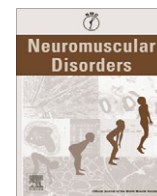




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Workshop report

170th ENMC International Workshop: Bone protection for corticosteroid treated Duchenne muscular dystrophy. 27–29 November 2009, Naarden, The Netherlands

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1. Introduction

The first ENMC workshop for bone protection in DMD patients treated with corticosteroids included 18 participants from Europe, USA and Canada. The participants were from diverse backgrounds including Paediatric Neurology, Endocrinology, Metabolic bone disease, Orthopaedics and Medical Physics. The objectives of the workshop were to discuss the problem of vertebral fractures with the following aims:

1. What is the prevalence of vertebral fractures in this population?
2. How are vertebral fractures defined and identified?
3. What is the predictive ability of DXA for vertebral fractures?
4. What interventions can be used to protect the skeleton and when should they start?

Two independent workshop reports on bone health in Duchenne muscular dystrophy (DMD) were previously published in 2004. Their conclusions were that children with DMD treated with corticosteroids should have bone mineral density (BMD) assessed every 1–2 years with Dual Energy X-ray Absorptiometry (DXA) and that symptomatic vertebral fractures should be treated with an intravenous bisphosphonate [1,2]. At the time, there was insufficient evidence to recommend the routine use of vitamin D and calcium supplementation or prophylactic oral bisphosphonates. Furthermore, the predictive value of BMD for the risk of developing a vertebral fracture in children was not understood, thus the working parties were unable to make recommendations for any specific intervention based upon BMD assessment alone.

In recent years it has become clear that painful vertebral fractures are a growing problem in patients with DMD treated with corticosteroids [3] and because there have been new developments in the paediatric metabolic bone field, this workshop was held to review the previous guidance in the light of any new or emerging evidence.

1.1. Corticosteroid-induced osteoporosis

Annemieke Boot reviewed the current literature on the effect of corticosteroids on bone. Corticosteroids affect both bone resorp-

tion and bone formation. There is an immediate increase of bone resorption markers with increases of CTx and urinary calcium creatinine ratio. The increase was maximal after 7 days of a 10 day methyl prednisolone regime and remained higher than baseline 3 months later [4]. Corticosteroids have a profound effect on osteoblasts; osteoprotegerin mRNA in explants of osteoblasts in vitro are down-regulated [5] and serum PINP fell significantly after 2 weeks of corticosteroid therapy in children with ulcerative colitis [6]. This phase of inadequate bone formation occurs due to apoptosis of osteoblasts and osteocytes, inhibition of both proliferation and differentiation of osteoblasts and inhibition of bone matrix production. Another effect of corticosteroids in children is a reduction of the effect of growth hormone and a reduction in IGF-1 synthesis in the growth plate which affects linear growth. Catch up growth occurs when treatment is stopped.

Corticosteroids also have extraskelatal effects on bone including increased excretion of calcium by the kidneys and reduced calcium absorption by the gastrointestinal tract, this leads to increased production of parathormone, which in turn activates osteoclasts. Vitamin D supplements can stimulate intestinal calcium absorption and inhibit parathyroid hormone secretion.

In a large population cohort study of 244,235 adults who were prescribed long-term corticosteroids, the relative risk (RR) of any fracture was 1.33 and the RR of a vertebral fracture was 2.60 [7]. There was a steep rise in vertebral fracture risk relative to the corticosteroid dose with the RR ranging from 1.55 for a prednisone dose of less than 2.5 mg/day, to a RR of 2.59 for 2.5–7.5 mg/day and to a RR of 5.18 for a dose of greater than 7.5 mg/day. A meta-analysis of studies of corticosteroid treated adults confirmed a significant negative association between cumulative dose of corticosteroid and BMD [8].

In the UK the incidence of any fracture in healthy children is 1.6–3.6% per year [9]. Large population studies have shown an increased risk of fracture in children treated with corticosteroids [10], the risk of fracture increases with higher cumulative doses. A case control study of 37,000 children treated with four or more courses of oral corticosteroids for a mean duration of 6.4 days compared with 340,000 untreated controls showed an RR for fracture of 1.32 (95% CI 1.03–1.69); the risk of a fractured humerus doubled, RR 2.17 (1.01–1.69) [10]. Fractures may therefore occur early after initiation of steroid treatment. In another study of young adults who underwent renal transplantation in childhood there was a significant negative association between cumulative prednisone dose

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and BMD Z-score [11], while another study of pQCT measurement in children with steroid sensitive nephrotic syndrome ($n = 55$) showed a low trabecular BMD compared with controls [12].

1.2. Definition of osteoporosis

Nick Shaw reviewed the literature defining osteoporosis, a systemic disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures [WHO technical report, 1994]. DXA is widely accepted as a quantitative measurement technique for assessing BMD status in adults. Reports of DXA scans of the lumbar spine for each vertebra include bone mineral content (BMC) in grams, bone area in centimeters and bone mineral density in grams per centimeter, data are usually collected for the lumbar spine and hip in adults and lumbar spine and whole body in children. In adults, the diagnosis of osteoporosis is often based on the comparison of a measured BMD result with the average BMD of young adults at the time of peak bone mass, defined as a *T*-score [13]. *T*-scores of less than 2.5 SD below the mean peak bone mass are associated with an increased fracture risk [13]. However, absolute fracture risk is multi-factorial and is also affected by genetics, gender and age in older people. The use of clinical risk factors is now being increasingly used in adult practice in the FRAX prediction model to assess fracture risk in conjunction with bone density measurements [14].

There are specific problems in interpreting DXA data in childhood. An artefactual reduction in BMD in small children may lead to an inappropriate label of osteoporosis because projectional techniques used with DXA measure area and not volumetric bone density. This can often be the case in children with chronic illness who are short and have delayed puberty. In children, BMD results should be expressed as a Z-score which is based upon age-matched comparative results with correction for body size. Although a number of different approaches have been advocated for body size correction there is still no consensus as to which method should be used for DXA scans in children and adolescents.

An additional problem in the interpretation of bone density results in children is the relationship between bone density and fracture risk. The first prospective cohort of BMD measurements in healthy girls, aged 3–15 years, correlated baseline DXA measures of BMD with frequency of subsequent fractures over a 4-year period [15]. Using multivariate models adjusted for age, weight and fracture history, each standard deviation below baseline total body BMD, equivalent to a 6.4% difference, almost doubled the risk of new fractures (hazard ratio [HR] per 1 SD decrease = 1.92; 95% CI, 1.31–2.81). Lumbar spine BMAD (an estimate of volumetric BMD) also predicted new fractures during the follow-up interval (HR per 1 SD decrease = 1.34; 95% CI, 1.02–1.75).

The ALSPAC fracture study included 6213 children, of whom 550 children (8.9%) reported a fracture. Fracture risk was inversely related to BMC adjusted for bone area, body size, volumetric BMD of humerus and a reduction in skeletal size in relation to body size [16]. A meta-analysis of similar studies confirmed a clear correlation between BMD and fracture risk in children [16]. The majority of studies which have examined fracture risk in relation to BMD have been undertaken in healthy children and there are currently few prospective studies in children with chronic disease.

In 2007 the ISCD published the following position statement: 'The diagnosis of osteoporosis in children and adolescents should NOT be made on the basis of densitometric criteria alone'. The diagnosis of osteoporosis in children requires the presence of both low BMC or BMD and a clinically significant fracture history (i.e., a long-bone fracture of the lower extremities, vertebral compression fractures or two or more long-bone fractures of the upper extremities).

Low BMD is defined as a BMD Z-score that is less than or equal to -2.0 , adjusted for age, gender and body size [17].

2. Bone turnover markers

Maria Luisa Bianchi reviewed the available literature on bone turnover markers. Bone turnover is characterized by two opposite activities: bone resorption and bone formation. During bone resorption, dissolution of bone mineral and catabolism of bone matrix by osteoclasts results in the formation of a resorption cavity and the release of bone mineral and matrix components [18]. During bone formation, the osteoblasts synthesize new bone matrix and promote mineralization, filling the resorption cavity with newly formed bone. Bone turnover is highly active during childhood and adolescence, with a net prevalence of bone formation over bone resorption and a net gain of bone mass. Bone mass reaches a peak at the end of growth and development, then bone turnover enters a steady state (where formation equals resorption) during early adulthood, which continues until menopause in women and about 60 years of age in men.

Bone turnover is affected by disorders of bone metabolism, for example, in osteoporosis there is often increased bone resorption; by contrast, osteopetrosis is characterized by decreased bone resorption. Bone turnover can be studied by measuring biochemical markers which are present in serum or urine [19,20]. Bone formation is mainly assessed by serum osteocalcin, serum alkaline phosphatase (better by "bone-specific" alkaline phosphatase) and serum N- and C-terminal propeptides of type I collagen. Bone resorption is mainly assessed by serum or urine pyridinium cross-links, N- and C-telopeptides of type I collagen, urine pyridinoline and deoxypyridinoline, serum tartrate resistant acid phosphatase. Biochemical markers of bone turnover may be useful in the clinical investigation of bone turnover in children and adolescents, both in health and disease [21–23]. However, the interpretation of bone markers in growing children is difficult because they depend on both clinical and assay-related variables, such as age, pubertal stage, growth velocity, mineral accrual, hormonal regulation, nutritional status, circadian variation, method of expression of results of urinary markers, specificity for bone tissue, sensitivity and specificity of assays [24]. These difficulties in the assays and their interpretation mean that as yet it is not advisable to use bone markers in children and adolescents in routine clinical practice.

There are some published data on bone markers in children with DMD; Bianchi et al. observed an increase in bone resorption markers, while a bone formation marker (osteocalcin) was within the normal range [25]. By comparison, Soderpalm et al. found a reduction in all biochemical markers of both bone formation and resorption in DMD [26,27]. These studies measured different clinical and treatment characteristics in their patients and the choice of different markers and assays makes the comparison of these results impossible.

When evaluating bone markers in DMD it is important to realize that the long-term use of corticosteroids have a significant effect on bone turnover, so that it can be difficult to understand whether the disease *per se* has a direct effect on bone remodeling in these children. To further this aim, large prospective studies on bone turnover in DMD before and during steroid therapy are needed to determine if they are clinically useful in management.

2.1. Definition of vertebral fracture

Mike Haddaway reviewed the literature on corticosteroid-induced vertebral fractures, indicating that defining an osteoporotic vertebral fracture can be difficult and is dependent upon visual assessment of vertebral shape seen on a lateral spine X-ray. Associated findings include the presence of osteopenia and wedging of

vertebrae, although differentiating a wedge fracture from a 'normal short vertebra' can be difficult [28]. Vertebral fractures can present with acute localized back pain or they can be completely silent, which poses a significant problem in the interpretation of prevalence data because clinicians may not routinely screen for asymptomatic fractures.

The criteria for measuring vertebral shape (morphometry) in adults are well known with grading of severity of vertebral fractures according to shape (biconcave, wedge and crush) and degree of deformity (mild, moderate or severe) [29]. However, this work has not been extended to paediatric practice.

Mike Haddaway and Mike Davie presented unpublished data on the assessment of vertebral morphometry in DMD children using a technique already established in adults. They chose to compare lateral spine images obtained by X-ray and MRI, the latter being an alternative method of monitoring which does not require exposure to radiation. Vertebral wedging (loss of anterior height as a ratio) rather than absolute dimensions were used to minimize age variation and inherent magnification from the X-rays. Observer variability in X-ray morphometry was evaluated in five patients' films, measured by two observers. Six dimensions were measured for each vertebra (anterior height, posterior height, superior width, inferior width, mid height (between inferior and superior surface), mid height (concavity) ranging from D4 to L5, a total of 270 measurements were made. Inter-observer variation was expressed in terms of intraclass correlation coefficient (ICC) where ICC of 1 = perfect agreement between observers, a measure of 0.984 was obtained for all 270 pooled measures. For the individual measures ($n = 45$) ICC was > 0.966 for all parameters. Taking the loss of anterior vertebral height- anterior wedging (ratio) ICC for all levels combined was 0.622 $p < 0.01$, there were insufficient results to split into individual vertebrae. The difference in wedging is from a mean of 2.6% to 4.6% (Fig. 1), but this was not statistically significant. Analysis of vertebral morphometry data in this patient group was not straightforward because of the following problems that are specific to the paediatric age-range:

1. A lack of information on the natural progression of vertebral shape with age.
2. The appearance of secondary ossification centres at about 10-12 years.
3. Small errors in measurement of vertebral dimension lead to greater errors in calculated ratios compared with adult assessment.
4. Parallax errors occur as the growing spine occupies larger areas on an X-ray film produced by a divergent beam.
5. More 'rounded' vertebral shape may suggest that standard 'deformity' shape indices may be less appropriate than area.
6. Quality of image.

7. Vertebral shape varies according to spinal level (Haddaway and Davie, unpublished data).

For observer ratings from the MRI images, ICC of the vertebral dimensions ranged from 0.67 (posterior height) to 0.93 (mid height). Scoliosis presented difficulties with interpretation of MRI images due to slice thickness. Precision of comparison with MRI was affected by low signal from vertebral endplate.

Further work is necessary to compare MRI and lateral spine X-ray from the same time point within patients to obtain agreement on comparative measurement. At present it is not clear whether the 'total' vertebral morphometry achieved with X-ray is better than the more specific measurement of MRI offers the best way of analyzing vertebrae in these children [Haddaway and Davie, unpublished data].

2.2. Risk of fractures in DMD treated with corticosteroids

Helen Roper reviewed the literature on long-bone fractures in DMD which are usually associated with falls and often lead to a loss of ambulation. Studies of DMD patients, before the use of corticosteroids, identified an increased fracture risk most frequently involving the humerus or femur [30,31]. In one study, fracture prevalence was 44% and associated with reduced femoral BMD [32]. MacDonald found a fracture prevalence of 20.9% with no difference in fracture prevalence in those using steroids, although no data was recorded on steroid regimen or duration of treatment [33].

Vertebral fractures were previously thought to be rare in this population with only a few individual case reports in the literature [34,35]. However, subsequent reports demonstrate an association with increased risk of vertebral fracture and cumulative corticosteroid dose in DMD [36]. In a more recent study the prevalence of vertebral fractures in corticosteroid treated DMD was 32% compared with zero in steroid naive patients [37]. The prevalence of long-bone fractures was 38.7% and 26.5% in steroid treated and steroid naive groups respectively, with lower limb fractures more common in the steroid group and upper limb fractures more prevalent in steroid naive patients. Another study confirmed that vertebral fractures were seen only in steroid treated boys, with a prevalence of 20% [38], while the prevalence of limb fractures was similar in both groups (24% steroid treated, 26% steroid naive).

Adnan Manzur presented cumulative data from 15 UK centres participating in the UK North Star Network. Two corticosteroid regimens are used: daily or intermittent (10 days on 10 days off) at a starting dose of 0.75 mg/kg/day. The total number of DMD patients was not known but 30 patients were identified with vertebral fractures, 26 were ambulant and four non-ambulant, three patients had been taking prophylactic oral bisphosphonates for less than

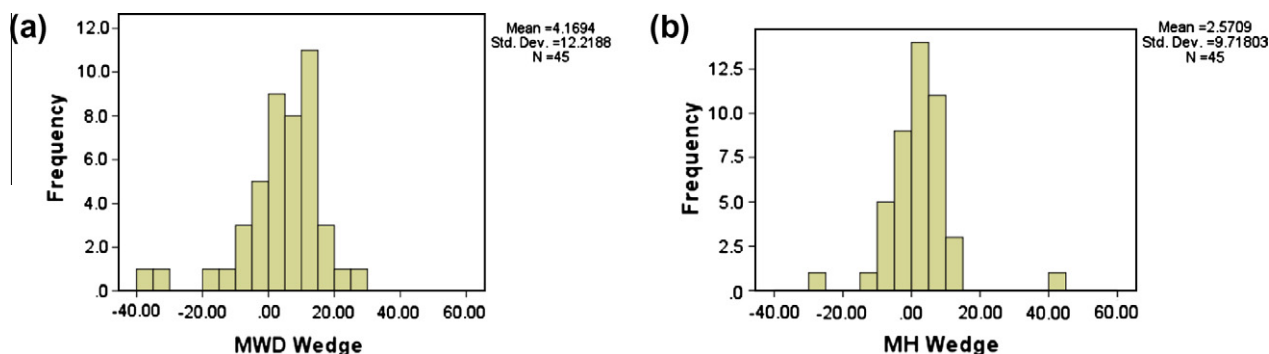


Fig. 1. Two histograms representing the range of anterior vertebral wedging and the mean difference between observers, as assessed by observer (a) (MH) and observer (b) (MWD) in all 270 vertebrae pooled. The difference in wedging is from a mean of 2.6% (MH) to 4.6% (MWD) which was not statistically significant.

1 year and four patients were taking calcium and vitamin D supplements. The mean dose of prednisolone was 0.56 mg/kg/day (range 0.21–0.8 mg/kg/day). The mean latency was 4.1 years (0.7–7.4 years). At the time of the vertebral fracture 28/30 were taking daily corticosteroids. 17/30 had started on intermittent corticosteroids but had been changed to a daily regimen because of declining function, 11 had only taken daily corticosteroids and two patients had only ever been on intermittent corticosteroids (latency 1.7 years). Data for the total number of patients treated with corticosteroids in the North Star dataset were not complete, however, data from the Dubowitz Neuromuscular Centre identified 17 boys with vertebral fractures out of a cohort of 118 corticosteroid treated boys; the rate of vertebral fracture in patients taking daily corticosteroids was 38% (16/42) compared with only 1/104 patients treated with intermittent corticosteroids, however it is not clear how many of these children had started on intermittent steroids and then changed to daily steroids. In 11/27 fractures, 41% followed a trivial fall and 21/27 (78%) were symptomatic with acute back pain in 52%. A previous long-bone fracture had occurred in 11/30 (37%). X-ray findings were available for 27/30 patients and identified a loss of vertebral height in 96% and wedging in 52%. The site was thoracic in 41%, lumbar in 44% and thoracolumbar in 15%. In 9/27 only single vertebrae were affected and in the remainder multiple vertebrae were affected. Results from DXA data were available for 15/30 patients within three months of the vertebral fracture, the mean Z-score was -2.8 (-0.8 to -3.8). Following a vertebral fracture six patients lost independent ambulation. Twenty-one patients were treated with a bisphosphonate, one with oral, three with a combination with oral and IV and the rest with IV treatment, 11/12 patients, where data were available, reported improvement in their back pain. The mean serum vitamin D levels were insufficient at 29.9 nmol/l, at the time of vertebral fracture (range 70 nmol/l to less than 12.5 nmol/l) [39].

In their study, Mike Davie and Mike Haddaway assessed levels of vertebral deformity and time to fracture after steroid initiation in relation to BMD. Asymptomatic vertebral deformities of $>20\%$ of vertebral height occurred in 9/22 (40%) patients, and in 2/22 (9%) patients symptomatic vertebral fractures occurred, one following a fall and the other spontaneously. Both children had been treated with daily prednisolone for more than 4 years. Vertebral deformities were most frequently seen at D7, followed by D5 and D6. By comparison D8 and D12/L1 are the most common sites for vertebral fracture in adult men. BMD Z-scores in the lumbar spine were negative in patients with vertebral deformities ($p = 0.01$, Fisher exact test) [40].

Imelda de Groot presented data from The Netherlands, prior to 2005; corticosteroids were rarely used in The Netherlands. Treatment regimens are either daily or intermittent (10 day on 10 day off treatment) starting with 0.75 mg/kg/day, reports of 162 children showed that 82 were on treatment, 76 were on the intermittent regimen (deflazacort $n = 7$, prednisolone $n = 69$), there were no children taking daily prednisolone and six were receiving daily deflazacort. Among the ambulant patients there were five long-bone fractures and no vertebral fractures. Of the non-ambulant patients there were one long-bone fracture and three vertebral fractures. The total number of ambulant vs non-ambulant children was not known. One vertebral fracture occurred in a child treated with intermittent prednisolone after 7 years and two vertebral fractures occurred in patients treated with daily deflazacort [de Groot, unpublished data].

2.3. Bone density in boys with DMD treated with corticosteroids

The relationship between bone health and DMD was investigated in a study of steroid naïve and corticosteroid treated patients [25]. Whole body BMD was reduced in both groups and lower limb BMD correlated with muscle strength score. Spinal BMD was sig-

nificantly lower in the steroid treated group and there was a correlation with cumulative steroid dose.

Data presented by Doug Biggar showed a dramatic reduction in L1–L4 vertebral BMD following a loss of independent ambulation in DMD regardless of whether the patient had been treated with corticosteroids, similar results were also presented by Nicola Crabtree. When all patients (corticosteroid treated and naïve) were also treated with vitamin D 1000 units and 750 mg calcium per day there was no difference in the long-bone fracture risk between the two groups, with a fracture rate of 25–35%. The corticosteroid treated boys were significantly shorter in final height compared with steroid naïve boys. Ninety percent of boys not treated with deflazacort developed scoliosis requiring spinal surgery [41]. Spinal surgery may help prevent vertebral collapse and fragility fractures despite reduced L1–L4 Z-scores. Most boys treated with deflazacort have reduced L1–L4 BMD and some have symptomatic vertebral fractures, however, only 10% of these patients required scoliosis surgery. One possible explanation for the greater incidence in vertebral fracture could be that because the spines of corticosteroid treated patient are not surgically stabilized they remain flexible and exposed to a variety of mechanical stresses [41].

Ann-Charlott Soderpalm presented data from Sweden, 24 DMD patients (most were treated with daily prednisolone 0.35 mg/kg/day) underwent DXA and DXL (DXA and laser) studies of total body, spine, hip, forearm and heel, the results were compared with healthy age and sex-matched controls [26,27]. Results showed that BMD in the DMD patients was generally lower than in the healthy controls and these differences significantly increased with advancing age. Furthermore, the normal age-related increase in BMD seen in the healthy boys did not occur in DMD, where the total body, spine and forearm BMD remained static and BMD in the hip and heel decreased with increasing age. The effect on age of the heel BMD was especially striking in the non-ambulant patients and showed poor calcaneal mineralization [26,27].

The long-bone fracture incidence in the DMD cohort was 25%, which interestingly was lower than age-matched controls, which was 37.5%. Nearly all fractures (9/11) in the DMD group occurred after loss of ambulation and the majority involved the lower limbs. In this study, 12 DMD patients, who were non-ambulant, were monitored with spinal X-ray with no vertebral fractures identified. A 4 year follow-up study of 18 patients conducted by the same group, showed a fracture rate of 39% among the DMD patients. Spinal radiographs were performed in 16 patients and vertebral fractures were observed in only one patient [26,27].

DMD children are smaller than average and bone accrual with age is reduced compared with controls. Significant correlations were found between lean mass (a surrogate for muscle mass) and whole body BMC. Also motor function and muscle strength were strongly correlated with BMD values in DMD [Soderpalm, unpublished data].

Dave Rawlings presented serial DXA data from Newcastle, UK, relating to 30 ambulant DMD patients with a mean age of 7.4 years (range 4.4–9.9) at baseline and 8.5 years (range 6.1–14.1) at follow up [Rawlings, Sarkozy and Bushby, unpublished data]. Lumbar spine BMD was nearly always lower than expected for age, with little if any of the normal age-related changes with the average increase in BMD over the follow-up period being close to zero.

Nicola Crabtree presented DXA data from corticosteroid treated DMD patients in Birmingham, UK. Lumbar spine and subcranial DXA was performed on 25 ambulant DMD patients (mean age 7.4 years) at baseline and after 30 months of intermittent (10 days on 10 days off) corticosteroid treatment. At baseline lumbar spine BMC was significantly low for projected bone area although appropriate for reduced lean body mass (LBM). Subcranial bone area for height and subcranial BMC for area and lean mass were all significantly reduced. After 30 months of steroid therapy there was a sig-

nificant increase in subcranial bone area for height but a significant reduction of subcranial BMC for area. At the lumbar spine there were no significant changes in bone area but small increases in lumbar spine BMC both for bone area and lean mass, suggesting no decrease in BMD after 30 months of intermittent corticosteroid treatment [42].

3. Vitamin D and calcium in bone health

Maria Luisa Bianchi reviewed the current literature on vitamin D and calcium supplementation. More than 60% of the variance of peak bone mass is genetically determined, while the remainder is influenced by modifiable factors with nutrition and physical activity being the most important. Their importance is particularly evident in the pre-pubertal years. Improving bone mass gain may reduce the fracture risk during adolescence, and maximizing peak bone mass is probably the best strategy to prevent osteoporosis and fragility fractures in later life.

Longitudinal, randomized studies demonstrated that, in healthy girls and boys, a high calcium intake has a positive effect on BMC and areal BMD, mainly of the appendicular skeleton (radial metaphysis and diaphysis and femoral neck, trochanter and diaphysis) [43,44]. With milk, but not with calcium supplements, positive effects were also observed on the forearm bone geometry and volumetric BMD [45]. The greatest benefit of high calcium intake for bone was observed in children who had the lower spontaneous calcium intake. Other intervention studies suggested that dairy products may have sustained effects on bone mass, probably related to the optimal rate of calcium and proteins present in milk: 3–5 years after the suspension of calcium enriched foods, BMC and BMD were still increased with respect to placebo [46]. In a meta-analysis of 21 randomized controlled trials, the authors concluded that increased dietary calcium/dairy products, with or without vitamin D, significantly increases total body and lumbar spine BMC in children with low baseline intakes [47]. A second meta-analysis of 19 randomized controlled trials including 2859 children aged 3–18 years, showed a positive effect of calcium supplementation on total body BMC and upper limb BMD [48].

Compliance to treatment with calcium supplements may limit the efficacy of such a measure, and probably the best way of intervention is with dietary intake. There are many more studies on calcium, and if we take all of them together, it seems that an increase in calcium intake during the pre-pubertal years (better if with milk products), may be able to induce a higher bone mass gain, with persistent effects, essentially in the appendicular skeleton [49].

Regarding vitamin D, there are few observational studies on its effects on bone mass gain. One study of girls aged 7–9 years demonstrated that those who had received vitamin D in the first year of life had a significantly increased areal BMD at six skeletal sites [50]. Another study on girls aged 9–15 years, followed for 3 years, found that the changes in spine areal BMD were clearly correlated with the serum levels of 25-OH vitamin D. The girls with higher levels of 25-OH vitamin D (more than 93 nmol/l) had a BMD change 27% greater than those with low levels (below 50 nmol/l) [51].

There are a few prospective studies of the effects of vitamin D. In one study a group of 11 year old girls, with adequate calcium intake, received either 5 or 10 mcg of vitamin D3 (200 or 400 U) for 1 year; there was a gain in femoral BMC dependent on the vitamin D dose. There was also a gain in vertebral BMC, but only with the higher dose [52].

There are no prospective studies on the use of calcium and vitamin D in children with DMD. However, on the basis of the studies on healthy children, we can assume that a correct calcium intake and adequate levels of vitamin D are necessary for bone health in this patient group. Appropriate longitudinal studies are needed

to define the optimal calcium intake and serum 25-OH vitamin D levels in this patient population [Bianchi, personal communication].

The optimal serum 25-OH vitamin D level for bone health is regarded as 50–80 nmol/l, vitamin D insufficiency is defined as 37.5–50 nmol/l, vitamin D deficiency less than 37.5 nmol/l and severe deficiency being <12.5 nmol/l [53]. Data presented by Adnan Manzur from the UK North Star Network national audit of 25-OH vitamin D levels from 157 DMD patients (mean age 6.9 years) prior to commencing corticosteroids, showed a median serum 25-OH vitamin D level of 35.8 nmol/l (range 4–155 nmol/l), 15% of patients had severe vitamin D deficiency (<17.5 nmol/l), 43% were vitamin D deficient (17.5–37.5 nmol/l), 20% were vitamin D insufficient (37.5–50 nmol/l) and only 22% were vitamin D sufficient (>50 nmol/l) according to Hollick [39,54].

Imelda de Groot explained that the bone protection strategy in The Netherlands includes the addition of calcium supplements (500 mg) to ambulant DMD children. This is increased to 1000 mg if intake of milk products is low. Vitamin D supplementation is given to boys who have low vitamin D levels or to those who prefer to play indoors.

Unpublished audit data of vitamin D supplementation in DMD children attending Cincinatti Children's Hospital were presented by Brenda Wong [Wong, unpublished data]. From 2006 vitamin D3 supplement dosage was titrated against serial serum 25-OH vitamin D levels. Initially, daily D3 supplements of 500 U was given to patients with 25-OH vitamin D levels of 50–72 nmol/l and 1000 U to patients with levels <50 nmol/l. For patients with severe vitamin D deficiency (25-OH vitamin D levels <12.5 nmol/l) a loading dose of Vitamin D2 50,000 U was given weekly for 8 weeks followed by maintenance daily vitamin D3 supplements. From mid-2009, patients with serum 25-OH vitamin D levels of 50–72 nmol/l have been prescribed 2000 U D3 supplements per day while those with levels <50 nmol/l are prescribed daily 4000 U D3. Data on serum 25-OH vitamin D levels in 298 DMD patients' first clinic visit between January 2003 and September 2009 and the impact of 6–12 months of vitamin D3 supplementation on serum 25-OH vitamin D levels and random second void urine calcium/creatinine ratio were presented. The mean age of the patients was 7.8 years (SD 4.0, range 0.6–25.0). Seventy percent of DMD patients not on D supplements had a 25-OH vitamin D level of <50 nmol/l (vitamin D deficient) and only 1 in 10 patients had a 25-OH vitamin D level > 75 nmol/l. Fifty percent of patients on a daily mean D3 intake of 1280 U had no increase in 25-OH vitamin D levels (mean change –1.1, 95% CI –2.4 to 0.2). The reasons for the lack of response (compliance issues vs poor bioavailability) were unclear. The remaining 50% on a mean daily D3 intake of 1267 U had responded with a mean increase in 25-OH vitamin D of 32 nmol/l (CI 10.9–14.8). These responders did not have hypercalciuria (random second void urine ca/cr ratios were unchanged (0.2) for pre- and 12 months' post-D3 supplements).

Studies of other patient groups with vitamin D deficiency suggest that 400 U per day of vitamin D supplementation might not be sufficient to restore 25-OH vitamin D levels to > 50 nmol/l [55]. Thus, there is a need to conduct prospective studies of vitamin D supplementation in DMD patients to determine the appropriate dosing requirements to address the high prevalence of vitamin D deficiency in this population.

3.1. The use of bisphosphonates in glucocorticoid treated DMD patients

Nick Shaw reviewed the literature on bisphosphonates, a group of drugs which act on bone by inhibiting the action of osteoclasts and thus reduce bone resorption. Studies of corticosteroid treated children have shown that intravenous pamidronate treatment increases BMD and reshapes collapsed vertebral bodies [56–58].

A placebo-controlled trial of oral alendronate in corticosteroid treated children (age 4–17 years, $n = 22$) showed that the drug was well tolerated and after 1 year of treatment there was an increase in lumbar spine BMAD [59].

A Cochrane systematic review of bisphosphonate therapy for secondary osteoporosis in children identified over 800 reports of their use in children but only nine studies fulfilled the inclusion criteria [60]. All of these studies had small sample sizes with the main reported outcome being change in lumbar spine BMD. It recommended that more natural history studies were required in children with chronic disease to establish the relationship of bone density to fractures. Further treatment trials are required with larger patient numbers to evaluate fracture rates and outcome measures other than BMD are required to assess bone structure and geometry such as the use of pQCT and vertebral morphometry. A recent review of bisphosphonate use in childhood osteoporosis concluded that current data are inadequate to support the use of bisphosphonates in children to treat reductions in bone mass/density alone [61].

Anna Sarkozy presented data from Newcastle UK, where six ambulant DMD patients had required treatment with intravenous bisphosphonates for painful vertebral fractures. The duration of steroid treatment ranged from 8 months to 6 years and all of the children were taking daily corticosteroids (prednisolone or deflazacort). Following this, the centre introduced a new bone protection protocol which included the use of prophylactic oral risedronate 35 mg weekly or 1 mg/kg/week for children weighing less than 20 kg and calcichew D3 forte in children taking long-term daily corticosteroids.

In total 53 patients have been treated with risedronate and 43 patients remain on treatment. The duration of treatment ranged from 2 to 23 months with a median duration of 19 months. There were 31 ambulant patients and 12 non-ambulant patients. Treatment was discontinued in eight patients because of side effects which included flu-like symptoms, joint pains, headaches and abdominal symptoms. In those patients who had previously complained of back pain there was symptomatic improvement on oral risedronate and there were no new complaints of back pain in any patient. There were no spontaneous vertebral fractures in patients treated with risedronate, two patients however, experienced vertebral fractures following trauma [Sarkozy and Bushby, unpublished data].

DXA scans were performed on 36 patients before and after 12 months of risedronate treatment and indicated a significant increase in lumbar spine BMD of 13.4% over a 12 month treatment period. The type of corticosteroid used (prednisolone vs deflazacort) did not affect the response to risedronate. The analysis of DXA results on this cohort of patients suggested a lower efficacy of risedronate on improving BMD with increasing duration of corticosteroid treatment. However, the numbers were small and analysis of additional patients is currently in progress to verify this.

Doug Biggar presented data from an open study of oral alendronate 0.08 mg/kg/day conducted on DMD children receiving daily deflazacort [62]. In addition all boys received 750 mg/day calcium supplementation and 1000 U/day of vitamin D. Patients were monitored with DXA and tablets were counted to determine compliance. Assessments were undertaken every 4–6 months with telephone calls in between to ask about adverse events. Sixteen patients who were taking deflazacort 0.69 mg/kg/day (mean 0.3–0.96) and a BMD Z-score of < -1.0 were recruited into the study. They had been on deflazacort for a mean of 2.6 years (range 0.25–7 years), the mean total body Z-score was -0.8 (range -3.73 to -0.77) and L1–L4 Z-score was -1.94 (range -1 to -5.12). No patient had suffered a vertebral fracture and two patients had had long-bone fractures. Side effects included headache, gastrointestinal and muscle/bone pain. Over the 2 year treatment period, whole body BMD scores remained stable and total body and L1–L4 Z-scores improved in the younger children who had

been taking deflazacort for a shorter time period. Less benefit was seen in the older boys and one possibility could be that they were relatively under-dosed. No conclusion could be made on the effect of alendronate on fracture risk in this study.

4. Conclusions

The management of bone health in boys with DMD, whether or not they are treated with corticosteroids remains a challenge. There remain more questions than answers. Osteoporosis may impact on quality of life and vertebral fractures may lead to pain, deformity and loss of function and, thus, deserves a high priority for further research. The balance between risk and benefit on the use of corticosteroids in DMD remains a delicate one, benefits include prolonging ambulation, improving respiratory function, reducing the need for scoliosis surgery but require counter balancing against the risk of side effects; highlighted here are the risks for the growing skeleton.

In healthy children there is an increase in bone mineral mass with advancing age and corticosteroid treatment is well known to interfere with this process. In children with DMD this effect is apparent but a clear impression of the workshop was that this appears to be less pronounced with intermittent than daily treatment. However, when walking is lost, there is a sharp decrease in bone strength and the risk of vertebral fractures is probably increased for all steroid regimens. Switching from an intermittent to daily steroid regimen at the point at which walking becomes more difficult may accelerate the risk of vertebral fracture. Painful vertebral fractures may accelerate the loss of independent ambulation.

The predictive value of imaging techniques such as DXA for fracture risk in DMD is not known, although these data are emerging for children as a whole. Puberty is a time when bone strength normally increases due to hormones such as testosterone. Delayed puberty is an additional risk factor for steroid treated children, thus, if the child is not showing signs of puberty by the age of 14 years then referral to a paediatric endocrinologist for testosterone treatment should be considered.

Weight bearing is important for maintaining bone strength, which is why lumbar spine BMD dramatically falls when walking stops, thus, maintaining walking or standing is important in children with DMD. Vitamin D is important for bone accrual in children and helps to maintain strong bones. Adequate blood levels of vitamin D should be maintained for all children taking steroids by giving daily vitamin D, aiming to maintain a level of 50 nmol/l. Calcium is also important for bone health and has a better effect when taken as dairy products, unless the child has a poor dairy intake, in which case a supplement should be given.

Bisphosphonates are used in children to treat vertebral fractures but they are not routinely used to prevent these fractures in children. They have the potential to remain in bone tissue for many years and the long-term efficacy and safety data are not known. Oral bisphosphonates appear to have an effect in maintaining BMD in DMD children, but this effect seems to lessen if bisphosphonates are started after a longer duration of corticosteroid treatment, however, these data are based upon open studies of small numbers of patients and further research in this area is needed. Bone markers can be assessed by blood and urine tests which can give an idea of the degree of bone loss or laying down of new bone. Their relationship with the risk of fracture is not known, but they may be useful to monitor the effects of bisphosphonate treatment.

The workshop consensus, summarized in Fig. 2, was that a DXA scan of the lumbar spine should be performed preferably every 1–2 years in all DMD children receiving corticosteroids. If the child complains of back pain and/or the BMD Z-score (adjusted for body size) is less than or equal to -2.0 , lateral spine imaging should be performed to look for vertebral deformity. Any changes of vertebral

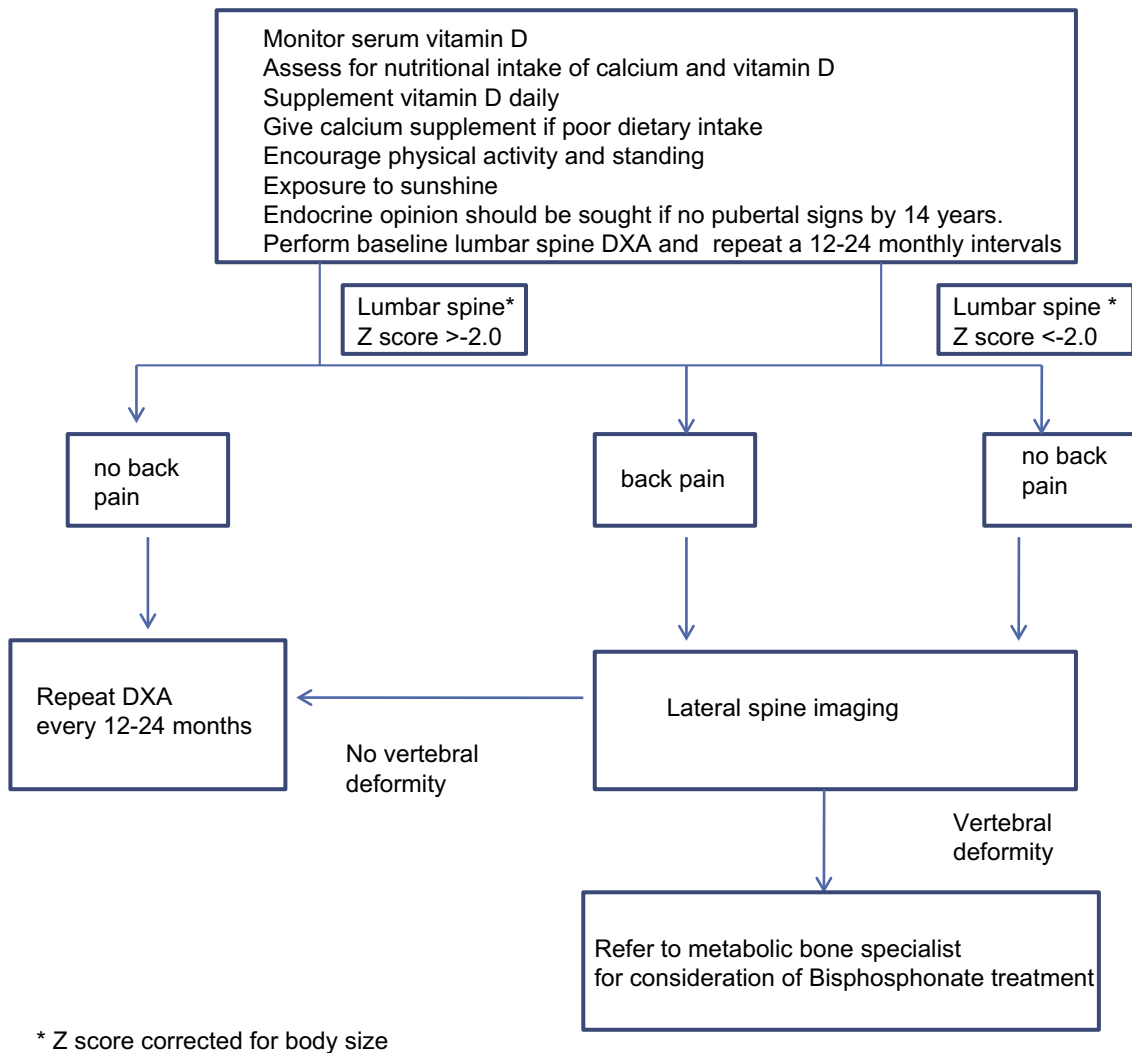


Fig. 2. Suggested care pathway for bone protection in DMD children treated with corticosteroids.

shape should be discussed with a metabolic bone expert for consideration of preventative treatment with a bisphosphonate.

Children presenting with spontaneous painful vertebral fractures should be treated with a bisphosphonate. On the other hand, children who have a single painful vertebral fracture following a fall on the buttock will require pain relief but may not necessarily require treatment with a bisphosphonate. At the moment there are no consistent data to suggest any increased risk of long-bone fracture in DMD treated with corticosteroids, however, there have been few systematic studies to define the risk and their numbers are small. In some older boys with recurrent long-bone fractures there might be an indication for treatment with a bisphosphonate.

When comparing studies of fracture in DMD, there are many causes of reporting bias- only reporting fractures which are symptomatic, not reporting the baseline frequency of fractures in the general population (though vertebral fractures are uncommon in children without major trauma). We do not understand the natural history of pain in the DMD population on steroids. Some back pain may be postural and not related to vertebral fractures. The impending NIH funded steroid trial will be a useful model to monitor the risk of fractures specifically with regard to corticosteroid regimen and longitudinal datasets such as the North Star in the UK and Italy also provides a tool to do this.

It should be noted that there remain many uncertainties about the investigation and management of bone health in corticosteroid

treated DMD children and that the current consensus on management may need to be reviewed in the future as new evidence emerges.

5. Participants

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- Maria Luisa Bianchi, Milan, Italy
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- Annemieke Boot, Groningen, The Netherlands
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- Helen Roper, Birmingham, UK
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- Ann-Charlott Soderpalm, Gothenburg, Sweden
- Mar Tuilinus, Gothenburg, Sweden
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