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Is endocrine surveillance important in the care of Duchenne Muscular Dystrophy? Results from a national survey to patients and families on endocrine complications

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ABSTRACT

Glucocorticoids are standard of care for patients with Duchenne muscular dystrophy (DMD). Although prolonged exposure is associated with multiple endocrine side effects, current guidelines related to monitoring and management of endocrinopathies are suboptimal. We aim to explore community perceptions of endocrine related complications in patients with DMD, assess current level of understanding, and desire for further education. A 31-item online survey was sent through Parent Project to Muscular Dystrophy (PPMD) to Duchenne Registry members to be completed by patients or their caretakers. Response rate was 55% ($n = 75$). Steroids were taken by 93%, but only 50% were followed by endocrinology and 21% report never been seen by endocrinology. Bone health was discussed with 87% of patients and 60% were diagnosed with osteoporosis. Delayed puberty was discussed with 41% of patients with 23% receiving testosterone therapy. About half the patients reported a diagnosis of slowed growth. Only 51% of the participants recalled discussing adrenal insufficiency. Obesity was discussed with 59% of participants. Families felt education about steroid-induced endocrinopathies to be very or extremely important and prefer to discuss about this at the beginning of their steroid therapy. This demonstrates significant gaps in education and access to endocrine care in patients with DMD.

1. Introduction

Duchenne muscular dystrophy (DMD), an x-linked recessive neuromuscular disease caused by variants in the dystrophin gene, is the most common hereditary neuromuscular disorder. Dystrophin is an essential cytoskeletal protein involved in sarcolemma stabilization and muscle integrity. Absent or insufficient dystrophin protein leads to progressive muscle damage and degeneration. Muscle fragility activates inflammatory pathways which cause muscle damage and progressive muscle wasting leading to progressive muscle weakness, loss of ambulation, cardiomyopathy and respiratory impairment [1,2]. Muscles are eventually replaced with fatty and connective tissue causing deterioration in muscle function and strength starting in early childhood. Management focuses on delaying disease progression and managing complications in order to optimize quality of life. Although there are promising novel disease modifying therapeutic targets including exon skipping and gene therapy, glucocorticoids remain the mainstay of therapy by suppressing causative inflammatory processes [3–5]. Glucocorticoids have been shown to delay loss of ambulatory milestones [6] and improve muscle function and strength [7]. However, chronic glucocorticoids also act at other sites causing multiple endocrine side effects including weight gain, insulin resistance, adrenal insufficiency, poor growth, delayed puberty and bone fragility [8–10].

Despite these systemic side effects, there is a paucity of data in the literature addressing the DMD community's perception and understanding of these complications. Until recently, endocrine involvement within DMD multidisciplinary muscular dystrophy clinics had been limited. As a result, there may have been less emphasis on education

Abbreviations: DMD, Duchenne muscular dystrophy; pDMD, Patients with Duchenne Muscular Dystrophy; cDMD, caretakers of patients with Duchenne Muscular Dystrophy; AI, Adrenal insufficiency; BMD, Bone mineral density.

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surrounding various endocrinopathies leading to delays in treatment.

Early intervention of endocrinopathies may promote better bone density, muscle function, mobility, weight management, psychosocial well-being, and overall improved quality of life. Timely engagement of endocrinology providers allows for routine screening of these complications with a focus on education and early intervention to improve quality of life. The objective of this study is to explore community perceptions about endocrine related complications for boys with DMD, identify gaps in education and care, and explore the most effective way to deliver education and care. We also hope to emphasize the importance of making endocrinology part of standard clinical practice as well as incorporate endocrine related complications as a measure in clinical trials and emerging treatments.

2. Materials and methods

2.1. Survey development

We designed a survey for parents/caregivers of children with DMD, or patients with DMD >18 years of age, in order to assess their knowledge gaps and barriers to endocrine management. The survey consisted of five sections pertaining to different endocrinopathies related to glucocorticoid exposure and chronic illness: 1) bone health, 2) puberty, 3) adrenal insufficiency (AI), 4) growth, 5) obesity and metabolic disorders. There were five to seven questions per section, and a total of 31 questions. Survey face and content validity were assessed by all authors including several experts in the field. Survey included multiple choice questions regarding prevalence of endocrinopathies, current level of knowledge, desire for further education, and preferred way of engagement. A five-point Likert scale was used for perception of importance (1, strongly disagree; 2, somewhat disagree; 3, neither agree nor disagree; 4, somewhat agree; 5, strongly agree).

2.2. Survey administration

A link to a RedCap survey was sent through Parent Project to Muscular Dystrophy (PPMD) to Duchenne Registry members Oct 7 and Nov 17, 2022. PPMD is an organization that focuses on supporting families and patients with DMD through sponsoring DMD-related research and maintaining a national registry of patients. Links for a one-time survey were sent to all members registered with PPMD via email, with no follow up required. For pediatric patients <18 years of age, survey was completed on their behalf by their caregivers, and their responses are abbreviated as cDMD (caregivers of patients with DMD). Patients that are over 18 years of age were asked to answer questions directly, and their responses are marked as pDMD (patients with DMD). Survey was accessible for up to 12 weeks since the initial email was sent, and only valid for one submission. Only exclusion criteria are inability to understand and read English. No financial compensation was provided for participation. All responses were anonymous and no identifying information was required. De-identified responses were captured into the REDCap database for storage and analysis. A copy of the survey is available on request. Participants were notified that responses were strictly voluntary and would be aggregated in future presentations and publications. This study was deemed exempt by the Institutional Review Board at the Children's National Hospital.

2.3. Data analysis

Survey data were managed using RedCap. Descriptive statistics are reported when applicable. Overall scores for perceived importance in receiving education for steroid induced endocrinopathies were calculated by averaging the Likert scale responses for items in each corresponding section.

3. Results

3.1. Survey response

The survey was sent to 3089 emails by PPMD, and 135 participants clicked on the survey. The response rate on the RedCap survey was 55% ($n = 75/135$), of which 96% were (71/75) cDMD and 4% (3/75) pDMD. The age distribution of responses were patients age < 5 years old was 4% ($n = 3/75$), age 5–10 was 28% ($n = 21/75$), age 11–15 was 27% ($n = 20/75$), over age 16 was 41% ($n = 31/75$) with 20% over age 20. Ninety three percent (93%, 70/75) of participants were on steroids, of which 32% (24/71) had been on steroids for over 10 years. Fifty percent (50%, 38/75) of the participants were regularly followed by an endocrinologist while 21% (16/75) reported never seeing this subspecialty (see Table 1). Main results from each section are summarized in Fig. 1. Endocrine complications were mostly perceived as extremely important or very important by majority of the survey across all domains (bone heath, adrenal, reproductive, growth, and weight) as shown in Fig. 2. The survey showed endocrine complications were not always discussed with team in Fig. 3.

3.2. Bone health

Bone health had been discussed with 87% (65/75) of patients; 59% (44/75) at initiation of steroid treatment. Twelve percent (12%, 9/75) reported not discussing bone health with DMD team but would have liked to. Only half of the participants were ambulatory (52% (39/75)). At least 60% (45/75) of the patients were diagnosed with low bone mineral density or osteoporosis, and 35% (26/75) already at least one fracture, whereas 12% (9/75) of participants never had a DEXA scan or spine x-ray. Eighty one percent (81%, 61/75) of participants had been on either vitamin D or calcium supplements, and up to 40% (30/75) had received bisphosphonates infusion.

3.3. AI

Only 51% (38/75) of the participants had discussed adrenal insufficiency, with 4% (3/74) having discussed after an episode of AI or during a hospitalization. Thirty percent (30%, 23/74) of the participants had not discussed AI but would have liked to learn more about it. Up to 31% (23/75) required stress dosing for illness or surgery, with up to 3% (2/74) having used emergency intramuscular steroids at least once. Fifty percent (50%, 37/75) of participants had an emergency letter and 30% (22/75) had IM hydrocortisone sodium succinate.

Table 1
Demographic characteristics of survey responders. DMD: Duchenne Muscular Dystrophy.

		People with DMD ($N = 75$)
Age of person with DMD	< 5 years	4.0% ($n = 3/75$)
	5–10 years	28.0% (n = 21/75)
	11–15 years	26.7% (n = 20/75)
	16–20 years	17.3% ($n = 13/75$)
	≥ 21 years	20.0% (n = 15/75)
Duration of steroid exposure	0 years	6.7% ($n = 5/75$)
	<1 year	9.3% (n = 7/75)
	1–5 years	26.7% (n = 20/75)
	6–10 years	25.3% ($n = 19/75$)
	≥ 10 years	32.0% ($n = 24/75$)
Patients followed by an Endocrinologist	Currently	50.7% ($n = 38/75$)
	In the past, but not anymore	22.7% ($n = 17/75$)
	Never	21.3% ($n = 16/75$)
	Unsure	5.3% ($n = 4/75$)

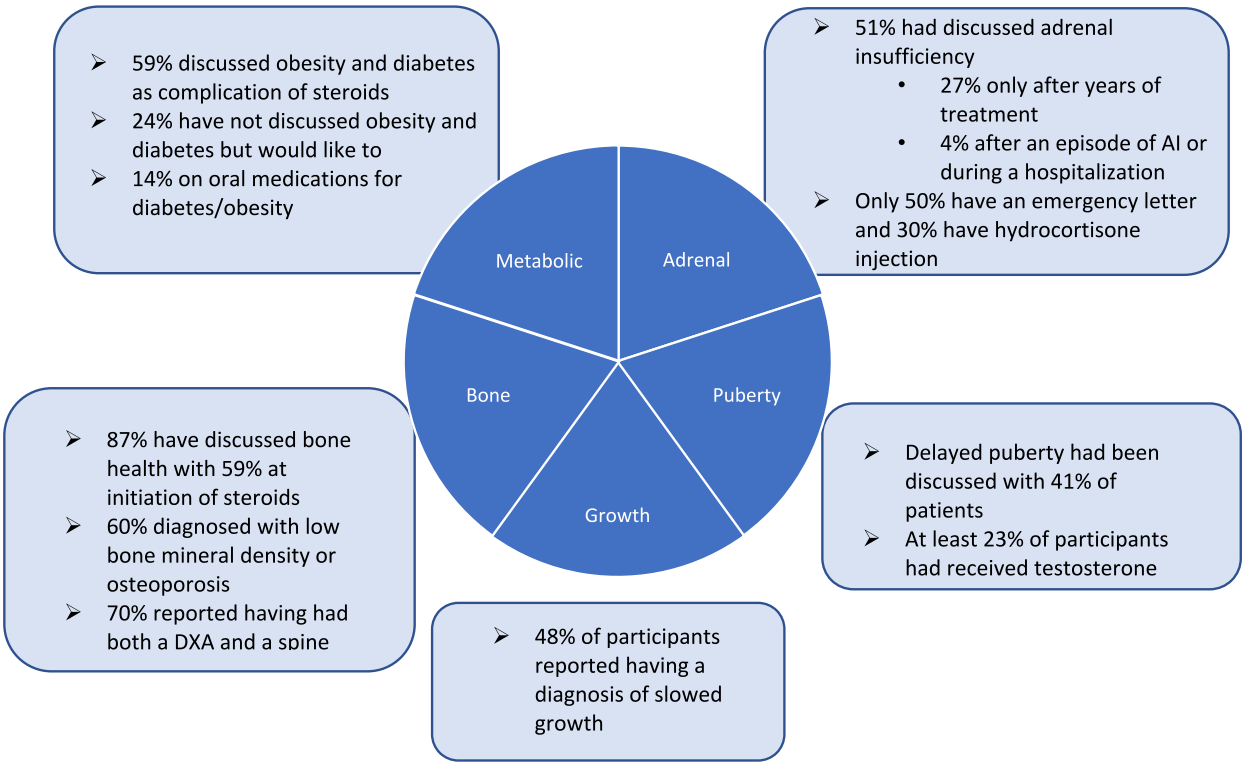

Fig. 1. Main results, per endocrine system. DM: Diabetes Mellitus, AI: Adrenal insufficiency, DXA: Dual-energy X-ray absorptiometry.

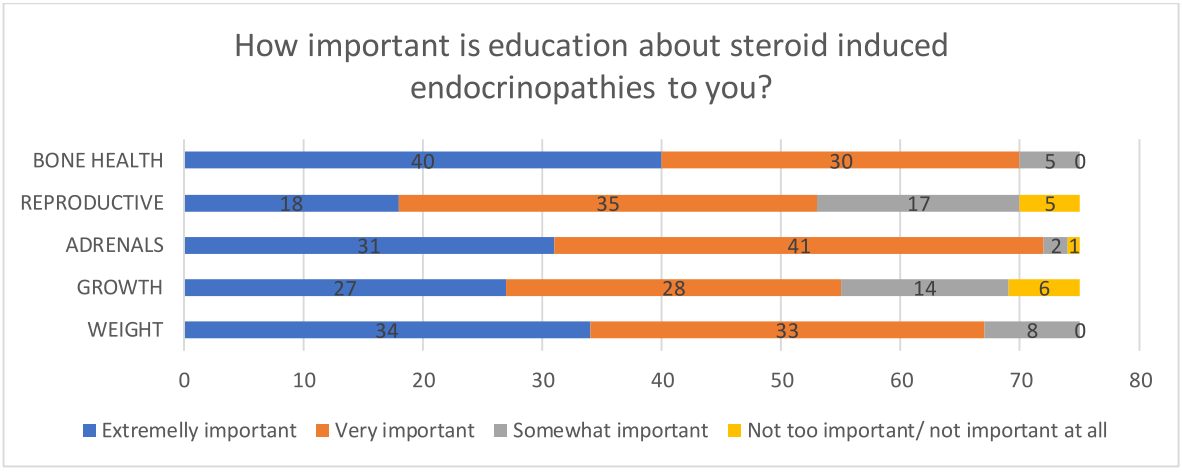

Fig. 2. Perception of importance of endocrine complications of steroid treatment, according to survey responders.

3.4. Puberty

Over half of the participants were pre-pubertal (44/75, 58%), with 20% of these patients being over 14 years old (n = 9/44). Forty one percent (41%, 31/75) learned about delayed puberty as a complication when starting steroids and 28% (21/75) after being on steroids for over one year. At least 23% (17/75) of participants received testosterone treatment.

3.5. Growth

Almost half of participants reported having a diagnosis of slowed growth (48% (36/75)). About a quarter (24% (18/75)) of participants said their provider had never discussed impact of steroids on growth but would have liked to.

3.6. Obesity and metabolism

Obesity or diabetes had previously been discussed with 59% (44/75) of participants. Up to 28% (21/75) had been diagnosed with either obesity or diabetes, with 14% (11/75) on oral medications for obesity and/or diabetes. Twenty four percent (24%, 18/75) of participants had not previously discussed obesity and diabetes but would have liked to.

3.7. Perceived importance of education regarding endocrinopathies and preferred methods of engagement

Participants wanted to learn about steroid induced complications at the time of steroid initiation (87% (65/75)), ideally from their primary Neuromuscular team (77% (58/75)). In-person education appears to be the preferred method for education (84% (63/75)), followed by printed/

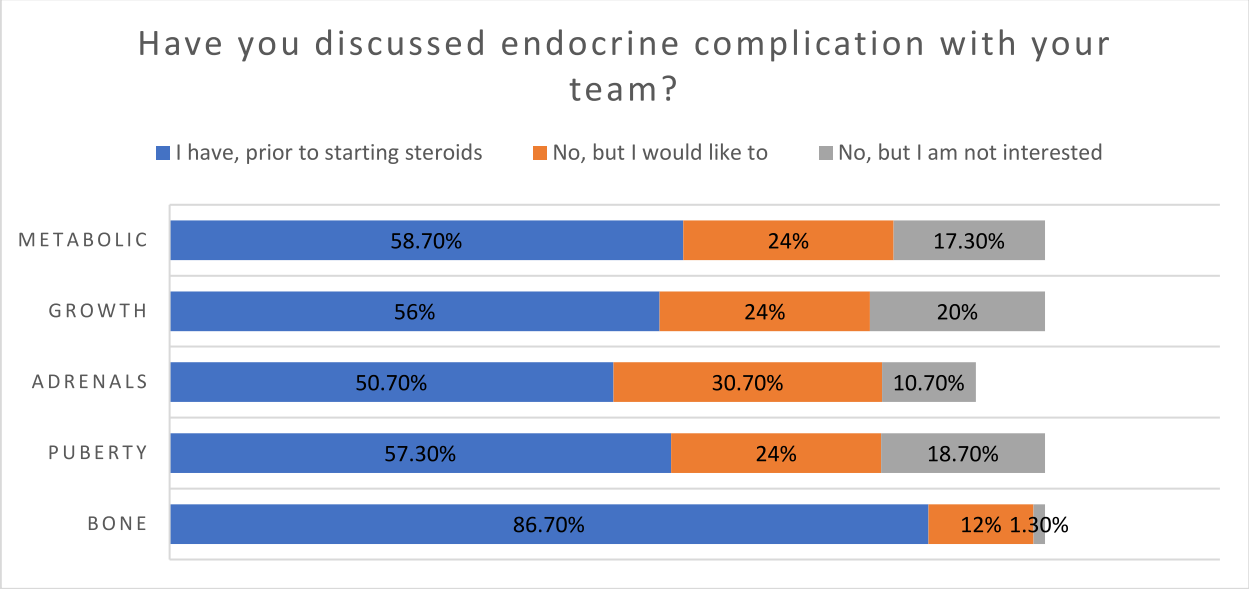

Fig. 3. Results on whether endocrine complications have been discussed, and patients' interest in being educated.

downloadable material (65% (49/75)), live webinars (64% (48/75)), online educational material (63%(47/75)), archived recorded presentation (49%(37/65)), or online support groups (47%(35/75)).

Families find education about steroid induced endocrinopathies to be very or extremely important (96% AI, 93% bone health, 89% weight/diabetes, 73% growth and 70% reproductive).

4. Discussion

With the changing landscape of DMD care and new treatment options becoming available like exon skipping and gene therapy, life expectancy has improved tremendously in the past 10 years for patients with DMD [4]. Therefore, there is a need to pivot approach towards focusing more on quality of life and minimizing complications secondary to treatments. It is well known that chronic exposure to steroids has an effect on almost all endocrine systems. This study highlighted that while almost all patients with DMD experience at least one endocrine complication from prolonged steroid treatment, most recall learning about these potential side effects after having already experienced them. Results showed that patients value early introduction and awareness of endocrine-related complications.

One of the primary complications that many of the patients with DMD face is low bone mineral density (BMD) and osteoporosis [8–10]. The essence of the disease itself is causing muscle wasting with most patients becoming non-ambulatory by the age of 13 if left untreated [11]. Bone undergoes constant remodeling, the rate of which is affected by many factors including physical activity, muscle tension, weight bearing load and pubertal hormones [12,13]. Steroids help delay disease progression, which prolongs ambulatory state. However, steroids cause osteoblastic apoptosis that hinders bone formation and induces osteoclastic activity, which overall results in predominant bone resorption and weaker bones [14]. At the same time, non-ambulatory state combined with excessive weight gain with increased physical load, can further weaken bones and specifically cause vertebral fractures [12,15,16]. Lastly, delayed puberty due to steroids delay bone maturation and remodeling.

Majority of the patients develop osteoporosis with fragility fractures either of the long bones or the vertebral bodies. Vertebral fractures can often be asymptomatic (up to 20% per Manzul et al) [17], therefore can often go unnoticed. Literature is sparse pertaining to the treatment and prevention of osteoporosis in DMD. There are several pharmacological and non-pharmacological treatments under investigation that are thought to improve outcomes in bone health for children with DMD. Starting with bisphosphonates, they are inorganic analogies of pyrophosphates that inhibit bone resorption by inducing osteoclastic apoptosis. They are generally well tolerated, and have been increasingly used in patients with DMD [18–20]. Small retrospective studies have shown improvement or slow in progression of deterioration of BMD in patients receiving bisphosphonates. However, large randomized trials are missing, and more data are needed to confidently justify earlier use of bisphosphonates in clinical care to treat or potentially prevent fractures. Other important factors to bone health in children with DMD are calcium and vitamin D supplementation. Data from large double blinded trials in healthy children, have indicated that although Vitamin D supplementation is not clinically beneficial in kids with normal values, it does help prevent bone loss of lumbar spine in those with low serum vitamin D levels [21]. Similar conclusion was drawn by the DIPART study in 2010 (vitamin D Individual Patient Analysis of Randomized Trials) [22]. Multiple studies have shown clear benefits in preventing bone loss, with the use of calcium in combination with vitamin D in adults over 50 years of age with chronic use of steroids [23–27]. Although no such studies exist in children with DMD, what is evident is that discussions about bone health, prevention and close monitoring for complications are of paramount importance. For that reason, the Parent Project Muscular Dystrophy (PPMD) program has been working to create centers that provide standardized care to patients and families living with DMD, in order to combat discrepancies in bone health monitoring and care across the nation [28].

Additionally, glucocorticoid treatment can cause hypogonadism and delayed puberty in patients with DMD [29]. This can have a significant impact not only in their bone health but also emotional and psychosocial wellbeing [30]. Although there is some data supporting the use of testosterone therapy for pubertal induction as a standard of care, at this time initiation of testosterone therapy is generally recommended by 14 years of age with consideration at 12 years of age for patients with absent pubertal development on glucocorticoid therapy [31]. Wood et al. recently performed a prospective single-arm study ($n = 15$) of patients with DMD and pubertal delay treated with a pubertal induction regimen (2 years of monthly testosterone injections). Their results showed improvement in contractile muscle bulk and function suggestive of overall improvement in the underlying disease process along with improved height gain and promotion of endogenous testosterone

production [32]. Families and patients have reported perceived benefit of therapy with good tolerability [30]. In our study, 12% of the participants were older than 14 years old and have yet to enter puberty, whereas 42% of participants have never discussed about puberty, and its benefits with their providers. Although further studies are required to determine the appropriate timing of pubertal induction, duration, and testosterone dosing in children with DMD, it is evident that it should become standard of care to at least monitor its progression and educate families early in the care model.

Children with DMD have decreased linear growth [33,34]. Vertebral fractures and non-ambulatory status as described above, play an important role in that [33]. However, exposure to steroids poses an even greater risk. Studies showed that ambulatory patients with DMD that are on steroids appear to have significantly shorter stature compared to ambulatory steroid-naïve patients, with early initiation, daily dosing, longer duration, and higher doses, all being predictors of poor growth [34]. The use of growth hormone to treat poor growth remains controversial as there have been no randomized control trials evaluating its efficacy and safety in this population and limited data that growth hormone improves growth while on high dose corticosteroids. It is important to counsel on expectations with family regarding growth in early childhood.

We know that boys with DMD have about two to six times higher risks of obesity than the general population, an observation found especially for steroid-treated, but even steroid naive patients, with incidence peak at the age of 10 years old [35]. Steroids may stimulate appetite and food intake, 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. This puts them at high risk of excessive weight gain, insulin resistance and type 2 diabetes mellitus, metabolic syndrome, hypertension and hyperlipidemia [36,37]. There is no data to safely assess the direct impact of weight gain in their overall cardiovascular complications. There is emerging evidence that a higher BMI and weight gain are associated with earlier fractures (independently of the steroid effect), worsening obstructive sleep apnea (OSA) and overall lung function [4,35]. Lastly, it is shown to play a pivotal role in their quality of life, by limiting the caregiver's ability to assist them and overall severely affecting their self-esteem [36]. A recent study by Walker et al. demonstrated that there are divergent views between families and physicians regarding obesity management and priorities of care which highlighted the significant psychosocial impact of obesity for patients and families living with DMD, which is frequently underestimated by health care providers [38]. A significant percentage of the participants in our survey have already been started on regimens for either obesity or diabetes and admit to considering weight and nutrition as extremely or very important to them.

Patients with DMD are inevitably at high risk of secondary adrenal insufficiency due to chronic high dose glucocorticoid use and suppression of the hypothalamic-pituitary-adrenal axis (HPA) [39]. It was particularly surprising to us to see that almost half of the participants have never discussed AI with their providers, and have never received any form of education, teaching, emergency letters or plans. Additionally, 4% of the participants were introduced to the concept of AI only after they experienced adrenal crisis or during a hospitalization. Of note, PPMD has now developed the “PJ Nicholoff Steroid Protocol” to aid health care providers in properly managing this condition, prompted by a patient with DMD that died because of an adrenal crisis [40]. Still, there is much work that needs to be done so that we can ensure that all the patients receive appropriate education and teaching on stress dosing and emergency injectable hydrocortisone in order to prevent life-threatening complications, which should become standard of care [41].

What this survey highlights, is that despite the well described complications of chronic steroid use, and the fact that the overwhelming majority of our patients and families want to discuss these matters as early as possible, only a small percentage of them receive the appropriate endocrine care and counseling. It is important for the medical community to acknowledge this gap in medical care and try to identify potential barriers. Unfortunately, the anonymity of our survey does not allow us to identify potential cofounders, such as age, geographic location, care in an academic or a community hospital, differences in socioeconomic or ethnic groups. Arguably, one of the most important factors would be whether these patients are seen in a multidisciplinary clinic setting, which typically includes endocrinology. It is understandable that not many centers have the capacity to accommodate this, which makes it even more important for the neuromuscular team to prioritize and facilitate such discussions. This also appears to be the preferred method of education based on our survey's results, primarily done in person or alternatively via downloadable/printed material. One feasible solution is to create standardized educational material which is easily accessible to all providers and can be distributed to all patients seen in neuromuscular clinics nationwide. Live webinars or archived presentations can also become available through PPMD for patients.

This survey has many limitations. Firstly, given the anonymity of the responders, it is not possible to take into account variability of practices in different places. We also were not able to make any associations between responders having received education and prevalence of complications to show that earlier education can prevent some of the complications such as adrenal crisis. Due to this being a community perception survey and importance of anonymity, we limited the number of questions to decrease survey burden. This survey was sent prior to clinical approval of new treatments for DMD such as gene therapy and vamorolone. We hope the descriptive results of this survey emphasize the importance of making endocrinology part of standard clinical practice as well as incorporate endocrine related complications as a measure in clinical trials and emerging treatments.

5. Conclusion

In conclusion, we have identified that the current educational approach to steroid induced endocrinopathies associated with treatment of children with DMD does not meet the needs of the DMD community. There is a need to increase awareness and advocate for improvement of endocrine care, by initiating these discussions early, and expanding the DMD multidisciplinary care teams to include endocrinology. The study underscores the need to improve delivery of care in order to meet the unique needs of this community, which is crucial in guiding patient-provider communications. It is important to include endocrinopathies and endocrine related complications as a measure in ongoing clinical trials and emerging experimental treatments.

Author's contributions

All authors conceived the idea, designed and validated the survey, and reviewed and edited the article. D.G. and V.S. wrote the original article and conduced the data analysis. N.M. supervised the process throughout. M.S. reviewed and edited the article.

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CRediT authorship contribution statement

Despoina Galetaki: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Vivian Szymczuk:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Melody Shi:** Writing – review & editing, Validation, Supervision, Formal analysis. **Nadia Merchant:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration,

Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

VS at NIDCR which receives funding from Amgen, Ultragenyx, and Kyowa Kirin. NM is on the advisory board of BioMarin, Pfizer, and Alexion; there is no conflict of interest in relation to this current paper or topic. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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