Meeting report

Report on the Second Endocrine Aspects of Duchenne Muscular Dystrophy Conference December 1–2, 2010, Baltimore, Maryland, USA

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1. Introduction

The Second Endocrine Aspects of Duchenne Muscular Dystrophy Conference convened at the Kennedy Krieger Institute in Baltimore, Maryland, USA from December 1–2, 2010. This annual meeting was established in 2009 in Florence, Italy for the purposes of promoting greater understanding of the endocrine issues surrounding Duchenne muscular dystrophy (DMD), identifying areas of research that are needed in this field, and developing unified treatment recommendations for patients and their families. The 34 attendees of this meeting included clinicians and researchers in the fields of adult and pediatric neurology, endocrinology, cardiology, and rehabilitative medicine, as well as members of Parent Project Muscular Dystrophy, the primary sponsor of the meeting. This report summarizes the presentations and highlights the major discussion points from this conference.

2. Background

The need for this meeting stems from a steadily increasing recognition of how the disease process in DMD and its treatment (namely corticosteroids) significantly impact the endocrine systems of affected patients. There is currently little evidence available to guide the management of this aspect of the disease. However, there is great potential to improve the quality of life of individuals with DMD through endocrine approaches, and multidisciplinary collaborations are needed to realize this potential. The proceedings of the inaugural endocrine conference in this series have recently been published and outline the key areas where further research and unified recommendations are most needed [1].

The conference included four major educational sessions in the following topics:

I. Growth, puberty, and self-esteem.
II. Metabolic issues and obesity.
III. Bone health.
IV. Endocrine treatments for muscle function.

Each of these sessions included presentations by endocrinology and neurology experts that were followed by round-table discussions involving all conference attendees. The meeting concluded with breakout sessions aimed at developing consensus recommendations for care and identifying future research projects and collaborations.

3. Growth, puberty, and self-esteem

The presentations in this session reviewed the function of the hypothalamic–pituitary–adrenal axis, the role of hormones in growth and puberty, and the side effects of
exogenous corticosteroid administration. The two most prominent issues discussed were: (1) the risks and benefits of treatment for delayed puberty/hypogonadism, and (2) the risks and benefits of treatment for short stature.

3.1. The treatment of delayed puberty and hypogonadism in DMD

Observational studies indicate that hypogonadism is common in DMD [2]. This is may be due to a number of factors including genetics, chronic disease, and suppression of pituitary function by exogenous corticosteroids. The effects of hypogonadism can include delayed puberty, diminished or late growth spurts, impaired emotional maturity, poor self-image, osteoporosis, and metabolic abnormalities.

The clinical approach and diagnostic workup of delayed puberty and growth failure in the DMD population were discussed. Specific emphasis was placed on accurately measuring height and weight, as well as correctly interpreting hormone levels. For the purposes of monitoring for delayed puberty, it was recommended that Tanner staging be directly assessed at routine clinic visits. Referral to an endocrinologist should be considered if a patient has not reached puberty by the age of 14. The initial workup for delayed puberty/hypogonadism includes early morning serum testosterone levels, thyroid function testing, and assessment of bone age from radiographs of the left hand and wrist.

Delayed puberty is most commonly treated with various forms of testosterone. Currently, there are no studies examining the outcomes of treating delayed puberty in patients with DMD. However, studies outside the DMD population suggest that there are multiple potential benefits to doing so, and many attendees strongly advocate treatment in all males with delayed puberty [3,4]. Among groups of hypogonadal boys, treatment with testosterone increased height velocity, lumbar spine bone mineral density, and lean body mass while decreasing fat mass. Patients with DMD may further benefit from improved maturity and greater social acceptance by their peers. The potential physiological effects of testosterone treatment include physical changes related to normal progression through puberty, such as acne and increased body mass index. These changes may make transfers and grooming more difficult for caregivers. Inducing puberty also increases libido, and there may be challenges for patients and families in addressing the subject of sexuality. Until further research provides a better understanding of the consequences of pubertal induction in the DMD population, the decision to treat with testosterone should be individualized.

3.2. The treatment of short stature/growth failure in DMD

Adult height is determined by a combination of genetics, endogenous and exogenous hormones, and nutritional factors, all of which can be abnormal in DMD. Natural history studies indicate that short stature is common in DMD. Although birth weight and length are normal, a gradual slowing of growth is observed in the first years of life [5]. At the age of 10, the median height of boys with DMD falls just below the 50th percentile. By the age of 18, most patients fall within the 5th percentile for height [6]. There is significant controversy regarding the treatment for short stature. A few reports have suggested that short stature in patients with DMD may be associated with increased strength and an improved clinical course overall [6,7]. This effect may be due to favorable mechanics related to smaller size in these patients. However, the possible adverse psychosocial effects of reduced height compel us to consider methods of improving growth in the DMD population.

The limited and conflicting data regarding growth hormone in DMD were reviewed [8–10]. Meilan Rutter presented original data on the use of growth hormone in patients with DMD and glucocorticoid-induced growth failure at Cincinnati Children’s Hospital Medical Center. This was a retrospective analysis of 39 subjects who were treated with recombinant human growth hormone. At baseline, the mean age of this cohort was 11.5 years, and the mean bone age was 8.3 years. 86% of patients were ambulatory, and all were on chronic daily glucocorticoid therapy. Follow-up at 12 months showed a significant increase in growth velocity and normalization in growth rate after treatment. Analysis of dual energy X-ray absorptiometry (DXA) scans in this cohort demonstrated an overall increase in lean mass without an increase in fat mass. There was marked variability in individual responses, but in general, patients did not completely catch up to baseline height percentiles prior to initiation of glucocorticoids. There were no significant changes in cardiac and respiratory function during the study period. Decline in performance of timed function tests (Gower’s and 30-foot run) was similar pre-growth hormone and at 12 months. Adverse events included intracranial hypertension in 1 subject, significant insulin resistance in 2 subjects, and progression of scoliosis in 3 subjects. Long-term follow-up of this cohort will provide valuable information in terms of final height, bone age status, and whether the phenomenon of “catch-down” growth (attenuated response with sustained growth hormone use) is observed.

Other potential treatments for short stature, including IGF-1 and testosterone, have not been studied extensively in DMD, and it was agreed that further investigation of these treatments is warranted. IGF-1 is a primary mediator of the effects of growth hormone and is approved for the treatment of patients with short stature due to growth hormone insensitivity or severe IGF-1 deficiency. It is speculated that IGF-1, like growth hormone, may increase growth and improve muscle function in patients with DMD, but without the risk of insulin resistance. A clinical trial to determine if IGF-1 improves or preserves muscle function (and secondarily increases growth) in DMD is currently being conducted at Cincinnati Children’s Hospital Medical Center.
For the purposes of tracking and managing issues of growth in a clinical context, it is recommended that height be measured at every clinic appointment and plotted on a growth curve. Standing height using a stadiometer is preferred. However, given that the disease eventually leads to loss of ambulation, an alternative measurement of growth is indicated. Ulnar length measured by a segmentometer was felt to be an appropriate second measurement. As this measurement should be obtainable regardless of ambulation status, it can be used for tracking growth and height velocity, monitoring for observational studies and clinical trials, and calculating predicted measurements for pulmonary function tests. Without further evidence of benefit, the decision to pursue treatment with growth hormone for short stature should be individualized, with the primary determinants being the opinions and feelings of the patient and his family regarding the impact of short stature on his quality of life.

4. Obesity and metabolic issues

4.1. Issues of weight in DMD

Obesity is a common clinical feature in patients with DMD and is primarily attributed to the use of corticosteroids and the progressive loss of exercise capability in these patients [11]. However, nutrition and other factors also contribute to the development of obesity, and observational studies have suggested that patients with DMD consume a significantly higher number of calories than their peers even before the initiation of corticosteroids [Escolar et al., unpublished data]. The presentations in this session reviewed the mechanisms of obesity and the possible adverse health consequences of chronic corticosteroid-induced obesity. These include: decreased linear growth, impaired mobility, decreased self-esteem, Cushingoid appearance, and metabolic issues such as hypertension, insulin resistance, and hyperlipidemia. The clinical picture is further complicated by the fact that ideal weight goals for patients with DMD have not been standardized. Decrements in lean muscle mass and immobility are factors that differentiate patients with DMD from their peers in ways that are likely to influence ideal body weight.

An important topic of discussion was the incidence of metabolic and cardiovascular complications in the DMD population. While it is well-established in other adult populations that chronic corticosteroid use can lead to insulin resistance and diabetes, the collective clinical experience of the conference attendees suggests that symptomatic hyperglycemia is uncommon in DMD patients. Likewise, the true incidence rates of hypertension, hyperlipidemia, and cardiovascular disease in the DMD population are unknown, but multiple clinicians felt that these conditions were rarely seen in their own practices. Multiple reasons for this were proposed. It is possible that there are unknown autonomic, vascular, and metabolic factors that distinguish patients with DMD from other adult populations. Another possibility is that patients with DMD may not have used corticosteroids in adulthood long enough for these complications to occur. It was agreed that further studies are needed in this field. However, until such data are available, prevention of vascular disease and/or metabolic syndrome may not be sufficient reasons for aggressively pursuing weight loss measures in this patient population. Likewise, the necessity of testing for indicators of metabolic syndrome (paired glucose and insulin levels, glucose tolerance tests, hemoglobin A1c, lipid profiles, etc.) was subject to debate among conference attendees. Many practitioners did some form of screening for these conditions, and among those practitioners it was felt that the detection of hyperlipidemia or insulin resistance requiring treatment was uncommon. However, there was agreement that the impact of obesity on motor, cardiac, and respiratory function in DMD patients was likely to be significant and should be examined further through clinical studies.

Another major topic of discussion was the fact that body habitus can vary markedly within the DMD population. While obesity remains the most prevalent obesity concern, many of the clinicians present have treated patients with DMD who do not have excessive weight gain or obesity. These patients may, in fact, develop “failure to thrive” and remain markedly underweight despite corticosteroid use [12]. Whether this presents a distinct subtype of DMD is unknown, as are the prognostic implications of this phenotype. Weight loss is also frequently seen in the later stages of DMD, and may be related to the cardiomyopathy and respiratory insufficiency that are characteristic of late-stage DMD [13]. The implications of treating patients who are underweight also merit further study.

4.2. Clinical management of weight in DMD

In terms of clinical management, it was agreed that at every visit, weight should be measured, plotted on a growth curve, and used to calculate a body mass index (BMI). A goal of maintaining a weight between the 10th and 85th percentiles for age was felt to be reasonable. Since this comprises such a wide range of weights, intervention is also indicated if weight velocity begins to increase exponentially. Alternatively, since normative BMI data for DMD do not exist, waist circumference is a good marker for obesity. Changes in the pattern of growth should be noted, particularly when a patient is on corticosteroids. Prior to

starting corticosteroids, patients and their families should understand that the decreased levels of activity in patients with DMD also reduces their caloric requirements compared to unaffected boys of the same age and that the addition of corticosteroids can precipitate marked weight gain. Nutritional counseling is recommended for all patients at the start of corticosteroid therapy, and caregivers should be advised to closely monitor caloric and sodium intake. Patients with excessive weight gain (greater than 10–25% of baseline weight) may require more frequent monitoring by a nutritionist or dietician. In selected cases, such as those in whom nutritional intervention is unsuccessful, a reduction in corticosteroid dosing should be considered.

4.3. Corticosteroid use in DMD

Many of the questions that were raised in this session dealt with various aspects of corticosteroid use. The differences between prednisone and deflazacort were discussed, and while it was felt that there were no differences between the drugs in terms of effect on muscle and cardiac function, some studies have found a lower incidence of weight gain with deflazacort [14–16]. Consequently, some attendees felt that switching from prednisone to deflazacort should be considered as an alternative to lowering the corticosteroid dose if obesity develops.

While the daily dose of corticosteroids for ambulatory patients is fairly standard (0.75 mg/kg for prednisone, 0.9 mg/kg for deflazacort), dosing schedules can vary significantly between practitioners. Some prescribe daily dosing, while others use intermittent drug dosing (such as “10 days on/10 days off”) in an effort to reduce weight gain and bone loss. A recent study has shown that a schedule of weekly high-dose corticosteroids is a viable alternative to daily dosing and may have fewer negative effects on linear growth [Escolar et al. Neurology. Accepted for publication February 2011]. A recent report from the DMD Care Considerations Working Group (DMD-CCWG) concluded that daily dosing is preferred and alternative dosing regimens should only be used if daily dosing is not tolerated [17]. It is anticipated that the upcoming FOR-DMD (Find the Optimal steroid Regimes in Duchenne Muscular Dystrophy) trial will clarify the efficacy of other dosing regimens [18].

Conference participants also discussed how corticosteroid dosing should be adjusted for weight. While measured weight is presumably used in most practices, it does not seem desirable to continue increasing the dose if excessive weight gain occurs. Alternatively, some attendees recommended using ideal body weight or lean body mass when calculating corticosteroid doses. A dosing cap can be employed, in which the dose is increased to a set limit (typically 30–40 mg/day for prednisone and 36–39 mg/day for deflazacort) and maintained at that limit despite further gains in weight [17]. Other participants recommended continuing the initial corticosteroid dose indefinitely without adjusting for increased weight over time, creating the effect of a very slow corticosteroid taper. The comparative effectiveness and toxicity of these systems is unknown at this time.

The question of when to start and stop corticosteroids is both extremely important and challenging. It is a common practice in some clinics to initiate corticosteroids when motor function begins to plateau and to taper them when a patient becomes wheelchair dependent. There are, however, many exceptions to this practice. Some clinics begin corticosteroid treatment soon after diagnosis in toddlerhood. It has been observed by some clinicians that when corticosteroids are given this early in the course of the disease (ages 2–5), the occurrence of obesity is rare. This is possibly due to parents having greater control of the patients’ diets from a very early stage, as well as the increased activity levels associated with the earlier stages of the disease. However, since there are no studies on the effects of corticosteroids in this age group, the DMD-CCWG recommends initiating corticosteroids when patients have stopped gaining motor function [17]. It is also becoming more common for patients and caregivers to request the continuation of corticosteroids into late adolescence and adulthood. There is evidence that continuing corticosteroids into adulthood may provide benefits in terms of respiratory or cardiac function [15]. Corticosteroid dosing in non-ambulatory patients is not standardized; however, two centers have reported using on average 0.3 mg/kg/day in this population [19,20].

The topic of stress-dose corticosteroids at times of illness was discussed. Chronic corticosteroid use causes adrenal suppression, which could place patients at risk for adrenal insufficiency in times of physiologic stress. The majority of patients with DMD are on corticosteroid doses that surpass levels needed at times of stress; therefore, corticosteroid coverage only becomes an issue when concomitant symptoms, such as vomiting, prohibit the intake of the usual corticosteroid dose. If this occurs, patients should receive intramuscular hydrocortisone (Solu-cortef). This can be administered by caregivers at home or in an emergency room/urgent care setting.

4.4. Directions for future research in growth and obesity in DMD

The discussion group felt that it was important to obtain data on the physical and psychosocial consequences of short stature, delayed puberty, and obesity in patients with DMD. While it is perhaps intuitive to assume that these issues will adversely and significantly affect a patient’s psychosocial condition, it is important to have patients independently identify the impact of these issues on their quality of life before recommending interventions that may have side effects or increase the burden of their care. The impact of these issues on parents and other caregivers should also be assessed. This will require the development of disease-specific research instruments and surveys that can accurately gauge quality of life, socialization, and independence.
It was agreed that the currently available data are not sufficient to develop unified clinical guidelines on the management of delayed puberty, short stature, and weight gain. Members of the discussion group felt that pre-existing databases (MD STARnet, PTC124 trial data, CINRG network data, the Utah Dystrophinopathy Project, and the Clinical Investigation of Duchenne Dystrophy study) could provide data on height, weight, and outcomes in DMD that would be useful in formulating care recommendations. The analysis of these data was therefore felt to be of high priority. Until evidence-based recommendations are available, members of this discussion panel will collaborate to produce fact sheets or Q and A discussions on the following issues:

- Short stature and the risks and benefits of starting growth hormone,
- Delayed puberty and the risks and benefits of starting testosterone, and
- The impact of obesity (and related co-morbidities) on care and mobility.

This literature will be directed toward patients, families, and health care providers with the goal of increasing awareness of endocrine issues and enhancing the multidisciplinary care of DMD patients.

5. Bone health

5.1. Osteoporosis and bone health in DMD

Osteoporosis-induced vertebral and extremity fractures are significant health issues in patients with DMD and are likely under-diagnosed causes of pain, loss of mobility, and skeletal deformity [21]. The speakers in this session reviewed the mechanisms of bone fragility and the causes of osteoporosis (including reduced mechanical loading, corticosteroid use, increased adiposity, nutritional deficiency, poor growth, and delayed puberty) [22,23]. Natural history studies show that reductions in bone mass (osteopenia) can be seen in DMD patients even prior to the initiation of corticosteroids and the loss of ambulation, and a review of historical data suggests that the prevalence of both long bone fractures and symptomatic vertebral compression in patients with DMD is around 20–30% [16,21,24–27]. The frequency of asymptomatic vertebral fractures (believed to be precursors to painful spine fragility) is unknown. Consensus statements from meetings on bone protection in DMD have previously been published, and this discussion is intended to complement those recommendations [28–30].

5.2. Clinical management of bone health

There was avid discussion regarding the appropriate diagnostic workup of osteoporosis in DMD. Although numerous imaging and laboratory tests are available, attendees felt that it was important to distinguish tests that significantly impact patient care for routine use. The discussion group concluded that at the time a diagnosis of DMD is made, baseline bone health information should be obtained. This includes a detailed nutritional history, fracture history, radiographic confirmation of any past fractures, and assessment of back pain. This history should be updated during routine visits. Serum vitamin D levels (i.e., serum 25-OH vitamin D) should also be obtained and vitamin D supplementation should be prescribed as needed with a target level $\geq 30$ ng/ml ($\geq 75$ nmol/L). It should be noted that there is controversy regarding optimum vitamin D levels, and other published guidelines recommend supplementation if the vitamin D level is less than 20 ng/ml (50 nmol/L) [30,31]. Until corticosteroids are initiated, vitamin D levels should be checked every 1–2 years.

At the time corticosteroids are initiated, a DXA scan of the lumbar spine and a lateral spine radiograph should be obtained to screen for reductions in bone mineral density and vertebral fractures, respectively. In pre-pubertal patients, bone age should be determined via radiograph of the left wrist and hand so that development may be factored into the interpretation of the DXA scan. These studies should be repeated on an annual basis while the patient is on corticosteroids. All patients should be counseled to report new onset back pain regardless of severity, and nutrition counseling should be provided to families in order to optimize calcium and vitamin D intake. Fall prevention strategies should also be considered.

5.3. Prevention and treatment of osteoporosis

A recent study from Bianchi et al. demonstrated the potential benefits of optimizing the intake of calcium and vitamin D in the DMD population [32]. Subjects that were given vitamin D supplements and achieved recommended levels of dietary calcium intake showed decreased bone resorption, decreased parathyroid hormone levels, and increased bone mineral density on lumbar spine and whole body DXA. It was agreed that for adult patients with DMD, dietary intake should include: 800–1000 IU of vitamin D3 per day, 1000–1200 mg of calcium per day, and 0.8 g/kg of protein per day. Dosing in pediatric patients should be based on recommended daily allowances for age. It was emphasized that calcium and vitamin D intake through food was felt to be superior to supplemental forms; however, supplementation should be considered in cases of inadequate dietary intake. Limiting sodium consumption was also recommended in order to reduce urinary calcium excretion, particularly during corticosteroid treatment.

Leanne Ward presented unpublished data from the DMD bone health monitoring program at the Children’s Hospital of Eastern Ontario (CHEO). Her retrospective analysis identified seven patients with DMD who were treated with intravenous bisphosphonate therapy for vertebral fractures and back pain localized to the site of fracture. Patients received either IV pamidronate (9 mg/kg/yr
divided into three doses given every 4 months) or IV zoledronic acid (0.1 mg/kg/yr, divided into two doses given every 6 months). Outcome measures included back pain and vertebral morphometry after 1 year of therapy. Four boys reported complete resolution of back pain and the remaining three boys reported significant improvement. Measurement of the height of the vertebral bodies and calculation of the change in the Spinal Deformity Index showed stabilization of vertebral fractures in five patients and improvement in the remaining two. With the first cycle of IV bisphosphonate therapy, side effects included fever, malaise, and bone pain (typical first-infusion symptoms associated with IV bisphosphonate therapy). Based on the results of this and other studies, it was felt that IV bisphosphonates should be considered in DMD patients with symptomatic vertebral fractures due to osteoporosis. The treatment of asymptomatic vertebral fractures or low bone density without fractures identified through routine screening was felt to be more controversial and should be considered on a case-by-case basis.

Other options for the treatment of osteopenia and osteoporosis were discussed, including oral bisphosphonates (such as alendronate), teriparatide (Forteo), recombinant human parathyroid hormone, and pubertal induction with testosterone (as previously discussed). Teriparatide is currently available for the treatment of osteoporosis in adults, particularly those who have failed bisphosphonates. However, the increased risk of osteosarcoma in patients with open epiphyses limits its use in children and adolescents. Currently, bisphosphonate therapy remains the most widely accepted treatment of osteoporosis (bone fragility) in the pediatric population, including patients with DMD.

5.4. Directions for future research in bone health in DMD

Members of the bone health working group discussed the establishment of a multi-center registry of standardized data on secondary osteoporosis in DMD. The working group identified several research parameters that would be important in characterizing longitudinal bone health in DMD, although they are not required for routine clinical care. These include imaging studies (DXA of the lumbar spine, lateral spine X-rays, and bone age assessment) at the time of diagnosis and every 2 years prior to the initiation of corticosteroids. The utility of bone turnover markers was extensively reviewed. These markers are frequently used to monitor outcomes in research studies of bone health; however, their role in the clinical management of patients with DMD is not clear. For the purposes of conducting bone health research in DMD, it was felt that serum bone turnover markers, including C-terminal cross-linking telopeptide of type I collagen (CTX) and bone-specific alkaline phosphatase (BSAP), should be collected at the time of diagnosis, every 2 years prior to the initiation of corticosteroids, and every year while a patient remains on corticosteroids. The inclusion of these parameters in a multi-center research database will be crucial to the development of further guidelines regarding preventative measures (such as nutrition, exercise, and medications) against osteoporosis and fracture in DMD, the management of subclinical vertebral fractures, and the criteria for treatment with IV and oral bisphosphonates.

6. Endocrine agents in muscle growth

Major clinical trials of endocrine-based treatment, including corticosteroids, anabolic androgenic steroids, and growth hormone-mediated medications for muscular dystrophy were reviewed in this session. Corticosteroids are currently the only medications that are widely-used to improve muscle strength in DMD. Although they are frequently discontinued when patients are no longer ambulatory, it is possible that adults with DMD will benefit from corticosteroid use in terms of cardiac and respiratory function. Whether there are any benefits to starting corticosteroids in adult patients (either those who have never taken corticosteroids or have discontinued them in the past) is a subject that warrants further study.

There are also many unanswered questions regarding the role of anabolic agents in the treatment of DMD. Testosterone and oxandrolone (a non-aromatizable analog of testosterone) have been studied in small-scale trials in DMD and other diseases that cause muscle wasting (such as HIV infection) [33–35]. These studies were able to demonstrate changes in disease biomarkers, but did not produce significant improvement in muscle function. Experimental agents, such as selective androgen receptor modulators (SARMs), are being developed with the goal of producing anabolic effects without androgenic effects, and may prove to be of interest in the DMD population. The interactions between growth hormone, GHRH, insulin, and IGF-1 as regulators of body composition also merit further study. It was recommended that longitudinal data on changes in testosterone, IGF-1, and possibly growth hormone stimulation testing in patients with DMD be collected and analyzed in order to optimize the timing of hormone treatment.

Kenneth Attie, VP of Medical Research at Acceleron Pharma, presented new data from clinical trials of ACE-031, an inhibitor of myostatin and other negative modulators of muscle growth. The activity of myostatin is mediated through its binding to the activin IIB receptor, and ACE-031 is comprised of the extracellular domain of the activin IIB receptor fused to human IgG serving as a decoy receptor to myostatin and other muscle regulators. A phase I trial of ACE-031 in post-menopausal women, demonstrated a trend for increased muscle mass, decreased bone resorption, and altered fat biomarkers. A phase II trial in patients with DMD has been initiated. The pharmacokinetic aspects and outcome measures studied in these trials were discussed in detail. With regards to endocrine issues, it was noted that phase I studies were done in post-menopausal women because activin stimulates pituitary synthesis of follicle stimulating hormone, which is involved in spermatogenesis and testicular function in males and...
7. Summary of research interests

Numerous potential avenues of clinical research were identified by the conference attendees. Those that were seen as having the greatest potential impact on the clinical management of endocrine issues in DMD are described.

7.1. Natural history and outcomes

A great deal remains unknown about the natural history of the endocrine system in DMD, and this information was felt to be vital to the development of unified recommendations regarding the management of endocrine issues in this population. Observational studies are needed to determine what significant health outcomes are associated with excessive weight gain, weight loss, short stature, and induction of growth. Measurements of hormone levels, bone turnover markers, and bone imaging studies at different stages of development should also be collected to determine how these markers change over time compared to unaffected individuals. From this data, ideal height and weight profiles could be defined for the DMD population.

7.2. Measurements

The importance of accurate and reliable measurements was emphasized throughout the conference. While the series of measurements described in the summary recommendations reflect the best measures of body composition, strength, and bone health that are currently available, it is possible that this battery of tests can be edited and augmented to be more accurate, replicable, efficient, informative, and convenient for patients and physicians. Many of the proposed interventions will also require investigators to obtain information from patients and caregivers about quality of life, socialization, patient self-image, and burden of care. While surveys and instruments do exist to assess these issues, it is possible that new methods of assessment that are specific to DMD will need to be developed and validated.

7.3. Corticosteroid use

Despite their widespread use, many questions remain regarding the optimal scheduling and dosing of corticosteroids, both in terms of improving function and minimizing side effects. As greater numbers of patients with DMD are living into adulthood, it will be vital to understand the risks and benefits of using corticosteroids in this stage of the disease. The effects – both positive and negative – of corticosteroids on cardiac, vascular, and metabolic disorders (glucose intolerance, diabetes, hypertension, hyperlipidemia, and cardiovascular disease) are of particular interest.

7.4. Novel medications and other interventions

Multiple endocrine-based treatments have been considered or are currently under investigation for use in DMD patients. These include existing medications, such as testosterone, oxandrolone, growth hormone, IGF-1, and IGF-1/IGFBP-3 complex, as well as investigational agents, such as myostatin inhibitors and SARMs. Prospective clinical trials with adequate sample sizes are needed to determine how they may affect outcomes in DMD, and all therapeutic trials should include measures to assess the impact of treatment on cardiac and pulmonary function. Further trials are also needed to clarify the role of bisphosphonates and other osteoporosis drugs in the treatment and prevention of bone mineral density reduction and fragility fractures in DMD.

8. Conference participants

Kenneth Attie, Cambridge, USA; Maria Luisa Bianchi, Milan, Italy; Genila Bibat, Baltimore, USA; Doug Biggar, Toronto, Canada; Carsten Bonnemann, Bethesda, USA; Todd Brown, Baltimore, USA; Filippo Bucella, Rome, Italy; Sarah Chen, Baltimore, USA; Lawrence Charnas, Cambridge, USA; Lisa Christopher-Stine, Baltimore, USA; Janet Crane, Baltimore, USA; Brian Denger, Biddeford, ME; Adrian Dobs, Baltimore, USA; Diana Escolar, Baltimore, USA; Pat Furlong, Middletown, OH; Emily Germain-Lee, Baltimore, USA; Tony Huynh, Canberra, Australia; Suzanne Jan De Beur, Baltimore, USA; Kathi Kinnett, Cincinnati, OH; Doris Leung, Baltimore, USA; Larry Markham, Nashville, USA; Elena Maria Mularoni, Turin, Italy; Katherine Mathews, Iowa City, USA; Craig McDonald, Sacramento, USA; Robert McDonald, Jefferson City, USA; Elyse Pine-Twaddell, Baltimore, USA; Alan Rogol, Indianapolis, USA; Meilan Rutter, Cincinnati, USA; Jay Shapiro, Baltimore, USA; Susan Sparks, Charlotte, USA; Carolina Tesi-Rocha, Washington DC, USA; Laura Tosi, Washington DC, USA; Kathryn Wagner, Baltimore, USA; Leanne Ward, Ottawa, Canada;

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