	3.4 (-4.2; 11.0)	-1.5 (-6.1-3.2)
$W_{max}$				
T = 0	107.3 (39.0)	128.6 (61.0)	21.3 (-15.3; 57.9)	
T = 1	122.7 (42.1)	134.0 (63.0)	11.3 (-27.0; 49.6)	<b>-10.3 (-20.0--0.5)</b>
T = 2	117.6 (39.4)	135.3 (63.4)	17.7 (-20.1; 55.4)	-3.6 (-13.0-5.8)
T = 3	114.9 (45.1)	135.6 (73.0)	20.7 (-22.7; 64.1)	-2.5 (20.2-15.1)
AT				
T = 0	0.79 (0.25)	0.89 (0.33)	0.1 (-0.1; 0.3)	
T = 1	0.94 (0.18)	0.97 (0.43)	0.0 (-0.2; 0.3)	0.0 (-0.2-0.1)
T = 2	1.0 (0.34)	0.90 (0.37)	-0.1 (-0.4; 0.2)	-0.2 (-0.4-0.0)
T = 3	0.89 (0.34)	0.86 (0.24)	-0.0 (-0.2; 0.2)	-0.1 (-0.3-0.1)
Muscle strength (N)				
T = 0	537.8 (183.7)	589.3 (187.7)	51.5 (-80.3; 183.4)	
T = 1	602.7 (182.6)	590.5 (184.5)	-12.2 (-142.6; 118.2)	<b>-61.4 (-96.7--26.2)</b>
T = 2	616.2 (169.8)	657.9 (196.6)	36.3 (-94.5; 167.1)	-5.2 (-53.0-42.5)
T = 3	621.3 (202.0)	680.1 (205.0)	58.8 (-85.8; 203.4)	6.5 (-49.7-62.8)

Regression coefficients are presented in bold when the *P* value is <.05.

administered to the parents. The questionnaire consists of 50 items in 14 dimensions. From these dimensions a physical and psychosocial summary score can be calculated. A higher score reflects a better HRQoL of the child.

### Statistical Analysis

Descriptions of data by treatment allocation were expressed as mean plus or minus SD and range. The effects of the intervention were analyzed by using linear regression statistics with a group indicator (intervention: yes/no) as independent variable and the outcome variables as dependent separate variables. Results are presented as linear regression coefficients representing mean group differences with their corresponding 95% CIs. Statistical significance was considered to be reached when 95% CIs did not include the null value. Nominal variables were analyzed with  $\chi^2$  analysis. All results were analyzed by intention to treat. Statistical analyses were performed with SPSS software version 12.0 (SPSS, Chicago, IL).

## RESULTS

The baseline anthropometric values and clinical characteristics of both groups are shown in Table I. Forty percent of the children had a located collagen type I mutation. Thirteen children had  $\geq 1$  intramedullary rods, all in the lower

extremities; 5 of these children were allocated in the intervention group. The reported intervention compliance, defined as the percentage of completed exercise sessions of the prescribed sessions, was 96.4%. All patients were able to complete the aerobic exercise test without adverse effects. No fractures occurred in the intervention group, whereas 3 children in the control group had a fracture during the study (Pearson's  $\chi^2 = 3.5$ ;  $P = .061$ ). The analysis of follow-up variables was adjusted for baseline differences in  $\dot{V}O_{2peak}$ ,  $\dot{V}O_{2peak/kg}$ ,  $W_{max}$ , AT, muscle force, subjective fatigue, perceived competence, and HRQoL. Table II shows that after 3 months of training (T = 1),  $\dot{V}O_{2peak}$ ,  $\dot{V}O_{2peak/kg}$ ,  $W_{max}$ , and muscle force were significantly improved in the intervention group compared with the control group (17%, 18%, 10%, and 12%, respectively). After adjustment for baseline differences, the  $\dot{V}O_{2peak}$  group difference increased statistically significantly with 0.192 L/min (95% CI, -0.3--0.1), the  $\dot{V}O_{2peak/kg}$  increased with 5.1 mL/kg/min (95% CI, -8.0--2.2),  $W_{max}$  increased with 10.2 W (95% CI, -20.0--0.5), and muscle force increased with 61 N (95% CI, -96.7--26.2). Table III shows that subjective fatigue levels were decreased with borderline statistical significance in the intervention group (adjusted for baseline measures, 4.2 points; 95% CI, -0.3-8.8,  $P = .068$ ). AT, perceived competence (CBSK), and HRQoL (CHQ physical and psychosocial summaries) showed some

**Table III. Total score and fatigue during the intervention and follow-up**

	<b>Intervention group Mean (SD)</b>	<b>Control group Mean (SD)</b>	<b>Mean group difference (95% CI)</b>	<b>Mean group difference (95% CI) adjusted for baseline (T = 0) measurements</b>
<b>Total score</b>				
T = 0	48.6 (16.0)	42.4 (15.3)	-6.2 (-17.2-4.9)	
T = 1	43.1 (17.9)	45.2 (16.8)	2.1 (-10.2-14.4)	6.1 (-4.3-16.5)
T = 2	48.2 (15.7)	46.1 (21.8)	-2.1 (-15.6-11.5)	2.3 (-9.3-13.8)
T = 3	50.4 (15.7)	42.3 (17.4)	3.3 (-8.6-15.2)	4.6 (-7.6-16.7)
<b>Fatigue</b>				
T = 0	20.7 (8.2)	17.9 (9.1)	-2.7 (-8.9-3.4)	
T = 1	16.7 (6.3)	19.3 (9.4)	2.6 (-3.1-8.3)	4.2 (-0.3-8.8)
T = 2	21.9 (7.7)	19.9 (8.7)	-2.1 (-7.9-3.8)	-0.6 (-5.5-4.4)
T = 3	21.3 (7.8)	17.5 (10.0)	3.9 (-2.4-10.2)	5.0 (-1.0-11.0)

Regression coefficients are presented in bold when the *P* value is <.05.

improvements (10%, 2.4%, 7.7%, and 6.2%, respectively), without being significant. Follow-up measurement 6 months after the start of the intervention (T = 2) showed a significant decrease of the gained improvements in  $\dot{V}O_{2peak}$  (6% decrease; adjusted  $\beta = 0.131$  L/min [95% CI, 0.0-0.3]) at T = 1.  $\dot{V}O_{2peak/kg}$ ,  $W_{max}$ , AT, perceived competence, subjective fatigue, and HRQoL showed, after adjustment, no significant difference as compared with T = 1. In the control group, total muscle force increased significantly because of an increase in muscle force in 1 girl (age 12 years) and 1 boy (age 18 years). Nine months after the start of the intervention (T = 3), measurements again showed a decrease of the gained improvements compared with the results immediately after intervention (T = 1).  $\dot{V}O_{2peak}$ ,  $\dot{V}O_{2peak/kg}$ , and muscle force showed a significant decrease ( $\beta = 0.16$  L/min [95% CI, 0.0-0.3],  $\beta = 4.4$  mL/kg/min [95% CI, 1.5-7.3], 71.1 N [95% CI, 7.2-134.9], respectively). Subjective fatigue also decreased at T = 3.  $W_{max}$ , AT, perceived competence, HRQoL showed no significant differences compared with T = 1. No significant differences in exercise capacity, muscle force, and subjective fatigue were found between the children who were given bisphosphonates and the children who used no medication. No significant differences were observed between the measurements of perceived competence and HRQoL (data not presented).

## DISCUSSION

In this study, a significant improvement in aerobic capacity and muscle force was found after 3 months of training in children with OI. However, the effects decreased with time after the intervention was stopped. The same pattern was also found for subjective fatigue. This clinically relevant improvement in aerobic capacity is greater than reported in healthy children, who after a comparable training period<sup>23</sup> in general improve approximately 8% in  $\dot{V}O_{2peak/kg}$ . These large improvements can be explained by the lower initial levels of  $\dot{V}O_{2peak}$  of children with OI.<sup>5</sup> Children with OI are relatively hypoactive and will improve to a greater extent during the first few months of training compared with healthy peers. Al-

though the intervention consisted only of low-resistance strength training without heavy weights, there was a 12% improvement in muscle force in the children in the intervention group during the training period compared with the children in the control group. This improvement is less than has been reported for healthy children after an 8-week resistance training program, for which improvements in muscle force between 5% and 40% were reported.<sup>24</sup> The smaller improvement in our study was expected because we only used very light resistance. However, the improvement in muscle force is clinically relevant for patients with OI because muscle force and the strength of bones are strongly associated.<sup>25</sup> In other chronic conditions, exercise interventions have been reported to be beneficial in improving exercise capacity and muscle force. The study of Klijn et al<sup>6</sup> in children with cystic fibrosis showed that a 12-week exercise training program was effective in improving aerobic performance, anaerobic performance, and HRQoL. The study of San Juan et al<sup>7</sup> showed in children with leukemia that a 16-week intra-hospital supervised conditioning program, including both strength and aerobic training, resulted in significant increases in aerobic capacity, muscle force, and functional ability.

In our study, 3 and 6 months (T = 2 and T = 3, respectively) after the completion of the intervention program, the children were not able to maintain the gained training effects. This is in contrast to findings in children with a congenital heart disease who maintained their exercise capacity 6 months after cardiac rehabilitation.<sup>26</sup> Elucidating the effects of detraining (reversibility) on children is confounded by the child's continued growth and development during the detrained period. As in adults, it seems that adaptations to training are transient and will steadily decay once training has stopped.<sup>27</sup> This decay is also seen in this study. A long-term benefit depends on the continuation of training sessions into adult life.<sup>27</sup>

Many of the included patients were not involved in regular exercise with sufficient intensity. Patients might avoid these exercises because of the risk of fractures or environmental concerns such as neighborhood safety.<sup>28</sup> This study indi-

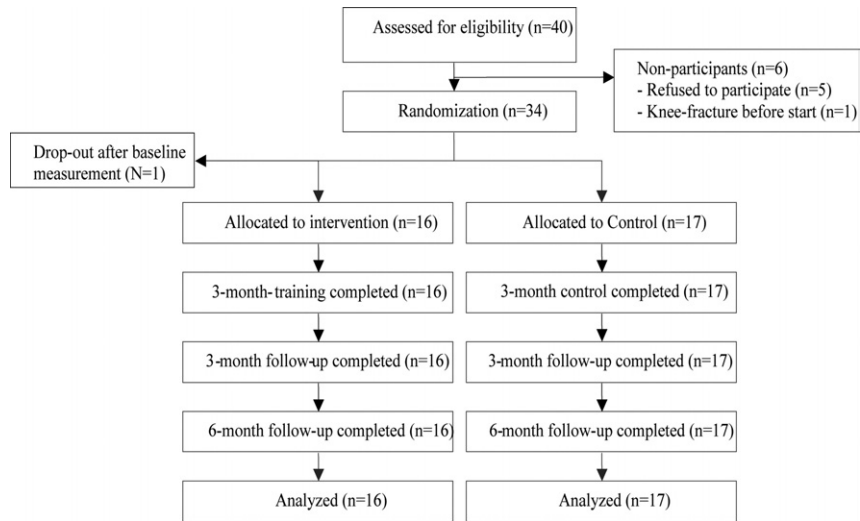
cates that children with mild to moderate OI can participate safely and effectively in a supervised and individual tailored training program. This form of training can be an important way of increasing fitness in children with OI, because participation in regular sport activities is not an option for most children because of their reduced exercise capacity and their increased fracture risk. Supervised training and close monitoring of patients is also likely to improve patient compliance. Future studies should focus on the perceived barriers of these children to participate in physical exercise in their own neighborhood or in school, on children with OI type IV and III who are wheelchair-bound, and when unsupervised training can be as safe and effective as the current training regimen. To maintain the improvement in exercise capacity and muscle force, the exercise regimen need to be continued.

For some of our secondary outcome measures, we did not find any improvements during training or follow-up. On the physical summary of CHQ, for example, the children had a score of almost 50 at baseline, which indicates normal function compared with healthy children.<sup>21</sup> The subscales that contribute mostly to the physical summary score are physical functioning, (physical) role/social limitations, bodily pain/discomfort, and general health. On the CHQ psychosocial summary, the patients scored >50, which is even higher than the healthy population.<sup>21</sup> The perceived competence of the patients did not change significantly. However, perceived competence seems not to be related to disease severity and impairment.<sup>29</sup> In the mildest form of OI (type I), a reduced athletic competence was previously reported.<sup>29</sup> In this study, no improvement on this subscale was observed after the intervention program. Individual supervised training can be advised as a safe and effective addition to current treatment methods in the short term. The long-term efficacy of this intervention requires further evaluation.

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**Figure.** Consort flowchart for intervention study in children with osteogenesis imperfecta.