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Nutrition in Duchenne muscular dystrophy 16–18 March 2018, Zaandam, the Netherlands

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1. Introduction

Twenty-six representatives of academia, clinics, patient organisations and industry from eight countries (Argentina; Australia; Belgium; Italy; the Netherlands; Switzerland; United Kingdom; United States) attended the workshop on 'Nutrition in Duchenne muscular dystrophy' organised by the Duchenne Parent Project the Netherlands (DPP). During the workshop current knowledge and clinical practice regarding nutrition in DMD was discussed, as well as research, preclinical and clinical, and guidelines for patients and caretakers.

The overall aim of the workshop was to evaluate the current knowledge concerning nutrition in DMD and to identify the existing gaps in research and information for patients. The objectives were to (1) discuss the existing literature concerning body composition, bone health, nutritional and metabolic aspects, the use of supplements and dental and swallowing problems in DMD; (2) determine priorities and Standard Operating Procedures (SOPs) for future research; (3) establish a task force to improve nutritional guidelines and information for patients and their caretakers.

1.1. Background

1.1.1. The pathology of Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a severe muscle wasting disorder, caused by a genetic defect in the DMD gene, which results in the absence of the dystrophin protein [1]. Currently research into potential treatments that address the primary defect is ongoing, but so far only ataluren (readthrough of primary stopcodons) and eteplirsen (exon 51 skipping) are on the market in the EU and the US, respectively. However, these medicines are not applicable to all patients [2]. Meanwhile mainly symptomatic treatment is available. Most widely used are corticosteroids, which have shown to slow down the disease progression [3].

The absence of dystrophin directly affects the muscular system and causes the gradual loss of muscle tissue over time, which is replaced by fibrotic and fat tissue [4]. However, the lack of dystrophin also has many secondary effects, including changes in metabolism that result from disturbances in intracellular signalling pathways and by the changes associated with the breakdown of muscle tissue. In both animal models and humans it has been shown that insulin signalling and mitochondrial function are perturbed [5–9]. Studies have further shown that in boys with Duchenne the body composition is altered and this may impact on energy expenditure and nutrient requirements [10,11]. In addition, the contribution of corticosteroids to metabolic changes needs to be considered.

In early stages of the disease overweight is a common feature resulting from metabolic changes, a decrease in physical activity, use of corticosteroids, and compensatory behaviour of family members. Obesity increases the risk of glucose intolerance and can worsen disease progression due to increased load on the already weak muscles [11]. Due to, among others, the use of corticosteroids and respiratory and cardiologic interventions the life expectancy of DMD patients has increased over the years [12]. However, nutritional complications worsen in later stages of the disease and patients be-

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come at risk for undernutrition due to decreased appetite and difficulties with chewing, swallowing and digestion. This can weaken the immune response to infection and cause osteoporosis [13,14]. Undernutrition further exacerbates the muscle wasting. These nutritional complications can have a great impact on the quality of life, making their management increasingly important [15].

1.1.2. Supplements

Over-the-counter nutritional supplements are widely taken by patients. However, there is little documentation of the types and extent to which they are used and how much they are used, since it is often an initiative of patients/caretakers themselves and is not discussed with clinicians. The only two supplements which are recommended in the current care guidelines are vitamin D and calcium if the serum level of 25-hydroxyvitamin D is less than 30 ng/mL and/or dietary calcium intake is low [16]. For these it is advised to follow the recommended dietary allowance for age [17]. Many other nutritional supplements have been studied in humans and animal models, but evidence of benefits is limited (for an overview see [13]). There is no standardised guidance for patients and their families around using additional supplements, such as where to buy supplements, what dose to take etc.

While supplements potentially might have beneficial effects, they could also have deleterious effects either in high dose or they could potentially cross-react with other drugs the patient is taking. Again, only limited information on this can be found in literature and the risk is underestimated due to the wrong perception about supplement safety. Furthermore the regulations surrounding supplement production and quality control are flexible. As such, the dose and purity of supplements may change per batch and among different manufacturers.

2. Session 1: Why do we need to set up nutritional guidelines and research agenda for DMD?

During the first session the current nutritional practices were discussed. The side effects of corticosteroids, including weight gain and osteoporosis were discussed extensively. It was recognized that even if these effects are severe, stopping steroids is not necessarily in the patient's best interest, since corticosteroids are proven to delay disease progression into adulthood [18–26]. A further difficulty that was addressed is the lack of reference anthropometric values for DMD, like height and weight. They are currently mostly adapted from the healthy population and may not be suitable. This makes assessment of *e.g.* nutritional status and quantifying the appropriate intake of nutrients difficult.

2.1. Current practice and challenges

Kathi Kinnett (Parent Project Muscular Dystrophy, US) presented the perspectives of Duchenne families and organisations. Parents often ask for advice and currently many different recommendations are given, resulting in both confusion and an abundance of supplements given. Furthermore, she addressed the influence of the corticosteroid use on weight and glucose metabolism. The best strategy for weight management during corticosteroid therapy is unclear.

Kathi Kinnett also discussed the current Care Considerations (supported by the Centers for Disease Control and Prevention in the US) regarding nutrition in DMD; a recent update has been published [16]. These guidelines contain recommendations for ideal weight, as well as energy, nutrition and fluid intake. Regular assessment by a registered dietitian is encouraged and gastrointestinal (GI), chewing and swallowing issues are discussed.

There is an underreporting of GI problems amongst DMD patients, even though they are very common [27–29]. Constipation is one of the most frequent complications, caused by weakness of the abdominal wall and intestinal muscles and exacerbated by dehydration. Laxatives are a possible treatment; however, long-term use can in turn cause metabolic acidosis (loss of bicarbonate in the gut), which is worsened by dehydration and inadequate food intake. Other issues include gastroesophageal reflux (GERD), often caused by smooth muscle weakness, and gastroparesis [15].

Nathalie Goemans (University Hospitals Leuven, Belgium) discussed the current challenges in young patients. Dietitians should be part of the multidisciplinary team to explain the importance of healthy eating habits, adequate nutrition and vitamin D and calcium intake. However, families are sometimes reluctant to see a dietitian because of feelings of guilt and difficulties with implementing the advice given.

Ros Quinlivan (National Hospital for Neurology and Neurosurgery, UK) talked about the challenges in older boys and adult men. Due to improvements in care the population of adult patients is rapidly growing; however, the standards of care are mainly for children [30]. Malnutrition is often seen when the disease progresses, mainly due to dysphagia and an inability to self-feed. Although gastrostomy feeding can be highly beneficial in this situation, many patients are reluctant to have a tube placed, despite its known benefits. Furthermore, this procedure requires either sedation or general anaesthesia, which has risks. Thus, there is an urgent need for anaesthetic guidance for DMD adults. She also discussed the frequency of renal calculi in the adult DMD population in association with other urinary symptoms such as urinary tract infection. Poor fluid intake by adults with DMD may be one of the reasons and should be addressed as part of the nutritional advice given to adult patients.

Justus Kuijer (27-year old DMD patient) gave the perspective of an adult patient. He has always been aware of the necessity of maintaining a healthy weight, but regrets that information is missing about what aspects in his diet require specific attention. Now he is older, he particular has to pay attention to eat enough. He also brought attention to the fact the DMD patients can develop problems not necessarily caused by DMD, but that have consequences that are more severe for a patient with the disease. For example a major problem is bloating, which causes difficulty breathing, since the intestines press against the lungs. Bloating does not necessarily

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have to be caused by DMD itself, but could have other causes as well. Thus, avoiding foods that cause gas formation should be considered.

Zoe Davidson (Monash University, Australia) described the key periods for dietary assessment and counselling for individuals with DMD and their families. She stressed that obesity is a major problem in DMD [31] and, therefore, better approaches for weight management are needed. She indicated the requirements for a successful prevention strategy, like building a good relationship between the dietitian and patient/caretakers, regular assessments to facilitate proactive not reactive nutrition strategies, and estimating the energy expenditure of the patient. There is little knowledge on how much energy is needed at different ages and activity levels (*i.e.* ambulatory *versus* non-ambulatory boys). Other challenges are a lack of evidence to support clinical practice, limited funding for dietitians in neuromuscular clinics and research, high turnover of dietitians working in neuromuscular clinics and difficulties in obtaining regular height and weight measures.

2.2. Discussion and action points

Nutrition plays a minor role in the current care for DMD patients, although it is becoming more and more clear that it has a large influence on disease pathology and quality of life. Nutrition guidelines are currently lacking. It was agreed that:

- More research is needed on the role of glucose intolerance (How prevalent is it? When does it start?) and if genetic predisposition plays a role in determining why some patients become obese while others do not. This requires an international follow-up study among DMD patients.
- The daily life habits of the patient/family should be taken into account when giving advice and the recommendations should be implemented by the whole family. This is essential to enhance change.
- It might be valuable to use a group approach to manage weight and other nutrition-related issues. In that way families may feel less reluctant and have the opportunity to share visions and solutions. This would facilitate more regular encounters with a dietitian when they are in short supply.
- An easier way to measure weight is needed. Alternatively, a potential surrogate measure of weight that could be used for individuals with DMD who are wheelchair dependent, would be helpful. Currently this is very difficult for wheelchair dependent patients seen in an outpatient setting, which hampers regular measurements that are necessary for good monitoring. Innovative ideas are needed to facilitate more frequent assessment.

3. Ongoing research and current knowledge

Presentations and discussions on the second day focussed on the current knowledge about nutrition. This included both preclinical and clinical research as well as research from other fields that might also be relevant for DMD. Furthermore, current practice was addressed.

3.1. Session 2: current knowledge preclinical

Maaike van Putten (Leiden University Medical Center, the Netherlands) and Marta Fiorotto (USDA/ARS Children's Nutrition Center, US) discussed the body composition and metabolism of the *mdx* mouse model. The genetic background has a major effect on the body composition of *mdx* mice. In contrast to the most used C57BL/10ScSn-*mdx*/J (BL10-*mdx*) mice, which exhibit muscle hypertrophy, D2.B10-*Dmd*^{mdx}/J (D2-*mdx*) mice show muscle atrophy and have a more pronounced dystrophic phenotype. This may make them resemble more the human disease and thereby make them a better model for future studies [32,33]. However, so far, few studies have been performed with the D2-*mdx* mouse, so little is known about their body composition and the effect of age and diet; more data on natural history of this background are needed. Most studies on this topic have used the conventional BL10-*mdx* mouse. While younger mice tend to be growth-retarded, when BL10-*mdx* mice age, lean body mass increases and their adiposity decreases compared to wildtype mice. Muscle damage leads to a higher protein turnover and contributes to a higher energy expenditure and amino acid oxidation. In young, growing mice the intake of a standard diet may be insufficient to meet their protein needs to support optimal rates of protein synthesis. This inadequacy would lead to reduced muscle and whole body growth, and may contribute to greater muscle damage observed at weaning. In non-growing adult mice, food intake is sufficient to sustain protein balance, but does not meet energy needs, thereby leading to reduced fat gain [34]. A high protein diet has no effect in both juvenile and adult mice as it results in a decrease in total food intake and accentuates the negative energy balance [35]. In contrast, a high fat diet (45 % kcal) increases lean body mass, but not fat mass, while in wildtype mice an increase in fat deposition is seen [van Putten et al.; unpublished data].

In humans, the skewed protein intake (protein intake is usually low at breakfast and lunch compared to dinner) does not support optimal skeletal muscle protein anabolism. Studies have shown that optimising feeding intervals can maximise muscle protein synthesis and may mitigate the development of sarcopenia during ageing and increase the anabolic response to exercise [36,37]. In young animals feeding meals at specific intervals *versus* continuous feeding of the same amount of food led to a higher lean body mass, weight and length. However, whether the dystrophic muscle responds similarly to meal feeding and can be translated to human DMD patients is uncertain [38].

Emma Rybalka (Victoria University and Australian Institute for Musculoskeletal Sciences, Australia) presented on mitochondrial dysfunction and mitochondria-targeting supplements. Mitochondrial dysfunction appears to be independent of the calcium-mediated pathology associated with DMD and may even exacerbate it [7]. When the calcium homeostasis

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is disrupted, ATP production is impaired in dystrophic mitochondria, while there is an overproduction of reactive oxygen species (ROS). This increases cell death [5,6]. One of the possible links between dystrophin deficiency and mitochondrial myopathy is nNOS signalling. Several compounds have been tested that target NO signalling via various pathways. PDE5-inhibitors like sildenafil and tadalafil have shown beneficial effects in *mdx* mice [39,40]; however these data were not translatable in clinical trials in DMD patients [41,42]. Other metabogenic compounds, which can enhance mitochondrial density and induce cytoprotective molecular signalling might be more beneficial. Since multiple complimentary pathways are involved in maintaining ATP, a combination of compounds targeting different aspects is probably the best strategy.

Annamaria De Luca (University of Bari, Italy) addressed the variability in preclinical experiments, which leads to different outcomes and hampers translation to humans. In addition, drugs that show some beneficial effects in animal models are often too quickly moved to clinical trials before their effects are thoroughly investigated [43]. Therefore SOPs are needed to bridge the gap between animal models and clinics and to enhance translation [44]. In 2007 a taskforce was established by TREAT-NMD to enhance translational research in DMD. This taskforce is among other things engaged in providing SOPs and guidelines for pre-clinical testing [45–47]. Protocols of chronic exercise according to SOPs can worsen pathology in the mildly affected *mdx* mouse and are useful in preclinical drug tests [48,49]. This approach also disclosed altered metabolic adaptation to physical activity in dystrophic muscles, which may sustain damaging signals, thereby being of interest when testing metabolic enhancers and supplements. In exercised *mdx* mice natural compounds like resveratrol, apocynin and taurine all showed positive effects on some of the functional outcome measures and biomarkers of inflammation and oxidative stress in a similar extent as prednisolone [50]. Results of other chronic interventions with taurine and metformin emphasised that food supplements and metabolic boosters should not be regarded as a lifelong treatment but used in specific phases of the disease.

Oliver Dorchies (University of Geneva-Lausanne, Switzerland) gave a presentation on experiments in dystrophic mice with repurposed drugs already on the market for use in the treatment of other disorders. Melatonin, used for sleep disorders, had moderate effects [51]. A more likely candidate for further development is green tea extract, of which the major component is epigallocatechin gallate (EGCG). EGCG has antioxidant, antifibrotic, anti-inflammatory and anti-apoptotic properties. Several studies have been performed in dystrophic mice showing beneficial effects like improved muscle function, stabilisation of the plasma membrane and prevention of kyphosis after long-term treatment. However a decrease in necrosis was only seen in young mice, suggesting that it only delays the pathology [52–54]. In addition, he stressed that in both wildtype and *mdx* mice the composition of the basal diet used to deliver the supplements can influence the results. Specifically, a semi-purified ingredient diet composed of starch, casein, lipids, minerals, and vitamins led to better functional outcomes than the cereal-based chow regularly fed to rodents. Currently, in Germany, a placebo-controlled clinical trial (NCT01183767) is ongoing to assess EGCG. Results are expected at the end of 2018, but so far no adverse side effects have been seen.

3.2. Session 3: ongoing research in other fields

The choice of methods to assess nutritional status can have a large impact on the research outcomes. Nicole de Roos (Wageningen University, the Netherlands) reviewed several methods. Here one can think of body composition, food intake, biochemistry, muscle function and energy requirements. For non-ambulatory Duchenne patients most regular methods are not suitable. As an alternative for measuring height, the ulnar length is most reliable and gives a reproducible result that shows agreement with the actual height [55]. Measuring body weight is a challenge if a person is wheelchair dependent. Body composition could be used as an alternative, *i.e.* by air displacement plethysmography (Bodpod) or bioelectrical impedance; however, alternative equations may be needed for DMD patients to estimate body composition from these measures [56]. Another complication is that reference charts of healthy individuals are not suitable, since DMD patients have relatively less muscle mass and more fat mass.

Vitalnext (Annemarie Rietman, the Netherlands) has developed a new medical nutrition product. This product, allowed on the EU market, is a powder formula that can be mixed into food or drinks, which may make it more consumer friendly than existing products (drinks). Its composition is aimed at improving or maintaining muscle mass and contains high levels of protein, vitamin D, free branched chain amino acids, ursolic acid [57]. In preclinical animal studies in wildtype mice it was showed to be more effective than standard medical nutrition by modulating protein synthesis and breakdown, and inflammatory pathways; however in *mdx* mice in a DBA background (D2-*mdx*) no beneficial effects were observed [van Putten et al., unpublished results]. A clinical trial with malnourished elderly people showed a relative higher increment in lean body mass *versus* fat mass. Only a small improvement during a walking test, but no change in other physical functions was seen. Results of muscle biopsy RNA analyses will come available soon.

The company Healx (Ian Roberts, UK) is specialised in computational models to discover novel connections between intervention and disease. This can be used for drug repurposing and/or biomarker discovery. A drug repurposing project generally consists of 3 stages: (1) gathering data about the disease, (2) drug matching, (3) pharmacological review by experts. Often gene expression profiles are used to identify candidate drugs for repurposing. The most promising candidates will thereafter be validated *in vitro* and those showing promising effects will progress to *in vivo* studies. If gene expression profiles are not available, indirect associations may be made to identify candidate treatments using other properties of drugs (chemical structure, target protein, side effects) and disease (ontology, phenotype, genes) through eval-

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uation of similarities. Additionally, metabolic profiling gives more insight in the disease (or drug) mechanisms, predicts biomarkers and can be used for personalised drug matching. This digital modelling approach could be attractive for DMD, where large gene expression datasets are available and much is published about the metabolic signature of the disease [58].

3.3. Session 4: current knowledge and practice – clinical

Leonie van den Engel-Hoek (Radboud University Medical Center, the Netherlands) presented on dysphagia and mastication problems, which are known to become problems in ageing Duchenne boys [59–61]. In DMD dysphagia (in oral and pharyngeal stages) can be caused by affected submental muscles and, in later stages, by hypertrophy of the tongue muscles. Problems are mainly observed in the oral and pharyngeal phase. In the oral phase drinking, eating and chewing takes place and in the pharyngeal phase food is transported to the oesophagus. Problems with mastication and the need for multiple swallows to clear the oral cavity is a sign of oral muscle weakness. In the pharyngeal phase, post-swallow residue has been observed [62,63]. Food adaptation, *e.g.* smaller pieces and changing consistencies (*i.e.* more fluid), could be beneficial and/or additional gastrostomy tube feeding is necessary. Additionally, there is a need for an easily applicable measurement to test chewing and swallowing abilities.

Elizabeth Vroom (Duchenne Parent Project, the Netherlands) explained the occurrence of dental problems in DMD. Patients have an altered facial morphology and wider dental arches resulting in malocclusions [64,65], caused by hypertrophy of the tongue and weakening of the orofacial muscles. Consequently there are few contact points between the lower and upper molars, thereby hampering chewing. Dental hygiene is often neglected, while caries and loss of teeth impair eating abilities even more. It is advised to rinse well after eating, regularly brush the teeth, take preventive measures and avoid certain types of food and drinks (*i.e.* sticky, sugar rich, especially in combination with low pH).

Jarod Wong (University of Glasgow, UK) presented on the impact of DMD and steroid use on bones. Osteoporosis is common in DMD as reflected by, among others, vertebral fractures [66]. Long bone fracture can lead to premature loss of ambulation. Severe and multiple vertebral fractures in postmenopausal women with osteoporosis can lead to progressive kyphosis and the development of restrictive lung disease [67]. This may also be the case in DMD patients. Previous focus on the use of dual energy absorptiometry (DXA) to assess skeletal fragility has been replaced by the call for routine lateral thoracolumbar spine X-ray in the new DMD care consensus [68]. Addressing bone health in DMD requires consideration of several factors, but nutrition is clearly important. Optimizing calcium intake through dietary measures and vitamin D supplementation is important. However, a study assessing the effect of vitamin D and calcium in DMD, showed only a marginal impact on the bone mineral density, while the effect on fractures was inconclusive [69].

Carola Saure (Hospital JP Garrahan, Argentina) discussed energy expenditure and body composition of DMD patients in relation to metabolic disorders. Measurement of body mass index (BMI) underestimates the prevalence of obesity, therefore the percentage of fat mass is a better measurement, although this also has limitations [11]. Various tools can be used to measure body composition, like DXA and MRI. These are accurate, appropriate and non-invasive, but they are not always available and unsuitable for routine practice. Bioelectrical impedance analysis (BIA) is a non-invasive, inexpensive technique that could be an adequate bedside method to routinely monitor body composition [56,70,71].

When indirect calorimetry is not an option, predictive equations may be used. In the DMD population the Schofield equation has been suggested to give the most accurate prediction of resting energy expenditure (REE) [72]. Some studies have shown a lower REE in DMD patients, which may be correlated with obesity [10,11,73,74]. Also insulin resistance is commonly seen. This is, however, difficult to determine in children, since standards are lacking and measures are influenced by race and pubertal stage [75]. The insulin sensitizing agent metformin is used in the treatment of type 2 diabetes [76] and may be beneficial to DMD patients [77]. However, there is limited evidence of the efficacy of metformin for weight management in DMD and overweight individuals. In addition, there is currently little known about the tolerability, risk of adverse effects, like lactic acidosis, and the action of metformin on non-normal muscle mass.

3.4. Discussion and action points

Research, both preclinical and clinical, into the dietary consequences of alterations in metabolism and the use of nutritional supplements for DMD is important. Hereby the DMD field can also learn from other fields. Some medicines acting on metabolism that are already on the market for other purposes, might also be beneficial in Duchenne. Furthermore, dysphagia and dental problems are often seen and can have a large impact on food and liquid intake. Key actions points of the day that were identified, include:

- Regarding preclinical animal models, SOPs are important for comparability and reproducibility of results between labs.
- When studying food supplements, it should be evaluated if the appropriate animal models, muscle type and age are used, taking into consideration their differences with human patients.
- Researchers using animal models should be aware of the influence of the type of diet used in their study. Therefore, the diet used should always be clearly described in the study methods.
- Natural history data on nutrition-related outcomes is needed to determine reference values and good outcome measures for nutritional interventions.
- There is a need for better methods to determine outcome measures. These methods should be tailored to DMD pa-

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tients in different disease stages, since many regularly used methods are not suitable.
- Simple guidelines for patients/caregivers are needed, specific for the different stages of the disease. Additionally, the potential risk of supplement use (especially when cocktails are taken) should be explained.
- Dental hygiene should be emphasised.
- Better understanding of the psychological barriers that impede more extensive use of GI tube feeding is needed.

4. Session 5: working groups on need for further research and guidelines

On the final day of the workshops, participants were divided in three discussion groups, addressing the development of a research agenda for clinical respectively pre-clinical research on nutrition and the improvement of the current guidelines on nutrition.

4.1. Group A: development research agenda clinical research on nutrition

The first group consisting of Lenie van den Hoek-Engel, Ros Quinlivan, Dorinda Snik, Jarod Wong, Nicole de Roos, Carola Saure, Annemarie Rietman and Mirjam Franken discussed the development of a clinical research agenda on nutrition. They concluded that there is a need for research on the natural history of DMD, regarding body composition, glucose metabolism, dental involvement and supplement use:

– A survey among patients/caregivers registered in the DMD patient registry would be a good tool, involving questions about, among others, disease severity, steroid regimen, supplement use, feeding-related problems (*e.g.* mastication, swallowing, dental, constipation), diets and dietary adjustment, and the occurrence of diabetes and liver disease.
– A more detailed prospective study should be done on the body composition of ambulant and non-ambulant children. Especially for non-ambulant children this will be difficult, due to the difficulty of weighing them. Therefore other methods, like waist or upper arm circumference, may be an alternative.
– Normative data for the non-ambulant population is needed (What is the optimal body composition and weight for these patients? What are their protein needs? What is their energy expenditure (total and resting)? What would be an optimal fluid intake?).
– The metabolic consequences of dystrophin deficiency and steroid therapy on glucose metabolism, energy expenditure, metabolic syndrome and non-alcoholic fatty liver disease and the development of acanthosis nigricans should be studied. Until such natural history studies are available, the group recommends consideration of evaluation of glucose homeostasis with an oral glucose tolerance test and lipid profile in those with significant obesity/weight gain. Treatment with metformin should not be used routinely in obese DMD boys, but can be considered on an individual basis where there is evidence of abnormal glucose homeostasis (type 2 diabetes, impaired glucose tolerance) or metabolic syndrome.
– Research into genetic markers to determine if there are predispositions to obesity, steroid complications including Cushingoid features, glucose intolerance and osteoporosis might make it possible to tailor diet and care and avoid complications.
– Outcome measures are needed to look at the effect of supplement use on specific muscle types, *i.e.* diaphragm, smooth and skeletal muscles.
– The psychological aspect of eating should also be addressed (How much should the quality of life improve by dietary adjustment to convince patients a change in diet is needed? What is the impact of comorbid psychiatric diagnoses [*e.g.* OCD and ADHD] on eating and does the diet play a role in the occurrence of these diagnoses?).
– Collecting data among older patients about gastrostomy tube feeding could help to get an overview of problems with anaesthetics and mouth opening during the surgical procedure.

4.2. Group B: development research agenda pre-clinical research on nutrition

The second group consisting of Annamaria De Luca, Marta Fiorotto, Fernanda De Angelis, Maaike van Putten, Olivier Dorchies and Ian Roberts, evaluated the pre-clinical research agenda for nutrition.

Firstly, they discussed the advantages and disadvantages of the available DMD animal models (mice [BL10-*mdx*, D2-*mdx*, *mdx/utrn*$^{-/-}$], rat, dog and pig) for nutritional research.

BL10-mdx mice are the most widely used and characterised model. There is a lot of data about the natural history, including body composition, and SOPs are available. This would make them an easy to use model, provided that the stage of the disease is correctly addressed and known disadvantages are taken into account. *Mdx-utrn*$^{-/-}$ and D2-*mdx* mice are less favourable, since *mdx-utrn*$^{-/-}$ have the additional mutation in the utrophin gene that does not occur in DMD patients and there is little known about the body composition of D2-*mdx* mice. There is a need for natural history data collection on the D2-*mdx* mouse.

The rat model is only used by a few labs [78,79]. Although some manifestations of the disease may mimic more closely those in the human, currently, there is little information about the natural history and body composition, and SOPs are not available. Furthermore, research with rats is relatively more expensive than with mice.

Dogs and pigs are very expensive and there is little known about the natural history and body composition, and metabolic consequences of the disease. In addition there is a large variability in disease severity among the *GRMD* (golden retriever) and *CXMDj* (beagle) dogs [80,81]. Pigs have the advantage

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that they closely resemble humans in size, anatomy, psychology and in their genome [82,83]. DMD pigs, however, can be more severely affected than human patients, which, therefore limits their usefulness [84].

Secondly, problems regarding reproducibility of results and knowledge gaps that should be addressed were discussed, as findings in animal studies are often difficult to reproduce. It would be important to implement the use of SOPs and more detailed description in publications on the animals and the type of diet used. Specific SOPs and more information about the influence of the type of diet on study results are needed.

Despite the increasing recognition that there are marked effects of the disease on nutrient metabolism, information is limited on how diet affects the pathophysiology of the disease. More focused and standardized studies using relevant methodologies should be devoted to the effects of diet on pathology course. Studies have shown that in young *mdx* mice food intake is insufficient to balance the protein and energy need of regenerating muscle [34]. However, many questions remain unanswered, such as the balance between intake and energy expenditure, the age-dependent effect of caloric or protein restriction on pathology progression and metabolism (*i.e.* would this worsen pathology if applied during regeneration phase?), as well as the effect of the different diets on body composition. Focused studies are necessary to answer part of these questions, although interpretation of results should consider that results may be confounded when commercial diets are used as they can vary in their nutritional value between different batches of the same chow, due to the use of whole food, rather than semi-purified ingredients, in their formulations.

Preclinical studies are also needed to evaluate the benefits of nutritional supplements of main interest for DMD patients. This is expected to be a multistep approach, involving first the identification of best candidates, based on clinical evidence of efficacy in other diseases and on supplements mostly used in DMD patients (on a registry-based survey). Then proper dose-dependent pre-clinical tests, according to SOPs, should be done in two independent labs to confirm reproducibility of efficacy on objective endpoints. Thereafter more detailed studies into insulin metabolism and energy be could be done for the most effective compounds. The age of the mice should be tailored to the specific supplement used, and combination with steroids or other drugs used in DMD standard care should be considered.

4.3. Group C: how to improve, expand and disseminate current guidelines on nutrition

The third group consisting of Kathi Kinnett, Zoe Davidson, Elizabeth Vroom, Ingrid Verhaart, Nicoletta Madia and Suzie-Ann Bakker, addressed the nutritional guidelines for patients and their caregivers. The current guidelines are very general. More detailed advice specific for the different disease stages is needed and should be better disseminated.

Different types of guidelines are needed for patients themselves, caregivers and clinicians/dietitians. Guidelines need to be provided in the context of potential harm as well (*e.g.* the harmful effects of taking [too many] supplements). The guidelines should be tailored to different ages and phases of the disease. Food recommendations need to be generic so that they could be applied internationally across different food cultures all over the world.

The most effective approach for disseminating the information was also discussed. Current guidelines are very scientific, while information that is simple, easily implementable is also needed for less scientifically educated people. Studies to evaluate the obstacles that prevent exploring behavioural changes in individuals with DMD would be very useful to determine the most suitable way of disseminating information.

It was agreed to make three videos and one-page information sheets for (a) childhood, (b) late childhood and adolescents (teens and twenties) and (c) adults. The three videos will discuss (1) weight (over- and underweight), (2) the use of nutritional supplements and (3) GI tube feeding. The videos can be translated by national organisations to make them accessible for patients in their country. It was also suggested to provide examples of daily meals for different cultures.

Additional information platforms are social media, like Facebook and Twitter, which are used by many, especially older, patients. These could be used to react to hypes and news in the field of nutrition.

Furthermore, a group education program for discussion groups of parents would be an easy, low threshold, approach to reach larger groups.

5. Summary and key action points

The workshop addressed the current state of knowledge and needs of research into the role of nutrition and metabolism in DMD and improved guidelines for nutrition. Key action points are:

- A budget should be made available to support nutritional research and improvement of information in DMD.
- Data on current dietary habits and supplement use should be gathered.
- SOPs, including diet use, are needed for pre-clinical animal research to improve outcomes.
- The awareness of the importance of nutrition should be increased. Therefore better guidelines are necessary. The development of an international network of dietitians would be helpful, since their help is needed for dissemination of information.
- Currently there is a big gap between scientists and the daily habits of patients/caregivers. A special workshop for clinicians has to be organised to involve them into bridging the gap.

6. Workshop participants

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6.1. Patient representatives

– Fernanda De Angelis, Parent Project Onlus, Italy.
– Suzie-Ann Bakker, World Duchenne Organisation (UPPMD), the Netherlands.
– Mirjam Franken-Verbeek, Duchenne Parent Project NL, the Netherlands.
– Ieke Ginjaar, Duchenne Parent Project NL, the Netherlands.
– Justus Kuijer, Adult DMD patient, Delft University of Technology, Delft, the Netherlands.
– Nicoletta Madia, World Duchenne Organisation (UPPMD), Italy
– Elizabeth Vroom, Duchenne Parent Project NL, and World Duchenne Organisation (UPPMD), the Netherlands.
– Kathi Kinnett, Parent Project Muscular Dystrophy, US.

6.2. ENMC representatives

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