

Bone Health in Children with Duchenne Muscular Dystrophy: A Review

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Abstract

Duchenne muscular dystrophy (DMD) patients are vulnerable to osteoporosis and fractures. This has significant impact on the mobility and quality of life of DMD patients, making the development of strategies to prevent or treat these complications critical. As such, this review incorporates a discussion of the determinants of bone health in healthy children, followed by an examination of bone health in DMD, with a particular focus of vitamin D deficiency and its implications. An illustrative case study highlights the bone-related complications that can occur in DMD and assessment approach.

Keywords: Duchenne muscular dystrophy; Bone health; Osteoporosis; Fracture; Vitamin D

Introduction

Children suffering from neuromuscular disorders such as Duchenne muscular dystrophy (DMD) are vulnerable to poor bone health and osteoporosis, a systemic disease characterised by low bone mass with a consequent increase in fragility and susceptibility to fracture [1]. This has significant implications for the quality of life and mobility of DMD patients, making the development of strategies to prevent or treat these complications critical. As such, this review incorporates a discussion of the determinants, assessment and management of bone health in healthy children followed by an examination of bone health in DMD, with a particular focus on vitamin D deficiency and its implications.

The Biology of Bone Health in Children

Childhood and adolescence are critical periods for the development of peak bone mass, which plays a large role in determining bone strength and later risk of osteoporosis [2,3]. Bone size, bone mineral density (BMD) and bone mineral content (BMC) are increased through the deposition of osteoid and its mineralisation with calcium and phosphate by osteoblasts [4]. Bone simultaneously undergoes resorption by osteoclasts during bone remodelling, which occurs in response to physical stress and endocrine signals [5]. The balance between bone deposition and resorption determines net bone formation; when there is a relative increase in bone resorption there is a decline in BMD, which can lead to weakened osteoporotic bones and an increased risk of fractures.

The Determinants of Bone Health in Children

Studies have established that peak bone density has a high genetic component, with about 70-80% of variability attributable to hereditary factors [6,7]. In addition, hormonal and lifestyle factors play a significant role in determining the bone health of children and adolescents. Understanding these determinants of bone health and the

pathophysiological mechanisms contributing to the development of osteoporosis is critical in improving strategies to reduce osteoporosis and fragility fractures long term, and are discussed below.

Endocrine Factors

Numerous hormones have been found to have an influence on bone health in children. The active form of vitamin D, 25-OH vitamin D (25-OHD), serves to enhance absorption of calcium from the intestine and hence promote skeletal mineralization [8]. In addition, parathyroid hormone (PTH) and calcitonin work in concert to regulate serum calcium levels by influencing bone deposition and resorption, as summarised in Figure 1.

The androgen and oestrogen hormones are of substantial importance during puberty. These hormones, particularly oestrogen, stimulate significant bone growth during early puberty and mediate the later closure of the epiphyseal growth-plates and hence peak bone size [9-12]. The timing of puberty consequently has an effect on the peak bone mass achieved, with delayed puberty associated with decreased BMD and BMC in adulthood [13].

Corticosteroids have varied and complex effects on bone health. Endogenous corticosteroids are necessary for the regulation of bone remodelling and differentiation of osteoblasts [5]. However, prolonged exposure to excess corticosteroids as occurs during the treatment of some conditions has negative impacts on bone health. These include the decreasing of bone formation through the suppression of osteoblasts, and the increasing of bone resorption via increased renal excretion and reduced gastrointestinal absorption of calcium; effects which consequently increase the risk of osteoporosis [14].

Nutritional Factors

Adequate levels of nutrients, particularly calcium and vitamin D, are critical for bone development during childhood and adolescence. Increasing dietary calcium, with or without vitamin D, significantly increased BMC in children with low baseline intakes in a recent meta-analysis of 21 randomised controlled trials [15]. Current Australian guidelines recommend that children and adolescents receive a daily

calcium intake of 500-1300 mg/day to promote adequate bone mineralisation [16].

As previously discussed, calcium absorption also requires adequate vitamin D. Over 80% of vitamin D in Australia is derived from skin

exposure to UVB radiation in sunlight, but small amounts of vitamin D can also be found in foods such as oily fish and egg [17]. Both the American Academy of Pediatrics and Australian guidelines currently recommend a daily vitamin D intake of 400 IU [18,19].

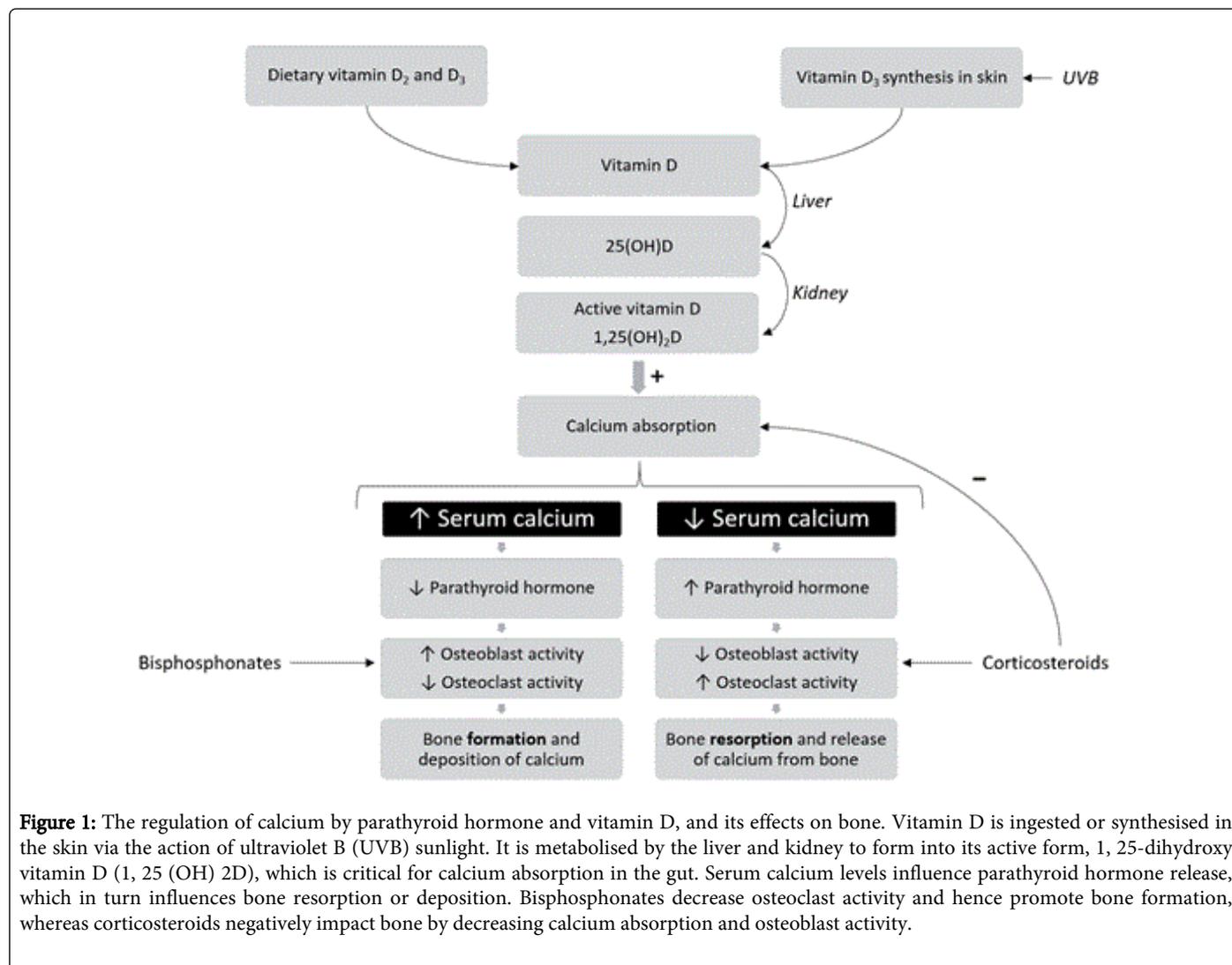


Figure 1: The regulation of calcium by parathyroid hormone and vitamin D, and its effects on bone. Vitamin D is ingested or synthesised in the skin via the action of ultraviolet B (UVB) sunlight. It is metabolised by the liver and kidney to form into its active form, 1, 25-dihydroxy vitamin D (1, 25 (OH) 2D), which is critical for calcium absorption in the gut. Serum calcium levels influence parathyroid hormone release, which in turn influences bone resorption or deposition. Bisphosphonates decrease osteoclast activity and hence promote bone formation, whereas corticosteroids negatively impact bone by decreasing calcium absorption and osteoblast activity.

Behavioural Factors

Weight-bearing physical activity promotes bone mineral accrual and maximises peak bone mass [20]. This appears particularly important during the pre-pubertal years, with several school-based exercise interventions demonstrating substantial positive effects on bone mineral content (BMC) and strength during this time [21-23]. Conversely, children who have limited ambulation have been found to suffer from low BMD and are at increased risk of fractures [24].

Exposure to sunlight is another important determinant of bone health given its effect on vitamin D levels. A recent Australian position statement recommended that adults walk for about 7 minutes with arms exposed during the summer to maintain adequate vitamin D [25]. Although the optimum duration of sunlight exposure for Australian children has not yet been established, is believed that it is less than in adults [19]. Risk factors for vitamin D deficiency in children include dark skin, malabsorption diseases, and behaviours

that limit sun exposure, such as the wearing of veils or chronic hospitalisation [17,26].

Evaluating Bone Health in Children

Assessing the factors discussed above can help guide management to reduce a child's risk of osteoporosis and fracture. Various investigations may be undertaken to give an overall understanding of the strength and condition of a child's bones, which are discussed below.

Biochemical Tests

Levels of serum calcium, 25-OH vitamin D (25-OHD) and PTH are routinely measured in assessing bone health. Bone health can also be assessed through biochemical markers of bone turnover, which reflect bone formation and resorption. Challenges are posed in interpreting these tests in children, as there is great variability in normal ranges due

to changes in skeletal metabolism induced by differences in age, growth rate, gender and maturity [27]. However, these tests can be useful in monitoring responses to treatment and determining underlying bone pathology.

Dual Energy X-ray Absorptiometry (DXA)

Dual energy x-ray absorptiometry (DXA) is the standard method used to assess bone mineral mass and density. This technique involves beaming low-intensity radiation through the body and determining BMC based on the degree of attenuation, from which an estimate of BMD can be calculated. While DXA is in widespread use, several issues exist surrounding its interpretation in children. DEXA scores are reported as "T-scores" and "Z-scores", which compare an individual's bone density with that of a healthy 30-year-old of the same gender and an average person of the same age and gender respectively. The values are expressed in units of standard deviations. DXA results are affected by bone size, maturity and body composition, with DXA tending to underestimate BMD in small subjects and overestimate BMD in large subject [28]. DXA results must therefore be adjusted based on subject size, but no consensus on the most appropriate correction method has been reached [28].

Another challenge lies in relating DXA to fracture risk in children. This is achieved in adults via the use of T-scores, which are derived by comparing BMD results to those of healthy young adults at peak bone mass [1]. T-scores cannot however be used in children who have not yet reached peak bone mass, and hence Z-scores, which use age and gender matched reference data for comparison, must be used. Currently, the International Society for Clinical Densitometry defines a size-adjusted BMD Z-score of <-2 as low in children [29]. However, although a clear inverse relationship between BMD Z-scores and risk of fractures has been found in healthy children [30], a precise estimate of fracture risk based on Z-scores in paediatrics is not yet well established.

Vitamin D Deficiency in Children

Although controversy exists over the optimum level of Vitamin D and how to define its deficiency, vitamin D deficiency is currently defined in Australia as a serum 25-OHD concentration of less than 50 nmol/L (or 20 ng/mL) [31]. This is best measured at the end of winter, when there is the greatest risk of deficiency [25].

Vitamin D deficiency leads to poor calcium absorption, inadequate bone mineralisation and an increased risk of pathological fracture [32], manifesting when severe as rickets or osteomalacia [19]. Vitamin D deficiency rickets has recently emerged as a significant problem in Australian children among known high-risk groups [33], highlighting the necessity for public health management strategies. In addition, vitamin D has been shown to influence the expression of hundreds of genes linked to inflammation, regeneration, autoimmune disorders, malignancies and cardiovascular disease [34,35], and may serve as an epigenetic factor in the progression of diseases such as DMD.

Despite increasing recognition that a significant number of children suffer from vitamin D deficiency, its prevalence is difficult to determine. Studies are complicated by the seasonal variability of vitamin D levels and variable access to sunlight in different locations [16,36,37]. Nevertheless, large population studies in Australia and the US have found the prevalence of vitamin D deficiency in adults to be around 32%-42% [36,38]. While studies on the prevalence of vitamin D deficiency in children within Australia are limited, several studies

have been conducted on children internationally (Table 1). These have generally shown that vitamin D deficiency is relatively lower during infancy at about 5.4%-12.1% [37,39], but increases in childhood and adolescence to around the same levels as those seen in adults [37,40,41]. Although many of these studies are limited by their small sample sizes, they demonstrate that vitamin D deficiency is a relatively common and significant health problem in children, highlighting the importance of developing further understanding of the pathophysiological role of vitamin D deficiency in neuromuscular disease.

Study	Population characteristics	Location	Sample size	Vitamin deficiency prevalence*
Gordon et al. [38]	Adolescents (age 11-18 years) in urban area	USA	307	42.00%
Gordon et al. [38]	Otherwise healthy infants and toddlers (age 8-24 months) in urban area	USA	380	12.10%
Andiran et al. [39]	Children and adolescents (age 0-16 years)	Turkey	440	40%
Zhu et al. [35]	Children and adolescents (age 0-16 years) subdivided into age groups	China	2116 (age 0-1)	5.40%
			2269 (age 2-5)	21.90%
			1440 (age 6-11)	40.40%
			183 (age 12-16)	46.40%

*Deficiency defined as <50 nmol/L or <20 ng/mL 25-hydroxyvitamin D

Table 1: Studies of vitamin D deficiency prevalence in healthy children and adolescents.

Age	Acute treatment
<1 month	1000 IU/day vitamin D for 3 months
1-12 months	3000 IU/day vitamin D for 3 months OR 300,000 IU over 1-7 days
>12 months	5000 IU/day vitamin D for 3 months OR 500,000 IU over 1-7 days

IU =International Units

Table 2: Recommended treatment protocol for vitamin D deficiency in children [18].

Management of Vitamin D Deficiency

Children at risk of vitamin D deficiency or who already suffer from deficiency may be treated with vitamin D supplements. Both the American Academy of Pediatrics and an Australian consensus statement recommend that children who are in at-risk groups or who do not have the recommended daily intake of 400 IU of vitamin D should receive a vitamin D supplement of 400 IU/day [18,19].

Methods for treating established vitamin D deficiency in children vary, but an Australian consensus statement recommends daily supplementation of between 1,000-5,000 IU vitamin D for 3 months (Table 2) [19]. High-dose stoss therapy, in which the total treatment dose of vitamin D (300,000-500,000 IU) is administered over 1-4 doses, has also been shown to be effective in treating vitamin D deficiency, although the best protocol has yet to be determined [19,42,43]. Calcium should be monitored and supplemented if low, and maintenance supplementation of 400 IU/day vitamin D should be continued after treatment [19].

Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disease affecting about 1 in 3600 to 6000 live male births, usually diagnosed at about 5 years of age [44,45]. The disease is caused by a mutation in the dystrophin gene which results in the absence or defect of dystrophin proteins and the consequent instability and degeneration of muscle fibres [46]. This leads to progressive muscle weakness, loss of independent ambulation by about 13 years of age, and premature death [47,48].

Bone Health Issues in DMD

Boys with DMD possess several major risk factors for poor bone health, including reduced weight-bearing exercise, delayed puberty, side effects of treatment with corticosteroids, reduced mobility and consequently the potential for reduced exposure to sunlight, and pathological effects of the disease itself [49-51].

Disturbances in bone health are evident in boys with DMD prior to their decline in mobility, related to their progressive muscle weakness [52,53]. The reduction in weight-bearing activity due to this weakness directly hampers bone mass accrual, with a decline seen in both lower limb strength and BMC prior to loss of independent ambulation [24,54]. When independent ambulation is no longer possible, BMD decline is dramatically accelerated. Larson et al. [24] demonstrated

that lumbar BMD dropped from a Z-score of -0.8 to -1.7 after the loss of ambulation, while BMD of the proximal femur dropped from -1.6 to a very low -3.9, increasing the risk particularly of long bone fracture. Without treatment, the majority of DMD patients are also at risk of developing severe scoliosis [55], which may require surgical stabilisation.

While corticosteroids (CS) are the standard therapy used to slow the progression of DMD, significantly prolonging ambulation, improving respiratory function and reducing the need for scoliosis surgery, the detrimental effect on bone mass may be profound [47,55]. BMD has been found to be considerably lower in CS-treated DMD patients than in steroid-naïve patients [53]. Studies have also demonstrated that CS therapy induces vertebral fractures in 19-38% of patients, which are very rare in steroid-naïve patients [55-57]. This may be partly accounted for by the protective effect of spinal surgery for scoliosis in steroid-naïve boys [49], but is difficult to ascertain. Delayed puberty, another side-effect of CS therapy, is an additional risk factor for poor bone health in this group [58]. It is clear that bone health protection in DMD warrants even greater attention due to the consequences of CS therapy, and studies are currently being undertaken to determine the best regimen of CS therapy which improves function while minimizing its negative impacts [49].

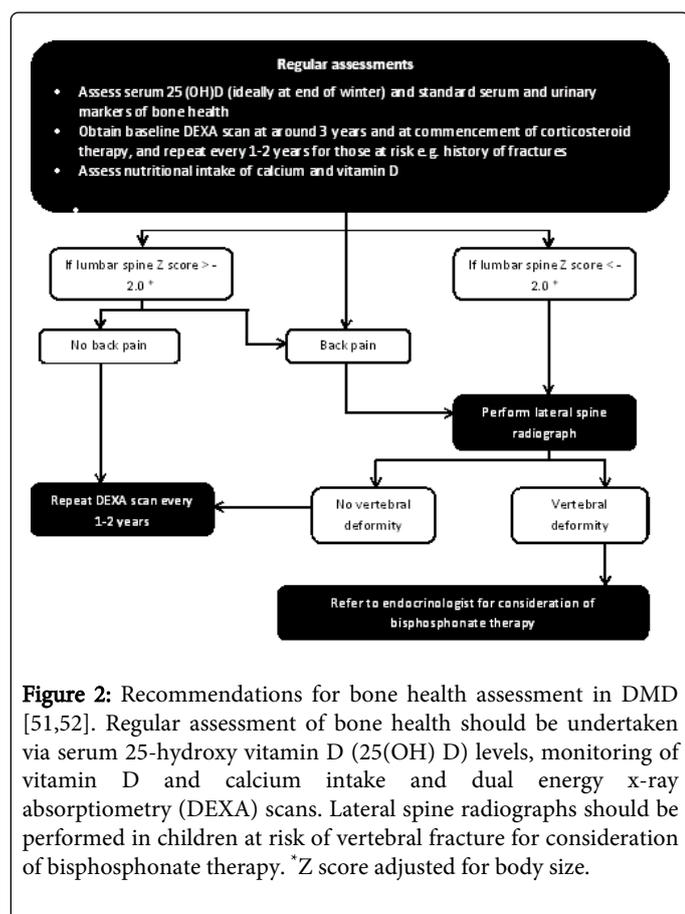
Vitamin D Deficiency in DMD

Vitamin D deficiency is another risk factor for poor bone health in DMD. While the prevalence of vitamin D deficiency in Australian DMD patients has not yet been established, remarkably only 22% of patients were vitamin D sufficient in a recent UK national audit [59]. Additional studies highlighting the frequency of vitamin D deficiency are summarised in Table 3. While correlations between low 25-OHD and low BMC have been found [58], little else is known about the association between vitamin D levels and bone health outcomes in DMD patients. This, and the prevalence of vitamin D deficiency in patients already prescribed supplements, is therefore areas in great need of further investigation.

Study	Study Objective	Patient number	Vitamin D status	Mean spinal BMD Z-score	Prevalence of fractures	Study conclusion
Mayo et al. [60]	To compare changes in lumbar spine BMD with deflazacort therapy	39	-	-1 ± 1.3 before CS treatment, -3.6 ± 1.1 after 7-8 years of CS treatment	21% (8) patients had long-bone fractures, 15% (6) patients had vertebral fractures	Patients on deflazacort therapy are at increased risk of vertebral fracture compared to steroid naïve patients, but not long-bone
Bianchi et al. [56]	To evaluate the effects of calcium and vitamin D supplementation on bone	33	60.6% < 50 nmol/L	-	21% (7) patients sustained fractures prior to enrolment	Vitamin D supplementation and adequate dietary calcium corrects vitamin D deficiency and increases BMC and BMD in most patients
Manzur et al. [57]	Audit on corticosteroid therapy, the prevalence of vitamin D deficiency, and vertebral fractures	157	78% < 50 nmol/L prior to corticosteroid commencement	-	-	Data was used to inform workshop recommendations
Bianchi et al. [51]	To evaluate BMD and calciotropic hormones	32	Mean 13 nmol/L in CS-treated group, 35 nmol/L in non-CS-treated group	-3.9 ± 1.4 in CS-treated group, -2.6 ± 1.3 in non-CS-treated group	18% (4/22) patients in CS-treated group and 20% (2/10) in non-CS-treated group sustained fractures	DMD patients experience decreased BMD and disturbed calcium metabolism, emphasized by CS therapy

McDonald et al. [59]	To determine the prevalence, circumstances, and outcomes of fractures	378	-	-	21% (79) patients sustained fractures	A fracture rate of 21% was found, most commonly caused by falls and associated with persistent functional loss. Early remobilization and aggressive therapy is recommended.
Soderpalm et al. [50]	To examine BMD, bone turnover, body composition and calciotropic hormones	22	Mean 52 nmol/L	-2.5 ± 1.9	24% (6) patients sustained fractures	DMD patients have reduced BMD and bone turnover, and interventions that increase bone formation should be considered
Larson et al. [24]	To assess the relationships between bone density, mobility, and fractures	41	-	-	44% (18) patients sustained fractures, 66% of which were in lower extremities	Low BMD is most profound in lower extremities and begins developing while still ambulating, which can result in fracture and early loss of ambulation
- = Not measured						

Table 3: Results of studies assessing bone health in Duchenne Muscular Dystrophy.



Fracture in DMD

Because of the risk factors discussed above, boys with DMD generally have significantly lower BMD than healthy controls and are more vulnerable to fractures and negative bone outcomes (Table 3)

[52,53,60]. Studies have found that between 21-44% of DMD patients experience fractures [24,61], which are generally long-bone in younger, ambulatory boys, and vertebral in older, non-ambulatory patients who have several years of corticosteroid therapy and significantly lower BMD [62]. These rates of fracture are considerably higher than the prevalence of fracture found in a large healthy cohort of children (8.9%) [30], suggesting that the reduced BMD of DMD patients are linked to increased fracture risk. However, just as there is difficulty ascertaining an accurate relationship between BMD Z-scores and fracture risk in healthy children, limited sample sizes in DMD studies mean that even less is known in this population.

As well as being painful, fractures in DMD have a significant impact on mobility. Prolonged immobilisation after a fracture can lead to the deterioration of muscle strength, with 20-44% of fractures resulting in the permanent loss of ambulation in previously walking patients [24,58,61]. Due to the positive effects of prolonged ambulation on quality of life in DMD, the development of strategies to optimise bone health and prevent fractures are consequently of great importance.

Assessment of Bone Health in DMD

While the need for assessment and management strategies for the protection of bone health in DMD is critical given the factors discussed above, there is currently no international consensus on this issue. However, several workshops have convened to develop recommendations for bone assessment and management, as summarised in Figure 2.

Despite the development of these guidelines, numerous areas of uncertainty exist. As previously discussed, bone assessments are very challenging to interpret even in healthy children, and DMD patients pose even greater challenges. The delayed growth and puberty and decreased muscle mass seen in DMD can skew DXA readings and bone turnover markers, emphasised further by corticosteroid use [50]. Although a few studies have evaluated bone turnover markers in DMD patients [52,53], these have produced inconsistent results. There is consequently little data which can be used to help prevent and predict fractures in DMD. Contractures and poor mobility also create

practical difficulties in performing DXA scans in more severe patients. Hence, while it is clearly important to monitor bone health in DMD, it is difficult to accurately do so.

Illustrative Case Study

The following case highlights the bone-related complications that can occur in DMD and assessment approach. A 12 year old boy with DMD presented with back pain during his regular check-up at the neuromuscular clinic. He had experienced intermittent lower back pain for the last 2 months, which had intensified after a fall 1 month previously. Despite still being capable of ambulation, the patient now preferred to use his wheelchair due to the severity of his back pain. He had been taking 2 paracetamol tablets daily to relieve the pain.

The patient had been treated with prednisone since the age of 5 to slow rate of decline of muscle strength. He was distinctly Cushingoid, with short stature, delayed puberty and obesity (weight 50.6 kg, height 1.2 m and BMI 35.2). He had a past history of moderate vitamin D insufficiency, with his lowest recorded 25-OHD level being 30 nmol/L. In response, he had been prescribed 1000 IU of vitamin D supplementation for 3 years and had also received stoss therapy. His most recent 25-OHD was sufficient at 78 nmol/L, which was measured at the time of his presentation with back pain.



Figure 3: Lateral radiograph showing vertebral crush fractures to T9 and T10 in 12 year old DMD patient.

Lumbar spine x-rays demonstrated marked osteopenia and stress fractures of his thoracic spine, with anterior wedging of the vertebrae T9 and T10 (Figure 3). Bone mineral scans were also undertaken. Interpretation of initial scans provided falsely high BMD results, as the DXA scan mode failed to take into account the patient's increased tissue depth due to his obesity, and his ischium and femoral neck were poorly positioned. Despite this, femoral neck BMD was very low: age adjusted Z-score -3.9, height adjusted Z-score -2.0 and weight adjusted

Z-score -4.8. These values met the International Society for Clinical Densitometry criteria for low BMD in children, which is a size adjusted Z-score of <-2.0. While the height and weight adjusted Z-scores of lumbar vertebrae BMD appeared normal at -1.2 and 1.0 respectively, the weight-adjusted Z-score was low at -2.3

Management of Bone Health in DMD

Current management of DMD bone health focuses on maximising bone mineralisation to prevent future fractures. Hence, it is important to ensure that dietary intake contains adequate calcium and is supplemented if necessary, and that adequate sunlight exposure is encouraged to maintain vitamin D levels. It is also recommended that patients receive a daily vitamin D supplement during corticosteroid therapy [48,63]. This has shown to be effective in treating vitamin D deficiency in DMD patients, with a study by Bianchi et al. [58] demonstrating that vitamin D supplementation over 2 years significantly increased mean 25-OHD levels from <50 nmol/L to well within the normal range. However, the optimum amount of supplementation has not yet been established due to the lack and variable design of studies in DMD patients. Similarly, while the importance of physical activity in improving bone health is understood, it is not completely known what the best level of activity is to prevent acceleration of muscle degeneration. It is currently recommended that exercise be submaximal, with care taken to avoid overexertion [48].

Bisphosphonates are the standard therapy used to treat osteoporosis in adults due to their ability to reduce bone resorption. Although they have not yet been established as safe in paediatric populations, protocols are now evolving for their use in children with DMD [51]. Studies in children suffering from osteoporosis have shown that intravenous bisphosphonates are well-tolerated except for transient first-dose side effects, and that they are associated with improved BMD and skeletal architecture but significantly decreased bone turnover [64,65]. It was also recently shown that the use of intravenous bisphosphonates to treat vertebral fractures in DMD was associated with significant improvements in back pain and vertebral height, although they do not completely protect from further vertebral fracture [66]. Hence, it is currently recommended that intravenous bisphosphonate infusions are only provided to DMD patients who have sustained a vertebral fracture [48].

The use of oral bisphosphonates as a treatment or preventative therapy in DMD remains controversial. A Cochrane review of bisphosphonate therapy for secondary osteoporosis in children concluded that while short-term (<3 years) bisphosphonate use appeared well-tolerated, bisphosphonates as standard therapy was not justified [67]. However, small studies in DMD patients have demonstrated mainly positive results. Hawker et al. [68] found that daily administration of the oral bisphosphonate alendronate in a group of steroid-treated DMD patients had positive effects on BMD, particularly amongst younger children. However, while no vertebral fractures were reported in the 2 year trial period, there was insufficient data in this study to draw conclusions about the effects of bisphosphonates on fracture risk. A recent study also demonstrated that bisphosphonate therapy was significantly associated with increased survival in children with DMD [69]. Bisphosphonate therapy hence appears promising, but further research is required to determine whether long-term bisphosphonate therapy in DMD is beneficial in reducing the risk of fractures and to investigate optimal doses and regimens.

Conclusion

Patients with DMD are predisposed to poor bone health, making them vulnerable to osteoporosis and fracture. It is therefore crucial to develop strategies which protect and optimise bone health in these patients. Despite increasing recognition of this, the assessment and management of bone health in DMD clearly remains a challenge. Many areas of uncertainty still exist, and the optimal management and treatment of bone health and its complications is not yet established. Addressing modifiable bone health determinants such as vitamin D levels has great potential to improve bone health in DMD patients, and is hence an area that would greatly benefit from further research.

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