Clinical Research on Foot & Ankle

Review Article Open Access

Clinical Recommendations to Improve Bone Health in Children with Duchenne Muscular Dystrophy

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Abstract

The X-linked recessive disease Duchenne muscular dystrophy (DMD) causes progressive muscle weakness that leads to eventual loss of ambulation and early death. Enhancing muscle strength, extending ambulation, and maintaining pulmonary function are all benefits of the approved corticosteroid therapy. However, the chronic use of corticosteroids has an osteoporotic effect that worsens the DMD-related reduced bone mass and increases the risk of long bone and vertebral fragility fractures. These severe consequences can have an impact on survival and negatively affect quality of life. This analysis discusses the current clinical concerns around bone health and approaches for bone health screening in DMD. Diagnostic procedures, such as dual energy X-ray absorptiometry (DXA), densitometric lateral spinal imaging, and biochemical markers of bone turnover and bone mineral density, as well as therapies to improve bone health in DMD patients, are reviewed. Bisphosphonate therapy offers a way to boost these kids' bone mass; both oral and intravenous bisphosphonates have been used successfully, though therapy is normally saved for kids with fractures and/or bone pain who have low bone mass according to DXA.

Keywords: Duchenne Muscular Dystrophy; Corticosteroid; Spinal Imaging; Bone Mass

Introduction

One of the dystrophinopathies, Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by mutations in the dystrophin gene, which codes for the dystrophin protein. A lack of dystrophin, a protein that maintains the cytoskeleton and extracellular matrix, outcomes from this mutation. Dystrophin depletion causes cell membrane instability, which causes myofiber necrosis and gradual muscular weakening. It is the most prevalent and severe type of muscular dystrophy, affecting roughly 1 in 3,500–5,000 males. DMD symptoms typically appear between the ages of 3 and 5 years. Early signs frequently involve a delayed onset of walking, toe walking, and/or a waddling stride. The level of serum creatine kinase (CK) is frequently 50–100 times higher than normal. In the past, ambulation was lost between the ages of 7 and 12 and people died by the end of the second decade [**1**]. Nearly 90% of the time, DMD is brought on by mutations that shorten the reading frame, preventing the expression of dystrophin.

Prior to receiving corticosteroid therapy, muscle weakness in DMD patients would undoubtedly worsen, resulting in these boys being nonambulatory at the beginning of their second decade of life and eventually needing breathing support. Prednisone and deflazacort, a prednisolone oxazolone derivative, are two corticosteroids frequently used to treat DMD. Five recently published, long-term controlled nonrandomized trials with prednisone or deflazacort (now extending beyond 3 years) showed that, with either drug, patients retain muscle function longer, ambulate 2 to 5 years longer, need less spinal stabilisation surgery, have a delayed need for noninvasive ventilation, and have less cardiac dysfunction than boys who are not receiving corticosteroid therapy [**2-5**].

According to a report released in 2010, corticosteroid medication and better supportive care for cardiopulmonary condition have increased survival in DMD from an average of 14.4 years in the 1960s to an average of 24.7 years. The beneficial effects of corticosteroids in DMD are thought to be caused by their strong anti-inflammatory activity, which lowers the inflammatory response in dystrophin-deficient muscle, delays the loss of muscle strength, and prolongs the ability to walk compared to boys not receiving corticosteroid therapy [**6**].

Regrettably, this treatment has a number of side effects, including detrimental effects on bone health such reduced bone mass and fractures due to bone fragility. The reader is directed to recent reviews for a more thorough discussion of corticosteroid therapy regarding timing of initiation, treatment after loss of ambulation, as well as the mechanism of corticosteroids, and other treatments in DMD. In this review, we outline the current threats to bone health, as well as the screening tools, research on the causes of bone problems, and approaches for treating DMD patients' poor bone health [**7**].

Health Risks for Bones [8]

The decline in bone health observed in DMD patients can be attributed to a variety of pathophysiological processes. The following mechanisms can affect a child with DMD's bone health: progressive muscular, effects of the cytokines generated as a Outcomes of the inflammatory response in muscles lacking dystrophin. Numerous factors are present in many individuals, and corticosteroid medication is linked to additional risk factors for weak bones. Genetic influences on inadequate bone mineralization or excessive bone mineral loss have not been investigated.

Mineral Density of Bone [9]

Additionally, they demonstrated that BMD was lower in DMD boys overall and at the spine compared to normal control patients, but no discernible difference was found in the spine-scores after adjusting

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Received: 1-Nov-2022, Manuscript No: crfa-22-81304, **Editor assigned:** 8-Nov-2022, PreQC No: crfa-22-81304 (PQ), **Reviewed:** 16-Nov-2022, QC No: crfa-22-81304, **Revised:** 21-Nov-2022, Manuscript No: crfa-22-81304 (R), **Published:** 30-Nov-2022, DOI: 10.4172/2329-910X.1000378

Citation: Jawn L (2022) Clinical Recommendations to Improve Bone Health in Children with Duchenne Muscular Dystrophy. Clin Res Foot Ankle, 10: 378.

for body surface area and vertebral volume followed 39 DMD boys on deflazacort therapy for roughly 8 years and found that there was a decline in the age-adjusted BMD score within the first 2 years of starting deflazacort (p0.05), with a consistent decline thereafter; in those who lost ambulation, the decline was greater. Height-adjusted BMD scores were less compromised in this population than age-based scores. Since children on corticosteroids tend to be short, this may reflect better bone health than what is expected in these DMD boys on corticosteroids.

Bone Fracture [10]

In DMD patients on steroids compared to steroid-free patients, long bone fractures occurred 2.6 times more frequently. Additionally, there were no vertebral fractures in the steroid-naive group, whereas 32% of those in the steroid-treated group did. About 20 to 25 percent of DMD patients experience long bone fractures, and those in the lower extremities frequently cause the development of a lifelong loss of mobility. Immobility, such as using a wheelchair continuously, can worsen bone demineralization, which in turn increases the risk of fracture.

Imperfect Osteogenesis

The incidence of osteogenesis imperfecta, a rare genetic condition, is about 1 in 25,000. Low bone mass, frequent fractures, deformed bones, short height, wormian bones, blue sclerae, hypermobility of joints, dentinogenesis imperfecta, and deafness are some of the clinical symptoms. According to the clinical severity, osteogenesis imperfecta comes in 5 different forms. Type 1 is the least severe and nondeforming; type 2 is fatal in the perinatal period due to respiratory insufficiency caused by multiple rib fractures; type 3 is associated with limb deformities and is progressively deforming; type 4 has an intermediate phenotype between types 1 and 3; and type 5 has a phenotype similar to that of type 4 but is linked to calcification of interosseous membranes and hypertrophic callus formation at healing fracture sites.

Juvenile Osteoporosis Idiopathic

The cause of idiopathic juvenile osteoporosis is unknown, but it is thought to have a genetically diverse aetiology. When girls or boys between the ages of 8 and 12 are affected, there may be minor damage and bone soreness. With varying remaining signs, symptom severity typically decreases on its own. differentiation between idiopathic juvenile disease and osteogenesis imperfect.

Prudent Management to Improve Bone Health

Nutrition, exercise, lifestyle, body weight, lean body mass, and hormone status are all modifiable factors that affect bone mass. To improve bone health, these conditions should be well maintained. Numerous studies have shown that giving children calcium and vitamin D supplements can help them develop more bone mass and BMD. In healthy youngsters, food should be used as a complement to these nutritional needs rather than medication. Calcium and vitamin D can be found in large quantities in a variety of foods. Healthy newborns should get most of their calcium from human milk or infant formula during their first year of life, and after that, they should primarily get it from milk and other dairy products. Other dietary sources include cereal, fruit juices, legumes, nuts, and green leafy vegetables. However, due to binding with oxalate in spinach, collard greens, and beans as well as with phytate in whole bran cereals, the bioavailability of calcium from vegetables is generally low. Weight-bearing exercises and mechanical forces on the skeleton both promote bone formation and mineral deposition. Children in good health can increase their femoral neck BMD by engaging in high-impact, low-frequency exercises like hopping, skipping, and jumping for 10 minutes three times per week. Walking, jogging, jumping, and dancing are weight-bearing exercises that are preferable to non-weight-bearing exercises like swimming or bicycling. Fast food, alcohol, caffeine, and smoking should all be avoided because they can all contribute to bone loss. Additionally, sedentary behaviours such as prolonged TV viewing, online gaming, and cell phone usage are detrimental to bone density. While excess glucocorticoids stimulate bone resorption, excess oestrogen, testosterone, growth hormone, and IGF-I can encourage bone production. Therefore, it is important to carefully analyse and manage the bone mineral depositions in kids with endocrine diseases such hypogonadism, Turner syndrome, GH insufficiency, and Cushing syndrome. In most healthy teenagers, body mass index and lean body mass are positively correlated with BMD; conversely, higher adiposity can be associated with an increased fracture risk.

Discussion

Denosumab and recombinant parathyroid hormone are two potential treatments for low bone density that haven't been examined in DMD patients. Denosumab is a human monoclonal antibody that fights nuclear factor-B ligand receptor activator. Less bone resorption happens when RANKL is inhibited, which outcomes in a drop in osteoclast activity and number. Several kids with osteogenesis imperfecta type VI as well as a child with Paget's disease have received denosumab treatment. Recombinant PTH r is another potential therapy. Teriparatide was utilised to raise BMD in a 19-year-old patient with osteoporosis pseudoglioma. Ataluren, a molecule that binds with ribosomes and may permit the insertion of an amino acid in the premature termination codon, and exon-skipping, a molecule that binds with ribonucleic acid (RNA) and excludes specific sites of RNA splicing, are two new treatments (for DMD in general) currently being studied in clinical settings. Studies are also being conducted to see if DMD symptoms can be mitigated by altering the levels of other muscular proteins like myostatin and utrophin. The treatment of DMD's muscle and bone metabolism may potentially use melatonin. The dystrophic mdx5Cv animal model for DMD showed increased muscular function after receiving intraperitoneal injections and subcutaneous implants of melatonin. This enhanced function may be attributable to melatonin's capacity to normalise proinflammatory cytokines, such as interleukin (IL-) 1 (IL-), IL-2 (IL-6), tumour necrosis factor (TNF), and interferon (IFN), as well as to lessen oxidative stress. Alizarin red S staining of mouse osteoblastic MC3T3-E1 cells in melatonin-cultured media revealed enhanced differentiation and mineralization. Pharmacological doses of melatonin produced a 36% increase in BMD (p0.05) in ddy mice, probably by lowering RANKL. Prior to widespread use, the advantages for muscle function and BMD in DMD patients need to be specifically studied.

Conclusion

Patients with DMD who have poor bone health should pay close attention because it can lead to a loss of ambulation, have a negative influence on quality of life, and even shorten life expectancy. The care of bone health in DMD patients requires the development of evidence-based practise guidelines. In all DMD patients, especially those receiving corticosteroid therapy, routine screening for vitamin D deficiency/sufficiency and low bone mass should be sought while maintaining adequate vitamin D and calcium intake. The timing of the first bone density test, the clinical utility of biochemical markers of bone turnover, and the accuracy of bone quality assessment using more modern imaging techniques like vertebral morphometry by DXA,

peripheral quantitative computed tomography, and micromagnetic resonance imaging are all areas that require further research. More research is needed to confirm the advantages of early vibration therapy for bone health improvement as shown in other neuromuscular illnesses. However, prospective randomised controlled studies with long-term follow-up are required to demonstrate the antifracture efficacy and safety of bisphosphonates, which have generally been advised to treat bone fragility. There should be further research into the effects of teriparatide, melatonin, or denosumab on BMD and fracture risk in this patient population. In both girls and boys, bone mineral deposition increases most during the pubertal stage and can significantly affect BMD in later life. Therefore, to ensure the best possible bone health in children and adolescents, modifiable determinants of bone mass, such as diet, exercise, lifestyle, body weight, lean body mass, and hormonal status, should be adequately maintained. Osteoporosis is defined differently in youngsters than it is in adults. Prior to considering conservative and pharmaceutical treatments for juvenile patients with primary or secondary osteoporosis, underlying problems should be treated.

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