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The functional muscle–bone unit in patients with osteogenesis imperfecta type I

Louis-Nicolas Veilleux [a,b,c,*], Annie Pouliot-Laforte [a,c,d], Martin Lemay [c,d], Moira S. Cheung [a,b], Francis H. Glorieux [a,b], Frank Rauch [a,b,c]

[a] Shriners Hospital for Children, 1529 Cedar Avenue, Montréal, Québec H3G 1A6, Canada
[b] Department of Pediatrics, McGill University, 1529 Cedar Avenue, Montréal, Québec H3G 1A6, Canada
[c] Centre de Réadaptation Marie-Enfant, Research Center, Hôpital Sainte-Justine, 5200 Bélanger Street East, Montréal, Québec H1T 1C9, Canada
[d] Département de Kinanthropologie, Université du Québec à Montréal, 141 Avenue du Président Kennedy Complexe des Sciences Pierre-Dansereau, Montréal, Québec H2X 1Y4, Canada

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ABSTRACT

Context: Osteogenesis imperfecta (OI) type I is a heritable bone fragility disorder that is caused by mutations affecting collagen type I. We recently showed that patients with OI type I frequently have muscle weakness. As muscle force and bone mass are usually closely related, we hypothesized that muscle weakness in OI type I could contribute to increase bone mass deficit in the lower extremities.
Objective: To assess the muscle–bone relationship in the lower extremities of children and adolescents with OI type I.
Setting: The study was carried out in the outpatients department of a pediatric orthopedic hospital.
Patients and other participants
Thirty children and adolescents with OI type I (20 females; mean age [SD]: 11.2 years [3.9]) were compared with 30 healthy age- and sex-matched controls (mean age [SD]: 11.1 years [4.5]).
Main outcome measures: Tibia bone mineral content (BMC; mg/mm) was measured by peripheral quantitative computed tomography to estimate bone strength at the 4% and 14% sites. Lower extremity peak force (kN) was measured by mechanography using the multiple two-legged hopping test.
Results: Compared with age- and sex-matched controls, patients with OI type I had 17% lower peak force (1.3 kN vs. 1.7 kN; $p = 0.002$) as well as a 22% lower BMC (128 mg/mm vs. 165 mg/mm; $p < 0.001$). Stepwise regression analysis showed that muscle force and tibia length were positively related to bone strength ($r^2 = 0.90$, $p < 0.001$) whereas there was no effect of the disease status (OI vs. control).
Conclusions: These results suggest that the muscle–bone relationship is similar between children and adolescents with OI type I and healthy age and sex-matched controls. It also suggests that muscle weakness may contribute to decreased bone strength in individuals with OI type I.

Introduction

Osteogenesis imperfecta (OI) is a congenital disorder characterized by low bone mass and increased bone fragility. Several types of the disorder are distinguished on the basis of clinical features and genetic findings, but OI type I is the most common type of OI [1]. OI type I is typically associated with a relatively mild phenotype with normal or near-normal height and absence of bone deformities [2]. OI type I is caused by mutations in one of the two genes that code for collagen type I alpha chains, *COL1A1* and *COL1A2*. Among these, stop or frameshift mutations in *COL1A1* are most commonly found [3,4].

Apart from deficits in bone mass, children with OI type I may also have decreased muscle force and endurance [5–8]. Impaired muscle forces may contribute to low bone mass, as muscle force is strongly correlated with measures of bone strength, both in health [9] and in disease [10]. For example, it has been shown that the maximal ground reaction force during hopping on the forefoot predicts as much as 84% of bone mineral content (BMC) of the tibia in healthy children, adolescents and adults [9]. Therefore, if the muscle–bone relationship is comparable between individuals with OI type I and healthy subjects, then decreased muscle force in OI type I may contribute to low bone mass.

Muscle–bone relationships can be assessed in many different ways, as a large number of muscle and bone parameters can be related to each other, resulting in a myriad of combinations. In order to limit the number of combinations that are tested and to guide the choice of muscle and bone parameters, it is useful to base the study set-up on a theoretical framework. The present study was based on Frost's mechanostat

* Corresponding author at: Shriners Hospital for Children, 1529 Cedar Avenue, Montréal, Québec H3G 1A6, Canada. Fax: +1 514 842 5581.
E-mail address: lnveilleux@shriners.mcgill.ca (L.-N. Veilleux).

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theory [11]. The central idea of this theory is that bone adapts to the largest physiological loads to which it is exposed. The largest physiological loads on bones result from muscle action. The peak forces generated by muscles are typically several fold higher than the static loads from body weight, because virtually all muscles work against unfavorable lever arms [11,12].

Peak muscle force is achieved when a contraction occurs while muscle fibers are elongated, i.e. during an eccentric contraction [13]. Peak eccentric force can be evaluated by measuring the maximal ground reaction force during hopping on tiptoes [14]. These forces are generated by the calf muscles and are transmitted to the foot via the Achilles tendon [15,16]. The eccentric contraction of calf muscle does not only generate ground reaction force, but also (much higher) forces in the tibia. It is therefore logical to relate eccentric muscle forces during tiptoe hopping to measures of bone strength of the tibia ('functional model' of the muscle–bone relationship).

Bone densitometry provides a variety of surrogate measures of bone strength, depending on which methodology is used. The present study employed peripheral quantitative computed tomography (pQCT) to analyze the tibia. This technique allows measuring BMC (mg/mm) in a cross-section of the tibia, which is one of the simplest measures of bone strength in compression [17]. As the largest forces applied to the distal tibia are presumably in compression [18], BMC at the distal tibia is a convenient bone parameter for the study of muscle–bone relationships.

Peripheral QCT cannot only measure bone parameters but also allows the quantification of calf muscle size and composition, which can be expressed as muscle cross-sectional area and muscle density, respectively. Muscle density as evaluated by pQCT is inversely related to muscle fat content, because fat attenuates radiation less than muscle [19]. As muscle cross-sectional area correlates positively with muscle force output [20] and lower muscle density has been associated with decreased muscle force production [21], these two pQCT-based muscle parameters can be combined with distal tibia BMC results to establish an 'anatomical model' of the muscle–bone relationship.

In the present study, we investigated the muscle–bone relationship in a group of individuals with OI type I. Using lower leg pQCT and force plate mechanography, we assessed the muscle–bone relationship with both a functional model and an anatomical model.

Methods

Study population

The study population comprised individuals with a diagnosis of OI type I aged 6 to 21 years who were followed in the outpatients department at the Shriners Hospital for Children in Montreal. The patient and control populations were subgroups of previously reported cohorts [8], with the difference that 24 individuals with OI type I who had received bisphosphonate treatment and their respective matched controls were excluded. Only patients with a confirmed mutation in *COL1A1* or *COL1A2* were included in this study. Exclusion criteria were: fractures of the lower limbs in the past 6 months; lower limb surgery in the past 12 months. Prior exposure to bisphosphonates was also exclusionary, as these drugs have a major effect on bone density and mass thereby altering the muscle–bone relationship.

Thirty individuals fulfilling these criteria (age range: 6.5 to 21.0 years; mean age [SD] 11.2 [4.0] years; 20 females) were enrolled in the study. Results in the OI group were compared with those of 30 healthy age- and sex-matched controls (age range: 6.5 to 22.8 years; mean age: 11.1 [4.1]) who were recruited among healthy siblings of patients and children of hospital employees. These healthy controls had previously participated in another study where they had performed the same pQCT and mechanographic tests (using the identical equipment) as the patients with OI type I. Data sets from 80 healthy children and adolescents were available, of which 30 data sets were selected for the present study. For each patient with OI type I, one control data set from an individual with the same sex and nearest age was selected. All study participants were of Caucasian origin. The study was approved by the Institutional Review Board of McGill University. Informed consent was provided by participants or, in minors, their parents. Assent was provided by participants aged 7 to 17 years.

Anthropometric measurements

Height was measured using a Harpenden stadiometer (Holtain, Crymych, UK). Body mass was determined using the Leonardo Mechanograph® ground reaction force plate. Height (m) and body mass (kg) 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 [22].

Peripheral quantitative computed tomography (pQCT)

Peripheral QCT was performed at the left tibia using the Stratec XCT2000® (Stratec Inc.; Pforzheim, Germany) as previously described [10]. The lower leg was scanned at 4%, 14% and 66% of tibia length. The tibia was analyzed at the 4% (metaphysis, trabecular bone) and 14% sites (metaphyseal–diaphyseal transition site, cortical bone) whereas muscle density (mg/mm^3) and muscle size (cross-sectional area, CSA; mm^2) were determined at the 66% site, where calf muscle CSA is at its maximum. The main parameters of pQCT analysis at the tibia were: total BMC, corresponding to the amount of mineral per mm of cross-sectional slice thickness (unit: mg/mm; measured at the 4% and 14% sites); total CSA, the surface area of the entire bone cross-section, including cortex and bone marrow space (unit: mm^2; 4% and 14% sites); cortical CSA, the surface area of the cortical bone cross-section excluding marrow space (unit: mm^2; 14% site); total volumetric bone mineral density (vBMD; bone mineral density averaged across the entire bone cross-section; unit: mg/cm^3; 4% site); trabecular vBMD, the average mineral density in the trabecular compartment (unit: mg/cm^3; 4% site); cortical vBMD, the average mineral density of the cortical compartment (unit: mg/cm^3; 14% site); cortical thickness calculated from total and cortical CSA using the ring model (unit: mm; 14% site). The reproducibility of muscle density and muscle CSA has been estimated at 0.8% [23] and 2.1% [24], respectively. Reproducibility of tibia bone parameters varies between 0.9% and 6.8% [25]. Peripheral QCT scans were visually inspected by an experienced technician in order to detect motion artifacts that are known to affect both muscle [26] and bone density measures [27]. The technician rated the scans according to the following scale: 1 (no motion), 2 (minimal motion), 3 (moderate motion), 4 (severe motion) and 5 (extreme motion). Scans rated 1 or 2 were deemed as acceptable whereas scans rated 3 to 5 were discarded and the measurement procedure was immediately repeated. The effective radiation dose from pQCT scans is lower than 0.01 mSv [28].

Mechanography

A force plate (Leonardo Mechanograph® Ground Reaction Force Plate; Novotec Medical Inc., Pforzheim, Germany) 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. All muscle function parameters reported here were derived from these force-time data using the software of the mechanography system (Leonardo Mechanography Ground Reaction Force Plate Research Edition® software, version 4.2-b05.53-RES; Novotec Medical Inc.), as described [14].

Participants performed the multiple two-legged hopping test. The test consists of jumping on the forefeet while keeping knees stiff and without the heels touching the ground (similar to rope skipping). It was repeated three times and the highest force achieved during hopping was recorded as the subject's test result, as described [14]. This

test assesses peak force during eccentric muscle contraction, which is the maximal force produced by a muscle. As bone is expected to adapt to the peak forces to which it is exposed, this is an appropriate parameter to investigate the muscle–bone relationship [9].

In contrast to studies in healthy subjects [9], multiple two-legged hopping rather than multiple one-legged hopping was selected to determine peak force in the present study, as some individuals with OI were unable to complete the more demanding one-legged hopping test [8]. The two-legged hopping test results in a slightly lower force per leg than the one-legged hopping test but nevertheless generates close to maximal voluntary forces [29,30]. The two-legged hopping test has also been investigated in detail in other studies on muscle–bone interaction in healthy subjects and has been shown to correlate well with indices of bone strength [15,16]. Peak force per body weight is the main mechanographic outcome of this test and is defined as the ratio between absolute peak force (N) and the participant's body weight (N). As this outcome measure is a ratio between two forces, the result is dimensionless and represents multiples of body weight. Specific force was computed as the ratio between peak force (measured in Newton; kN) during multiple two-legged hopping relative to muscle cross-sectional area (cm^2). 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 [31]. Rate of force development was defined as the slope of the force time curve between initial feet contact and occurrence of peak force (kN/s). This variable was used to provide an estimate of the strain rate imposed by muscle contractions. Evidence from animal studies indicates that strain rate can constitute an osteogenic stimulus independent of strain magnitude [32].

Statistical analyses

Descriptive statistics are presented as means and standard deviations. Anthropometrics of patients with OI and those of control participants were compared through paired t-tests. Muscle parameters were assessed through univariate analysis of variance (ANOVA), with disease status (OI type I vs control) as the between-subject factor. Data were adjusted for sex, age, height z-scores and tibia length. To test for the impact of OI on bone parameters, we computed random-block ANOVA on the main outcome parameters at both the 4 and 14% tibia bone sites. The block factor was the sample group (OI type I vs. control). Age and sex were already accounted for by our matched control design.

To determine whether the difference between patients with OI and control participants is influenced by the mutation type, the percent differences in bone parameters between one patient with OI and his respective matched control was computed at both the 4 and 14% sites. Using the percent difference for each bone parameter as a dependent variable, multiple stepwise regression analyses were conducted. Along with mutation type (haploinsufficiency = 0; other = 1), age (years), sex (male = 0; female = 1) height (expressed as age- and sex-specific z-scores; a disease severity marker in OI) and tibia length (cm) were set as independent predictors to take into account the expected difference between patients and controls for these bone parameters.

To assess the muscle–bone relationship we first used bivariate correlation analyses. Two analyses were performed: 1. BMC was correlated with peak muscle force; and 2. bone strength was correlated with muscle CSA. In addition, independent stepwise regression analyses were used to assess predictors of bone strength as estimated by BMC. Independent predictors were peak muscle force and rate of force development ('muscle function model') or physiological markers of muscle quantity and quality (muscle CSA and muscle density; 'muscle anatomy model'). Other independent predictors were disease status (control = 0; OI = 1), sex (male = 0, female = 1), age (years) and tibia length (mm). All tests were two-tailed and throughout the study $p < 0.05$ was considered significant. The same models were used to determine predictors of trabecular bone mineral density (trabecular BMD) at the 4% tibial site and cortical thickness at the 14% tibial site. These calculations were performed using the PASW Statistics software version 18.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Among the 30 study participants with OI type I, 15 had haploinsufficiency mutations (frameshift or stop mutations) in *COL1A1*. In 15 patients other types of mutations were found (splice mutations, glycine substitutions in the triple helical domain of the collagen type I alpha chains). An intramedullary rod was present in the tibia of two patients. The OI type I and the control cohorts did not differ significantly in height and weight (Table 1). The OI group had lower muscle force and lower specific force in the multiple two-legged hopping test, as well as smaller muscle size (after adjusting for tibia length) (Table 2) [8].

The ANOVA computed on bone parameters revealed that at the 4% tibia site total bone CSA did not differ between the OI type I and the control groups, whereas all other parameters at this site were approximately 20% lower in OI type I. At the 14% site, total CSA and cortical density did not differ between groups, whereas BMC, cortical thickness and cortical CSA were about 20% lower in the OI group (Table 2).

Next we determined whether the type of disease-causing mutation in OI patients (haploinsufficiency vs. other mutations) influenced the observed group differences in bone parameters. These analyses showed that the percent difference for bone parameters at the 4% site were independent of sex, height z-score, tibia length and mutation types. However, age was negatively associated with the percent difference in total CSA (total CSA [mm] = 42–3.4 [age; years]; $R^2 = 0.18$; $p = 0.02$) and in total BMC (total BMC [mg/mm] = 16–2.8 [age; years]; $R^2 = 0.16$; $p = 0.03$), indicating that the relative deficits in OI patients decreased with age. At the 14% site, regression analyses showed that cortical thickness, cortical area and BMC were independent of all factors included in the model. It also indicated that the percent difference in total CSA was significantly influenced by age and height z-score (total CSA [mm] = 32–2.8 [age; years] + 5.1 (height z-score); $R^2 = 0.34$; $p = 0.003$) and cortical density was positively associated with age (cortical density [mg/cm^3] = −9.8 + 0.9 [age; years]; $R^2 = 0.26$; $p = 0.04$).

The relationship between peak muscle force and BMC was similar between groups (Fig. 1a), but the relationship between muscle size and BMC indicated that at a given muscle size individuals with OI type I had less BMC than healthy age- and sex-matched controls (Fig. 1b). The reason for the difference in muscle–bone relationship between muscle force and muscle size is that the OI cohort produced less force per muscle CSA than controls (Table 2 and Figs. 1 and 2).

The stepwise regression analysis on the muscle function model indicated that BMC at the 4% site was predicted by peak force and age, whereas BMC at the 14% site was determined by peak force and tibia length. Disease status, rate of force development and age were not independently associated with BMC at either site. In the muscle anatomy model, disease status and muscle CSA were significant predictors of BMC at the two measurement locations (Table 3) whereas muscle density, age and rate of force development were not. Tibia length was a significant additional predictor only at the 14% site.

Table 1
Anthropometric data in patients with OI and age- and sex-matched healthy controls.

	OI type I	Controls	P
N (female/male)	30 (20/10)	30 (20/10)	
Age (years)	11.20 (3.89)	11.02 (4.15)	0.10
Height (m)	1.38 (0.20)	1.42 (0.24)	
Height (z-scores)	−0.68 (1.59)	−0.16 (1.35)	0.21
Body mass (kg)	38.5 (17.0)	40.6 (18.2)	
Body mass (z-scores)	−0.14 (1.14)	0.24 (1.15)	0.28
Tibia length (mm)	334 (55)	326 (60)	0.24

Table 2
Results of mechanography and pQCT analyses.

	OI type I	Controls	% difference	P
Mechanography				
Peak force (kN)	1.31 (0.56)	1.73 (0.96)	−24	<0.001
Peak force (relative to body weight)	3.52 (0.67)	4.29 (0.83)	−18	<0.001
Specific force (kN/mm^2)	16 (3)	19 (4)	−16	<0.001
Rate of force development (kN/s)	11 (5)	16 (8)	−32	<0.001
pQCT calf muscle				
Muscle CSA (mm^2)	4021 (1452)	4289 (1532)	−6	0.03
Muscle density (mg/cm^3)	73 (2)	72 (3)	1	0.12
pQCT tibia 4% site				
Total CSA (mm^2)	652 (196)	681 (303)	−4	0.14
Total vBMD (mg/cm^3)	245 (51)	297 (36)	−17	<0.001
Total BMC (mg/mm)	157 (48)	200 (88)	−22	<0.001
Trabecular vBMD (mg/cm^3)	160 (33)	203 (25)	−21	<0.001
pQCT tibia 14% site				
Total CSA (mm^2)	270 (77)	296 (111)	−9	0.10
Total BMC (mg/mm)	132 (43)	161 (63)	−18	<0.001
Cortical CSA (mm^2)	93 (33)	118 (44)	−21	<0.001
Cortical vBMD (mg/cm^3)	993 (89)	990 (53)	0	0.78
Cortical thickness (mm)	1.80 (0.55)	2.16 (0.48)	−18	0.01

BMC: bone mineral content; CSA: cross-sectional area; pQCT: peripheral quantitative computed tomography; vBMD: volumetric bone mineral density.

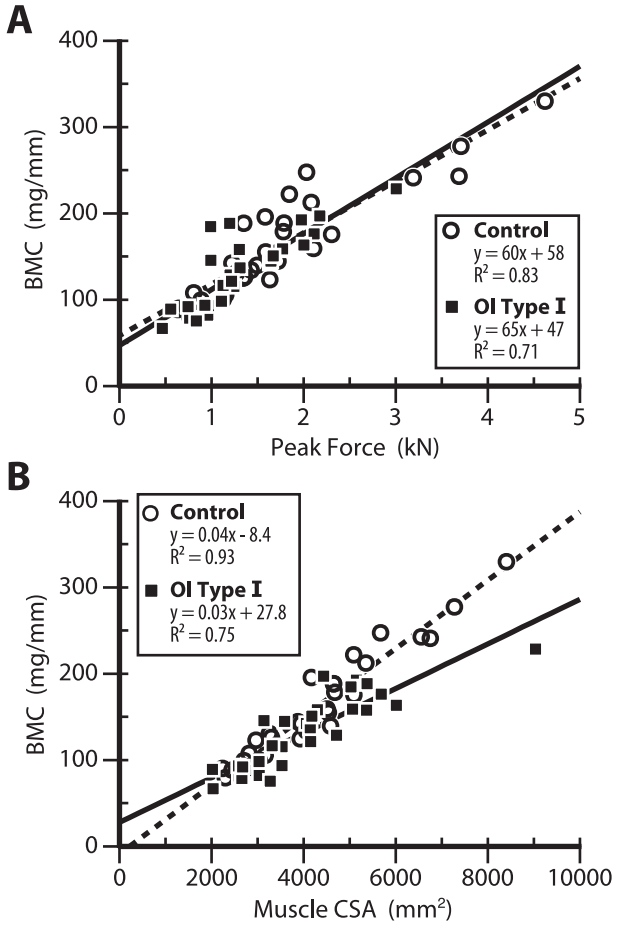

Fig. 1. Illustration of the correlation between (a) Total BMC (mg/mm) at the 14% site of the tibia and peak muscle force (kN) as measured during the multiple two-legged hopping test and between (b) Total BMC (mg/mm) at the 14% site of the calf muscle cross-sectional area (mm^2) as measured by pQCT.

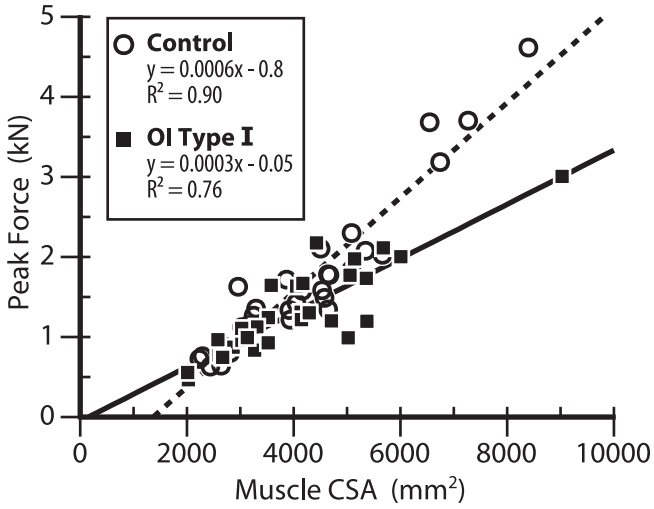

Fig. 2. Illustration of the correlation between peak muscle force (kN) and calf muscle cross-sectional area (mm^2).

BMC is influenced by bone geometry (estimated by total or cortical bone cross-sectional area and cortical thickness) and bone tissue properties (estimated by vBMD). Total bone cross-sectional area was similar between groups at both the 4% and the 14% site and there was also no group difference in cortical vBMD at the 14% site (Table 2). However, we observed deficits in trabecular vBMD and cortical thickness at the 4% and 14% sites, respectively (Table 2). To evaluate whether these parameters were influenced by the same determinants as BMC, additional stepwise regression analyses were performed. Predictors of trabecular vBMD (at the 4% site) and cortical thickness (at the 14% tibial site) were determined using the 'muscle function' and 'muscle anatomy' models (Table 3). The only predictor of trabecular vBMD was disease status. Predictors of cortical thickness in the muscle function model were peak force and tibia length. In the muscle anatomy model, muscle size, tibia length and disease status were independent predictors of cortical thickness.

Discussion

The present results show that the previously reported muscle force deficit in OI type I [8] is paralleled by a proportional deficit in BMC. These results were similar between individuals with haploinsufficiency mutations in *COL1A1* and those with other types of *COL1A1/COL1A2* mutations. Regression analyses also indicated that the muscle–bone relationship did not differ between OI type I and healthy controls. Together, these results are compatible with the view that the muscle force deficit in OI type I contributes to the low bone mass that is commonly seen in this disorder.

Although the current study was not designed to provide mechanistic data on the muscle–bone interaction, it can nevertheless be interpreted in the framework of the mechanostat theory. According to this theory, bone adapts to muscle forces in a manner that maintains bone tissue deformation caused by mechanical muscle loads within safe limits (setpoint). It has been suggested that the collagen defect in OI leads to an abnormally elevated mechanostat setpoint [33,34]. However, the results of our 'muscle function' model would suggest that the setpoint in patients with OI type I is normal and that bone mass is well adapted to the (lower) forces that the surrounding calf muscle contractions apply on the tibia.

To evaluate the muscle bone relationship, we used two different regression analysis models: the 'muscle function' and the 'muscle anatomy' models. The 'muscle function' model uses peak force generated during dynamic hopping as an index of muscle force whereas the anatomy model uses muscle size as a surrogate of muscle force and muscle

Table 3
Predictors of bone strength parameters at the 4% and 14% sites of the tibia.

	Regression equations	R^2	P
Muscle function model			
4% site			
BMC (mg/mm)	33.4 + 59.5 (F_{M2LH}; kN) + 4.9 (age; years)	0.78	<0.001
Trabecular BMD (mg/mm^3)	203–42 (disease status: 0,1)	0.35	<0.001
14% site			
BMC (mg/mm)	−43.7 + 41.2 (F_{M2LH}; kN) + 0.39 (tibia length; mm)	0.87	<0.001
Cortical thickness (mm)	0.466 + 0.32 (F_{M2LH}; kN) + 0.003 (tibia length; mm)	0.54	<0.001
Muscle anatomy model			
4% site			
BMC (mg/mm)	21 + 0.023 (mCSA, mm^2)–39 (disease status; 0,1) + 7.4 (age; years)	0.78	<0.001
Trabecular BMD (mg/mm^3)	203–42 (disease status; 0,1)	0.35	<0.001
14% site			
BMC (mg/mm)	−51 + 0.015 (mCSA, mm^2) + 0.36 (tibia length; mm) −29 (disease status; 0,1) + 2.8 (age; years)	0.91	<0.001
Cortical thickness (mm)	0.432 + 0.0002 (mCSA, mm^2)–0.371 (disease status; 0,1) + 0.003 (tibia length; mm)	0.67	<0.001

density a surrogate of intra- and inter-muscle fat infiltration. The results of the 'muscle function model' showed no difference in the muscle–bone relationship between the OI and control groups, indicating that at a given muscle force, individuals with OI type I and controls had the same BMC. In this model we also assessed the rate of force development as a marker of bone strain rate but this parameter did not emerge as a significant predictor of BMC. This suggests that the absolute amount of force rather than its rate of increase is the main factor that contributes to bone mass modifications. In contrast, the 'anatomy' model did show a different muscle–bone relationship between both populations indicating that for a given muscle CSA healthy controls will have higher BMC than OI patients. This difference between models may result from differences in muscle/tendons properties in both populations. Indeed, as shown previously and as reported in the current study, patients with OI type I have lower specific force, i.e. at equivalent muscle size, muscle force will be lower for individuals with OI type I than healthy controls (as shown in Fig. 2). This difference between models supports the idea that muscle size is an imperfect surrogate of muscle force in OI type I.

Among the limitations of this study are the relatively small sample population and the wide range of age. Pubertal status was not determined, but as OI type I does not affect sexual maturation, matching by chronological age can be expected to lead to two groups with similar maturity status. Physical activity was not measured in this study and, therefore, it is difficult to estimate its influence on the results of the current study. However, in a separate study we have determined physical activity by accelerometry and found no difference between children and adolescents with OI type I and their healthy age- and sex-matched peers (unpublished observation). We therefore think it is more likely that the group differences presented here are caused by the primary musculoskeletal disorder of OI type I rather than being secondary to lack of exercise.

Conclusion

The results of the current study suggest that the muscle force–bone strength relationship is similar between children and adolescents with OI type I and healthy age and sex-matched controls and indicate that bone strength is normally adapted to muscle force in patients with OI type I. In light of these results it is suggested that muscle weakness contribute to decreased bone strength in patients with OI type I.

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