Muscle Anatomy and Dynamic Muscle Function in Osteogenesis Imperfecta Type I

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Context: Results of previous studies suggested that children and adolescents with osteogenesis imperfecta (OI) type I have a muscle force deficit. However, muscle function has only been assessed by static isometric force tests and not in more natural conditions such as dynamic force and power tests.

Objective: The purpose of this study was to assess lower extremity dynamic muscle function and muscle anatomy in OI type I.

Setting: The study was performed in the outpatient department of a pediatric orthopedic hospital.

Patients and Other Participants: A total of 54 individuals with OI type I (6–21 years; 20 male) and 54 age- and sex-matched controls took part in this study.

Main Outcome Measures: Calf muscle cross-sectional area and density were measured by peripheral quantitative computed tomography. Lower extremity muscle function (peak force per body weight and peak power per body mass) was measured by jumping mechanography through 5 tests: multiple two-legged hopping, multiple one-legged hopping, single two-legged jump, chair-rise test, and heel-rise test.

Results: Compared with age- and sex-matched controls, patients with OI type I had smaller muscle size ($P = .04$) but normal muscle density ($P = .21$). They also had lower average peak force and lower specific force (peak force/muscle cross-sectional area; all $P < .008$). Average peak power was lower in patients with OI type I but not significantly so (all $P > .054$).

Conclusions: Children and adolescents with OI type I have, on average, a significant force deficit in the lower limb as measured by dynamic force tests. Nonetheless, these data also show that OI type I is compatible with normal muscle performance in some individuals. (J Clin Endocrinol Metab 99: E356–E362, 2014)

Osteogenesis imperfecta (OI) is a heritable disorder characterized by low bone mass and increased bone fragility (1). Several types of OI are commonly distinguished on the basis of clinical features and genetic findings, but OI type I is the mildest and most common form of the disorder (1). Patients with OI type I typically have no deformities of the long bones, and they have fewer fractures than patients with other OI types (2). Height is typically normal or only slightly below the percentile curves. OI type I is usually caused by mutations in one of the 2 genes that encode collagen type I, COL1A1 and COL1A2 (1).

In addition to bone fragility, OI type I may be associated with muscle function deficits. One study on 17 chil-
Children and adolescents showed that isometric muscle force of the shoulder abductors, hip flexors, and ankle dorsiflexors and grip force were lower in patients with OI type I than in healthy age- and sex-matched control participants (3). Another study on 20 children with OI type I observed a trend for lower plantar flexor muscle force and decreased resistance to fatigue (4). Animal experiments have shown that a mouse model of OI type I has slightly lower muscle force than that of wild-type littermates (5).

The available clinical studies on muscle function in OI type I are, however, limited by small study cohorts and the use of isometric force tests. From a functional perspective, isometric muscle contractions represent a rather rare situation. Most everyday movements are performed in a dynamic fashion consisting of a sequence of eccentric, isometric, and concentric contractions of muscles, also known as the stretch-shortening cycle (6, 7). For this reason, isometric force test results do not correlate well with performance in dynamic movement tests (8, 9). Assessment of muscle performance using dynamic tests may therefore provide information that reflects everyday activities better than isometric tests.

Jumping mechanography is a method to assess dynamic muscle function through vertical ground reaction force measurements (10, 11). From these force-time measures, basic muscle function parameters such as maximal muscle force, power, and velocity can be determined (12). These tests evaluate movements involving the stretch-shortening cycle (eg, countermovement jump), eccentric contractions (eg, hopping on the forefoot), or concentric contractions (heel-rise test) (13). To interpret muscle function test results, it is useful to simultaneously obtain muscle anatomical data. Peripheral quantitative computed tomography (pQCT) can be used to determine the cross-sectional area and density of calf muscles. Muscle density is inversely related to im fat content and is thus regarded as a marker of muscle quality (14).

Thus, the goal of the present study was to assess muscle dynamic function and muscle anatomy in young individuals with OI type I, using mechanography and pQCT. Even though mechanography results are highly reproducible in healthy children and adolescents (12), reproducibility has yet to be established in a pediatric OI population and was therefore also assessed in the present study.

Materials and Methods

Study population

The study population comprised young patients with a diagnosis of OI type I who were followed in the outpatient department at the Shriners Hospital for Children in Montreal. Only patients with a confirmed mutation in COL1A1 or COL1A2 were included in this study. Patients with such mutations were diagnosed as having OI type I if they did not have long-bone deformities and no major scoliosis (Cobb angle <30°). Patients with a diagnosis of OI type I were eligible for this study if they were between 6 and 21 years of age. Exclusion criteria were fractures of the lower limbs in the past 6 months or lower limb surgery in the past 12 months.

Of the 58 consecutive patients with OI type I who were screened for this study, 4 were not eligible because of a recent fracture. The other 54 patients (34 female and 20 male; age range, 6.4 to 21.3 years; mean [SD] age, 12.6 [4.2] years) agreed to participate. Of these, 23 patients had received bisphosphonate treatment before the time of testing and 1 patient was still receiving this treatment at the time of testing. Four patients had undergone femoral intramedullary rodding surgery after repeated femur fractures (unilateral in 3 patients and bilateral in 1 patient). In 31 patients, OI was due to haploinsufficiency mutations (frameshift or stop mutations) in COL1A1, whereas 23 patients had other types of mutations (glycine substitutions in the triple helical domain or splice mutations) in either COL1A1 or COL1A2. Age- and sex-matched control participants (age range, 6.4–24.2 years; age, 12.6 [4.6] years) were recruited among unaffected siblings of patients (ie, not presenting clinical signs of OI) and children of hospital employees.

The study was approved by the institutional review board of McGill University. Informed consent was provided by participants or for minors by their parents. Assent was provided by participants aged 7 to 17 years.

Anthropometric measurements

Height was measured using a Harpenden stadiometer (Holtain). Weight was determined using the Leonardo Mechanograph Ground Reaction Force Plate (Novotec Medical Inc). Height and weight measurements were converted to age- and sex-specific Z scores on the basis of reference data published by the Centers for Disease Control and Prevention (15).

Biochemical analyses

Serum samples were obtained for 53 of the 54 study participants. Serum 25-hydroxyvitamin D concentrations were measured by RIA (Osteo SP; Incstar Corp).

pQCT

pQCT was performed at the left lower leg (XCT2000; Stratec Inc) as described previously (16). The angle between the foot and lower leg was set at 120°. Tibia length was measured as the total distance between the medial condyle and the medial malleolus of the tibia, using a rular. A pQCT scan was performed at the site whose distance to the distal tibial articular surface corresponded to 66% of tibia length, matching the region of the largest outer calf diameter (17). From this scan, muscle and bone were separated from fat using a density threshold of 40 mg/cm³, and muscle was further separated from bone using a density threshold of 280 mg/cm³. After this separation procedure, the cross-sectional area of muscle and bone (fibula and tibia) was determined. Muscle cross-sectional area (mm²) was calculated by subtracting the bone cross-sectional area from the combined muscle and bone cross-sectional area. Muscle density (milligrams per cubic millimeter) was calculated as the mean density of the tissue that was included in the measurement of muscle cross-sectional area (16).
Mechanography

A force plate (Leonardo Mechanograph Ground Reaction Force Plate) was used to measure vertical ground reaction forces. The force plate was connected to a laptop computer, and force measurements were sampled at a frequency of 800 Hz. As described in detail elsewhere, all muscle function parameters reported here were derived from these force-time data using proprietary software (Leonardo Mechanography GRFP Research Edition software (version 4.2-b05.53-RES; Novotec Medical Inc) (12).

Five different tests were performed: (1) multiple one-legged hopping and (2) multiple two-legged hopping, representing vertical hopping on one or both forefeet (similar to rope-skipping), respectively (the aim of these hopping tests is to achieve maximal ground reaction forces during eccentric muscle contraction); (3) single two-legged jump, a vertical countermovement jump to achieve maximum jump height during a stretch-shortening cycle movement; (4) heel-rise test, consisting of 5 bilateral heel rises with the aim to achieve maximal speed during the upward movement; and (5) chair-rise test, a sit-to-stand test repeated 5 times, with the aim to achieve maximal speed during the upward movement (the chair-rise test made use of a bench that was anchored to the force plate).

Each test was repeated 3 times and the “best” result was retained as the participant’s test result. The definition of the best result was “highest peak force for a given hop in the multiple one-and two-legged hopping, highest peak power during the take-off phase during a single two-legged jump, during the first rise of the heel-rise test and for the second rise of the chair-rise test” (12). For the multiple one- and two-legged hopping, the main outcome parameter was peak force relative to body weight (“force tests”), whereas for the single two-legged jump, the heel-rise test, and the chair-rise test, the main outcome parameter was peak power relative to body mass (“power tests”).

The reproducibility of the 5 mechanography tests was assessed in a group of 15 individuals with OI type I (8 female and 7 male; age range, 7–21 years; mean [SD] age, 14.4 [4.7] years; body mass, 52.4 [22.2] kg; and height, 1.27 [0.55] m. Participants took part in 2 testing sessions within the same day, separated by a 1-hour resting period.

Specific force was computed as the ratio between peak force (newtons) during multiple two-legged hopping relative to muscle cross-sectional area (square centimeters). The multiple two-legged hopping test was selected over the multiple one-legged hopping test because all patients could perform the former test, whereas 13 and 12 patients were unable to perform the multiple one-legged hopping on the left and right leg, respectively. Specific force is thought to reflect the intrinsic force-producing capacity of a muscle and may be influenced by neuromuscular factors or muscle fiber type composition (18).

Statistical analyses

To assess reproducibility, coefficients of variation (CVs) and intraclass correlation coefficients (ICCs) were calculated (12). A two-way mixed-effects model with a consistency definition was used to calculate ICCs, following the algorithm proposed by McGraw and Wong (19). In the mixed model, the participant is treated as a random effect, whereas measurement error is considered as a fixed effect. Thus, ICC(C, 1) and the 95% confidence intervals were computed. The SEM was also calculated to compute the minimal detectable difference (MDD) (20). The MDD represents the smallest intraindividual change that can be detected, given the test-to-test variability of the measure. It was calculated as follows:

\[
\text{SEM} = \frac{SD}{\sqrt{1 - ICC}} \quad (1)
\]

\[
\text{MDD} = \text{SEM} \cdot 1.96 \cdot \sqrt{2} \quad (2)
\]

Paired t tests were used to detect significant differences between the first and the second test session.

For the main study, descriptive statistics are presented as means and SD. Paired t tests were used to assess differences between the OI cohort and the individually matched group of controls. All tests were two-tailed and throughout the study, a value of \( P < .05 \) was considered significant. To investigate the effects of sex, treatment, and type of disease-causing COL1A1/ COL1A2 mutations on mechanographic outcome parameters, the difference of the results (as a percentage) between each patient and the matched control was computed for each of the 5 tests as well as for muscle cross-sectional area and muscle density. Stepwise multiple regression analyses were then performed with percent differences for each mechanographic test and muscle parameters as dependent variables. Bisphosphonate treatment status (history negative for bisphosphonate exposure = 0; history positive for bisphosphonate exposure = 1), molecular diagnosis (haploinsufficiency = 0; other = 1), age (in years), and height (expressed as age- and sex-specific Z scores) were set as independent variables to take into account the expected difference between patients and controls for these variables. To determine predictors of muscle function, stepwise multiple regression analysis was used. Mechanographic measures were set as the dependent variable whereas disease status (control = 0; OI = 1), muscle cross-sectional area, muscle density, and tibia length (used as a surrogate of muscle fiber length) were used as independent variables. Finally, to determine whether the 25-hydroxyvitamin D serum concentration was related to muscle function, correlations between mechanographic outcome parameters and 25-hydroxyvitamin D serum concentrations were computed (in the OI group only). All statistical analyses were performed using PASW Statistics software (version 20.0; SPSS Inc).

Results

Reproducibility of mechanography in OI type I

Force was significantly lower in session 2 than in session 1 in the multiple two-legged hopping (by 5%) and in the multiple one-legged hopping on the left leg (by 3.5%), but no significant intersession differences were observed in the power tests (Table 1). All 3 force tests showed low CVs and high ICCs, indicating high reproducibility. For power tests, the single two-legged jump was the most reproducible test. When the MDD was expressed as a percentage of the group mean, it was lowest for the single two-legged jump (8%) and highest for the heel-rise and chair-rise tests (29% in both cases).

Comparison between individuals with OI type I and controls

As expected, patients with OI type I were shorter and lighter than age- and sex-matched controls (Table 2). Of
the 54 patients, 39 (72%) had sustained ≥1 (mean, 2.4) tibia or femur fractures before testing, but none had deformities of the lower extremities. All patients were able to perform the power tests (single two-legged jump, heel-rise test, and chair-rise test), but for technical reasons, the results for 2 patients had to be excluded from the analysis of the heel-rise and chair-rise tests. Because of ankle instability in the context of ligamentous laxity, 13 and 12 patients were unable to perform the multiple one-legged hopping test on the left and right leg, respectively. These test results were treated as “missing values.” All control participants were able to complete all the tests.

For all mechanographic tests, group averages were numerically lower in the OI cohort than in control participants (Table 2). These group differences were significant for all the force tests but not for the power tests, even though P values ranged between .05 and .09 for the 3 power tests. Regarding pQCT analyses, the calf muscle cross-sectional area was on average 7% smaller in the OI group than in control participants, after correction for differences in tibia length, but no difference was observed for muscle density (Table 2). Patients with OI type I generated on average 16% less force per unit of muscle cross-sectional area than control participants.

The percent differences in force and power between patients with OI and control participants were computed for results on all 5 mechanographic tests and for muscle density and muscle cross-section data. Using the percent difference in each parameter as a dependent variable, multiple regression analyses were conducted to determine which factors influenced the difference between patients with OI and control participants. These analyses showed

| Table 1. Comparison of Results Between Patients With OI Type I and Control Participants |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Force tests (peak force per body weight) | Session 1, Mean (SD) | Session 2, Mean (SD) | Δ% | P |
| Multiple two-leg hopping | 4.22 (0.48) | 4.01 (0.47) | -5.2 | .009 |
| Multiple one-leg hopping—right* | 2.60 (0.33) | 2.55 (0.28) | -1.9 | .14 |
| Multiple one-leg hopping—left* | 2.60 (0.30) | 2.51 (0.27) | -3.6 | .04 |
| Power tests (peak power per body mass, W/kg) | 39.6 (7.7) | 39.0 (7.8) | -1.6 | .18 |
| Single two-legged jump | 5.52 (1.17) | 5.51 (1.39) | -0.1 | .98 |
| Chair-rise test | 12.3 (3.4) | 11.5 (3.4) | -0.8 | .09 |

Abbreviation: CI, confidence interval.

a n = 14 (1 and 2 participants were unable to perform the multiple one-legged hopping on the right and left leg, respectively).

b n = 13.

c MDD is given in the unit of the measurement; it represents the smallest intraindividual change that can be detected, given the variability of the measure.

d Though values ranged between .05 and .09 for the 3 power tests.
that the percent differences for all 5 mechanographic tests as well as for muscle density were independent of sex, age, height Z score, type of mutation (frameshift vs other mutation), or bisphosphonate treatment status (data not shown). In contrast, the percent difference in muscle cross-sectional area was positively associated with height Z score (muscle cross-sectional area /H11005 \(/H11006 5.86 \text{ (height; Z scores)}; r^2 \approx 0.14; P \approx .005\).

In the single two-legged jump, 18 patients (33%) had a result above the mean value of the age- and sex-specific reference data (21) (Figure 1). Reference data were not available for the other tests, but comparison of individual results of matched pairs showed that a substantial proportion of patients with OI type I had better results than their age and sex-matched control participants (Figure 2).

Stepwise regression analyses were performed to determine factors influencing mechanographic test results. The potential predictive factors included in the stepwise regression analysis model were muscle cross-sectional area, tibia length (surrogate of muscle fibers length), muscle density, and disease status (ie, OI vs control). These analyses showed that disease status was the only significant predictor of force test results (Table 3). In contrast, the results of power tests were independent of disease status. Calf muscle cross-sectional area and density were significant predictors of single two-legged jump results, whereas power in the heel-rise test was associated with muscle cross-sectional area only. The result of the chair-rise test was correlated only with tibia length.

The average serum concentration of 25-hydroxyvitamin D in the OI cohort was 69.6 mmol/L (SD, 18.8); 6 patients had a level <50 mmol/L. Regression analyses showed that the 25-hydroxyvitamin D serum concentration was not significantly associated with any of the muscle function outcomes (\(P > .11\) for each mechanographic test result).

**Discussion**

In this study, we found that patients with a clinical diagnosis of OI type I and known mutations in the \(COL1A1/\COL1A2\) genes produced less force during hopping tests. Results for the 3 power tests tended to be lower in the OI type I group, although the differences from control participants did not achieve statistical significance for these tests. Regression analyses confirmed these results, because disease status predicted the force test results but not the power test results.

Lower muscle function in OI type I might be partly due to smaller muscle size, but this is probably not the sole explanation for lower muscle force because the maximum force per unit of muscle cross-sectional area, ie, specific force, was also 16% lower in patients with OI type I than in control participants. Specific force is influenced by muscle fiber size and muscle fiber composition (23), and differences in these characteristics may thus contribute to lower muscle force in patients with OI type I. It is not known whether patients with OI type I have abnormalities in muscle fiber composition, but muscle fiber size and composition appeared to be normal in a mouse model of OI type I (5).

The mechanical properties of tendons may also play a role in determining the results of force tests in OI type I. Forces generated by muscle contractions are transmitted to the bones via tendons, which contain abundant amounts of collagen type I (24). Mutations in collagen type I encoding genes may alter the structural and mechanical properties of tendons. In a model of severe OI, tendons contain an abnormally low amount of collagen...
type I and are biomechanically compromised (25). Even though tendon properties do not seem to have been studied systematically in patients with OI type I, joint hyperlaxity is a typical feature of OI. Collagen type I is also present in the extracellular matrix surrounding muscle fibers (26) and plays an important role in transmitting muscle force to tendons (27). More detailed studies on the effect of collagen type I mutations on tendons and muscle extracellular matrix are required to clarify these issues.

In some patients with OI type I, low levels of physical activity may have contributed to lower muscle function. Physical activity was not measured in the present study, but some children and adolescents with OI type I do not participate in physical education activities because of a fear of fractures (28). In that respect, it is interesting to note that even though patients with OI type I as a group had decreased muscle performance, a substantial proportion of individuals with OI type I had normal results, independently of the putative predictors of muscle function that were assessed in this study. This finding suggests that these individuals had better performance owing to characteristics that were not captured in the present study, of which the level of physical activity is an obvious candidate. Nutrition, such as the level of protein intake, also may influence muscle performance. Future studies should therefore capture physical activity and nutritional data in more detail.

It has been reported previously that IV bisphosphonate treatment increased isometric grip force in children and adolescents with OI, which was possibly related to decreased bone pain (29, 30). Therefore, at first it may be surprising that no effect of bisphosphonate treatment was observed in the present study. However, we did not evaluate the effect of bisphosphonate in a prospective fashion, but rather in a retrospective cross-sectional analysis that compared patients with and without a history of bisphosphonate treatment. Because bisphosphonate treatment is usually used for more severely affected patients (32), it is not surprising that this group of individuals did not have better muscle function than the group without prior exposure to bisphosphonates.

Vitamin D is important for muscle function, and adolescents with very low 25-hydroxyvitamin D serum levels have low performance in mechanographic testing (22). However, the large majority of the participants in the present study had 25-hydroxyvitamin D serum concentrations >50 nmol/L, and thus their vitamin D status was deemed adequate (31), which may explain why we did not observe a relationship between 25-hydroxyvitamin D serum levels and muscle function.

In contrast to peak force, the results of peak power are more equivocal, because group differences were not achieved for any of the power tests. However, all 3 power tests pointed in the same direction and taken together these results suggest that there is some muscle power deficit in patients with OI type I.

Regarding the reproducibility of mechanography in OI type I, the results presented here are similar to those reported previously in a healthy pediatric population (12). However, a force decrease was observed between the 2 test sessions in 2 of the 3 force tests. It is possible that fatigue played in role in the decreased muscle force during the second test session (3). The MDD data nevertheless indicate that the single two-legged jump is sensitive to performance changes, because a change of 3.19 W/kg of body mass (8% of the measured mean) is detectable. For the 3 force tests, a change of about 10 to 13% of the measured means is required, whereas it is about 29% for both the heel-rise and the chair-rise test.

In summary, this study on a group of relatively highly functional children and adolescents with OI type I found deficits in eccentric muscle force that can be partially attributed to smaller muscles. Of note, however, some patients had entirely normal muscle function. Future studies should address the question of whether muscle function in these individuals depends on physical activity levels and

### Table 3. Predictors of Mechanographic Tests Results

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Regression Equation (n = 54)</th>
<th>$r^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Force tests (peak force per body weight)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple two-legged hopping</td>
<td>$4.28 - 0.463 \times \text{disease status (0, 1)}$</td>
<td>0.06</td>
<td>.01</td>
</tr>
<tr>
<td>Multiple one-legged hopping-left leg</td>
<td>$2.90 - 0.460 \times \text{disease status (0, 1)}$</td>
<td>0.27</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multiple one-legged hopping-right leg</td>
<td>$2.89 - 0.507 \times \text{disease status (0, 1)}$</td>
<td>0.26</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Power tests (peak power per body mass, W/kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single two-legged jump</td>
<td>$24.0 + 0.003 \times \text{muscle CSA (mm}^2) + 0.933 \times \text{muscle density (mg/mm}^3)$</td>
<td>0.40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heel-rise testa</td>
<td>$3.20 + 0.001 \times \text{muscle CSA (mm}^2)$</td>
<td>0.19</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chair-rise testa</td>
<td>$3.37 + 0.026 \times \text{tibia length (mm)}$</td>
<td>0.14</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: CSA, cross-sectional area. The predictive factors included in the stepwise regression analysis model were muscle CSA, tibia length (surrogate of muscle fibers length), muscle density, and disease status.

a Data for 2 OI patients had to be removed because of invalid data acquisition.
whether muscle function in OI type I can be improved by physical activity interventions.

Acknowledgments

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