BODY COMPOSITION AND BODY MASS INDEX IN DUCHENNE DYSTROPHY: ROLE OF DIETARY INTAKE

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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None of the authors has any conflict of interest to disclose.

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ABSTRACT:

Introduction: In Duchenne muscular dystrophy (DMD) muscle is replaced by adipose tissue. The role of dietary intake (DI) in DMD has not been evaluated. We examined body composition , BMI and adequacy of DI in patients with DMD and evaluated the influence of DI on body composition.

Methods: Patients (n=101; age 3 to 18 years; BMI 11.8 to 29.5 kg/m^2) completed a dietary recall to determine DI and underwent dual-energy x–ray absorptiometry to determine body composition.

Results: Preschool–age and school–age boys with DMD had high total energy intake. Protein intake/kg exceeded recommendations. As age increased, the percentage of boys with abnormal BMI and fat mass increased, while lean mass decreased. Dietary intake did not predict body fat or lean mass.

Discussion: Age dependent changes in BD in boys with DMD may be due to endogenous metabolic factors related to the underlying disease process and to disease-related mobility impairments.

Key words: Duchenne muscular dystrophy, dietary intake, body composition, body mass index, pediatric patients, obesity.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most prevalent dystrophy, occurring in 15.9 to 19.5 cases per 100,000 live male births.[1] Mutations in the dystrophin gene affect smooth and striated muscles of the digestive tract, impairing its function.[2] A range of nutritional states, varying from over nutrition to under nutrition (malnutrition)[3] occurs with disease progression.[4] Although patients with DMD are at high risk of being overweight or obese in early life, undernutrition risk rises as they become adults.[5,6] The international approach to assess nutritional status is to take body or anthropometric measurements related to an individual's age to construct indices, which enable comparison of a child with a reference such as the body mass index (BMI).[7] Prevalence of obesity based on weight > 90th percentile by 13 years of age has been reported to be from 44% to 73% in boys with DMD, whereas at 17-18 years of age, undernutrition (weight <10th percentile) affected 47-65% of boys with DMD in steroid-naïve cohorts.[5,8,9] In patients receiving steroids, obesity can reach 50% based on BMI,[10] and 70% using percentage of fat mass.[11] In patients with DMD this is most likely because the myofibers are susceptible to necrosis and they become replaced by fibrous and adipose tissue.[1,12] Thus, DMD is associated with an increase in body fat mass with ageing.[5,6] Furthermore, muscle degeneration results in reduced lean mass and probably decreased resting energy expenditure as a result. The lower energy requirement is also associated with decreased physical activity due to loss of ambulation.[1] In addition, excess caloric intake may be related to the caregiver compassion and the increase of appetite caused by corticosteroids, considered a key contributor of obesity and its complications such as dyslipidaemia, insulin resistance, and hypertension.[4,6,13] Conversely, being underweight has been attributed to the cumulative effects of feeding difficulties, as well as to the age-related increase of resting energy expenditure associated with cardiorespiratory complications.[5,8]

Nutrient imbalance, and consequently energy imbalance can be contributing factors to adverse changes in body composition and in nutritional status assessed as BMI.[1] However, the influence of dietary intake has not been evaluated in boys with DMD nor compared with dietary reference intake (DRI) values, which help individuals to avoid under or overconsumption of a nutrient and prevent malnutrition, especially as related to age.[2,14] Therefore, the aim of this study was to compare dietary intake with DRIs at different ages; to examine BMI and body composition according to age, and to evaluate the role of dietary intake as a predictor of body composition in patients with DMD.

METHODS

Study Population

A cross–sectional study was carried out between January 2011 and July 2016. All patients with DMD were recruited from the National Rehabilitation Institute, the Paediatrics Hospital of the "Siglo XXI" National Medical Centre, "Dr. Gaudencio González Garza" General Hospital, and "La Raza" National Medical Centre of the Instituto Mexicano del Seguro Social (IMSS) in Mexico City. One hundred and one male patients (aged 3─18 years) with a confirmatory molecular diagnosis of dystrophy were eligible for inclusion in the study if they had a deletion in the DMD gene analysed by multiplex polymerase chain reaction. All patients had a clinical diagnosis of DMD and were not taking steroids or other medications, as described in a report on these same patients.[13] This study was approved by the Institutional Ethics Committee, IMSS. Parents of the participants and patients signed a written consent (or assent) form prior to the boys' inclusion in the study.

Procedures

On the day of the study visit, a medical history was obtained and anthropometric measurements and body composition were determined as described later. Finally, a 3–day, 24–hour dietary recall was obtained by an interviewer. At the end of the day of the study visit, all patients received individual dietary counselling.

To identify disorders in nutritional status based on BMI at different ages, subjects were divided into three groups: preschool–age (2 to < 6 years, $n = 20$); school–age (6 to < 12 years, $n = 64$), and adolescents (12 to ≤ 18 years, $n = 17$).

Dietary Intake Analysis

A multiple–pass, 24–hour recall method was obtained by a nutritionist, including 2 non–consecutive mid–weekdays and 1 weekend day to estimate energy and nutrient intakes per day on the first study visit. Patients and parents were asked to recall everything the child ate according to the reported method, including, in the second pass, the type of food and amount eaten, as well as any type of additional food that accompanied it, brands, and method of preparation and/or cooking. Food models were employed to estimate the amount of meat and beverages consumed.[15,16]

The current DRIs for energy (kcal/day) for healthy pre–schoolers, school–age children, and adolescents with a sedentary physical activity level are 1142–1308, 1308–1666, and 1773–2358, respectively.[14] For protein intake, the recommendation is 0.76 g/kg/d for pre–schoolers and school–age children and 0.73 g/kg/d for adolescents.[14]

Average caloric intake, macronutrient intake, and percentage of the adequacy of intake were computed by Food Processor software (version 10.11.0; Salem, OR, USA) and compared with the DRI. Dietary intake was analysed at different ages stratified into three groups: preschool–age (*n* = 20); school–age (*n* = 64), and adolescents (*n* = 17). Dietary intake was also examined stratifying by ambulatory and non-ambulatory ability and by categories of Vignos scales as detailed later, as well as the association with physical rehabilitation.

Nutritional Status Based on BMI

Anthropometric measurements were performed by trained personnel using standardized procedures. Ambulatory patients were weighed using a digital scale (Tanita model BWB–700). Height was measured with a wall–mounted stadiometer (Seca model 208). Non–ambulatory patients were weighed on a chair scale (Seca model 954). To measure length in these patients, the summation of body–parts method was utilized with a Seca tape measure.[17] Nutritional status based on BMI has emerged as the most practical, universally applicable, inexpensive, and non–invasive anthropometric indicator for classifying patients as being thin, overweight, or obese.[18] In this study, BMI was determined as z–score employing Epi Info software (version 3.5.3; Atlanta, GA, USA) according to the following cut–offs: ≤ 2 SD (thin); ≥ −1.99 to ≤ 0.99 SD (normal); ≥ 1 SD (overweight); ≥ 2 SD (obese) for children aged 6–19 years, and ≥ 2 SD (overweight), ≥ 3 SD (obese) for children aged 3–5 years.[19,20] The identification of disorders in nutritional status based on BMI was performed using the same age groups and by 3 Vignos scales detailed below.

Body Composition: Fat and Lean Mass Measurement

Body fat and lean mass compartments were determined by dual–energy x–ray absorptiometry (DEXA) (Lunar Prodigy; GE Medical Systems, Madison, WI, USA) and Encore version 2004 software (Lunar Corporation). These compartments were expressed as both kg and percentage of body weight. The percentage of body fat was also categorized as normal, overweight or obese for children and adolescents as described by Taylor.[21] The sum of thinness, overweight and obesity based on BMI was considered as malnutrition.[3]

Muscle Function Measurement and Physical Rehabilitation

There are scales to evaluate muscle function in DMD patients; these are considered as a measurement of the degree of functional dependence of the patient. One of the most utilized is the Vignos scale that measures lower limb function. It is painless, quick to conduct, and affordable. Scores range from 1−10, and a higher score indicates poorer muscle function.[22] This scale was grouped into three categories, A (scores of 1-5), B (6-8) and C (9-10).[23] Non-ambulatory and ambulatory ability was also recorded. Physical rehabilitation was evaluated as frequency of sessions of therapy (days per week), considering that each session had a median duration between 25 to 30 minutes of the stretching of upper and lower limbs.

Statistical Analyses

Statistical analysis was performed using SPSS Statistical software (ver. 20.0). A p value ≤ 0.05 was considered significant. Results are presented as median [minimum, maximum] because data did not fit a normal distribution determined by Shapiro-Wilk test. To identify differences in variables among age groups, the Kruskal–Wallis test and, where that was significant, the Mann−Whitney U test was utilized for group−wise comparisons. To identify differences in categorical variables, Pearson's Chi−square test was used. Association between dietary intake and physical rehabilitation was analysed with Spearman correlations. To evaluate the effect of non-ambulatory ability or muscle function on dietary intake, but considering the age group effect, and its interaction, two-way ANOVA test with Bonferroni pair-wise correction was applied. Multivariate linear regression analysis was applied to determine whether dietary intake was related to body fat and lean mass, after adjusting for confounding covariates, such as the degree of functional dependence of the patient, age, non-ambulatory ability, and physical rehabilitation.

RESULTS

A total of 101 male patients with confirmed DMD were included in this study. Characteristics of boys stratified according to age are shown in Table 1.

Dietary Intake

Median energy intake (kcal/day) was high relative to the DRI for preschool–age and school–age boys, although there was no significant difference in energy intake among the age groups (Table 2). The percentage of energy from proteins and carbohydrates as well as fiber intake was adequate and not statistically different among the age groups (Table 2). However, protein intake in g/kg/d was higher than the DRI in all age groups and was also different among them ($p < 0.001$) decreasing with age (Table 2). The opposite was observed for fat intake expressed as g/kg/d (Table 2). Although the median energy intake from fat was according to the DRI in all age groups, it was lower in adolescents than in the younger age groups ($p < 0.001$). Dietary intake was also analysed stratifying by ambulatory ability and age group. The two-way ANOVA showed that the school-age group had higher protein, carbohydrate and fat intake compared with adolescents (Table 3). However, patients who were non-ambulatory consumed less energy and carbohydrate compared with ambulatory patients. There were no interactions between age group and ambulatory ability (Table 3). There were no differences in energy and fibre intake. Likewise, dietary intake was not different among the 3 categories of Vignos scale (Table 4), but the differences in macro-nutrients were confirmed among each age group ($p < 0.01$, Table 4). Dietary intake was not associated with physical rehabilitation ($p > 0.200$).

Nutritional Status Based on BMI and Body Composition

The percentage of boys with normal nutritional status based on BMI showed a trend to decrease with age (Table 5), while boys with malnutrition (the sum of thin, overweight, and obese) showed a trend to increase with age (pre−schoolers 15%, school−age 40.6% and adolescents 47.1%, $p = 0.072$). Adolescents were more likely than other age groups to be overweight, but not obese, when evaluation was based on BMI (Table 5). They also had the highest percentage of fat mass. Accordingly, 81% of adolescents showed high body fat content corresponding to overweight or obesity, followed by school−age, and finally, pre−schoolers (Fig. 1). Lean mass analysed as percentage of body weight decreased significantly with increasing age (Table 5). Likewise, the patients grouped in Vignos scale C had higher percentage of fat mass and consequently a lower percentage of body lean mass compared with those in Vignos Scale A and B (Table 6).

Multivariate linear regression analysis revealed that macronutrient (protein $\beta = 0.0121$, $p = 0.324$; carbohydrate $\beta = 0.0059$, $p = 0.103$; fat $\beta = -0.0061$, $p = 0.205$) and energy intake (Supplementary Table 1) had no significant effect on the percentage of body fat mass after adjusting for confounders such as the degree of functional dependence of the patient evaluated with Vignos scale, age, non-ambulatory ability, frequency of physical rehabilitation, and nutritional status based on BMI. However, body fat mass was higher in overweight patients and highest in obese patients compared with normal nutritional status, showing a positive linear trend between body fat and overnutrition (Supplementary Table 1).

Similar to fat mass, macronutrient (protein $\beta = 0.0047$, $p = 0.710$; carbohydrate $\beta = -0.0030$, $p = 0.414$; fat $\beta = -0.0052$, $p = 0.306$) and energy intake (Supplementary Table 2) did not determine lean mass. Nonetheless, lean mass was negatively associated with thinness, overweight and obesity after adjustment for the confounders mentioned above, except for the frequency of physical rehabilitation, which demonstrates that a higher frequency of rehabilitation favoured greater lean mass (Supplementary Table 2).

DISCUSSION

In this study, we observed that body composition in boys with DMD was not related to dietary intake at different ages, and that the standard reference BMI cut–offs from WHO[18-20] are not suitable to establish the nutritional status of patients with DMD. Previous investigations have described BMI using the Centers for Disease Control (CDC) cut-offs[8,5] or body composition through DEXA[24,25] in school–age or adult patients with DMD with a limited sample size. Although steroids are not used in all neuromuscular centres, they remain the mainstay of DMD therapy.[1] The degree of functional dependence measured with the Vignos scale and non-ambulatory ability were more frequent in adolescents, which was expected due to the evolution of the disease with time.[22] In the present study, it was identified that non-ambulatory status is associated with lower carbohydrate and energy intake, possibly due to reduced energy expenditure.[1] We analysed this with two-way ANOVA because intake also strongly depends on age group. We examined whether Vignos scale was associated with lower dietary intake (probably due the decline of muscle function), but there was no effect. This analysis also showed an inverse relation between macronutrients intake and age, as younger patients had higher macronutrient intake which declined with the increase of the age in these groups. Energy and macronutrient intake were estimated by 24–h recall because this method is practical, inexpensive, and relatively quick to use with large groups of patients. In addition, the respondent's burden is low compared with other methods, such as weighed dietary records, and typically, this measurement is well–accepted by parents and children. Finally, when the recall is applied without previous advice there is a low risk that food patterns are changed to "please" the measurer.[15]

There is a lack of information concerning whether boys with DMD, especially at different ages, have an adequate energy intake according to the DRIs. Our findings demonstrate that pre–school and school–age groups had a high energy intake while that of adolescents was adequate according to the DRI.[14] Hankard *et al*. analyzed the macronutrient intake in healthy subjects (n = 9), obese DMD patients (ODMD, n = 8), and non–obese DMD patients (NODMD, n = 5) aged 8−13 years, and reported that patients in the ODMD group had a lower energy, carbohydrate and fat intake compared with healthy subjects.[26] It is well known that Mexico has an obesogenic environment and a high prevalence of overweight and obesity: in pre-school age children combined overweight and obesity was 9.7%, while in school-age children overweight and obesity prevalence was 19.5% and 17.4%, respectively, and in adolescents 19.6% and 14.5%, respectively.[27] In our patients with DMD, only the prevalence of overweight in adolescents is higher than the national average determined by BMI (41% vs 19.6%). Nonetheless, the average energy intake reported in a nationally representative sample of Mexican children was similar to or slightly higher than that of DMD boys (1,494 kcal/day vs. 1,431 kcal/day in pre-schoolers, 1,908 kcal/day vs. 1,807 kcal/day in schoolers, and 1,976 kcal/day vs. 1,837 kcal/day in adolescents, respectively).[28,29] It is important to highlight that the high energy intake at pre–school and school–age, as observed in the current study, could result in obesity.

Additionally, all age groups had a higher protein intake (expressed as g/kg/d) than the DRI. These findings are in agreement with the elevated protein intake in adolescents reported by Okada *et al*, who observed a lower energy intake and a high (1.34−1.40 g/kg/day) protein intake in patients with DMD aged between 11−29 years.[30] Boys with DMD in our study had also higher protein intake compared with Mexican children through all age groups (233 kcal/day vs. 207 kcal/day in pre-schoolers, 292 kcal/day vs. 252 kcal/day in schoolers and 326 kcal/day vs. 245 kcal/day in adolescents, respectively).[28,29]

In healthy children aged 9−14 years, it has been reported that macronutrients are not significantly related to weight gain.[31] However, this information is controversial, because excessive protein intake was positively associated with a trend toward an increase in overweight and obesity when energy intake was adequate.[32] Furthermore, we should consider some factors that affect the reporting of dietary intake, such as socioeconomic status, food habits, and the ability of the primary caregiver to determine portion size, resulting in intake under– or overestimation.[33]

Adequate energy intake was found in adolescents, but 81.2% of them had excessive body fat mass, although there were no obese adolescents detected based on BMI. Furthermore, the school–age group showed a higher percentage of thin subjects compared with the pre–school age group, based on BMI, whereas the reverse was observed with DEXA (i.e. fat mass was higher in school–age compared with pre–school). These conflicting results strongly suggest that common anthropometric measures, such as BMI, are not suitable for dystrophic patients perhaps because they do not evaluate the progressive intramuscular fat deposition in both the central and peripheral regions that characterizes the disease.[34,35] Moreover, muscle mass loss can mask fat mass accumulation. BMI is therefore misleading in DMD patients. It has been recommended that the adapted weight–for-age charts of Griffiths and Edwards be used,[36] which take into account the muscle mass loss in DMD. We applied the standard reference BMI classification to evaluate the impact of misclassification on fat mass measured by DEXA as the gold standard.

In the present study, we evaluated BMI according with World Health Organization (WHO) rather than the CDC growth references, because it is well known that the CDC charts reflect a heavier and somewhat shorter sample of children than the WHO sample, which results in lower rates of undernutrition and higher rates of overweight and obesity when based on WHO standards.[37] Typically DMD patients have a higher percentage of body fat and a lower percentage of lean mass compared with healthy subjects.[2,38] Results from our patients were consistent with these reports but with a difference in pre-school age. This group showed a lower median of fat mass compared with the cut-off for overweight non-DMD children from 2-5 years (13.5% vs. 18.7% of fat mass), but higher fat mass in school-age children and adolescents with DMD than in non-DMD subjects of the same age who were overweight (28.8% vs. 19.7% and 51.1% vs. 21.9%, respectively).[21] The lean mass was lower in boys with DMD from our study compared with non-DMD school-age children (16.9 kg vs. 24.5 kg),[39,38] and even compared with other boys with DMD (19.8 kg)[38] Moreover, the percentage of fat mass showed an increase from school–age to adolescence,[40] with a decrease in the percentage of lean mass in the same age groups.[38] These findings are explained by the replacement of skeletal muscle by adipose tissue, generated by inadequate muscle regeneration in patients with DMD.

However, the limitations were the cross–sectional design, which makes it difficult to establish a cause–and–effect relationship compared with a prospective longitudinal study, and the lack of concurrent age matched control groups. Additionally, the dietary intake was not measured with a questionnaire of food frequency, so that we were not able to examine food groups, or specific foods such as meat, which may be difficult to chew, or if the intake of food groups changed among age groups. Furthermore, dietary intake measured in boys with DMD in this study may be different from in other countries, as dietary intake and body composition may vary among geographic regions and population subtypes, and therefore our findings may not be generalizable. However, the identification that younger children have nutritional alterations indicates that this age group needs more attention to avoid health complications in later life.

Our findings suggest that total energy or macronutrients are not significant factors for the development of nutritional disorders in boys with DMD. However, we observed that nutritional alterations may start in pre–school age, and not later as has been reported.[8] Moreover, the severity of nutritional alterations increases with age in boys with DMD. Therefore, it is best to offer individual nutritional treatment, starting from pre-school age in patients with DMD. There has been little or no investigation into the optimal dietary patterns for boys with DMD. In the context of obesity and related metabolic alterations, country specific dietary guidelines should be used to guide dietary intake. Patients and their families should practice healthy eating habits and life styles to improve dietary compliance.[1,4] Therefore, we recommend diets that have shown positive effects to prevent overweight/obesity, control insulin resistance and dyslipidaemia. Specifically, a diet based on consumption of complex carbohydrates with high fibre such as non-starchy vegetables, legumes, whole-grain breads and cereals, most fruits with peel, and raw nuts should be adopted along with control of portion size. Oils should be limited to cooking and simple sugars restricted by controlling intake of high caloric foods such as sugar-sweetened beverages and fatty meals.[41,42] Consistent with our results, there is no evidence suggesting that patients require additional protein intake compared with DRI.[43] Hypertension control is achieved by reducing weight, avoiding coffee and cola beverages and limiting sodium intake. Eating slowly along with fluid intake allows better perception of satiety.[44] The loss of ambulation may cause constipation and weight gain; therefore intake of high fibre foods along with plenty intake of plain water may help to reduce constipation and favour satiety. Weight should be monitored to guide the energy prescription with adequate intake of macronutrients as per DRI, adjusting for activity level and to prevent excess weight gain or loss.[4] Swallowing dysfunction, constipation, gastro-oesophageal reflux disease and delayed gastric emptying are consequences of decreased muscle strength, and, along with increased energy expenditure, result in insufficient intake and undernutrition. Adequate fluid intake and modifications of food options/texture might also be useful.[43,45] Nutritional guidance should be mandatory prior to steroid therapy prescription which can increase appetite, promote weight gain, mainly in adipose tissue leading to obesity and insulin resistance.[1,4] In turn, nutritional guidance may improve disease progression and, in the long term, quality of life.

In conclusion, all age groups of boys with DMD had a protein intake/kg above the DRI. Preschool−age and school−age boys with DMD had high energy intake, whereas adolescents had adequate energy intake. Body composition data confirmed that as age increases, there is an increase in fat mass, but a decrease in lean mass. Nevertheless, dietary intake did not predict body fat and lean mass in boys with DMD, possibly due to the greater impact of the disease itself or of disease–related confounding factors such as immobility.

Abbreviations

BMI: Body Mass Index

DEXA: Dual–Energy X–ray Absorptiometry

DMD: Duchenne muscular dystrophy

IMSS: Instituto Mexicano del Seguro Social

DRI: Dietary Reference Intake

REFERENCES

1. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, Case LE, Clemens PR, Hadjiyannakis S, Pandya S, Street N, Tomezsko J, Wagner KR, Ward LM, Weber DR, Group DMDCCW. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol 2018;17(3):251-267.

2. Davidson ZE, Rodden G, Mázala DAG, Moore C, Papillon C, Hasemann AJ, Truby H, Grange RW. Practical Nutrition Guidelines for Individuals with Duchenne Muscular Dystrophy. In: Childers MK, editor. Regenerative Medicine for Degenerative Muscle Diseases. New York, NY: Springer New York; 2016. p 225-279.

3. Haddad L, Achadi E, Bendech MA, Ahuja A, Bhatia K, Bhutta Z, Blossner M, Borghi E, Colecraft E, de Onis M, Eriksen K, Fanzo J, Flores-Ayala R, Fracassi P, Kimani-Murage E, Nago Koukoubou E, Krasevec J, Newby H, Nugent R, Oenema S, Martin-Prevel Y, Randel J, Requejo J, Shyam T, Udomkesmalee E, Reddy KS. The Global Nutrition Report 2014: actions and accountability to accelerate the world's progress on nutrition. J Nutr 2015;145(4):663-671.

4. Davidson ZE, Truby H. A review of nutrition in Duchenne muscular dystrophy. J Hum Nutr Diet 2009;22(5):383-393.

5. Martigne L, Salleron J, Mayer M, Cuisset JM, Carpentier A, Neve V, Tiffreau V, Guimber D, Gottrand F. Natural evolution of weight status in Duchenne muscular dystrophy: a retrospective audit. Br J Nutr 2011;105(10):1486-1491.

6. Davis J, Samuels E, Mullins L. Nutrition Considerations in Duchenne Muscular Dystrophy. Nutr Clin Pract 2015;30(4):511-521.

7. de Onis M, Blossner M. The World Health Organization Global Database on Child Growth and Malnutrition: methodology and applications. International journal of epidemiology 2003;32(4):518-526.

8. Willig TN, Carlier L, Legrand M, Riviere H, Navarro J. Nutritional assessment in Duchenne muscular dystrophy. Dev Med Child Neurol 1993;35(12):1074-1082.
9. McDonald CM, Abresch RT, Carter GT, Fowler WM, Jr., Johnson ER, Kilmer DD, Sigford BJ. Profiles of neuromuscular diseases. Duchenne muscular dystrophy. Am J Phys Med Rehabil 1995;74(5 Suppl):S70-92.
10. Davidson ZE, Ryan MM, Kornberg AJ, Sinclair K, Cairns A, Walker KZ, Truby H. Observations of body mass index in Duchenne muscular dystrophy: a longitudinal study. Eur J Clin Nutr 2014;68(8):892-897.
11. Saure C, Caminiti C, Weglinski J, de Castro Perez F, Monges S. Energy expenditure, body composition, and prevalence of metabolic disorders in patients with Duchenne muscular dystrophy. Diabetes Metab Syndr 2018;12(2):81-85.
12. Deconinck N, Dan B. Pathophysiology of duchenne muscular dystrophy: current hypotheses. Pediatr Neurol 2007;36(1):1-7.
13. Rodriguez-Cruz M, Sanchez R, Escobar RE, Cruz-Guzman Odel R, Lopez-Alarcon M, Bernabe Garcia M, Coral-Vazquez R, Matute G, Velazquez Wong AC. Evidence of Insulin Resistance and Other Metabolic Alterations in Boys with Duchenne or Becker Muscular Dystrophy. Int J Endocrinol 2015;2015:867273.
14. Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Jennifer JO, Jennifer Pitzi H, Linda DM, editors. Washington, DC: The National Academies Press; 2006.
15. Johnson RK, Driscoll P, Goran MI. Comparison of multiple-pass 24-hour recall estimates of energy intake with total energy expenditure determined by the doubly labeled water method in young children. J Am Diet Assoc 1996;96(11):1140-1144.
16. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler WV, Paul DR, Sebastian RS, Kuczynski KJ, Ingwersen LA, Staples RC, Cleveland LE. The US Department of Agriculture

Automated Multiple-Pass Method reduces bias in the collection of energy intakes. Am J Clin Nutr 2008;88(2):324-332.

17. Adams KM, Kohlmeier M, Powell M, Zeisel SH. Nutrition in medicine: nutrition education for medical students and residents. Nutr Clin Pract 2010;25(5):471-480.

18. de Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? Int J Pediatr Obes 2010;5(6):458-460.

19. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85(9):660-667.

20. Group WHOMGRS. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl 2006;450:76-85.

21. Taylor RW, Jones IE, Williams SM, Goulding A. Body fat percentages measured by dual-energy X-ray absorptiometry corresponding to recently recommended body mass index cutoffs for overweight and obesity in children and adolescents aged 3-18 y. Am J Clin Nutr 2002;76(6):1416-1421.

22. Vignos PJ, Jr. Diagnosis of progressive muscular dystrophy. J Bone Joint Surg Am 1967;49(6):1212-1220.

23. Stevens PM. Lower Limb Orthotic Management of Duchenne Muscular Dystrophy: A Literature Review. JPO: Journal of Prosthetics and Orthotics 2006;18(4).

24. McDonald CM, Carter GT, Abresch RT, Widman L, Styne DM, Warden N, Kilmer DD. Body composition and water compartment measurements in boys with Duchenne muscular dystrophy. Am J Phys Med Rehabil 2005;84(7):483-491.

25. Zanardi MC, Tagliabue A, Orcesi S, Berardinelli A, Uggetti C, Pichiecchio A. Body composition and energy expenditure in Duchenne muscular dystrophy. Eur J Clin Nutr 2003;57(2):273-278.

26. Hankard R, Gottrand F, Turck D, Carpentier A, Romon M, Farriaux JP. Resting energy expenditure and energy substrate utilization in children with Duchenne muscular dystrophy. Pediatr Res 1996;40(1):29-33.
27. Gutiérrez JP R-DJ, Shamah-Levy T, Villalpando-Hernández S, Franco A, Cuevas-Nasu L, Romero-Martínez M H-ÁM. National Survey of Health and Nutrition. National Results [Spanish: Encuesta Nacional de Salud y Nutrición 2012. Resultados Nacionales]. Cuernavaca, México: Instituto Nacional de Salud Pública (MX); 2012.
28. Taillie LS, Afeiche MC, Eldridge AL, Popkin BM. The contribution of at-home and away-from-home food to dietary intake among 2-13-year-old Mexican children. Public Health Nutr 2017;20(14):2559-2568.
29. Denova-Gutierrez E, Ramirez-Silva I, Rodriguez-Ramirez S, Jimenez-Aguilar A, Shamah-Levy T, Rivera-Dommarco JA. Validity of a food frequency questionnaire to assess food intake in Mexican adolescent and adult population. Salud publica de Mexico 2016;58(6):617-628.
30. Okada K, Manabe S, Sakamoto S, Ohnaka M, Niiyama Y. Protein and energy metabolism in patients with progressive muscular dystrophy. J Nutr Sci Vitaminol (Tokyo) 1992;38(2):141-154.
31. Rodríguez G, Moreno LA. Is dietary intake able to explain differences in body fatness in children and adolescents? Nutrition, Metabolism and Cardiovascular Diseases 2006;16(4):294-301.
32. Pimpin L, Jebb S, Johnson L, Wardle J, Ambrosini GL. Dietary protein intake is associated with body mass index and weight up to 5 y of age in a prospective cohort of twins1,2. The American Journal of Clinical Nutrition 2016;103(2):389-397.
33. Collins CE, Watson J, Burrows T. Measuring dietary intake in children and adolescents in the context of overweight and obesity. Int J Obes (Lond) 2010;34(7):1103-1115.
34. Leroy-Willig A, Willig TN, Henry-Feugeas MC, Frouin V, Marinier E, Boulier A, Barzic F, Schouman-Claeys E, Syrota A. Body composition determined with MR in patients with Duchenne muscular dystrophy, spinal muscular atrophy, and normal subjects. Magn Reson Imaging 1997;15(7):737-744.

35. Pichiecchio A, Uggetti C, Egitto MG, Berardinelli A, Orcesi S, Gorni KO, Zanardi C, Tagliabue A. Quantitative MR evaluation of body composition in patients with Duchenne muscular dystrophy. Eur Radiol 2002;12(11):2704-2709.
36. Griffiths RD, Edwards RH. A new chart for weight control in Duchenne muscular dystrophy. Arch Dis Child 1988;63(10):1256-1258.
37. de Onis M, Garza C, Onyango AW, Borghi E. Comparison of the WHO child growth standards and the CDC 2000 growth charts. J Nutr 2007;137(1):144-148.
38. Skalsky AJ, Han JJ, Abresch RT, Shin CS, McDonald CM. Assessment of regional body composition with dual-energy X-ray absorptiometry in Duchenne muscular dystrophy: correlation of regional lean mass and quantitative strength. Muscle Nerve 2009;39(5):647-651.
39. Ramirez E, Valencia ME, Bourges H, Espinosa T, Moya-Camarena SY, Salazar G, Aleman-Mateo H. Body composition prediction equations based on deuterium oxide dilution method in Mexican children: a national study. Eur J Clin Nutr 2012;66(10):1099-1103.
40. Mok E, Letellier G, Cuisset JM, Denjean A, Gottrand F, Hankard R. Assessing change in body composition in children with Duchenne muscular dystrophy: anthropometry and bioelectrical impedance analysis versus dual-energy X-ray absorptiometry. Clin Nutr 2010;29(5):633-638.
41. Bianchi ML, Biggar D, Bushby K, Rogol AD, Rutter MM, Tseng B. Endocrine aspects of Duchenne muscular dystrophy. Neuromuscul Disord 2011;21(4):298-303.
42. Freeland-Graves JH, Nitzke S, Academy of N, Dietetics. Position of the academy of nutrition and dietetics: total diet approach to healthy eating. J Acad Nutr Diet 2013;113(2):307-317.
43. Salera S, Menni F, Moggio M, Guez S, Sciacco M, Esposito S. Nutritional Challenges in Duchenne Muscular Dystrophy. Nutrients 2017;9(6).
44. Ogata BN, Hayes D. Position of the Academy of Nutrition and Dietetics: nutrition guidance for healthy children ages 2 to 11 years. J Acad Nutr Diet 2014;114(8):1257-1276.

45. Messina S, Pane M, De Rose P, Vasta I, Sorleti D, Aloysius A, Sciarra F, Mangiola F, Kinali M, Bertini E, Mercuri E. Feeding problems and malnutrition in spinal muscular atrophy type II. Neuromuscul Disord 2008;18(5):389-393.

FIGURE LEGEND

Figure 1. Percentage of boys with Duchenne muscular dystrophy (DMD) with low, adequate or high fat mass[21] according to age group.

Table 1. Characteristics of boys with Duchenne muscular dystrophy patients according to age group.

Child characteristics	Preschool–age (n = 20)		School–age (n = 64)		Adolescents (n = 17)		*P*
	Median	Min., Max.	Median	Min., Max.	Median	Min., Max.	
Age (y)	5.0[a]	3.12, 5.9	8.5[b]	6.0, 11.7	13.7[c]	12.0, 18.9	<0.001*
Weight (kg)	16.2[a]	11.8, 21.7	25.2[b]	14.3, 58.2	52.3[c]	28.1, 79.4	<0.001*
Height (cm)	104.1[a]	87.0, 114.3	123.1[b]	102.0, 152.0	153.0[c]	129.0, 175.0	<0.001*
BMI							
kg/m^2	15.0[a]	13.29, 18.3	16.0[b]	11.8, 28.9	22.5[c]	21.8, 29.5	<0.001*
Z–score	-0.13	-2.38, 2.13	0.10	-4.92, 2.80	0.63	-13.9, 1.97	0.586*
Vignos scale	3.0[a]	0.0, 7.0	7.0[b]	0.0, 9.5	9.0[c]	0.0, 10.0	<0.001*
Physical therapy (sessions/week)	3	2, 7	4	1, 7	6	1, 7	0.904
Non- ambulatory boys, n (%)	0 (0)		16 (25)		13 (45)		<0.001**

Preschool-age (2 to < 6 years); school-age (6 to < 12 years), and adolescents (12 to ≤ 18 years)

BMI, body mass index

Min.: Minimum, Max.: Maximum

*Determined using Kruskal–Wallis test.

**Determined using Chi–Square test.

Median values not sharing a superscript letter are significantly different (P < 0.001; Mann–Whitney U–test).

Table 2. Dietary intake of boys with Duchenne muscular dystrophy according to age group.

	Preschool–age (*n* = 20)		School–age (*n* = 64)		Adolescents (*n* = 17)		*P***
Energy							
DRI Ref. (kcal/day)*	1,142 – 1,308		1,308 – 1,666		1,773 – 2,358		
Intake of patients (kcal/day)	1,431	[1,169; 2,946]	1,807	[937; 4,411]	1,837	[1,034; 2,875]	0.307
Interquartile range (kcal/day)	620		684		1,139		
Protein							
DRI Ref. (g/kg/day)*	0.76		0.76		0.73		-
Intake of patients (g/kg/d)	3.8[a]	[2.0, 8.5]	2.8[b]	[1.0, 6.8]	1.6[c]	[1.0, 2.9]	<0.001
Interquartile range (g/kg/d)	1.30		1.70		0.50		
Reference (% of E/day)*			10 – 30				-
Intake of patients (% of E/day)	14.7	[11.2, 23.1]	15.9	[10.6, 30.8]	18.5	[11.8, 23.3]	0.197
Carbohydrates							
Intake of patients (g/kg/d)	12.2[a]	[8.4, 18.6]	9.3[b]	[2.3, 21.6]	5.1[c]	[2.0, 13.3]	<0.001
Interquartile range (g/kg/d)	5.36		4.75		2.49		
Reference (% of E/day)*			45 – 65				-
Intake of patients (% of E/day)	52.3	[38.7, 64.1]	53.4	[28.7, 78.7]	57.4	[37.8, 74.0]	0.099
Fibre							
Intake of patients (g/1000 kcal)	10.4	[2.4, 18.5]	9.9	[3.3, 38.0]	10.7	[3.5, 18.7]	0.913
Interquartile range (g/1000/kcal)	6.14		6.61		6.72		
Fat							
Intake of patients (g/kg/d)	4.1[a]	[1.9, 7.7]	2.5[b]	[0.6, 7.4]	1.1[c]	[0.5, 1.9]	<0.001
Interquartile range (g/kg/d)	2.57		1.72		0.49		
Reference (% of E/day)*			25 – 35				
Intake of patients (% of E/day)	31.8[a]	[20.3, 48.1]	30.9[a]	[9.9, 51.8]	25.3[b]	[11.3, 37.5]	0.033

Data are presented as median [minimum, maximum] unless otherwise stated.

Preschool-age (2 to < 6 years); school-age (6 to < 12 years), and adolescents (12 to ≤ 18 years)

*Estimated Requirement for boys with sedentary physical activity level according to Dietary Reference Intakes (DRI).

E: energy

**Determined using Kruskal−Wallis test.

Median values not sharing a superscript letter are significantly different (*P*< 0.001; Mann−Whitney *U* test).

Table 3. Relation of age group and ambulatory ability on dietary intake of boys with Duchenne muscular dystrophy.

Dietary intake	Age group	Ambulatory ability		*P* value*		
		No *n* = 52	Yes *n* = 29	*P*1	*P*2	*P*3
Energy (kcal/d)	School-age	1,897 ± 84	1,747 ± 145			
	Adolescents	2,406 ± 289	1,734 ±160	0.184	0.029	0.163
Protein (g/kg/d)	School-age	3.2 ± 0.2	2.4 ± 0.3			
	Adolescents	1.9 ± 0.5	1.6 ± 0.3	0.002	0.102	0.487
Carbohydrates (g/kg/d)	School-age	9.8 ± 0.5	8.2 ± 0.9			
	Adolescents	8.8 ± 1.7	4.7 ± 0.9	0.041	0.012	0.281
Fibre (g/1000 kcal)	School-age	10.7 ± 0.8	12.0 ± 1.4			
	Adolescents	9.0 ± 2.8	11.2 ± 1.6	0.484	0.344	0.794
Fat (g/kg/d	School-age	2.9 ± 0.2	1.9 ± 0.3			
	Adolescents	1.1 ± 0.6	1.1 ± 0.3	0.001	0.178	0.200

Mean ± Standard deviation

School-age (6 to < 12 years), and adolescents (12 to ≤ 18 years)

*Two-way ANOVA. P1: between age groups, P2: between ambulatory ability or not; P3: interaction between age groups and ambulatory ability.

Levene´s test of equality of error variances was < 0.05 for protein, carbohydrates and fat intake.

Table 4. Relation among age group and Vignos scale on dietary intake of boys with Duchenne muscular dystrophy.

Dietary intake	Age group	Vignos Scale A (n = 41)	Vignos Scale B (n = 27)	Vignos Scale C (n = 19)	*P* value* *P*1	*P* value* *P*2	*P* value* *P*3
Energy (kcal/d)	Preschool–age	1706 ± 158	1660 ± 360	--			
	School-age	2023 ± 681	1698 ± 417	1873 ± 514			
	Adolescents	2105 ± 379	2150 ± 981	1845 ± 540	0.311	0.702	0.644
Protein (g/kg/d)	Preschool–age	4.6 ± 0.4	3.4 ± 0.6	--			
	School-age	3.2 ± 0.2	3.0 ± 0.3	2.6 ± 0.4			
	Adolescents	1.5 ± 1.0	1.9 ± 0.8	1.5 ± 0.5	0.002	0.644	0.631
Carbohydrates (g/kg/d)	Preschool–age	12.5 ± 1.0	13.2 ± 1.6	--			
	School-age	10.1 ± 0.7	9.1 ± 0.8	8.2 ± 1.1			
	Adolescents	6.7 ± 2.4	7.8 ± 2.0	4.9 ± 1.2	0.002	0.253	0.772
Fibre (g/1000 kcal)	Preschool–age	10.5 ± 1.5	10.8 ± 2.5	--			
	School-age	10.7 ± 1.1	12.2 ± 1.3	9.4 ± 1.8			
	Adolescents	9.5 ± 3.9	8.5 ± 3.2	10.6 ± 1.8	0.817	0.987	0.689
Fat (g/kg/d)	Preschool–age	4 3 ± 0.4	4.0 ± 0.6	--			
	School-age	3.1 ± 0.3	2.4 ± 0.3	2.4 ± 0.4			
	Adolescents	0.9 ± 1.0	1.0 ± 0.8	1.0 ± 0.5	< 0.001	0.745	0.906

Mean ±Standard deviation.

Vignos categories were grouped as scale A (scored 0-5), Vignos scale B (scored 6-8), Vignos scale C (scored 9-10).

--There are patients in preschool-age with scale C.

Preschool-age (2 to < 6 years); school-age (6 to < 12 years), and adolescents (12 to ≤ 18 years).

*Two-way ANOVA. P1: between age groups, P2: between Vignos scales; P3: interaction between age groups and

Vignos scales

Levene's test of equality of error variances was < 0.05 for protein, carbohydrates and fat intake.

Table 5. Nutritional status based on BMI and body composition of boys with Duchenne muscular dystrophy according to age group.

Nutritional status	Preschool–age (*n* = 20)	School–age (*n* = 64)	Adolescents (*n* = 17)	*P*[a]
Normal	17 (85)	38 (59.4)	9 (52.9)	
Thin	1 (5)	8 (12.5)	1 (5.9)	
Overweight	1 (5)	12 (18.8)	7 (41.2)	
Obese	1 (5)	6 (9.4)	0	0.080

Body composition	Median	Min., Max.	Median	Min., Max.	Median	Min., Max.	*P*[b]
Fat mass							
kg	2.2[a]	0.9, 3.7	6.9[b]	1.3, 31.1	27.0[c]	5.3, 31.8	<0.001
%	13.5[a]	7.6, 54.8	28.8[b]	8.5, 7.2	51.1[c]	12.7,60.0	<0.001
Lean mass							
kg	13.0[a]	10.1, 16.2	16.9[b]	11.2, 28.2	25.0[c]	10.7, 36.6	<0.001
%	81.8[a]	75.9, 86.7	67.4[b]	41.3, 85.6	50.0[c]	13.5, 84.1	<0.001

Data for nutritional status is shown as frequency (%)

Min.: Minimum, Max.: Maximum

Preschool-age (2 to < 6 years); school-age (6 to < 12 years), and adolescents (12 to ≤ 18 years)

[a] Determined using Chi−square test

[b]Determined using Kruskal−Wallis test.

Median values not sharing a superscript letter are significantly different (Mann−Whitney *U* test).

Table 6. Nutritional status and body composition stratified by Vignos scale.

	Vignos scale A (*n* = 40)	Vignos scale B (*n* = 27)	Vignos scale C (*n* = 18)	*P*
BMI, z-score	-0.04 [-2.7, 2.2]	0.40 [-3.2, 2.5]	0.78 [-4.9, 2.8]	0.765
Fat mass				
Kg of body weight	4.8^{a} [1,31.2]	4.8^{a} [0.9, 30.7]	15.5^{b} [1.3,32.1]	0.006
% of body weight	20.1^{a} [9.0,55.3]	23.6^{a} [7.6, 54.8]	46.3^{b} [8.5, 60.0]	0.005
Lean mass				
Kg of body weight	16.0^{a} [10.1, 36.6]	16.6^{a} [10.7, 33.2]	20.5^{b} [10.7, 29.6]	0.005
% of body weight	75.5^{a} [42.9, 85.7]	72.0^{a} [44.3, 86.7]	51.9^{b} [13.5,85.6]	0.005

Data are presented as Median [Minimum, Maximum]

Vignos categories were grouped as scale A (scored 0-5), Vignos scale B (scored 6-8), Vignos scale C (scored 9-10).