J Musculoskelet Neuronal Interact 2017; 17(2):1-7

Journal of Musculoskeletal and Neuronal Interactions JMNI

Original Article

Muscle abnormalities in osteogenesis imperfecta

L-N. Veilleux, P. Trejo, F. Rauch

Shriners Hospital for Children and McGill University, Montreal, Quebec, Canada

Abstract

Osteogenesis imperfecta (OI) is mainly characterized by bone fragility but muscle abnormalities have been reported both in OI mouse models and in children with OI. Muscle mass is decreased in OI, even when short stature is taken into account. Dynamic muscle tests aiming at maximal eccentric force production reveal functional deficits that can not be explained by low muscle mass alone. However, it appears that diaphyseal bone mass is normally adapted to muscle force. At present the determinants of muscle mass and function in OI have not been clearly defined. Physiotherapy interventions and bisphosphonate treatment appear to have some effect on muscle function in OI. Interventions targeting muscle mass have shown encouraging results in OI animal models and are an interesting area for further research.

Keywords: Children, Fractures, Mobility, Muscle, Osteogenesis Imperfecta

Introduction

Muscles and bones are closely linked, both on the anatomical and on the functional level. From an anatomical perspective, skeletal muscles in the extremities are usually attached to at least two bones, typically with a broad base that inserts into a large surface area of a proximal bone and a much more circumscribed insertion into a distal bone via a tendon[1]. The middle part of many muscles is in direct contact with a periosteal bone surface. This anatomical proximity between muscles and bones allows for direct interaction through paracrine and endocrine factors[2].

From a functional perspective, muscle contraction generates forces that act on bones. As muscles use unfavorable lever arms, the 'internal' forces that muscles exert on bones are much larger than the forces that can be measured externally on a limb, for example with a ground reaction force plate or a dynamometer. As the largest forces on bones result from muscle action, bone strength needs to be adapted to peak muscle forces. This close mechanical relationship between muscle and bone is encapsulated in the term 'functional muscle-bone unit', as coined by Schoenau[3].

Given these intricate links between muscle and bone, it is not surprising that developmental disorders affecting one of these tissues are often associated with deficits in the other tissue as well. Indeed, many pediatric studies have documented skeletal abnormalities in conditions that primarily affect muscles or the neuromuscular system, such as Duchenne muscular dystrophy, spina bifida or cerebral palsy[4-8]. Much less is known about muscle deficits in conditions that are regarded as primary bone disorders.

One of the most common primary bone disorders in children is osteogenesis imperfecta (OI), a connective tissue disorder that is characterized mainly by bone fragility. OI is usually caused by mutations in *COL1A1* or *COL1A2*, the two genes encoding collagen type I alpha chains (alpha 1 and alpha 2), but mutations in a large number of other genes can also cause an OI phenotype[9]. The severity of OI can vary widely, as captured in the traditional Sillence classification that distinguishes four major types of OI[10]. OI type I is the mildest form of OI with absent or minimal bone deformities and normal or near-normal final height (Figure 1). Type II is lethal in the perinatal period. Type III is the most severe non-lethal form of OI, with very short stature as well as limb and spine deformities. Patients with short stature and moderate-to-severe phenotype who do not fit into one of the previously described types are classified as OI type IV. Three more OI types have been identified based on phenotypic and later genotypic criteria (OI types V, VI, VII)[11]. Many additional OI types have subsequently been proposed, based on which gene contains the disease-causing defect, but the resulting large number of OI types makes the classification unmanageable and confusing. The present review focusses on OI types I,

The authors have no conflict of interest.

Corresponding author: Frank Rauch, Shriners Hospital for Children, 1003 Boulevard Decarie, Montreal, Québec, Canada H4A 0A9
E-mail: frauch@shriners.mcgill.ca

Edited by: F. Rauch
Accepted 30 May 2017

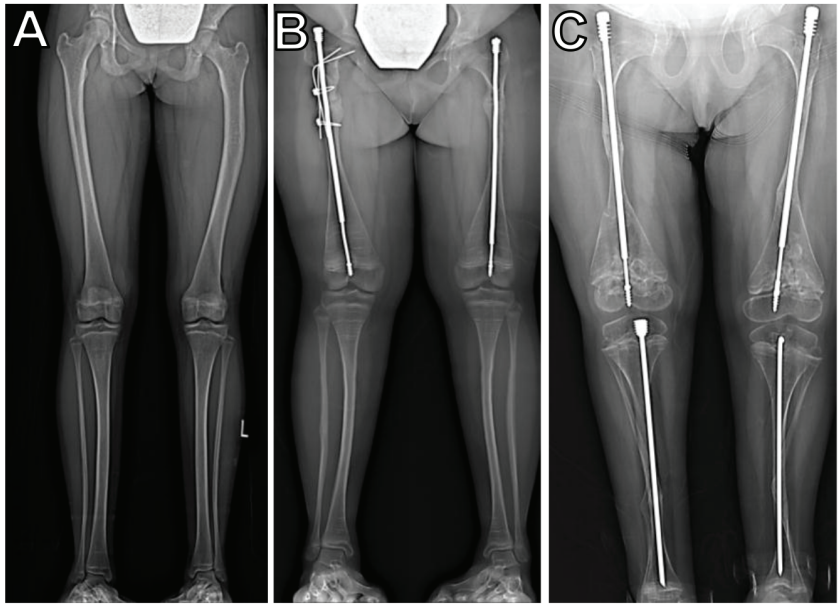


Figure 1. Anteroposterior radiographs of lower extremities. **(A)** 11-year old girl with OI type I who has not received bisphosphonate treatment and has not had intramedullary rodding surgery. There is a mild deformity of the left femur following a fracture at the age of 12 months. **(B)** 10-year old girl with OI type IV. Intravenous bisphosphonates had been given since the age of 4 years and both femurs have intramedullary nails. Coxa vara corrective surgery had been performed on the the right femoral neck. **(C)** 10-year old girl with OI type III. She had received intravenous bisphosphonate treatment since the age of 2 months. Both femurs and tibias have undergone rodding surgery.

III, and IV, as the other OI types are much rarer[9] and little is known about muscle characteristics in these disorders.

Although muscle weakness has been described as a presenting symptom of OI[12], muscle weakness is usually not the most conspicuous characteristic of OI. Nevertheless, muscle abnormalities have been reported both in OI mouse models and in children with OI. Here we review the evidence for muscle deficits in OI and discuss therapeutic approaches.

Muscle studies in animal models of OI

The *oim* mouse is the most widely used animal model of OI. This mouse has a frameshift mutation in the *Col1a2* gene that gives rise to a dysfunctional alpha 2 chain[13]. The heterozygous *oim/+* mouse has a very mild bone phenotype[14], whereas the homozygous *oim/oim* mouse is a model of severe OI, characterized by growth restriction and spontaneous fractures.

Gentry et al reported that muscle mass relative to body mass was low in the *oim/oim* mouse, whereas the *oim/+* mouse had normal muscle mass[15]. Some muscles of the *oim/oim* mouse contained less fibrillar collagen than wild type mice, but muscle fiber size and muscle fiber type distribution seemed to be normal. Nevertheless, electrophysiological testing showed that peak tetanic force relative to muscle cross-sectional area was much lower in *oim/oim* mice than in wild type mice, and that the tetanic tension decreased rapidly during the stimulation period. Similar but much milder functional abnormalities were present in *oim/+* mice. The authors suggested that disordered contractility may point to alterations of intracellular calcium handling by myocytes, but no further experiments seem to have been performed on this topic.

In contrast to *oim* mice, no muscle defect was found in the heterozygous G610C mouse[16]. This mouse model of dominant OI has a glycine-to-cysteine substitution in the triple helical domain of the collagen type I alpha 2 chain, but the bone phenotype is very mild[17]. G610C mice have normal locomotor activity, muscle mass and muscle fiber size and they have normal force production in electrophysiological tests[16]. Given these normal baseline characteristics, it is perhaps not surprising that a physical activity intervention involving running did not have a positive effect on bone mass or strength[16]. The marked discrepancy in muscle phenotype between *oim* mice and the G610C model suggests that the muscle abnormality in OI mouse models depend on the specific collagen mutation.

Even though the cause of the muscle abnormalities in *oim* mice is not entirely clear, pharmacological and genetic rescue experiments have been undertaken to correct them. Myostatin is a peptide secreted by muscle cells that has potent anti-anabolic effects on skeletal muscle itself[18]. Blocking myostatin function can increase muscle mass and improve muscle regeneration[19]. Myostatin and other compounds from the same family of proteins signal through the activin receptor

2B, which thus is a therapeutic target for inhibiting myostatin activity[20]. One approach to inhibit myostatin signaling uses a soluble form of the activin receptor 2B. This soluble receptor interacts with myostatin before it can bind to its functional receptor on the cell surface. This increases muscle mass, as shown in mouse models of various disorders, such as muscular dystrophy[21] and cancer cachexia[22].

A pilot study in *oim/oim* mice observed that injections of soluble activin receptor 2B increased muscle and bone mass[23], but muscle function and biomechanical tests of bone strength were not reported. Another study crossed the *oim/+* mouse with a heterozygous myostatin knockout mouse to assess the effect of partial genetic myostatin inhibition[24]. This increased muscle mass as well as trabecular bone volume in the proximal tibia and energy to failure in the femur. Thus, it appears that myostatin inhibition is a promising treatment avenue that warrants further exploration in OI mouse models.

Muscle studies in children with OI

There are many potential reasons for muscle deficits in children with OI. Mutations affecting collagen type I may have a direct effect on muscle, as collagen type I is present in the extra-cellular matrix surrounding muscle fibers[25], which plays an important role in transmitting muscle force to tendons[26]. Collagen type I is also abundant in tendons and ligaments and these tissues may therefore have altered structural and mechanical properties[27,28], as evidenced by the fact that joint hyperlaxity is a common clinical feature of OI[29]. Bone deformities can lead to muscle shortening, which could make muscle contraction inefficient. Fractures lead to periods of physical inactivity, which may lead to muscle atrophy. Even outside of the context of recent fracture, reduced mobility limits the opportunities for physical exercise for many individuals with OI, further limiting muscle development. Finally, it is possible that there is a direct negative effect of bone matrix abnormalities on muscle through paracrine effects. For example, TGFbeta signaling appears to be increased in OI[30], and release of TGFbeta from bone can decrease muscle mass[31].

Muscle in mild OI

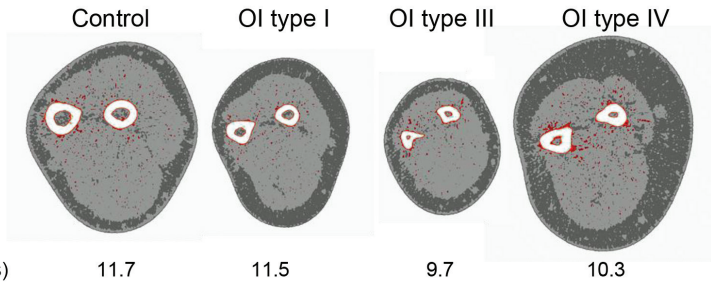
Rehabilitation specialists have long noticed that children with moderate to severe OI can have muscle weakness that interferes with therapeutic efforts to improve mobility[32]. More quantitative assessments of muscle function have shown that muscle deficits can be associated even with mild OI. One study on 17 children and adolescents with OI type I found lower isometric force of the shoulder abductors, hip flexors, ankle dorsiflexors as well as grip force than in healthy age- and sex-matched controls[33]. Another study on 20 children with OI type I observed a trend to lower plantar flexor muscle force and decreased endurance[34].

In more detailed studies, calf muscle anatomy and dynamic muscle function of the lower extremities were assessed in 54 children and adolescents with OI type I[35]. Peripheral quantitative computed tomography (pQCT) showed that, compared to age- and sex-matched controls, individuals with OI type I had smaller muscle size but normal muscle density. This indicated that OI type I is associated with decreased muscle mass, but normal muscle fat content as reflected by muscle density. Functional dynamic muscle testing using mechanography revealed that the OI group had lower average peak force and lower peak force relative to muscle cross-sectional area in hopping tests that evaluate maximal eccentric force production. However, peak power during tests involving concentric muscle contraction did not show a significant difference to controls. Despite these significant differences in group mean values, many children with OI type I had entirely normal muscle function test results, which is in accordance with the hypothesis that muscle involvement in OI varies with the disease-causing *COL1A1/COL1A2* mutation. The study also suggested that lower muscle mass was not the only explanation for lower muscle force in OI type I, because some force deficit persisted after adjustment for muscle cross-sectional area[35].

The origin of the muscle mass and function deficit in OI type I remains unclear. Lack of physical activity might contribute to lower muscle function in some individuals with OI type I. However, a study that assessed physical activity in 14 children with OI type I using both questionnaires and accelerometer data observed similar physical activity levels in youth with OI type I and in healthy controls[36]. Despite this, mechanography showed significant muscle function deficits in the OI type I group, both with regard to muscle force and, to a lesser extent, muscle power.

Disturbances in postural control might be another explanation for muscle function deficits in OI type I. One study performed static balance tests in 22 individuals with OI type I using a force plate[37]. Compared to healthy controls, the center of force in individuals with OI type I showed longer and faster displacements, indicating less efficient postural control. The difference between OI type I and controls was even larger when the tests were repeated with closed eyes. This suggests the presence of a proprioceptive deficit in OI type I. The cause of this putative proprioceptive deficit in OI type I was not elucidated. However, collagen type I is present in many tissues that are involved in postural control, such as skin, tendons, ligaments and muscles. For example, ankle instability, a frequent problem in OI, could affect postural control[38,39]. Alternatively, changes in biomechanical properties of the skin or changes in tendon properties are both likely to affect the sensory feedback that is required for postural control.

As muscle force and bone mass are usually closely related and the studies mentioned above provide evidence for some muscle weakness in OI type I, it can be surmised that muscle function deficits contribute to the bone mass deficit in OI type I. One study assessed the muscle-bone relationship in 30 children and adolescents with OI type I using mechanography and distal lower extremity pQCT[40]. This revealed that individuals with OI type I had 17% lower peak force and 22% lower tibia bone mineral content than age- and sex-matched



	Control	OI type I	OI type III	OI type IV
Age (years)	11.7	11.5	9.7	10.3
Bone CSA (z)	0.2	-3.8	-5.8	-2.7
Muscle CSA (z)	0.9	-2.4	-3.3	+0.1
Height (z)	+1.3	-1.4	-6.4	-3.2
FA Length (mm)	230	210	170	200

Figure 2. Peripheral quantitative computed tomography scan images at the 65% forearm site in a healthy control and in boys with OI. Cortical bone is shown in white, muscle in light grey and fat in dark grey. Bone CSA represents the cross-sectional area of the radius, including the marrow cavity. Muscle CSA is the cross-sectional area of the forearm muscle. FA length corresponds to the forearm length, as measured from the tip of the ulnar styloid process to the tip of the olecranon.

controls. However, the relationship between muscle force and bone mineral content was similar between the OI and the control cohorts. These data are in accordance with the view that the muscle function deficit impairs bone strength in OI type I, but that OI bone is able to adapt to mechanical forces in a similar manner as healthy bone.

Muscle in moderate to severe OI

The available information on muscle abnormalities in OI focusses on OI type I, because individuals in this diagnostic category typically are able to perform standard muscle function tests, and densitometric assessment of muscle mass or size is feasible. Evaluating muscle function in individuals with moderate to severe OI (i.e., OI types III and IV) is more difficult because they often do not have the level of functional mobility that is required for many dynamic muscle function tests. The presence of bone pain and bone deformities as well as frequent fractures and orthopedic interventions also interfere with muscle tests. Even simple tests of isometric muscle force are sometimes not possible due to the fear of causing a fracture during the test.

Analysing muscle mass in moderate to severe OI also is often not straightforward. One issue is that many individuals with moderate to severe OI have metal implants in their legs or spine as a consequence of intramedullary rodding or spinal fusion surgery (Figure 1). Such metal implants can interfere with whole-body scans using dual-energy x-ray absorptiometry, a widely used method for determining lean mass. Similarly, intramedullary rods make it impossible to analyse lower extremities with methods such as pQCT. However, few children with OI have major deformities or permanent metal rods in forearm bones, making this limb segment accessible for analysis. It is therefore usually possible to determine muscle size at the forearm, even in severe OI (Figure 2). Forearm muscle cross-sectional area provides a reasonable estimate of total body lean mass in children and adolescents with OI[41].

In a study of 266 children with OI types I, III and IV, muscle cross-sectional area adjusted for forearm length was significantly lower in patients with OI types I and III than in healthy controls but was similar to controls in patients with OI type IV[41]. The lower forearm muscle size in OI type I was expected, given similar previous findings at the calf muscle[35]. It is also intuitive that individuals with OI type III should have low muscle size. Bone fragility in OI type III often is so severe that physical exercise and ambulation are very limited. However, it was less expected to find normal muscle size in patients with OI type IV. One possible explanation is that many individuals with OI type IV are ambulatory but often require assistive devices such as walkers or crutches and therefore load their upper extremity during ambulation[42]. The increased use of arms for mobility may have a beneficial effect on arm muscle mass and function. In accordance with this hypothesis, one study found that individuals with OI type IV had normal grip force when compared to height-matched references[43]. Conversely, impaired upper extremity function is often the cause for reduced mobility in individuals with moderate to severe OI[42].

In contrast to preserved muscle mass and function at the upper extremities, children and adolescents with OI type IV often have weakness in the lower extremities. This was observed in a recent study on mechanography in 27 children and adolescents with OI type IV[43]. As expected, patients with the lowest scores on functional mobility testing were unable to perform one or several of the mechanography tests and thus the results of the study represent only the highest performing individuals with OI type IV. Among those OI type

IV patients who could perform the tests, both maximal muscle force on hopping tests and maximal power were significantly lower than in OI type I or in healthy controls. Not surprisingly, the number of previous fractures was a significant negative predictor of lower limb muscle function in OI type IV. Fractures lead to periods of physical inactivity and thereby may interfere with muscle development. Muscle function deficits in turn may contribute to limitations in mobility despite multidisciplinary treatment with bisphosphonates, intramedullary rodding surgery and rehabilitation[42].

Effect of treatments on muscle function in OI

If muscle function is impaired in OI and is associated with lower bone mass and decreased mobility, then muscle is a logical treatment target in OI. What are the muscle-targeting treatment options in OI and do they work?

Exercise: One randomized trial assessed the effect of a 12-week graded exercise program in children with OI type I or IV[44]. The intervention consisted of two weekly 45-minute exercise sessions with a physiotherapist for a duration of 12 weeks; during the last 6 week of the intervention, one weekly home-based exercise session was added to the program. Strength training was performed with weights of less than 1 kg. At the end of the intervention period, isometric muscle force had increased significantly and subjective fatigue had decreased. As expected, the positive effects of this intervention disappeared in the months following treatment discontinuation.

Vibration treatment: Whole-body vibration (WBV) treatment is a specific physiotherapy treatment approach that has generated a great deal of interest over the past decade. WBV is usually applied through a vibrating platform on which the user stands in a static position or moves in dynamic movements. Many devices and protocols providing very different forms of vibration exposure have been used to treat a wide range of conditions, including osteoporosis[45]. A study on the *oim/oim* mouse found that one form of vibration exposure had a positive effect on OI bone[46].

Several studies have assessed side-alternating WBV in human OI. 'Side-alternating' refers to the fact that the vibration is applied through a platform that rotates around a pivot in the middle of the plate[47]. Therefore, while one side of the plate is moving upwards, the other is moving downwards. Observational studies have suggested that side-alternating WBV has a beneficial effect on muscle function and mobility in children and adolescents with OI[48,49]. However, given the observational nature of these studies, the effect of WBV could not be isolated from that of other treatments that were given at the same time. A randomized controlled trial on 24 children and adolescents with OI applied side-alternating WBV twice daily over a period of 5 months[50]. It was observed that lean body mass increased faster in the WBV group than in the control group, but there was no detectable effect on muscle function or any bone parameters[50]. It is possible that different WBV approaches and different selection criteria for study participants may yield different results, but at present there is no clear evidence that WBV is effective in treating muscle and bone deficits in children and adolescents with OI.

Bisphosphonate treatment: Many children with OI are receiving treatment with intravenous bisphosphonates such as pamidronate or zoledronate[11]. These drugs attach to mineralized bone surfaces, inactivate bone-resorbing osteoclasts and thereby increase bone density. Given that the mechanism of action of bisphosphonates is quite specific to bone, it is somewhat surprising that grip force increased rapidly after a single pamidronate infusion cycle[51]. It can not be excluded that pamidronate has a direct effect on muscle cells, but pamidronate infusions lead to very low concentration of the drug in muscle tissue[52]. The positive effect of bisphosphonate treatment on muscle force in OI is quite rapid and therefore seems to be caused by an increase in muscle function rather than muscle muscle mass. In accordance with this hypothesis, no relationship between bisphosphonate treatment status and forearm muscle size was found in a pQCT-based study[41]. Possibly, antiresorptive treatment with pamidronate increases muscle function by inhibiting the release of factors from the bone matrix that have an inhibitory effect on muscle action, such as transforming growth factor beta 1. Such a mechanism has been demonstrated in experimental models of tumor cachexia, where bisphosphonate treatment improved muscle function and mass[31]. The apparent effect of bisphosphonate infusions on muscle force in OI might also be due to decreased skeletal pain. Pain can affect muscle function through inhibition by the central nervous system or peripheral accumulation of inflammatory factors[53].

Conclusions

Although muscle weakness is usually not a major characteristic of OI, there is evidence both from mouse models and from human studies that at least some forms of OI are associated with low muscle mass and function. Many factors could potentially explain muscle development in children and adolescents with OI, but at present the determinants of muscle mass and function in OI have not been clearly defined. Physiotherapy interventions and bisphosphonate treatment appear to have some effect on muscle function in OI. Interventions targeting muscle mass have shown encouraging results in OI mouse models and are an interesting area for further research.

References

1. Berendsen AD, Olsen BR. Bone development. Bone 2015;80:14-8.
2. Goodman CA, Hornberger TA, Robling AG. Bone and skeletal muscle: Key players in mechanotransduction and potential overlapping mechanisms. Bone 2015; 80:24-36.
3. Schonau E, Werhahn E, Schiedermaier U, Mokow E, Schiessl H, Scheidhauer K, et al. Influence of muscle

strength on bone strength during childhood and adolescence. Horm Res 1996;(45 Suppl)1:63-6.
4. Wong BL, Rybalsky I, Shellenbarger KC, Tian C, McMahon MA, Rutter MM, et al. Long-term outcome of interdisciplinary management of patients with Duchenne muscular dystrophy receiving daily glucocorticoid treatment. J Pediatr 2017;182:296-303 e1.
5. Ma J, McMillan HJ, Karaguzel G, Goodin C, Wasson J, Matzinger MA, et al. The time to and determinants of first fractures in boys with Duchenne muscular dystrophy. Osteoporos Int 2017;28:597-608.
6. Trinh A, Wong P, Brown J, Hennel S, Ebeling PR, Fuller PJ, et al. Fractures in spina bifida from childhood to young adulthood. Osteoporos Int 2017;28:399-406.
7. Dosa NP, Eckrich M, Katz DA, Turk M, Liptak GS. Incidence, prevalence, and characteristics of fractures in children, adolescents, and adults with spina bifida. J Spinal Cord Med 2007;(30 Suppl)1:S5-9.
8. Mughal MZ. Fractures in children with cerebral palsy. Curr Osteoporos Rep 2014;12:313-8.
9. Bardai G, Moffatt P, Glorieux FH, Rauch F. DNA sequence analysis in 598 individuals with a clinical diagnosis of osteogenesis imperfecta: diagnostic yield and mutation spectrum. Osteoporos Int 2016;27:3607-13.
10. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979;16:101-16.
11. Trejo P, Rauch F. Osteogenesis imperfecta in children and adolescents-new developments in diagnosis and treatment. Osteoporos Int 2016;27:3427-37.
12. Boot AM, de Coo RF, Pals G, de Muinck Keizer-Schrama SM. Muscle weakness as presenting symptom of osteogenesis imperfecta. Eur J Pediatr 2006; 165:392-4.
13. Chipman SD, Sweet HO, McBride DJ, Davisson MT, Marks SC, Shuldiner AR, et al. Defective pro alpha 2(I) collagen synthesis in a recessive mutation in mice: a model of human osteogenesis imperfecta. Proc Natl Acad Sci U S A 1993;90:1701-5.
14. Saban J, Zussman MA, Havey R, Patwardhan AG, Schneider GB, King D. Heterozygous oim mice exhibit a mild form of osteogenesis imperfecta. Bone 1996; 19:575-9.
15. Gentry BA, Ferreira JA, McCambridge AJ, Brown M, Phillips CL. Skeletal muscle weakness in osteogenesis imperfecta mice. Matrix Biol 2010;29:638-44.
16. Jeong Y, Carleton SM, Gentry BA, Yao X, Ferreira JA, Salamango DJ, et al. Hindlimb skeletal muscle function and skeletal quality and strength in +/G610C mice with and without weight-bearing exercise. J Bone Miner Res 2015;30:1874-86.
17. Daley E, Streeten EA, Sorkin JD, Kuznetsova N, Shapses SA, Carleton SM, et al. Variable bone fragility associated with an Amish COL1A2 variant and a knock-in mouse model. J Bone Miner Res 2010;25:247-61.
18. Lee SJ. Regulation of muscle mass by myostatin. Annu Rev Cell Dev Biol 2004;20:61-86.
19. Elliott B, Renshaw D, Getting S, Mackenzie R. The central role of myostatin in skeletal muscle and whole body homeostasis. Acta Physiol (Oxf) 2012;205:324-40.
20. Lee SJ, Reed LA, Davies MV, Girgenrath S, Goad ME, Tomkinson KN, et al. Regulation of muscle growth by multiple ligands signaling through activin type II receptors. Proc Natl Acad Sci U S A 2005;102:18117-22.
21. George Carlson C, Bruemmer K, Sesti J, Stefanski C, Curtis H, Ucran J, et al. Soluble activin receptor type IIB increases forward pulling tension in the mdx mouse. Muscle Nerve 2011;43:694-9.
22. Zhou X, Wang JL, Lu J, Song Y, Kwak KS, Jiao Q, et al. Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. Cell 2010;142:531-43.
23. DiGirolamo DJ, Singhal V, Chang X, Lee SJ, Germain-Lee EL. Administration of soluble activin receptor 2B increases bone and muscle mass in a mouse model of osteogenesis imperfecta. Bone Res 2015;3:14042.
24. Oestreich AK, Carleton SM, Yao X, Gentry BA, Raw CE, Brown M, et al. Myostatin deficiency partially rescues the bone phenotype of osteogenesis imperfecta model mice. Osteoporos Int 2016;27:161-70.
25. Gillies AR, Lieber RL. Structure and function of the skeletal muscle extracellular matrix. Muscle Nerve 2011;44:318-31.
26. Huijing PA. Muscle as a collagen fiber reinforced composite: a review of force transmission in muscle and whole limb. J Biomech 1999;32:329-45.
27. Misof K, Landis WJ, Klaushofer K, Fratzl P. Collagen from the osteogenesis imperfecta mouse model (oim) shows reduced resistance against tensile stress. J Clin Invest 1997;100:40-5.
28. Sims TJ, Miles CA, Bailey AJ, Camacho NP. Properties of collagen in OIM mouse tissues. Connect Tissue Res 2003;44 Suppl 1:202-5.
29. Brizola E, Staub AL, Felix TM. Muscle strength, joint range of motion, and gait in children and adolescents with osteogenesis imperfecta. Pediatr Phys Ther 2014;26:245-52.
30. Grafe I, Yang T, Alexander S, Homan EP, Lietman C, Jiang MM, et al. Excessive transforming growth factor-beta signaling is a common mechanism in osteogenesis imperfecta. Nat Med 2014;20:670-5.
31. Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, et al. Excess TGF-beta mediates muscle weakness associated with bone metastases in mice. Nat Med 2015;21:1262-71.
32. Binder H, Conway A, Hason S, Gerber LH, Marini J, Berry R, et al. Comprehensive rehabilitation of the child with osteogenesis imperfecta. Am J Med Genet 1993;45:265-9.
33. Takken T, Terlingen HC, Helders PJ, Pruijs H, Van der Ent CK, Engelbert RH. Cardiopulmonary fitness and muscle strength in patients with osteogenesis imperfecta type I. J Pediatr 2004;145:813-8.
34. Caudill A, Flanagan A, Hassani S, Graf A, Bajorunaite R, Harris G, et al. Ankle strength and functional limitations

in children and adolescents with type I osteogenesis imperfecta. Pediatr Phys Ther 2010;22:288-95.
35. Veilleux LN, Lemay M, Pouliot-Laforte A, Cheung MS, Glorieux FH, Rauch F. Muscle anatomy and dynamic muscle function in osteogenesis imperfecta type I. J Clin Endocrinol Metab 2014;99:E356-62.
36. Pouliot-Laforte A, Veilleux LN, Rauch F, Lemay M. Physical activity in youth with osteogenesis imperfecta type I. J Musculoskelet Neuronal Interact 2015;15:171-6.
37. Pouliot-Laforte A, Lemay M, Rauch F, Veilleux LN. Static postural control in youth with osteogenesis imperfecta type I. Arch Phys Med Rehabil 2017.
38. Engelbert RH, Uiterwaal CS, Gerver WJ, van der Net JJ, Pruijs HE, Helders PJ. Osteogenesis imperfecta in childhood: impairment and disability. A prospective study with 4-year follow-up. Arch Phys Med Rehabil 2004;85:772-8.
39. Rombaut L, Malfait F, De Wandele I, Thijs Y, Palmans T, De Paepe A, et al. Balance, gait, falls, and fear of falling in women with the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken) 2011; 63:1432-9.
40. Veilleux LN, Pouliot-Laforte A, Lemay M, Cheung MS, Glorieux FH, Rauch F. The functional muscle-bone unit in patients with osteogenesis imperfecta type I. Bone 2015;79:52-7.
41. Palomo T, Glorieux FH, Schoenau E, Rauch F. Body composition in children and adolescents with osteogenesis imperfecta. J Pediatr 2016;169:232-7.
42. Montpetit K, Palomo T, Glorieux FH, Fassier F, Rauch F. Multidisciplinary treatment of severe osteogenesis imperfecta: Functional outcomes at skeletal maturity. Arch Phys Med Rehabil 2015;96:1834-9.
43. Veilleux LN, Darsaklis VB, Montpetit K, Glorieux FH, Rauch F. Muscle function in osteogenesis imperfecta type IV. Calcif Tissue Int 2017.
44. Van Brussel M, Takken T, Uiterwaal CS, Pruijs HJ, Van der Net J, Helders PJ, et al. Physical training in children with osteogenesis imperfecta. J Pediatr 2008;152:111-6, 6 e1.
45. Cheung AM, Giangregorio L. Mechanical stimuli and bone health: what is the evidence? Curr Opin Rheumatol 2012;24:561-6.
46. Vanleene M, Shefelbine SJ. Therapeutic impact of low amplitude high frequency whole body vibrations on the osteogenesis imperfecta mouse bone. Bone 2013;53:507-14.
47. Rauch F, Sievanen H, Boonen S, Cardinale M, Degens H, Felsenberg D, et al. Reporting whole-body vibration intervention studies: Recommendations of the International Society of Musculoskeletal and Neuronal Interactions. J Musculoskelet Neuronal Interact 2010; 10:193-8.
48. Semler O, Fricke O, Vezyroglou K, Stark C, Stabrey A, Schoenau E. Results of a prospective pilot trial on mobility after whole body vibration in children and adolescents with osteogenesis imperfecta. Clin Rehabil 2008;22:387-94.
49. Hoyer-Kuhn H, Semler O, Stark C, Struebing N, Goebel O, Schoenau E. A specialized rehabilitation approach improves mobility in children with osteogenesis imperfecta. J Musculoskelet Neuronal Interact 2014; 14:445-53.
50. Hogler W, Scott J, Bishop N, Arundel P, Nightingale P, Mughal MZ, et al. The effect of whole body vibration training on bone and muscle function in children with osteogenesis imperfecta. J Clin Endocrinol Metab 2017.
51. Montpetit K, Plotkin H, Rauch F, Bilodeau N, Cloutier S, Rabzel M, et al. Rapid increase in grip force after start of pamidronate therapy in children and adolescents with severe osteogenesis imperfecta. Pediatrics 2003; 111:E601-3.
52. Hoggarth CR, Bennett R, Daley-Yates PT. The pharmacokinetics and distribution of pamidronate for a range of doses in the mouse. Calcif Tissue Int 1991; 49:416-20.
53. Hodges PW, Smeets RJ. Interaction between pain, movement, and physical activity: short-term benefits, long-term consequences, and targets for treatment. Clin J Pain 2015;31:97-107.