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Growth, pubertal development, and skeletal health in boys with Duchenne Muscular Dystrophy

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Abstract

Purpose of review—Glucocorticoid therapy is currently the most widely used treatment for Duchenne muscular dystrophy (DMD), having consistently shown to prolong ambulation by 2 years, reduce the frequency of scoliosis, and improve cardiorespiratory function. Among the most frequent side effects of glucocorticoids are fractures due to osteoporosis, linear growth retardation or arrest, and pubertal delay, the subjects of this review.

Recent findings—The diagnosis of osteoporosis has shifted in recent years away from a bone mineral density-centric to a fracture-focused approach, with particular emphasis on early vertebral fracture identification (one of the key triggers for osteoporosis intervention). Delayed puberty should be addressed in an age-appropriate manner, with numerous options available for sex steroid replacement. Growth impairment, however, is a more challenging complication of glucocorticoid-treated DMD, one that is most likely best addressed through growth-sparing therapies that target the dystrophinopathy.

Summary—With glucocorticoid prescription an increasingly prevalent component of DMD care, early attention to management of osteoporosis and delayed puberty are important components of multidisciplinary and anticipatory care. The treatment of short stature remains controversial, with no accepted therapy currently available to over-ride the toxic effects of glucocorticoids on the growth axis.

Keywords

bisphosphonates; bone mineral density; Duchenne muscular dystrophy; growth; growth hormone; osteoporosis; puberty; testosterone; fractures

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Conflicts of interest

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INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder, occurring in 1 of 5 000 live male births [1]. Loss-of-function mutations in dystrophin cause progressive degeneration of skeletal and cardiac muscle so that untreated patients typically lose ambulation by 12 years of age, and succumb to respiratory insufficiency in the late second and third decades [2]. There is no cure for DMD; the only treatment that has consistently shown benefit is glucocorticoid therapy [3]. Glucocorticoids slow disease progression, prolong ambulation by 2 years [4,5], reduce the frequency of scoliosis, and improve cardiorespiratory function [6–9]. Many patients with DMD now live well into their 30 s on long-term glucocorticoids. Despite their benefits, glucocorticoids nevertheless hold a narrow therapeutic window, resulting in frequent side effects affecting numerous organ systems. Many boys with glucocorticoid-treated DMD develop a Cushingoid appearance, testament to the high and prolonged doses that are used to treat this condition.

Among the most frequent side effects of glucocorticoids, including those that are the most disconcerting to patients and families, are fractures due to osteoporosis, linear growth retardation or arrest, and pubertal delay. With multidisciplinary and anticipatory care, osteoporosis and pubertal delay can be effectively managed. Growth impairment, however, is a more challenging complication of glucocorticoid-treated DMD, one that will most likely only be addressed through growth-sparing therapies that specifically target the dystrophinopathy. In this review, we discuss what is known about growth, pubertal delay, and osteoporosis in glucocorticoid-treated DMD, including best practices for diagnosis, monitoring, and treatment, and the doors that are open for improved approaches in the future.

SHORT STATURE

Reduced growth and short stature are common clinical manifestations of DMD even in the absence of glucocorticoid therapy. Natural history studies performed in glucocorticoid-naïve DMD populations have shown that slow growth is apparent early in the disease course, and that final adult height is reduced by approximately one standard deviation (SD) score relative to the healthy average [2,10–12,13]. Growth failure is magnified by the high glucocorticoid doses used to treat DMD, and is one of the most commonly reported glucocorticoid-related side effects [14]. Short stature can be emotionally distressing to patients, to the point that there are concerns it may contribute to diminished quality of life [15] and affect child and caregiver decisions regarding choice of glucocorticoid regimen and adherence to therapy [16]. A representative growth curve of a boy with glucocorticoid-treated DMD and growth failure is shown in Fig. 1.

The degree of growth failure has varied widely among reports and appears to be influenced by duration of glucocorticoid therapy, dosing regimen (daily versus intermittent), and specific agent (prednisone vs. deflazacort). At one center, 40 boys treated with daily deflazacort for an average of 5.5 years were shorter by an average of 10 cm at 18 years of age compared to a matched glucocorticoid-naïve group [8]. Another center reported that the prevalence of short stature (height <3rd percentile) climbed from less than 10% of the 97

boy cohort prior to glucocorticoid initiation, to 72% following 8.5 years of daily glucocorticoid therapy [16[■]]. Both observational and clinical trial data have shown that daily glucocorticoid regimens resulted in greater growth impairment compared to intermittent dosing [17[■],18]. A natural history study that analyzed the clinical outcomes of subjects on 14 different glucocorticoid regimens found that growth delay was more commonly reported in subjects on deflazacort compared to prednisone [19].

Mechanisms of impaired growth

The mechanisms underlying DMD-related growth failure are unclear. Both circulating levels of growth factors and skeletal maturation during childhood have been normal [10,20]. Studies that reported the growth hormone (GH) response to provocative testing were not in line with a primary defect in GH secretion, although mild deficits in peak GH levels were observed in some subjects [21,22]. Emerging data suggest a possible link between the dystrophin genotype and growth. Two recent studies reported that growth was more severely impaired in subjects with mutations in the distal segment of the dystrophin gene, mutations that were predicted to alter the expression of the Dp71 isoform [12,13[■]]. The mechanism by which altered Dp71 expression may contribute to growth failure is not known, as this isoform is not present in fully differentiated skeletal muscle [23].

The growth suppressive effects of glucocorticoids are complex and multifactorial [24]. The primary detrimental effect of glucocorticoid exposure on growth appears to be growth plate toxicity. Glucocorticoids are suspected to impair growth plate activity via inhibition of chondrocyte and osteoblast differentiation [25], induction of chondrocyte and osteoblast apoptosis [26], and disruption in the local production of paracrine hormones including insulin-like growth factor 1 (IGF-1) and C-type natriuretic peptide [27,28]. The GH-IGF-1 axis is also disrupted by glucocorticoid excess, characterized by impaired GH secretion and increased peripheral resistance to both GH and IGF-1 [29,30]. Disrupted GH secretion has been shown in patients with glucocorticoid-treated DMD, as evidenced by a study in which 45% of subjects had peak stimulated GH levels < 7 ng/ml [31].

Treatment of short stature

The use of recombinant human (rh)GH to treat short stature in DMD is controversial. The anticipated benefit of exogenous GH in the setting of ongoing glucocorticoid-mediated growth plate toxicity is unclear and there are theoretical concerns that rapid growth or tall stature may worsen muscle function in DMD [32,33]. Insulin resistance is common in boys with DMD [16[■],34], and could progress with rhGH therapy. There have been no randomized, controlled trials evaluating the safety and efficacy of rhGH to promote growth in DMD. The largest report of rhGH included 39 boys with DMD on daily glucocorticoid therapy [31]. Growth velocity increased from 1.3 cm/year pretreatment to 5.2 cm/year over 12 months. No detrimental effects on neuromuscular function were observed; however, suspected rhGH-related side effects included insulin resistance in two boys and increased intracranial hypertension in one boy. rhGH was reported to be well tolerated in an RCT investigating its use to improve cardiac output; however, growth outcomes were not reported [35].

The published literature suggests significant variability in the use of rhGH in clinical practice. A review of data from 683 boys with DMD living in five regions of the United States reported that 1.9% of subjects had been treated with rhGH [36[■]]. This is in contrast to a single-center report where 37% of subjects on daily glucocorticoid therapy had received rhGH [16[■]]. In the absence of robust safety and efficacy data, current guidelines do not recommend the routine use of rhGH in the DMD population [37[■]]. The recommendations do note, however, that growth should be monitored closely until attainment of final height, and they allow for rhGH therapy to be considered on a case-by-case basis [37[■],38].

DELAYED PUBERTY

Hypogonadotropic hypogonadism is another common endocrine abnormality encountered in the management of DMD. Observational studies have consistently reported that the majority of adolescents with DMD on daily high-dose glucocorticoid therapy have delayed or absent puberty [31,39,40]. Unlike growth, pubertal development does not appear to be affected in the absence of glucocorticoid use. Similar to short stature, delayed pubertal maturation may adversely affect self-esteem and impair quality of life during adolescence. Prolonged testosterone deficiency may additionally have negative implications for bone strength, cardiovascular health, and cognitive development, although these associations have not been formally investigated in DMD.

Treatment of delayed puberty

Testosterone replacement is specifically recommended for the treatment of glucocorticoid-induced hypogonadotropic hypogonadism in adults [41] and has been shown to increase lean body mass in adults with other forms of muscular dystrophy [42], but has not been well studied in DMD. There have been no RCTs investigating the safety and efficacy of testosterone for any indication in patients with DMD [43[■]], and published clinical experience is currently limited to a single center review of 14 boys treated with testosterone for pubertal delay [44]. In that cohort, growth velocity increased and therapy was reported to be well liked by subjects; side effects were minor and consistent with known effects of testosterone [44].

Current guidelines recommend that all boys with DMD undergo close monitoring for pubertal development and that testosterone therapy should be initiated by age 14 years in those with confirmed hypogonadism [37[■]]. This recommendation was based upon the wealth of clinical experience supporting the use of testosterone to manage hypogonadism in other populations, and the perception of an international expert panel of a favorable benefit-to-risk ratio in boys with DMD. There were insufficient data to support the choice of one testosterone preparation over another; however, it was recommended that therapy be started at a low dose and increased slowly to adult levels over a few years. Currently it is not known whether testosterone requirements will be lifelong in some patients, or whether a short course of testosterone during adolescence will be the bridge to normal endogenous production through adulthood. The recommended clinical approach to growth failure and delayed puberty in boys with DMD is outlined in Fig. 2.

SKELETAL HEALTH AND OSTEOPOROSIS

Bone health monitoring and diagnosis of osteoporosis in Duchenne muscular dystrophy

Up to 60% of boys with DMD will have low-trauma extremity fractures even without glucocorticoid therapy [16[■],17[■],45–47,48[■]], a risk that is doubled when receiving glucocorticoid treatment [46]. In addition, as many as 50% of boys with glucocorticoid-treated DMD will have symptomatic vertebral fractures [46,49[■]]; the true vertebral fracture prevalence may be even higher, because vertebral fractures are frequently asymptomatic, especially in their earlier phases of development. As a result, vertebral fractures frequently go undetected in the absence of monitoring with periodic spine radiographs [48[■],50–53]. In children, including in boys with DMD, vertebral fractures are most frequent in the mid-thoracic region and the upper lumbar spine [54,55]. Lumbar fractures are an additional osteoporosis feature in DMD [55], hypothesized to result from the exaggerated lumbar lordosis typical of this condition.

Vertebral fractures are more severe at first identification if boys have not been monitored with periodic spine radiographs during the asymptomatic phase [48[■]]. To identify the earliest signs of vertebral fractures, recent guidance encourages periodic lateral thoracolumbar spine radiographs starting around the time of diagnosis or glucocorticoid initiation, followed by spine radiographs every 1 to 2 years for those on glucocorticoids, and every 2 to 3 years for glucocorticoid-naïve boys or those who have stopped glucocorticoid therapy [56[■]]. Spine x-rays should be carried out sooner if there is back pain or a decline in spine bone mineral density (BMD) Z-score by at least 0.5 SD in a 12-month period. For vertebral fracture detection, the Genant semiquantitative method is now recognized as a valid method in children, given numerous pediatric studies showing that the Genant method for vertebral fracture identification is associated with biologically logical vertebral fracture predictors including a history of prior vertebral fractures, low or declining spine BMD Z-scores, and back pain [52,53,57]. Overall, these recommendations are in line with the move away in recent years from a BMD-centric to a more fracture-focused diagnostic approach to osteoporosis in children [58[■],59].

Vertebral fractures can occur as early as 6 months following glucocorticoid initiation (on average between 2–3 years) in DMD when monitored with routine spine radiographs from the time of glucocorticoid initiation [48[■]]. Untreated, vertebral fractures are linked to chronic back pain and spine deformity [48[■]], whereas leg fractures can cause permanent, premature loss of ambulation and challenges in daily care for those in wheelchairs [45]. Death because of fat embolism syndrome after long bone injuries has also been reported [60,61]. Osteoporosis treatment with bisphosphonates has been linked to survival [62], an observation which provides further rationale for effective osteoporosis diagnosis, surveillance, and treatment strategies. Because vertebral fractures typically do not undergo reshaping in the DMD setting, the importance of early identification and treatment in order to prevent the ‘vertebral fracture cascade’ is further underscored [56[■]].

Studies have shown that total body BMD Z-scores decline early in the course of the disease [63[■]], whereas spine BMD declines more significantly once ambulation is lost [63[■]]; both are adversely impacted by glucocorticoid exposure [55]. With solidification of

glucocorticoid exposure in the care plan of patients with DMD, attention has now turned to the relative effects of different glucocorticoid regimens on various organ systems, including bone strength and growth. Crabtree *et al.* [17[■]] recently showed that there was a trend for boys on daily glucocorticoids to retain ambulation longer than boys on intermittent glucocorticoids, but at the cost of more frequent vertebral fractures, increases in body mass index Z-scores and reductions in height Z-scores.

In view of these collective observations, the international consortium of experts in DMD and skeletal health that informed the recent Centres for Disease Control (CDC) guidances concluded that bone morbidity was sufficiently high in DMD to warrant early identification and intervention, and that trials are now needed to investigate strategies for the prevention of first-ever fractures in pediatric DMD [56[■]]. As a first step, boys with DMD are diagnosed with osteoporosis in the presence of at least one low-trauma long bone or vertebral fracture, which in turn triggers consideration for osteoporosis therapy [56[■]]. Given the high risk of fractures in DMD, the international CDC consortium concluded it was not necessary to await multiple long bone fractures by a certain age before diagnosing osteoporosis, in contrast to the suggestion by the International Society for Clinical Densitometry that two or more long bone fractures by age 10 or three or more long bone fractures by age 19 are required before diagnosing a child with osteoporosis [59].

Prevention and treatment of osteoporosis: standards of care and emerging therapy

To date, there are no drug trials that have been adequately powered to assess the prevention of first-fractures in DMD, despite the need. Therefore, the management of osteoporosis follows principles of secondary prevention that are applicable to any child with risk factors for bone fragility, including timely identification of vertebral fractures with periodic spine radiographs and integration of bone pain and fracture histories into routine care [58[■]]. With this approach, boys will be referred to an osteoporosis expert at the first sign of low-trauma fractures in order to discuss initiation of osteoporosis treatment. Osteoporosis therapy falls into two broad categories—antiresorptive and anabolic treatment.

The current standard of care for the first-line treatment of fragility fractures in childhood including DMD is intravenous (IV) bisphosphonate therapy (pamidronate, zoledronic acid, and neridronate). Neridronate is only available and approved for use in children with osteogenesis imperfecta in Italy, whereas zoledronic acid and pamidronate are prescribed off-label the world over) [58[■]]. Oral bisphosphonate therapy during childhood is not recommended because of data from controlled trials in pediatric osteogenesis imperfecta showing improvements in the height of vertebral bodies with IV bisphosphonate therapy [64–66], but not with oral agents [67–69]. These observations are likely influenced by the relatively low bioavailability of oral agents [70]. The lack of improvement in vertebral height with oral bisphosphonates is highly relevant to DMD where the frequency of vertebral fractures is high. Degrees of vertebral body reshaping following IV bisphosphonate therapy have been described in pediatric DMD [55], a phenomenon which is growth-dependent and thereby limited by both the patient's growth velocity and residual growth potential. Early treatment of vertebral fractures is paramount to maintaining the structural integrity of vertebral bodies as far as possible in DMD, because intervention that starts once

there are more advanced stages of vertebral collapse may be unable to prevent further loss of vertebral height in some cases [55]. Bisphosphonates should be prescribed by an expert knowledgeable in the potential side effects and their management, contraindications and appropriate dosing regimens, all of which have been reviewed in detail elsewhere [56[■], 58[■],71[■]]. The overall approach to bisphosphonate administration in DMD is summarized in Fig. 3.

Denosumab is a newer antiresorptive agent that targets RANKL to prevent the activation of RANK, thereby inhibiting bone resorption [72]. Denosumab is approved in Canada and the United States for postmenopausal women and osteoporotic men with a high risk for fracture, and for adults with glucocorticoid-induced osteoporosis [73]. Denosumab is particularly interesting in DMD, given observations that RANKL activation is implicated in the inflammatory pathway arising from the dystrophinopathy [74[■]].

To date, denosumab has been used on compassionate grounds in children with osteogenesis imperfecta [75,76], giant cell tumors [77], aneurysmal bone cysts [78], fibrous dysplasia [79], and in a 13-year-old boy with DMD [80[■]]. Although lumbar spine BMD increased significantly following 18 months of denosumab and the drug was well tolerated in this boy [80[■]], this study raises concern about one of the known precautions of denosumab – break-through re-activation of bone turnover markers on six monthly denosumab. As a monoclonal antibody, denosumab's effect is much shorter than bisphosphonates, with cessation resulting in rebound of bone turnover markers, declines in BMD, and even increases in vertebral fractures (the rebound phenomenon) in women with postmenopausal osteoporosis [81,82[■]]. These observations appear to result from re-activation of osteoclasts in the face of denosumab's waning effect. Osteoclast re-activation has even been clinically evident between serial denosumab doses in children with osteogenesis imperfecta, resulting in overt hypercalcemia and hypercalciuria [83[■]]. The rebound phenomenon is an important consideration for any patient embarking on the use of denosumab. Currently off-label for the treatment of glucocorticoid-induced osteoporosis in children, denosumab requires further study in the DMD setting.

Teriparatide – recombinant human PTH (1–34) – is approved by the Food and Drug Administration for initial treatment of women with postmenopausal osteoporosis who are at high risk of fracture or who have failed prior osteoporosis therapy, and for glucocorticoid-associated osteoporosis [84]. DMD is a compelling clinical scenario for osteoanabolic therapy such as teriparatide, since bone turnover on trabecular surfaces is reduced in boys with DMD even prior to bisphosphonate therapy, falling dramatically to 10% of the healthy average after 2 years of pamidronate or zoledronic acid when given to treat painful vertebral fractures [55,85[■]]. Unfortunately, this anabolic agent has a black box warning against its use in children because of the observation of osteosarcoma in growing rats treated with doses three to 50 times higher than the adult human equivalent and for much longer durations [86]. A recent case report of teriparatide in a 20-year-old male with DMD described complete resolution of vertebral fracture-induced back pain following 6 months of therapy, along with increases in lumbar spine BMD, in bone biomarkers and improved quality of life [87[■]]. It should be noted, however, that the effect of PTH on bone appears to be blunted in adults when administered following bisphosphonate therapy [88], an observation which may be a

limiting factor in adults with DMD who received bisphosphonates as children. Like denosumab, teriparatide warrants further study in DMD, in this case restricted to the postpediatric population.

CONCLUSION AND FUTURE DIRECTIONS

Although glucocorticoids are the current mainstay of DMD treatment, this class of drugs nevertheless hold a narrow therapeutic window, a fact that behooves prescribing clinicians to carefully monitor and treat myriad glucocorticoid-related side effects. Although the treatment of delayed puberty and osteoporosis in DMD are now formally integrated into routine clinical care [71■■,89■■], short stature in this setting remains an unresolved issue, one that is likely best-targeted by glucocorticoid-sparing therapies [89■■]. Further studies are needed to determine the optimal timing of pubertal induction for those with delayed physical maturation, the relative benefits and risks of growth-promoting therapy to mitigate glucocorticoid-induced short stature, and the prevention of first-fractures in DMD.

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KEY POINTS

- Through multidisciplinary and anticipatory care, osteoporosis and delayed puberty due to glucocorticoid therapy in DMD can be effectively managed.
- The diagnosis of osteoporosis in DMD has shifted away from a bone mineral density-centric to a fracture-focused approach. Vertebral fractures are key signs of bone fragility that, like low-trauma long bone fractures, signal a need for osteoporosis treatment.
- Monitoring for vertebral fractures should begin around the time of diagnosis, and no later than the time of glucocorticoid initiation.
- Intravenous rather than oral bisphosphonates are preferred as first-line treatment for osteoporosis in DMD, given the lack of evidence for efficacy with oral agents at the fracture-prone spine in numerous clinical trials targeting pediatric osteoporotic diseases.
- While delayed puberty can be effectively managed with sex steroid replacement, to date the treatment of short stature remains controversial, with no accepted therapy currently available to over-ride the toxic effects of glucocorticoids on the growth axis.

FIGURE 1.

A representative growth curve of a boy with glucocorticoid-treated Duchenne muscular dystrophy (DMD) and growth failure.

	Growth Failure	Pubertal Delay
Surveillance	- Assess height every 6 months until pubertal completion - Ambulatory: standing height - Non-ambulatory: ulnar length or other measure - Evidence of growth failure should prompt referral to endocrinologist and includes: - Downward crossing of height percentile - Height velocity < 4 cm/yr - Height < 3rd percentile	- Assess puberty by Tanner Stage every 6 months starting by age 9 years - Absence of pubertal changes (testicular volume ≥ 4 cm³) by age 14 years should prompt referral to endocrinologist
Evaluation	- Recommended for all boys with growth failure: - Bone age X-ray of L hand - Labs: thyroid function tests, celiac panel, growth factors, comprehensive metabolic panel, complete blood count - Growth hormone stimulation testing to be considered with severe growth failure	- Recommended for all boys with delayed puberty: - Labs: luteinizing and follicle stimulating hormone and testosterone (using appropriate pediatric assay) - Bone age X-ray of L hand to be considered if will guide management
Therapy	- Growth hormone therapy is not recommended for routine use - Can be considered on case-by-case basis after discussion of risks and benefits	- Testosterone replacement is recommended for all boys ≥ 14 years with confirmed hypogonadism - Can be considered starting at 12 years - Initiate at low dose and slowly increase
Monitoring	- Regular visits to assess clinical progress and evaluate for side effects - Annual + PRN testing of glycemic status with hemoglobin A1c and/or blood/urine glucose	- Regular visits to assess clinical progress and evaluate for side effects - Monitor testosterone levels to adjust dose, target mid-normal range on full replacement - Consider annual testing of blood counts, lipids

FIGURE 2.

The recommended clinical approach to growth failure and delayed puberty in boys with DMD.

FIGURE 3.

The approach to the diagnosis and treatment of osteoporosis in boys with Duchenne muscular dystrophy (DMD). Reproduced with permission from [56].