SCOTTISH MUSCLE NETWORK PATHWAY FOR BONE HEALTH MONITORING

Summary of bone morbidity in boys with DMD

The key aspects are as follows:

• The high fracture incidence in DMD, ranging from 20 - 40 % is well recognised. (1,2) With long-term glucocorticoid use in extended non-randomised studies, a high incidence of vertebral fractures has been reported (3). In patients not treated with glucocorticoids, these fractures are almost exclusively in the limbs and spare the vertebrae. Current fracture studies in DMD only report symptomatic vertebral fractures (VF). Current studies of symptomatic vertebral fractures in DMD suggest that they can present as early as two years after initiation of glucocorticoid. Studies, where systematic screening of the spine with x-ray was carried out in other groups of children with chronic disease (e.g., ALL, inflammatory rheumatic conditions, nephrotic syndrome treated with glucocorticoids, show a high incidence of asymptomatic vertebral fractures (4). It is very likely that the incidence of vertebral fractures is, therefore, higher in DMD, and results from the ScOT-DMD study will clarify this issue.

• Several published studies have demonstrated that in boys with DMD, the bone mineral density (BMD) as measured by DXA scanning is lower(5-10). Low BMD can also exist before the introduction of glucocorticoid, which might reflect the poor muscle function and low-grade chronic inflammatory state on bone development (11).

• The recent position statement by the ISCD (2013) emphasises that osteoporosis in childhood should not be diagnosed by densitometry findings alone. Osteoporosis in childhood is defined by the presence of clinically significant fracture history accompanied by a low DXA BMD Z-score ≤ -2.0, although it also recognises that BMD may be within normal limits in children with pathological fractures. A clinically significant fracture history is defined as either ≥ two long bone fractures by ten years old or ≥3 long bone fractures at any age up to 19 years old. The finding of ≥1 VF irrespective of densitometry z-score is indicative of osteoporosis, which emphasizes the importance of detecting VF(12).

• There are pitfalls of DXA scanning (13). The interpretation of DXA bone density z-scores using appropriate paediatric normative data is crucial. DXA bone mass results in boys with DMD need to be size corrected (e.g., height, bone age, bone area, lean mass, etc.). The current ISCD (2013) guidance recommends size adjusted DXA parameters for height although other methods may be appropriate and indeed necessary especially in non-ambulant boys with DMD (14).

• At present, in the paediatric age group, the precise correlation /threshold (if any) of bone density z-scores and risk of vertebral fractures is not known. There is a poor correlation between DXA BMD and fracture occurrence in children with chronic disease (15). Serial DXA scans in an individual patient can identify trends of change, and may be used to monitor the effect of specific treatment. An “abnormal” DXA scan in the absence of pathological fracture is not an indication to commence bone protective therapies but should prompt a careful evaluation of possible pathological fractures (i.e. evaluation of the spine).

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• In patients on glucocorticoid treatment, there is no evidence base to demonstrate prevention of osteoporosis/fractures with the routine use of calcium or Vitamin D. (This will obviously not apply to the individual patient who is calcium or Vitamin D deficient). Vitamin D and calcium affect the mineralizing of bones, whereas other risk factors like glucocorticoid, immobility, poor growth, and hypogonadism play a bigger role in the acquisition of bone mass and bone geometry. However, given the severe and irreversible threats to skeletal health in boys with DMD, it is good clinical practice to optimise vitamin D levels and ensure adequate calcium intake.

• There is not enough paediatric data to support the routine prophylactic use of bisphosphonate in boys with DMD on glucocorticoids. Boys with DMD treated with glucocorticoid have reduced bone turnover due to the effect of glucocorticoid on bone growth such that bone formation and bone resorption are both reduced (10). Treatment with bisphosphonate as prophylactic therapy in DMD, therefore, may not be physiological as published data shows that bone turnover is further suppressed with bisphosphonate therapy (16).

• Symptomatic vertebral/pathological fractures can be treated effectively with IV bisphosphonate treatment. It does not, however, prevent new fractures, although vertebral reconstitution and improvement in bone mass may be seen in some, more likely in those who are younger and have good linear growth (17). Therefore, this supports a case for an early identification of vertebral fracture. Hence, this new guidance recommends early detection of vertebral abnormalities.

• Blood tests should be performed for the bone profile, 25-hydroxy Vitamin D, Parathyroid Hormone (PTH) before starting glucocorticoid and then annually. All boys commencing glucocorticoid should receive vitamin D replacement (600-1200 IU) depending on local availability of preparation. The aim is to keep vitamin D levels ≥ 50 nmol/L.

• DXA with lateral vertebral morphometry or DXA and lateral thoracolumbar spine x-ray should be performed just before starting glucocorticoid. DXA should be repeated annually, and lateral thoracolumbar spine x-ray should be repeated every two years to allow early identification of vertebral compression fractures.

• Bone age assessment should be done once from age 13 years onwards. Pubertal assessment with the examination of the testicular volume is also recommended although challenging. Boys with bone age delay of > 3 years and those with delayed puberty should be referred to paediatric endocrinology for further assessment. Sex steroid contributes to bone accrual, and it is crucial that the pubertal delay is addressed.

• Boys with evidence of delayed puberty will require testosterone replacement therapy and should be managed jointly with the paediatric endocrinologist. Testosterone therapy for delayed/absent puberty should be considered from age 14 years. Preliminary data suggest that young men with DMD have persistent hypogonadism requiring testosterone therapy even in adulthood (18).
References


12) ISCD (The International Society for Clinical Densitometry). 2013 ISCD official position brochure.


14) Crabtree NJ, Hogler W, Cooper MS, Shaw NJ. Diagnostic evaluation of bone densitometric size adjustment techniques in children with and without low trauma fractures. SC Wong, SF Ahmed, A Mason, S Joseph
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This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient’s case notes at the time the relevant decision is taken.