Bones and muscular dystrophies: what do we know?

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Purpose of review
Muscle and bone are intrinsically linked, and therefore, it is not surprising that many muscular dystrophies are associated with impaired bone health and increased risk of osteoporosis. Osteoporotic fracture is an important and preventable cause of morbidity and mortality. This article will firstly review the general causes of impaired bone health in muscular dystrophies and then focus on the evidence available for the diagnosis and treatment of osteoporosis in specific conditions.

Recent findings
With the exception of DMD, there is a paucity of data regarding bone health in muscular dystrophies. However, it appears that in common with all types of muscular dystrophies that cause a significant level of muscle weakness and disability there is an increased risk of falls, fractures and decreased vitamin D levels. A better understanding of the extent of the impaired bone health and underlying causes could help to identify potential new therapeutic agents and aid clinical care.

Summary
It would be prudent for clinicians to assess fracture risk in their muscular dystrophy patients and if appropriate, arrange surveillance and recommend vitamin D supplementation. Additionally, fracture should be considered in any patient presenting with new-onset bone pain.

Keywords
muscle–bone interaction, muscular dystrophies, osteoporosis

INTRODUCTION

Muscular dystrophy is the term given to a rare and highly heterogeneous group of genetic muscle diseases, characterized by progressive skeletal muscle wasting and weakness from congenital through to adult-onset. As many muscular dystrophies are extremely rare, information about bone health in the individual conditions remains sparse. However, there are many causes in common across the group.

CAUSES OF IMPAIRED BONE HEALTH IN MUSCULAR DYSTROPHIES

Bone mineral density (BMD) in adulthood depends predominantly on growth and mineralization of the skeleton and the resultant peak bone mass achieved and then, to a lesser extent, on the subsequent loss. In healthy individuals, 80% of bone mass is accrued by 18 years of age [1] and a reduced peak BMD in childhood has been proposed as one of the strongest predictors of later life fractures [2]. Healthy bone is metabolically active and undergoes continuous remodelling to maintain the balance between bone formation and bone resorption. If this finely tuned process is disturbed, then osteoporosis can result. Osteoporosis is characterized by the depletion of bone mineral mass, combined with bone microarchitecture deterioration, enhanced bone fragility and a resultant increased fracture risk [3]; a 10% loss of vertebral bone mass can double the risk of a vertebral fracture [4].

Genetic predisposition only accounts for up to 50% of the variance in bone mass. Other important influences on bone health include lifestyle and sociodemographic factors (such as alcohol and tobacco use), nutrient intakes (including vitamin

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KEY POINTS

- Bone health and fracture risk should be assessed and vitamin D supplementation recommended in all patients with muscular dystrophy.
- With the exception of DMD, there is a paucity of data regarding bone health in muscular dystrophies.
- There is limited evidence for the use of any interventions to prevent or treat osteoporosis in this cohort.
- Consider fracture in any patient presenting with new-onset bone pain.

D and calcium intake), physical activity and bone stress, and comorbidities and drug treatments. Although impaired bone health in muscular dystrophies has been recognized for almost 80 years [5], it is only relatively recently that the importance of assessment and diagnosis of osteoporosis in these conditions has been recognized [6]. It is likely that several co-existing factors are responsible for the impaired bone health in muscular dystrophies:

The muscle–bone interaction

Bone and muscle are intrinsically linked and the mechanostat model [7] is a widely accepted theory; normal bone mineral accrual depends on a regulatory circuit sensing the bone deformations that are produced by muscle contractions to regulate osteocyte activity and modulate bone strength. The muscle weakness and reduced mobility that result from muscular dystrophies, and in particular those which are congenital or paediatric-onset, cause reduced loading forces on the bone, diminished bone growth and mineral accrual and result in osteopaenic/osteoporotic bone and low-trauma fractures, fractures that result from mechanical forces that would not ordinarily result in fracture [8,9]. A concise review has recently been published about the muscle–bone interaction [10▪]. In particular, once a patient becomes nonambulatory, and no dynamic or gravitational bone loading occurs, bone resorption exceeds bone formation; often termed disuse osteoporosis [11]. In support of this, retrospective data from the the Muscular Dystrophy Surveillance, Tracking and Research (MDSTAR) network combining Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy patients, shows that full-time wheelchair use increased the risk of first fracture by 75% for every 3 months of use [12].

The myotendinous junction (MTJ) is also a major site of force transfer in skeletal muscle. There are two independent transsarcolemmal linkage systems present at the MTJ, the dystrophin–glycoprotein complex and the a7ß1 integrin complex. Therefore, if a muscular dystrophy involves a mutation encoding for components of this linkage then MTJ function will be impaired, further contributing to abnormal bone loading. Examples include DMD, Becker muscular dystrophy and limb girdle muscular dystrophies (LGMD)2I. However, even if two muscular dystrophies appear to be phenotypically very similar, for example, Becker muscular dystrophy and LGMD2I, they can have very different contractile properties [13]. Costameres are also important for the conduction of force during muscle contraction [14]. The lateral force generated through these is impaired in a number of muscular dystrophies, therefore directly reducing bone loading.

Glucocorticoids

Glucocorticoids (GCs) are currently the mainstay of treatment in DMD and are the only pharmacological intervention proven to stabilize muscle strength for at least a number of years. They are offered before muscle function starts to decline and overall slow the progression of disease [15▪▪]. Therefore, by adulthood, in addition to the effects of the muscular dystrophy itself, most patients with DMD have also been on high-dose GCs for over 10 years.

The combination of progressive myopathy and osteotoxic GC therapy in DMD contributes to significant growth retardation [16] and fragility fractures [17], which can be very challenging to manage. GCs are not widely used in other muscular dystrophies, and in fact have been shown to be ineffective in some, such as dysferlinopathy [18].

GC-induced osteoporosis is associated with considerable morbidity and even mortality; a reduction in BMD of up to 40% can occur with GC therapy, and it is estimated that up to half of those on long-term GC therapy will experience fractures [19]. The use of GCs within the previous 6 months increased the risk of fracture three-fold and osteoporotic fracture by almost five-fold compared with nonexposed patients in a retrospective cohort study of patients with muscular dystrophies [6]. Data suggests that the greatest bone loss is experienced in the first year of treatment [20] and particularly in trabecular bone [19], but ongoing loss continues with prolonged treatment [21].

Vitamin D deficiency

Vitamin D is essential for skeletal health and regulates calcium absorption, and may also have

Table 1. Evidence for bone involvement and published data on bone health in muscular dystrophies

Disease	Primary bone involvement	Specific secondary risk factors for bone involvement	DXA data	Guidelines for monitoring bone health
DMD	Impaired osteoblast function [33,48] Activation of NFKB pathway and increased osteoclastogenesis	Glucocorticoid use Delayed puberty Inflammation and cytokine release	Many studies, including: LS BMD decreased compared with controls, further decreased when nonambulatory [39] GC dose and motor function correlated with BMD [49] LS BMD greater in BP-treated cohort of patients [50]	At each clinic visit [40▪▪]: ask about back pain/fractures At initial visit (with follow-up as required): serum calcium, phosphate, magnesium, alkaline phosphatase, parathyroid hormone Annually: calcium/vitamin D intake and vitamin D level Spine BMD by DXA Lateral thoracolumbar spine X-ray (1–2 yearly on GC, 2–3 yearly if not) Do lumbar spine X-ray if back pain or at least 0.5 SD decline in LS BMD *z*-score/12m)
FSHD	Not known	Increased incidence of vitamin D insufficiency	BMD not uniformly reduced but moderately correlated with strength and function [42▪]	No published guidelines
LGMD	Not known	Increased fall risk Greater than expected levels of vitamin D insufficiency [43]	None found	No information re monitoring bone health in guidelines [44]
Myotonic dystrophy	Not known	Testicular atrophy and hypogonadism Instability causing increased falls and fracture risk Increased incidence of vitamin D insufficiency	BMD comparable with control population [47▪]	No information regarding bone health in guidelines [51]

DMD, Duchenne muscular dystrophy; FSHD, facioscapulohumeral muscular dystrophy; LGMD, limb girdle muscular dystrophies.

an additional role in muscle strength [22]. Low vitamin D levels in patients with muscular dystrophies are likely to be multifactorial and may result from reduced sunlight exposure (especially in nonambulant patients), reduced oral motor function [23] and obesity. Vitamin D absorption is also reduced by GC use, and so it is, recommended that vitamin D levels are checked routinely in DMD before commencing GCs and annually thereafter (Table 1; [24]). Adequate dietary calcium to meet the reference nutrient intake should also be advised and supplementation considered if this is unlikely to be reached [25].

Instability and fall risk

Postural abnormalities are found in almost all patients with muscular dystrophies and the abnormal vertebral load further contributes to an abnormality of bone loading; the resulting impairment of balance further increases fracture risk. Muscle instability also plays an indirect role in bone health, via an increased fall risk. For example, it has been shown that people with myotonic dystrophy fall 10 times more frequently than their healthy counterparts [26].

Effects of chronic disease and inflammation

The inflammatory process and cytokine release associated with muscular dystrophies may also contribute further to low bone density, as is demonstrated in other chronic diseases [27]. In particular in DMD, the activation of the NF-KB pathway may also cause altered muscle metabolism and activation of osteoclastogenesis [28].

Pubertal delay and hypogonadism

Testosterone acts via its conversion to 5-alpha dihydrotestosterone or oestradiol to enhance osteoblast differentiation and action and reduce osteoclast activity. Puberty is a crucial time for bone mineral accrual and pubertal timing is an important determinant of peak bone mass. Puberty is often delayed in many childhood chronic conditions and is almost universally delayed or absent in GC-treated DMD [16,29]. Over half of patients were found to

have low testosterone levels when total and free serum levels were measured in 59 men with different dystrophinopathies [30].

Genetic defects associated with both muscle function and bone activity

It is possible that in certain neuromuscular conditions, the genetic defect may also have additional deleterious effects on bone health, or interact with other markers of osteoporosis [31], but this has not been studied in detail. For example, in spinal muscular atrophy, an interaction between osteoclast-stimulating factor (OSF) and survival motor neuron (SMN) protein may occur, thus causing an additional increase in bone resorption [32]. Studies of the dystrophin deficient mouse model for DMD (*mdx*) have also suggested a reduced bone mass and strength and higher osteoclast number and bone resorption rate, independent of GC use [33–35]. These findings have been demonstrated prior to the onset of significant muscle weakness in young mice, therefore suggesting an intrinsic bone abnormality in addition to the reduced bone loading.

Whilst the above factors are likely to be common to most of the muscular dystrophies, the next section highlights the disease-specific evidence and guidance available on bone health.

Becker muscular dystrophy

Becker muscular dystrophy is caused by a reduction, rather than complete absence of dystrophin expression, thus resulting in a less severe phenotype compared with DMD. There is limited evidence regarding the increased fracture risk in Becker muscular dystrophy, but it follows that as disease progression occurs and muscle weakness worsens, osteopaenia/osteoporosis may occur [12].

Congenital muscular dystrophies

There does not appear to be any published data regarding bone health in congenital muscular dystrophies, probably because of the heterogeneity and rarity of the individual conditions. These individuals are at high risk of osteoporosis; however, because of the chronicity and severity of the muscle weakness and resultant effects on bone accrual.

Duchenne muscular dystrophy

DMD is the most common and best characterized form of muscular dystrophy and affects 1 in 4000 live male births [36]. As quality of life and survival rates continue to improve, bone health has become an increasingly important issue [37]. The presence of fractures in the DMD population and the risk factors for osteoporosis have been well documented [17,38,39] and the recently updated standards of care for DMD include comprehensive information for the monitoring of bone health (Table 1) [40▪▪]. Bone pain and fractures (long bone and vertebral) are common and can occur after minimal or no trauma. It has been predicted that by 100 months of high-dose daily GC therapy as many as 75% will have at least one vertebral fracture [41]. Loss of ambulation occurs in up to half after their first fracture.

Facioscapulohumeral muscular dystrophy

A recent cross-sectional study of 94 adults from two sites aimed to determine whether BMD is reduced in individuals with facioscapulohumeral muscular dystrophy (FSHD) and whether or not BMD and fractures correlate with muscle strength or function [42▪]. They found that 30% had insufficient vitamin D levels, with reduced levels from the US cohort compared with Australia, possibly explained by latitude. The disease severity score, BMD, muscle strength and functionality were not uniformly reduced and were all highly variable, but whole-body and regional BMD were found to be moderately correlated with strength and function. Their conclusion was that effective treatment plans must be tailored based on individual BMD and strength to prevent fractures and promote optimal bone health.

Limb girdle muscular dystrophies

LGMDs are a genetically heterogeneous group of diseases characterized by muscle weakness and wasting in the arms and legs. A recent cross-sectional survey endeavoured to determine the risk factors for osteoporosis, falls and fractures in various muscle conditions, including LGMD. The data suggested an increased risk of falls in LGMD patients and osteoporosis in nonambulatory patients with myopathies and increased prevalence of vitamin D insufficiency with decreased levels in 55% of patients with LGMD. However, the authors stated that, 'Their conclusions were limited by the low number of participants with different myopathies, cross-sectional design and retrospective nature and that larger, multicentre study of patients with limb girdle muscular dystrophies seems to be warranted' [43]. The recently published guidelines do not provide any evidence regarding monitoring for osteoporosis with bone-density testing. [44]

Myotonic dystrophy

Myotonic dystrophy type 1 (DM1) is the most common adult-onset muscular dystrophy, whereas type

2 (DM2) is rarer and tends to have a milder phenotype with later onset of symptoms. Severe cases of DM1 may also present in childhood and congenital forms can occur. Approximately 80% of patients with myotonic dystrophy will develop primary hypogonadism, which often occurs later in adulthood and is frequently associated with low testosterone levels [45]. Although hypogonadism is usually associated with low BMD, a study of 32 myotonic dystrophy patients found lower vitamin D levels compared with the control group but comparable BMD scores when measured using dual energy X-ray absorptiometry (DXA) of the femoral neck [46]. There appears to be an increased fracture risk in DM1 patients regardless of BMD, because of the higher fall rate compared with some other muscular dystrophies [6]. A web-based survey of 573 adults with DM1 [47▪] found they had a 2.3 times increased risk of falling compared with a healthy adult over 65 years of age, although like any voluntary, questionnaire-based study, this will be subject to significant recall bias. Seventeen percent had sustained a fracture in the previous 12 months, with the ankle and foot accounting for the majority of fractures, but there was no data available regarding bone density.

INVESTIGATIONS INTO BONE HEALTH

When reviewing patients with muscular dystrophies, consideration should be given to their bone health and where available, guidelines followed to further assess their risk of osteoporosis. In the rarer dystrophies, where there are no clinical guidelines available, assessment of individual risk factors should be used to determine which, if any of the below investigations are performed, either as screening tools or as a response to bone pain or reduced function.

Fracture incidence

Fracture is the most clinically relevant endpoint when assessing bone health. Fractures are an important cause of morbidity and reduction in quality of life. Some can occur after minimal trauma, or even just on handling. Death because of fat embolism after long-bone fracture has also been reported in DMD [52]. The pathogenesis of fragility fracture is multifactorial. Assessment of fracture risk depends not only on BMD but also on several other factors including bone remodelling, morphology and architecture and muscle function and balance. Using fracture incidence as a proxy for bone health has important limitations. Firstly, the fracture pattern in muscular dystrophies is likely to differ from the healthy population. For example, lower participation in sports activities will lead to fewer upper extremity fractures. Falls also contribute to an increased risk of lower extremity fracture and particularly femoral fracture, which are otherwise rare in the young population. It is likely that vertebral fractures in DMD are under-diagnosed and any acute back pain or focal tenderness as well as sudden deterioration in mobility should warrant further investigation. Vertebral fractures usually cause change in the shape of the vertebrae and scoring systems such as the Genant semi-quantitative method [53] can be useful to determine the severity of vertebral fractures. In this method, fracture severity is assessed solely by determining the extent of vertebral height reduction and morphological change; type of deformity (such as wedge or compression) is not used to determine fracture grade.

Dual energy X-ray absorptiometry

Current standards of care recommend assessment of spinal BMD by DXA on an annual basis in DMD. Evidence for its use is less clear in the other muscular dystrophies (Table 1). The exact correlation between BMD and fracture risk remains unclear, although it probably remains the best clinically available proxy for fracture risk. Models like the Fracture Risk Assessment Tool (FRAX) can be useful in combination with DXA to predict fracture risk in adults [54], but this cannot be used in children. Furthermore, interpretation of DXA results in DMD patients can be technically challenging because of their small size, body composition and the possibility of contractures and spinal instrumentation. Appropriate software to enable size adjustment and longitudinal readings for the patients are essential for accurate interpretation of risk. Vertebral fractures can also cause spuriously high BMD readings because a given bone volume has effectively been compressed into a smaller area.

Bone turnover markers

Bone turnover markers can be useful in addition to BMD to estimate fracture risk and to determine response to therapy and treatment adherence, but have limited use in children because of variations in normal range. Markers of bone formation include bone-specific alkaline phosphatase, osteocalcin (which is the most abundant noncollagenous protein in the extracellular matrix) and P1NP (a propeptide of type 1 collagen). The most frequently used markers of resorption are C-telopeptide (CTX) and N-telopeptide (NTX), which are released from the C-terminal and N-terminal ends of type 1 collagen,

respectively. CTX is recommended by the National Osteoporosis Foundation as the reference marker of bone resorption [55]. Many bone turnover markers, however, are not readily available in clinical practice, thus limiting their use.

Spinal X-ray

The new standards of care in DMD place an increased emphasis on the use of spinal X-ray as a surveillance tool to try and improve detection of vertebral fracture (Table 1). Newer methods of vertebral fracture assessment are also being developed, including the use of lateral DXA images [56], which may reduce the necessity for spinal X-rays in the future.

Other imaging modalities

Peripheral quantitative computed tomography, MRI and ultrasound have currently only been used in the research setting when investigating bone health in muscular dystrophies. A novel study using ultrasound to comparing muscle and bone parameters in DMD, Becker, LGMD and FSHD found that Becker and DMD patients had significantly lower bone health scores [57]. There were no observed differences in LGMD and FSHD, but the authors felt that this may be because of sample sizes or limitations of ultrasound as a measurement technique because it cannot provide absolute measure of BMD, bone mineral content, or bone geometry or distinguish between cortical and trabecular bone. These limitations preclude its clinical use.

POTENTIAL TREATMENT STRATEGIES

There are very limited treatment strategies currently available for the treatment of osteoporosis associated with muscle diseases. The impaired osteoblast function described in both the *mdx* mouse and patients with DMD suggest that an anabolic bone treatment would be optimal, but there are no current options clinically available. A recent Cochrane review [58▪▪] concluded that, 'We know of no evidence from high-quality randomised controlled trials (RCTs) about the efficacy of interventions to prevent or treat corticosteroid-induced osteoporosis and prevent osteoporotic fragility fractures in DMD in children and adults.'

The next section focuses on some of the therapies that are currently in use, with examples highlighting their use in DMD.

Bisphosphonates

There is limited evidence for the use of bisphosphonates in DMD and their use varies by centre; some advocate prophylactic bisphosphonate use whereas in other institutions, they are reserved for the treatment of fractures and there is no consensus regarding timing of initiation, drug regimen or cessation of treatment. The efficacy of BP therapy on BMD appears to depend on the age at time of treatment and the amount of bone growth remaining [59]. Generally, they appear to be a well tolerated and effective therapy in cases of severe bone loss, although the long-term effect of inhibition of bone turnover remains unknown [60–62].

Prophylactic bisphosphonates in DMD in those receiving GCs has been reported to be associated with increased survival [63] but evidence from this study should be interpreted with caution as it was a retrospective review of only 16 patients, 12 of whom were on intravenous bisphosphonates. Although bisphosphonates are frequently used to treat osteoporosis in DMD, they do not primarily affect osteoblast function and their use does not prevent the development of new vertebral fractures [64]. Sbrocchi *et al.* [65] found that using intravenous bisphosphonate therapy to treat vertebral fractures in DMD was associated with an improvement in back pain and stabilization/improvement in vertebral height ratios of previous vertebral fractures, but that it did not completely prevent the development of new vertebral fractures. A retrospective review of patients treated with risedronate for a mean of 3.6 years showed significantly less vertebral fractures in the treated cohort compared with a control group [50]. The lumbar spine (age and size adjusted) BMD *z*-scores also remained unchanged in treated patients, and were significantly greater than in the untreated cohort [50]. Recent work utilizing trans-iliac biopsy samples, however, suggests that caution needs to be taken before prophylactic bisphosphonates are used, particularly in a condition such as DMD, where there are additional risk factors for ongoing bone turnover suppression including myopathy and GCs [48]. They found that bone turnover was already low before the initiation of bisphosphonates and then as expected, the antiresorptive bisphosphonate treatment decreased bone formation indices further. An unexpected drop in trabecular bone volume, however, was also noted and unlike in osteogenesis imperfecta, no structural improvements were seen.

In view of the risk of fracture in children with DMD and the impact of fracture on health and long-term mobility, prophylactic use of bisphosphonates may, therefore, be beneficial [65–67] but the method of administration and when to start, stop or pause treatment remains unclear [68]. It is likely that bisphosphonates are effective in the initial period of GC-induced bone loss when there is

increased bone remodelling but become less responsive as osteoclast function reduces with prolonged treatment and bone remodelling ceases. After this time, bisphosphonates may further dampen bone remodelling and instead compromise skeletal quality, predisposing to fracture.

Parathyroid hormone

High levels of parathyroid hormone (PTH) stimulate osteoclastic bone resorption but intermittent low-dose PTH can stimulate osteoblast function by increasing PGE_2 and TGF-β release from bone [69]. This could, therefore, be a useful anabolic agent to counteract the adverse effects of GCs in osteoblasts. However, recombinant parathyroid hormone treatment using teriparatide requires daily subcutaneous injections and is currently contraindicated in children with a 'black box' warning, limiting its use to 2-year duration in adults [70] because of the risk of osteosarcoma.

Testosterone

The use of testosterone therapy in DMD has recently been reviewed [29] and it appears to be well tolerated in adolescents with DMD but our evaluation of practice found that neither growth nor pubertal developmental were optimal and few patients had adult endogenous testosterone levels posttreatment. There remains much variability in clinical practice regarding whether oral, topical or intramuscular preparations are used, and the age at initiation and duration of treatment vary greatly by centre. The importance of testosterone in the maintenance of muscle mass as well as bone density is critical, and testosterone supplementation should be considered when hypogonadism is present in adults with muscular dystrophies.

Vitamin D and calcium

There are multiple risk factors and evidence for vitamin D deficiency in this population as discussed above and so vitamin D supplementation should routinely be recommended to all patients with a muscular dystrophy. Whilst an adequate dietary calcium is required to satisfy reference intake levels, there is no evidence in the DMD population to indicate that additional calcium will have a beneficial impact on bone health. Patients with DMD are at risk of hypercalciuria and additional calcium may simply increase susceptibility to nephrocalcinosis [71].

CONCLUSION

With the exception of DMD, there is a paucity of data regarding bone health in muscular dystrophies. A better understanding of the extent of the impaired bone health and underlying causes could help to identify potential new therapeutic agents and aid clinical care. However, it appears that in common with all types of muscular dystrophies that cause a significant level of muscle weakness and disability, there is an increased risk of falls, fractures and decreased vitamin D levels. It would, therefore, be prudent for clinicians to assess fracture risk in their muscular dystrophy patients and if appropriately arrange surveillance and recommend vitamin D supplementation. Additionally, fracture should be considered in any patient presenting with new-onset bone pain.

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Conflicts of interest

There are no conflicts of interest.

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