COMMUNITY REPORT:
APRIL 2023
ENDOCRINE AND BONE HEALTH WORKSHOP

Parent Project Muscular Dystrophy
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Parent Project Muscular Dystrophy and Duchenne Parent Project, Italy-Sponsored International Workshop

Endocrine and Bone Issues in Duchenne Muscular Dystrophy: An Ever-Changing Landscape

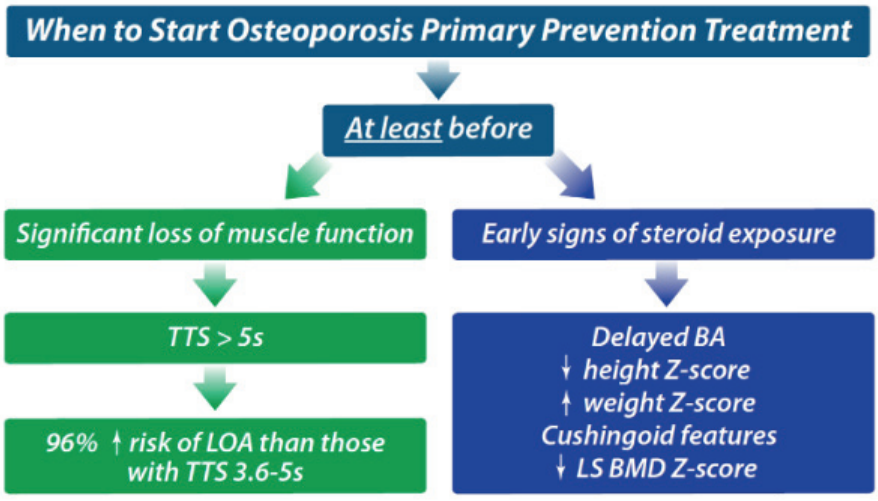
Led by Dr. Leanne Ward, Pediatric Endocrinologist from Children's Hospital of Eastern Ontario (CHEO), over 30 health care professionals and patient advocates from four countries (Canada, Italy, UK and USA) met in April 2023 to discuss current standards and unmet needs in the endocrine and bone health care of individuals living with Duchenne and Becker muscular dystrophy.

While there have been significant advances in muscle targeted therapies for Duchenne and Becker, the use of long-term and high-dose corticosteroids (steroids) remain the backbone of treatment for the foreseeable future. While steroid therapy is helpful, there can be serious consequences with long term use including: adrenal suppression, compression fractures of the vertebrae, long bone fractures, fat embolism syndrome, weight gain and the psychosocial impact of growth and pubertal delay.

Pat Furlong, PPMD, and Filippo Buccello, Duchenne Parent Project, Italy, emphasized the need to "do better" than the current minimum Standards of Care. This includes two important areas: prevention of first-ever fracture, and the need to prevent unexpected death from unrecognized adrenal suppression & crisis. They highlighted the challenges that families face in receiving inconsistent messages from health care providers about the best course of action for optimal bone and endocrine care. Furlong and Buccello reminded workshop attendees that families do not have time for advances to arise slowly, and that the collaborative efforts of health care professionals need to be nimble and quick to positively impact the families living today, as well as the families of the future.

The main drivers of bone strength loss

The following image shows that bone strength loss occurs with a combination of declining muscle function and steroid use. Workshop attendees agreed that it is time to implement a primary osteoporosis prevention (POP) strategy.



LOA = loss of ambulation; LS = lumbar spine; TTS = time to stand; S = seconds

Moving from current steroids to vamorolone

Vamorolone, an investigational dissociative steroid for individuals with Duchenne, was recently approved in Europe (EMA) and is currently under review by the FDA in the U.S., with a regulatory decision expected by October 26, 2023.

During this workshop, Dr. Leanne Ward reviewed the evidence from the randomized, controlled trial of vamorolone 2 mg/kg and 6 mg/kg daily versus daily prednisone and placebo over 24 weeks in young, ambulatory boys with Duchenne in terms of adrenal insufficiency. Dr. Ward noted that suppression was evident in all treatment groups except placebo. This was based both on first morning cortisol values at 12 and 24 weeks and on standard dose ACTH stimulation testing at 24 weeks. It was agreed that all individuals on vamorolone should be considered at risk of adrenal suppression given the life-threatening nature of this complication.

Clinicians agreed that management for vamorolone-treated patients can be divided into four key concepts.

The first concept was that vamorolone given at 6 mg/kg daily shows comparable efficacy for muscle strength with oral daily prednisone at around 0.75 mg/kg/day (standard Duchenne-treatment dose). Therefore, clinicians may advise individuals for whom it is appropriate to switch, a transition from classic daily steroids to a vamorolone dose of 6 mg/kg/day in order to avoid signs and symptoms of adrenal suppression during the switch from one medication to the other. Patients should be monitored for signs and symptoms of adrenal suppression as a precaution when transitioning to vamorolone 6 mg/kg until more information is available about patients' symptoms during this time.

The second concept was that if at any time a patient who is transitioning from classic steroids (prednisone or deflazacort) to vamorolone 6 mg/kg/day, or who is tapering the vamorolone dose for any reason, has symptoms that could represent adrenal insufficiency (fatigue, headache, abdominal pain, nausea, weakness), they should be presumed to have adrenal insufficiency and be treated with steroid stress dosing accordingly. This is the safest course of action and was therefore considered to be in the best interest of the patients.

The third concept was that clinicians are not advised to carry out stress dosing using vamorolone. This is because there is no available experience with vamorolone doses higher than 6 mg/kg/day. The group advised that stress dosing should ideally be carried out with hydrocortisone or prednisone if hydrocortisone is not available.

The fourth concept was that because vamorolone causes adrenal suppression, gradual tapering would be required for any patient transitioning off vamorolone (like the approach when discontinuing classic steroid therapy).

Going forward, it will be crucial to get messaging out to health care professionals and patients that the signs and symptoms of adrenal insufficiency are "the great pretenders" of other diseases. Given their frequency in the general population and lack of specificity for adrenal insufficiency, symptoms of fatigue, weakness, headache, nausea, vomiting and abdominal pain may be overlooked. One could argue that this is particularly problematic in Duchenne and Becker, where fatigue and weakness are common symptoms at baseline. This highlights the importance of adrenal insufficiency awareness and education.

It is for this very reason that decision-making around the possible signs and symptoms of adrenal insufficiency must always err on the side of caution, with a low threshold to activate steroid stress dosing protocols. These principles were recently summarized in a slogan contest through *Defeat Duchenne Canada*, with the winner's submission as follows:

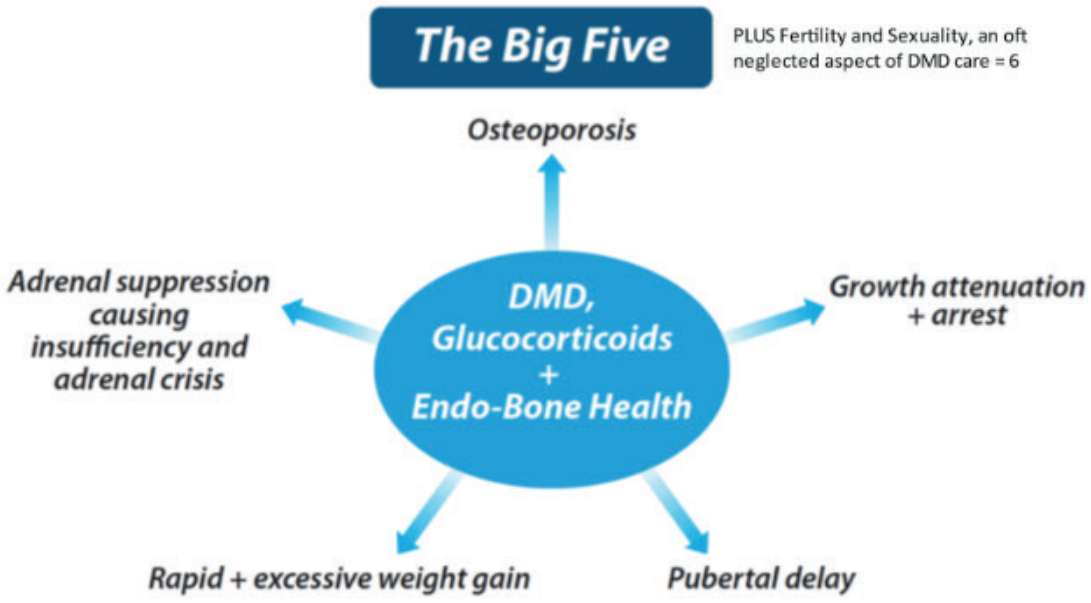
"Don't cut it close, take another dose"

by Rachel Witzke, Ottawa

DEFEAT DUCHENNE CANADA

Duchenne Endocrine-Bone Working Groups

This workshop resulted in the creation of a Duchenne Endocrine-Bone Consortium of Working Groups to address various aspects of endocrine and bone health including osteoporosis, growth, puberty, weight management, and addressing issues related to adrenal suppression and insufficiency. Additionally a working group was established to look at fertility, gender identity and sexuality.



The impact of early steroid initiation on endocrine and bone health: thinking about the future

The average age for a Duchenne diagnosis (4.4 years) and the average time from symptom onset to diagnosis (2.2 years) have not changed in recent decades. This fact, coupled with the FDA approval of the creatine kinase (CK)-MM blood spot assay (a tool to facilitate blood testing in babies), have re-invigorated the push to implement newborn screening with the hope that earlier diagnosis and initiation of disease modifying therapies will improve outcomes. Exon-skipping and gene therapies are typically given with steroids, raising the possibility that earlier diagnosis could lead to initiation of steroids at younger ages. Infancy and early childhood are times of rapid growth and bone development. It is expected that earlier steroid initiation will further reduce height and bone mass and may result in earlier fractures. There are also challenges of bone health monitoring in young children. Some centers use BoneXpert, which provides a "Bone Health Index assessment" from a hand X-ray to measure bone strength and may be simpler to obtain in young children.

Weight management in muscular dystrophy

Excessive weight gain and obesity are common in Duchenne due to a combination of steroids, decreased physical mobility, and increased calorie intake relative to physical activity levels. Support for more aggressive interventions for weight management may require a change in perspective for both families and healthcare professionals. The risks and benefits of potential medications for weight loss need to be carefully considered prior to updating the guidelines

The impact of testosterone therapy on muscle-bone health in Duchenne

There were 4 main takeaways from the discussion around testosterone therapy in Duchenne and Becker.

1. Testosterone improves muscle bulk, protects bones, and is important for overall well-being. Young people rated their quality of life as improved after pubertal induction with monthly testosterone injections.
2. Current recommendations for those with Duchenne are to induce puberty when the individual is ready. It is important for clinicians to start conversations with their patients around the time of a typical pubertal onset(12 to 13 years of age) and ensure the patient is open to the having the conversation.
3. Medically induced puberty promotes hormone (testosterone) release, but this is not always sustained. It is important to continue monitoring testosterone levels and supplement as needed.
4. It will be important to study the long-term effects of testosterone.

It was acknowledged that moving forward there needs to be greater emphasis in clinicians speaking to teens about medically inducing puberty in a private and appropriate manner during routine clinical care. In addition, there was consensus that many questions remain around best timing of testosterone intervention, the psychosocial aspect of pubertal delay and short stature, and the impact of inducing puberty on the individual's overall physical and emotional health and well-being.

Sexuality, fertility, and gender identity in Duchenne

The group agreed that individuals with Duchenne should participate in discussions around sexual wellness, fertility, and gender identity at age- and readiness-appropriate times, while respecting the patient's right to privacy and ensuring they have access to appropriate resources. In addressing the intersections of these topics within the context of Duchenne, it is essential to integrate these discussions into the broader framework of adult care while acknowledging that the transition of a child with Duchenne to adulthood can be a challenging and emotional time for parents and caregivers. While some families may experience feelings of pride and accomplishment, others may experience grief and anxiety. It is important to provide sensitivity and resources to individuals and their families during this time, acknowledging and addressing their complex emotions and needs.

The path forward: clinical care, research, and advocacy

Pat Furlong, Filippo Buccella and Dr. Ward led a group discussion to wrap up the meeting. To achieve the identified goals, it was agreed that a Duchenne Endocrine-Bone Consortium of Working Groups would be established to develop an endocrine- and bone-specific patient registry. The goal of the registry is to better understand the endocrine and bone comorbidities while looking at different muscle-targeted therapeutic regimens. In addition, the Duchenne Endocrine-Bone Consortium of Working Groups plans to develop collaborative clinical care pathways, identify synergies to enable research initiatives that answer critical questions, and create patient and health professional educational materials that address the issues outlined by the delegates and speakers in the report. With steroid treatment as a standard of care for the foreseeable future, efforts to optimally manage their co-morbidities are essential and welcomed by the Duchenne and Becker community.