



## Workshop report

## Endocrine Aspects of Duchenne Muscular Dystrophy

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## 1. Introduction

In October 2009, the United Parent Projects Muscular Dystrophy (UPPMD) organized the First Conference on the Endocrine Aspects of Duchenne Muscular Dystrophy (DMD), as these topics had never been thoroughly discussed until then. Children and adolescents affected by DMD, and consequently their parents, are currently requiring increasing attention, because of the new clinical problems related to longer survival and long-term corticosteroid treatment. The conference was attended by 17 participants (8 from the USA; 2 each from Canada, Italy, and UK; 1 each from Australia, Germany, The Netherlands; of these, 5 were representatives of the United Parent Project, and 12 were clinicians and researchers from 12 different centers).

This first meeting was focused on what is known, which preliminary studies are ongoing, and what needs to be done on four main topics: growth, puberty, weight gain and bone health.

This article is a summary of these four topics, with some concluding remarks. It is a starting point to stimulate attention, debate and specific studies on the endocrine challenges in DMD and their treatment.

In the last few years, the remarkable expansion in clinical and therapeutic capabilities has changed the natural history of many chronic diseases starting in childhood, with increased survival rates and increased numbers of subjects living for a much longer time, often into adulthood. These changes have also been observed in DMD, for which corticosteroids (CS) are now widely used to slow the progression of disease.

The counterpart of these positive medical achievements has been the appearance of treatment-related adverse events with multiple organ involvement of a wide spectrum of severity. In the follow-up of boys with DMD, we are now confronting endocrine system issues never considered before (e.g. delayed puberty, short stature, obesity, osteoporosis, etc.). This increases the problems and needs of patients, and poses novel challenges to caregivers and physicians. For this reason, there is an urgent need to create collaborative teams of different specialists.

The first meeting concerning the endocrine aspects of DMD (Florence, Italy, October 2009) was a starting point to initiate dialogue on relevant issues and to increase the collaboration of neurologists with endocrinologists and bone experts.

## 2. DMD and corticosteroids

Dr. Brian Tseng presented the historical background and clinical features of DMD, and underlined how supportive medical efforts have changed the perspective of these patients, offering a longer survival. Irrefutable evi-

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dence of this fact is the growing population of men with DMD who are active, happy, social, educated and some even working full-time. For this reason, the need of multidisciplinary, interdisciplinary (coordinated) and transitional (pediatric to adult medical care) strategies was emphasized.

Dr. Doug Biggar reported that today, only CS (prednisone and deflazacort) slow the progression of muscle weakness in boys with DMD. Most agree that CS should be given daily to be most effective. He summarized the main benefits of long-term daily use of CS (improved skeletal muscle, cardiac and pulmonary functions, delayed onset of scoliosis and contractures, and preserved upper extremity function), and underlined that the side-effects of daily CS on endocrine function are common and significant. Reporting his experience with deflazacort, he noted that the side-effect profile with daily deflazacort might be less than with daily prednisone, but nevertheless the side effects are significant. The boys' height velocity is slowed significantly by 12–18 months after starting deflazacort, and by 13–15 years of age, their height might be reduced to 20–25 cm below the 50th percentile. While shorter stature might help preserve muscle function, walking and stair climbing, it is a significant concern for most boys and their families. Increased weight for age is another concern, as well as the fact that the onset of puberty may be delayed by 3–5 years or more. Boys who are ambulating in their teens are frustrated because people often think they are much younger than they are. Their voice remains high and they have little facial hair. Their small penis is often a concern voiced by parents, even if usually not by the boys themselves. Their bone age can be delayed significantly (by 2–4 years). The impact of deflazacort compared to prednisone on bone health is less well understood. Prolonged ambulation during CS treatment clearly benefits bone health. To date, the incidence of long bone fractures has not increased significantly. This might change with longer follow-up as the boys are ambulating 3–5 years longer and therefore at greater risk for fragility fractures from falling. The increased incidence of vertebral fragility fractures in the CS-treated boys may not be explained by CS alone. Boys not treated with CS have reduced spinal BMD and most have had spinal surgery to stabilize their spine. This procedure might protect the vertebrae from fractures secondary to osteoporosis and mechanical stresses. Further studies are needed. Finally, it should be noted that the boys and their families want more effective strategies for the prevention and treatment of the side-effects commonly associated with CS.

### 3. Growth and DMD

Dr. Alan Rogol reported the anabolic effects of growth hormone (hGH) on striated muscle. In subjects with myotonic muscular dystrophy and limb-girdle muscular dystrophy, recombinant (r)hGH is anabolic with positive changes in the balances of nitrogen, phosphorus, sodium, potas-

sium and body weight. However, in boys with DMD, hGH is suspected of playing a role in the pathogenesis of the condition [1,2]: with relatively high doses of rhGH there are negative balances of sodium, potassium and sometimes phosphorus; none of the boys with DMD exhibited any anabolic responses to any dose of rhGH.

There is some evidence suggesting that hGH could be detrimental to muscle in subjects with DMD. However, several trials with Mazindol, a weak inhibitor of hGH secretion, did not show a positive effect on the course of muscle function decline [3,4]. Treatment strategies based on the physiology of hGH release are mainly theoretical at this time, but there are several agents that have been used in humans or can be tested in mdx mice.

Dr. Meilan Rutter reported that short stature secondary to chronic CS in DMD boys may negatively impact psychosocial health, quality of life and clinical outcome. In DMD, baseline height velocity and growth hormone testing are typically normal in the absence of CS therapy [5]. However, chronic CS therapy results in growth failure, due to suppression of GH production and/or GH or insulin-like growth hormone-I (IGF-I) resistance, as well as direct effects on bone [6].

Management of short stature and growth failure in DMD should be individualized to address the needs of each patient. Management options include: (1) no intervention (standard of care and acceptable for many), (2) reduction of CS dose or intermittent regimens (not an option in most cases), or (3) GH (or IGF-I) therapy.

Dr. Rutter and the other participants debated the lack of data regarding GH in DMD, and the conflicting opinions about them [7]. Although an isolated case report from the 1980s [2] suggested that GH might be detrimental in DMD, this hypothesis was not held up by subsequent studies (including a randomized controlled study of 83 boys) using a GH inhibitor which failed to show a benefit [3]. A case report of GH treatment of a DMD boy with GH deficiency showed improved growth velocity and motor function [8], while a small, short-term study of GH in DMD and Becker MD suggested cardiovascular benefits with improved systolic function [9]. Dr. Rutter reported her experience with GH in 39 DMD boys: during the first year on therapy, there was improved linear growth and body mass index (BMI), with no detrimental effects on neuromuscular and cardiopulmonary function [10]. Finally, IGF-I (a hormone which mediates many of the actions of GH) has been shown to improve muscle strength and survival in mdx mice [11–13].

### 4. Puberty and DMD

Dr. Rutter also discussed that chronic high-dose CS therapy for DMD frequently results in absent, delayed or arrested puberty. Typically, without CS therapy, boys with DMD progress through puberty appropriately. However, CS excess inhibits production of hypothalamic-pituitary hormones regulating puberty, resulting in testosterone

deficiency due to hypogonadotropic hypogonadism. Lack of puberty may have a significant negative impact on both body image and bone health, which are already adversely affected by DMD itself and its treatment. Dr. Rutter reported that at the Neuromuscular Center at Cincinnati Children's Hospital, 44 DMD boys treated with long-term daily CS aged 13 years or greater (including 31 boys aged at least 14 years), were evaluated for puberty by measuring serum testosterone concentrations and/or a genital examination performed by a pediatric endocrinologist. All but one boy were prepubertal, which underscores the potential scope of this problem in DMD.

Treatment comprises replacement therapy with testosterone, starting with low doses by age 14 years, or perhaps earlier, approximating a more normal age of onset of puberty. Doses are gradually increased over 3–4 years until adult replacement doses are attained. Low-dose testosterone replacement can be administered by monthly intramuscular injections or by daily transdermal application.

In general, testosterone promotes virilization and growth, with gains in bone density, muscle strength and energy levels. However, promotion of growth in the setting of CS-induced growth failure, and gains in muscle strength in the presence of a progressive myopathy may not be realistic expectations for DMD boys. Adverse effects in this age group are infrequent and minor, including acne, oily skin and adolescent mood changes.

Management of puberty in DMD boys on CS presents some additional pertinent issues which require consideration before embarking on therapy. Osteoporosis may prompt the decision to initiate treatment due to beneficial effects for bone health. Conversely, in cases with extreme short stature, testosterone replacement will eventually bring about bone age advancement and epiphyseal fusion, and final height will be further compromised. The decision to undertake treatment should involve a frank discussion of the pros and cons, and individualized according to the boy's concerns and wishes. Fundamentally, there needs to be awareness by neurologists and timely referral to endocrinologists, so that this issue can be addressed. The evaluation and management of puberty in DMD is complex, and should be addressed together with other endocrine issues.

## 5. Weight gain and DMD

Dr. Rutter emphasized that boys with DMD are at high risk of excessive weight gain, insulin resistance and type 2 diabetes mellitus, due to chronic treatment with CS and progressive muscle weakness. CS may stimulate appetite and food intake, and act on metabolic pathways in liver and fat cells to promote insulin resistance, hyperglycemia and visceral adiposity. Progressive muscle weakness limits physical activity and results in eventual loss of independent ambulation, exacerbating weight gain. Excessive weight gain negatively impacts DMD boys in many ways. It may lead to carbohydrate intolerance and diabetes, and be detrimental for pulmonary and cardiac function. Excess

weight affects motor function and mobility, and limits the caregivers' ability to lift and transfer boys, affecting the quality of life and functioning of the entire family.

In DMD the mainstays of prevention and treatment of excessive weight gain involve addressing CS dose and formulation and dietary control, due to the limited practical value of exercise recommendations. In individuals with significant insulin resistance, medications could be considered.

CS are typically initiated using weight-based dosing at supra-pharmacological doses (prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day). In some institutions, the doses may be periodically increased in line with weight gain, aside from clinical response. In general, the smallest dose to achieve a desired effect should be used, and caution should be exercised before increasing doses based on weight alone.

Nutritional intake is a key component of management. DMD boys require fewer calories compared to average healthy children (ambulatory boys need about 80%, while non-ambulatory boys about 70%). It is important to individualize recommendations based on physical ability and ambulatory status. Nutritional counseling should ensue from the outset, well before CS are initiated. General principles which underlie a low glycemic index diet may help with weight control and prevention of hyperinsulinemia. These include avoidance of simple sugars, portion control, increased fiber and whole grains, and limited fat intake.

Medications, such as metformin, could be considered in select cases in whom weight gain is severe and insulin resistance or glucose intolerance are present. Metformin is an insulin-sensitizing agent which is effective in type 2 diabetes and insulin resistance, and may result in associated weight loss. A case series of DMD boys on CS who had extreme weight gain and insulin resistance were treated with metformin at Cincinnati Children's Hospital Neuromuscular Center [14], and showed short term weight loss or slowing of the rate of weight gain, with improvement in body mass index. While this is an option which could be considered, currently there are insufficient data to recommend metformin as standard of care for treatment or prevention of excessive weight gain in DMD.

## 6. Bone and DMD

Dr. Maria Luisa Bianchi emphasized that among the endocrine problems related to DMD, alterations of bone metabolism, with a reduction of bone mineral content (BMC, also referred to as "bone mass") and bone mineral density (BMD), are particularly relevant (see Note 1). For this reason, bone density measurement should be considered part of the normal clinical evaluation in these boys.

It is necessary to remember that the evaluation of bone mass and its change in growing subjects is very complex, as the growth process implies rapid changes in bone size, shape and mineral content. Considering these physiological changes, that may be altered by the presence of pathological

conditions, BMC and BMD are very difficult to evaluate in children and adolescents.

Dual X-ray absorptiometry (DXA) is the most widely used densitometric technique in children. A limitation of DXA is that it only calculates an “areal” BMD (the ratio of BMC to the projection area of the scanned bones). This, for mathematical reasons, overestimates the true BMD value (BMC/bone volume) for increasing bone volume, thus requiring appropriate corrections to evaluate the actual BMD value in subjects with a small body size for age, and the actual BMD changes during growth. To overcome this limitation, different correction methods have been proposed [15,16]. Since boys affected by DMD (especially receiving CS treatment) have a reduced growth, their DXA values must always be adequately corrected in order to avoid incorrect estimates.

Lumbar spine and total body measurements are the most widely used in children, and those with more published data. However, Dr. Bianchi reported a recent development of DXA, the scanning of lateral distal femur, that is quite promising for children with motor disabilities such as cerebral palsy and also for children with DMD with limited mobility [17].

An important aspect of DXA is that it can be used to predict the risk of fractures before they occur. There is evidence for a strong relationship between low BMD and fracture risk in adults, and some recent studies have also found a similar relationship in children [18,19]. This aspect may be very relevant in DMD, in which the fracture rate seems to be increased, even if a precise estimate of the vertebral fractures incidence is lacking.

The treatment options in glucocorticoid-induced osteoporosis (GIO) and disuse osteoporosis were also discussed, given their relevance in DMD.

Dr. Bianchi stressed that bone loss is 6–12% within the first year of CS treatment, and that the fracture risk increases rapidly in the first 3 months of treatment. Fractures may occur in up to 30–50% of adult subjects receiving chronic CS therapy. Vertebral fractures are often asymptomatic, probably because of CS-induced analgesia. There are only few epidemiological data about fractures in children treated with long-term CS [20]. No safe dose seems to exist, since an increase in vertebral fractures has been observed with as little as 2.5 mg of prednisone daily. King et al. [21] observed that CS-treated boys with DMD have an increased risk of vertebral and lower limb fractures with respect to untreated DMD boys. Vertebral compression fractures were observed in 32% of the CS-treated group, compared with none in the CS-naïve group. Long bone fractures were 2.6 times more frequent in CS-treated patients.

Bisphosphonates (BPs) are the current standard of care for the prevention and treatment of GIO. Alendronate and risedronate were the first BPs used in GIO and their efficacy was demonstrated in both female and male patients over a wide age range (17–85 years) [22]. In a recent double-blind study on adults with GIO [23], a single intrave-

nous infusion of zoledronic acid (5 mg) once a year seemed effective for both the prevention and treatment of bone loss associated with CS.

The fact that most data on BP use in children come from the treatment of osteogenesis imperfecta, essentially with intravenous pamidronate was discussed. One of the first studies with an oral BP in children was performed by Dr. Bianchi: CS-treated children affected by juvenile rheumatoid arthritis showed a significant increase in BMD and a reduction of fractures with alendronate treatment. Alendronate proved to be safe and had no negative effects on growth or pubertal spurt [24].

Recently, the efficacy of intermittent (pulse) therapy with teriparatide (recombinant form of parathyroid hormone) has been demonstrated in adult GIO [25].

Regarding disuse osteoporosis, its most common causes are prolonged bed confinement, immobilization due to motor paralysis and fracture casts. Rehabilitation, including bed positioning, therapeutic exercise and electrical stimulation are the basic treatments to avoid disuse OP. Animal studies [26] and double-blind studies on small groups of children with cerebral palsy [27,28], demonstrated the efficacy of BPs in inhibiting bone resorption in disuse osteoporosis.

Many studies have demonstrated the influence of physical activity on bone during growth. Especially in prepubertal children, exercise increases bone density and bone strength [29]. More recently it was demonstrated that low-magnitude mechanical stimuli are anabolic to bone in young females with low bone density and increase BMD at the spine and lower limbs [30]. Following this, there are ongoing trials in children with disabilities, including one by Dr. Bianchi in children with DMD using a vibration platform.

## 7. Concluding remarks

Until recently, the physicians' approach to the endocrine complications of DMD was essentially inactive. Currently, some centers are in favor of a more reactive approach. But on the basis of the latest clinical and research developments, it is probably time to be proactive, that is, to think about preventing the undesirable secondary manifestations of the disease before their appearance and to implement strategies to avoid or reduce the effects of these complications.

It must be noted that, until now, the endocrine problems of DMD have not been explored in depth. At the Florence 2009 meeting, there was a very lively debate, and even though no definitive conclusions could be reached, the experts agreed on some starting key-points.

1. Regarding height, there is evidence that DMD does influence height and that short stature is not detrimental to function. In addition, chronic CS treatment may cause growth failure. However, data on height are not regularly collected in DMD patients, and this must be



changed. It is also important to remember that linear height measurement is not trivial in children with difficulty to stand-up normally. Thus, it is necessary to standardize the methods for measuring height in boys with DMD and to widely disseminate these standards to obtain comparable data. National specific growth charts should be used to evaluate height deficits. In the presence of reduced height, serum GH screening indices should be evaluated, with consideration given to more detailed GH testing if indicated. If GH treatment is decided, timing and therapeutic goals should be individualized, and therapy should be carefully monitored, considering the difficulties of accurate height measurement in boys with DMD, and the fact that there are inadequate data regarding benefit or harm of rhGH in the DMD-affected muscle.

2. Pubertal delay or complete suppression of puberty may accompany prolonged CS use in DMD, as in many other chronic diseases. Testosterone replacement is possible, and preliminary experience (see above) has been positive. Like growth, pubertal stage must also be regularly assessed. The choice to treat and the timing of interventions must take into account the individual's specific needs. Presently, there are no data on the psychological impact of reduced height and pubertal delay. All these aspects become relevant for boys with DMD especially during adolescence and in young adulthood when socialization and comparison with same-age subjects are common. The requests of being "like the others" must be taken into account, and the risks and benefits of interventions (including psychological well-being) must be carefully individualized.
3. Excessive weight gain is very frequent in boys with DMD due to chronic treatment with CS and also to reduced mobility. Dietary evaluation by skilled dietitians should be part of the routine evaluation. Glucose metabolism should be evaluated: paired glucose and insulin levels, with glycosylated hemoglobin levels, and oral glucose tolerance testing (OGTT) could be considered in the presence of excessive weight gain, increased laboratory values (serum glucose, insulin or glycosylated hemoglobin). The experts agreed on the relevance of diet and careful weight monitoring. Some experts suggested that, in DMD boys, caloric intake should be about 80% of normal intake for ambulant boys, and 70% for non-ambulant boys. Some preliminary data suggest that metformin may be useful in patients with proven insulin resistance and extreme weight gain.
4. Regarding bone health, the relationship between BMC/BMD and future fracture risk in children/adolescents underscores that bone mass evaluation should become a standard in the follow-up of children with DMD. General measures to optimize bone mass gain should be started as soon as possible. They include individualized physical exercises, appropriate calcium and protein intake, supplementation of vitamin D (if needed, after measuring 25-hydroxyvitamin D levels). The dose and

regimen of CS administration may have important effects on bone, and this aspect will be addressed in a forthcoming international study ("Duchenne muscular dystrophy: double-blind randomized trial to find optimum steroid regimen (FOR-DMD)" – Study Chair: Kate Bushby and Robert C. Griggs). In the presence of vertebral fractures and reduced BMD, BPs should be considered as a treatment option, with due caution for children. However, there are no large randomized double-blind studies to support decisions about the drug, the administration route, the dose and the duration of therapy.

In conclusion, we must be fully aware that we are moving within an unexplored area. This article is only a preliminary contribution, and a partial response to the "cry for help" coming from the patients and their families, who would like to see a more rapid progress than is normally achieved by evidence-based medicine.

Considering the difficult problems that the "older" subjects with DMD are currently posing and would like to see resolved (fewer side effects of CS therapy, improved self-esteem and quality of life), more active collaboration between different specialists and different centers is imperative.

Large, longitudinal, controlled studies are urgently needed to give scientifically valid answers to the many open questions.

## Participants

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