Muscle abnormalities in osteogenesis imperfecta

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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. 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.

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.

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. 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. The severity of OI can vary widely, as captured in the traditional Sillence classification that distinguishes four major types of OI. 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). 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,

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

Although muscle weakness has been described as a presenting symptom of OI, 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. The heterozygous oim/ mouse has a very mild bone phenotype, 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. 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. 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. G610C mice have normal locomotor activity, muscle mass and muscle fiber size and they have normal force production in electrophysiological tests. 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. 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. Blocking myostatin function can increase muscle mass and improve muscle regeneration. 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. 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 and cancer cachexia.

A pilot study in oim/oim mice observed that injections of soluble activin receptor 2B increased muscle and bone mass, 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. 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, which plays an important role in transmitting muscle force to tendons. Collagen type I is also abundant in tendons and ligaments and these tissues may therefore have altered structural and mechanical properties, as evidenced by the fact that joint hyperlaxity is a common clinical feature of OI. 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, and release of TGFbeta from bone can decrease muscle mass.

**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. 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 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. Another study on 20 children with OI observed a trend to lower plantar flexor muscle force and decreased endurance.

In more detailed studies, calf anatomy and dynamic muscle function of the lower extremities were assessed in 54 children and adolescents with OI. Peripheral quantitative computed tomography (pQCT) showed that, compared to age- and sex-matched controls, individuals with OI had smaller muscle size but normal muscle density. This indicated that OI 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 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, because some force deficit persisted after adjustment for muscle cross-sectional area.

The origin of the muscle mass and function deficit in OI remains unclear. Lack of physical activity might contribute to lower muscle function in some individuals with OI. However, a study that assessed physical activity in 14 children with OI using both questionnaires and accelerometer data observed similar physical activity levels in youth with OI and in healthy controls. Despite this, mechanography showed significant muscle function deficits in the OI 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. One study performed static balance tests in 22 individuals with OI using a force plate. Compared to healthy controls, the center of force in individuals with OI showed longer and faster displacements, indicating less efficient postural control. The difference between OI and controls was even larger when the tests were repeated with closed eyes. This suggests the presence of a proprioceptive deficit in OI. The cause of this putative proprioceptive deficit in OI 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. 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, it can be surmised that muscle function deficits contribute to the bone mass deficit in OI. One study assessed the muscle-bone relationship in 30 children and adolescents with OI using mechanography and distal lower extremity pQCT. This revealed that individuals with OI had 17% lower peak force and 22% lower tibia bone mineral content than age- and sex-matched controls.
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 focuses 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.

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. The lower forearm muscle size in OI type I was expected, given similar previous findings at the calf muscle. 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. 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. Conversely, impaired upper extremity function is often the cause for reduced mobility in individuals with moderate to severe OI.

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. 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 rehabilitation42.

**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 IV44. 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 osteoporosis15. A study on the oim/oim mouse found that one form of vibration exposure had a positive effect on OI bone46.

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 plate47. 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 OI48,49. 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 months50. 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 parameters50. 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 zoledronate11. 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 cycle51. 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 tissue52. 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 mass. In accordance with this hypothesis, no relationship between bisphosphonate treatment status and forearm muscle size was found in a pQCT-based study11. 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 mass11. 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 factors53.

**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.

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