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ORIGINAL RESEARCH

The Effect of Adiposity on Cardiovascular Function and Myocardial Fibrosis in Patients With Duchenne Muscular Dystrophy

Sarah E. Henson, MD; Sean M. Lang, MD; Philip R. Khoury, PhD; Cuixia Tian, MD; Meilan M. Rutter, MD; Elaine M. Urbina, MD, MS; Thomas D. Ryan, MD, PhD; Michael D. Taylor, MD, PhD; Tarek Alsaied, MD, MSc

BACKGROUND: Patients with Duchenne muscular dystrophy (DMD) develop cardiomyopathy because of a dystrophin deficiency causing fibrofatty replacement of the myocardium. Corticosteroid use and mobility limitations place these patients at risk for increased adiposity. We sought to determine the association of adiposity with cardiovascular dysfunction in patients with DMD.

METHODS AND RESULTS: This was a retrospective review of patients with DMD who underwent both cardiac magnetic resonance imaging and dual-energy x-ray absorptiometry within 1 year. The cardiac magnetic resonance imaging parameters included left ventricular ejection fraction and the presence of late gadolinium enhancement (LGE positive [LGE+]). The adiposity indices, measured by dual-energy x-ray absorptiometry, included percentage of body fat, whole body fat mass indexed to height, and body mass index. A total of 324 patients were identified. Fifty-two percent had LGE+, and 36% had cardiac dysfunction (left ventricular ejection fraction <55%). Patients with cardiac dysfunction had higher whole body fat mass indexed to height and body mass index on univariate analysis (mean difference between patients with and without cardiac dysfunction: +2.9 kg/m, P=0.001; and +1.5 kg/m^2, P=0.03, respectively). whole body fat mass indexed to height remained independently associated with cardiac dysfunction on multivariable analysis after adjusting for age, LGE+, and corticosteroid duration. High whole body fat mass indexed to height and percentage of body fat were associated with LGE+ on univariate analysis (mean difference between patients with and without LGE+: +2.0 kg/m, P=0.02; and +2.4%, P=0.02, respectively). Using multivariable analysis, including age and cardiac dysfunction, high percentage of body fat remained independently associated with LGE+.

CONCLUSIONS: This study demonstrates an independent association of adiposity with cardiac dysfunction and LGE+ in patients with DMD. Preventing adiposity may mitigate the later development of ventricular dysfunction in DMD.

Key Words: adiposity ■ Duchenne muscular dystrophy ■ ventricular dysfunction

Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy and affects 1 in 5000 males. This X-linked recessive disease leads to the absence of dystrophin, affecting skeletal muscles and myocytes, including cardiomyocytes. As cardiomyopathy is a leading cause of morbidity and mortality in patients with DMD,[1–3] complete cardiac evaluation is recommended biannually in early childhood and annually from 10 years of age.[4,5] Because of poor acoustic windows on echocardiograms, many children and teenagers with DMD undergo cardiac magnetic resonance (CMR). Evaluation for the presence of late gadolinium enhancement (LGE positive [LGE+]) is routinely performed to detect myocardial fibrosis in patients with DMD.[6] Our group and others have shown a correlation between left ventricular ejection fraction decline and LGE+.[7–9]

Correspondence to: Sarah E. Henson, MD, Heart Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 2003, Cincinnati, OH 45229. E-mail: sarah.henson@cchmc.org

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CLINICAL PERSPECTIVE

What Is New?

- This retrospective study demonstrates that higher whole body fat indexed to height and percentage of body fat are associated with cardiac dysfunction and late gadolinium enhancement on cardiac MRI in patients with Duchenne muscular dystrophy.
- Body mass index is routinely used as a measure of obesity; however, in patients with Duchenne muscular dystrophy, body mass index was not associated with cardiac dysfunction and was likely inaccurate because of the use of surrogate height measures once ambulation is lost.

What Are the Clinical Implications?

- Delaying ventricular dysfunction in patients with Duchenne muscular dystrophy may be accomplished by avoiding excess weight gain.
- Percentage of body fat and whole body fat obtained by dual-energy x-ray absorptiometry scans should be used to develop nutritional and physical treatment plans for patients with Duchenne muscular dystrophy.

Nonstandard Abbreviations and Acronyms

DMD	Duchenne muscular dystrophy
LGE	late gadolinium enhancement
NHANES	National Health and Nutrition Examination Survey
PBF	percentage of body fat
WBF	whole body fat mass indexed to height

Childhood obesity has been shown to cause changes in cardiovascular structure and function in children without DMD, but there have been no studies of the association of obesity with cardiovascular function in patients with DMD.[10] Patients with DMD are at high risk of developing increased adiposity attributable to decreased mobility, corticosteroid therapy, and the fibrofatty replacement of muscle. Corticosteroids are part of current care recommendations and are routinely used to preserve ambulation, cardiac and pulmonary function, and muscle strength.[11–13] However, the long-term use of corticosteroids may result in endocrine side effects such as obesity and growth deceleration.[14] Despite nutrition counseling and close monitoring of growth,[2,11] the ability to lose weight in this population is limited because of continued supra-physiologic corticosteroid therapy and mobility limitations with decreased energy expenditure.[15,16] Quantifying adiposity in this population can be challenging because of difficulty assessing body mass index (BMI), especially in nonambulatory patients. Dual-energy x-ray absorptiometry (DXA) scans are performed routinely to evaluate and monitor osteoporosis and provide an opportunity for serial measurement of adiposity indices including body fat mass and percentage of body fat (PBF).

The objective of this study was to determine if adiposity is associated with the development of cardiac dysfunction in patients with DMD. We hypothesized that adiposity indices measured by DXA are associated with LGE+ and cardiac dysfunction in patients with DMD.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Design

Patients with DMD (confirmed by genetic analysis or muscle biopsy) who underwent clinical CMR studies from January 1, 2006, to December 31, 2018, at Cincinnati Children's Hospital were eligible if they had at least 1 DXA scan performed within a year of their CMR. A retrospective chart review was performed to collect patients' demographic information, medical histories, medications, heights, and functional mobility scores.[17] This study was approved by the Institutional Review Board at Cincinnati Children's Hospital and qualified for waiver of informed consent.

DXA Scans

Whole body DXA scans were obtained using a Hologic Densitometer (Discovery/Horizon) calibrated to a common manufacturer standard and analyzed using Apex 2.3 software. To account for normal growth over time whole body mass measures were indexed to height (kg/m).[18] We recorded weights, PBF, BMI, and whole body fat mass indexed to height (WBF). Weights were obtained at the time of DXA, and heights were obtained using ulnar length.[19] PBF, BMI, and WBF from the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES) were used for normal control values. The Centers for Disease Control and Prevention conducts these surveys of the health and nutrition status of the US population. Cross-sectional whole body DXA examinations were conducted on participants aged ≥8 years. Pediatric participants were considered overweight if their BMI for age was at or above the male-specific 85th percentile, but less than the 95th percentile. Obesity was defined as BMI for age at or above the male-specific 95th percentile. Overweight for adult participants was defined as BMI of 25.0 to 29.9;

30.0 to 39.9 was used to define obesity; and 40.0 or higher was used to define extreme obesity.[20–22]

Cardiac Magnetic Resonance

CMR studies were obtained using a 1.5 T scanner (Ingenia; Philips Healthcare, Best, The Netherlands) using a phased array coil and R5.4.1 software. LGE images were obtained using a standard inversion recovery sequence protocol 8 to 10 minutes after injection with 0.2 mmol/kg gadolinium diethylenetriamine pentaacetic acid or gadoterate meglumine. A study was considered LGE+ if any left ventricular segments showed LGE in 2 separate imaging planes. Patients who did not have the presence of LGE were considered LGE negative. Right and left ventricular ejection fractions, and LGE images were collected for each patient.

Statistical Analysis

Statistical analysis was performed using JMP (version 14, SAS Institute Inc., Cary, NC) and SAS (version 9.4, SAS Institute Inc., Cary, NC). Patients' CMR and DXA scans were analyzed longitudinally across all visits if they had multiple studies and at the time of their last CMR visit. Each CMR and DXA scan were paired to within 0 to 365 days of each other. Patient characteristics were summarized using frequencies and percentages for categorical variables and median (25th, 75th percentile) for continuous variables. Covariates were obtained at each relative scan. Two sample t tests and chi-square tests were used to compare the means of adiposity indices from participants with and without DMD using the NHANES data set.[20–22] Analysis of covariance was used to compare characteristics of patients with and without cardiomyopathy adjusting for age. For bivariate analysis, correlation analyses were used to assess the strength of association between 2 continuous variables using Pearson correlation for normally distributed variables and Spearman for variables that were not normally distributed. Cohorts were grouped into patients with and without the presence of LGE and with and without the presence of cardiac dysfunction defined as left ventricular ejection fraction <55%.[23,24] For multivariable analysis, logistic regression was used for outcomes left ventricular dysfunction and LGE+. To take advantage of multiple CMR and DXA scans per patient, longitudinal mixed-effects models were employed, with subject accounted for as a random effect for all outcomes.

RESULTS

Patient Characteristics

A total of 324 patients with DMD were included in the study. The median age at last CMR was 14.9 years (interquartile range, 12.3–17.9); 164 patients (52%) had LGE+, and 116 patients (36%) had cardiac dysfunction (left ventricular ejection fraction <55%) on last CMR. The median age at the first LGE+ study was 12.9 years. Two hundred fifty-eight patients had multiple scans available. The median time between the CMR and DXA scan pairs was 1 day (interquartile range, 1–18.5). Ninety-eight percent of the patients were on corticosteroids, with a median age of 6.1 years at the initiation of corticosteroids and median total duration of 9.1 years. Patient characteristics at the time of their last CMR visit are summarized in Table 1. Comparisons of patient characteristics by cardiac dysfunction and presence of LGE are presented in Table S1. At the last CMR visit, the mean WBF was 16.6 kg/m (11.5–22), PBF was 49.2% (41–55.7), and BMI was 24 kg/m^2 (20.3–27.7). Patients with DMD had significantly higher WBF, PBF, and BMI

Table 1. Patient Characteristics at Their Last CMR

Patient characteristics (n=324)	Median (25th, 75th percentile)
Age at CMR, y	14.9 (12.3, 17.9)
Height, cm	140 (129.1, 152.4)
Weight, kg	48.9 (37.3, 60.4)
BMI, kg/m^2	24.0 (20.3, 27.7)
Systolic blood pressure, mm Hg	111 (102, 117)
Functional Mobility Score	5 (2, 6)
LV end-diastolic volume index, mL/m^2	72.3 (62.6, 85.6)
LV end-systolic volume index, mL/m^2	30.8 (24.7, 39)
LV mass index, g/m^2	38.1 (30.8, 44.8)
LV ejection fraction (%)	57 (53.8, 61.9)
LV ejection fraction <55%, n (%)	116 (36)
WBF, kg/m	16.6 (11.5, 22)
WLM, kg/m	17.1 (15.4, 19.4)
PBF	49.2 (41, 55.7)
Number of patients on corticosteroids, n (%)	316 (97.5)
Corticosteroid duration, y	9.1 (6.5, 11.6)
Age at start of corticosteroids, y	6.1 (4.5, 7.7)
Treated with an ACE inhibitor, n (%)	121 (37)
Treated with a beta blocker, n (%)	110 (34)
Treated with an ARB, n (%)	27 (8)
Treated with spironolactone, n (%)	75 (23)
Number of CMRs per patient	3 (2, 5)
Age at first CMR, y	10.1 (8.8, 11.7)
Number of patients with LGE+	164 (52)*
Age at first LGE+ CMR, y	12.9 (11.1, 15.4)
Number of DXA scans per patient	6 (4, 8)
Time between CMR and DXA scan pairs	1 (1, 18.5)

Data are presented as median and interquartile range for all variables. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CMR, cardiac magnetic resonance; DXA, dual-energy X-ray absorptiometry; LGE, late gadolinium enhancement; LV, left ventricular; PBF, percentage of body fat; WBF, whole body fat mass indexed to height; and WLM, whole body lean mass indexed.

*Percent of the sample.

Table 2. Comparison of Percentage of Body Fat and Whole Body Fat in Patients With and Without DMD Using the NHANES Data Set

Age, y	Percentage of body fat (%)			Whole body fat, kg*		
	DMD Mean±SD	NHANES Mean±SD	*P* value	DMD Mean±SD	NHANES Mean±SD	*P* value
8–11	41.8±9.6	28.0±0.4	<0.0001	16.6±8.0	11.5±0.3	<0.0001
n	73	1067		73	1067	
12–15	48.4±8.2	25.2±0.3	<0.0001	24.6±10.4	16.1±0.3	<0.0001
n	132	1726		132	1726	
16–19	51.0±9.2	22.9±0.3	<0.0001	29.8±11.0	18.7±0.4	<0.0001
n	86	1751		86	1751	
20–39	52.4±8.7	26.1±0.1	<0.0001	34.9±15.8	23.4±0.3	<0.0001
n	33	2183		33	2183	

DMD indicates Duchenne muscular dystrophy; and NHANES, National Health and Nutrition Examination Survey.
*Whole body fat mass indexed to height was not available for NHANES, whole body fat mass indexed for DMD patients available in Table S2.

when compared with the NHANES data (Tables 2 and 3, Figures 1 and 2). Indexed whole body fat was not available for the NHANES participants. WBF in patients with DMD by age group is presented in Table S2. It is important to note that the PBF is almost double compared with the general population, while BMI was only slightly different (mean difference of 1.8 kg/m^2). A total of 33.6% of pediatric patients with DMD met the criteria for obesity compared with 19.1% of NHANES pediatric participants; 30.3% of adult patients with DMD met the criteria for obesity, which was comparable with 31.1% of NHANES adult participants (Table 3). In our cohort, only 10 patients were deceased at the end of the study period. Four were over the age of 20 (1.2%), and only 1 of the 4 patients was obese. The remaining 6 patients were in the 12 to 19 years age group and 5 of the 6 patients were obese.

Factors Associated With Adiposity

On bivariate analysis, WBF and PBF increased with corticosteroid duration (r=0.1, P=0.02; and r=0.3, P<0.0001, respectively). WBF (r=0.2, P=0.01), PBF (r=0.4, P<0.0001) and BMI (r=0.2, P<0.0001) also increased with age (Table 4). On multivariable analysis, including age and corticosteroid duration, corticosteroid duration was associated with high PBF (P=0.02), while age was associated with both high WBF and PBF (P<0.0001).

Adiposity and Cardiac Dysfunction

Patients with cardiac dysfunction had higher WBF and BMI on bivariate analysis (+2.9 kg/m, P=0.001; and +1.5 kg/m^2, P=0.03) and WBF after adjusting for age (P=0.001) (Tables 4 and 5). WBF and PBF remained independently associated with cardiac dysfunction after adjusting for age, LGE+, and corticosteroid duration on multivariable analysis (Table 6). Of note, corticosteroid duration was not associated with the development of ventricular dysfunction on multivariable analysis.

Adiposity and Late Gadolinium Enhancement

Higher WBF and PBF were associated with LGE+ on bivariate analysis (mean difference between patients with LGE+ and LGE negative at last CMR: +2.0 kg/m, P=0.02; and +2.4%, P=0.02) (Table 4). On multivariable

Table 3. Comparision of Participants With Normal Weight, Overweight, and Obesity With Duchenne Muscular Dystrophy and Without Using NHANES BMI Data

Age, y	6–11		12–19		20–39	
	DMD (n=65)	NHANES (n=463)	DMD (n=210)	NHANES (n=1138)	DMD (n=33)	NHANES (n=756)
Normal weight,* n (%)	34 (52)	202 (44)	88 (42)	511 (45)	15 (46)	51 (7)
Overweight,† n (%)	13 (20)	169 (36)	39 (19)	419 (37)	8 (24)	470 (62)
Obese,‡ n (%)	18 (28)	92 (20)	83 (39)	208 (18)	10 (30)	235 (31)
P value	0.028		<0.00001		<0.0001	

The DMD values are numbers of individual participants from their last cardiac magnetic resonance visit data. BMI indicates body mass index; DMD, Duchenne muscular dystrophy; and NHANES, National Health and Nutrition Examination Survey.
*Defined as BMI <85th percentile for participants aged 6 to 19 years or BMI (in kg/m^2) <25.
†Defined as BMI ≥85th and <95th percentile for participants aged 6 to 19 years or BMI (in kg/m^2) ≥25 and <30 for participants aged 20 to 39 years.
‡Defined as BMI ≥95th percentile for participants aged 6 to 19 years or BMI (in kg/m^2) ≥30 in participants aged 20 to 39 years.

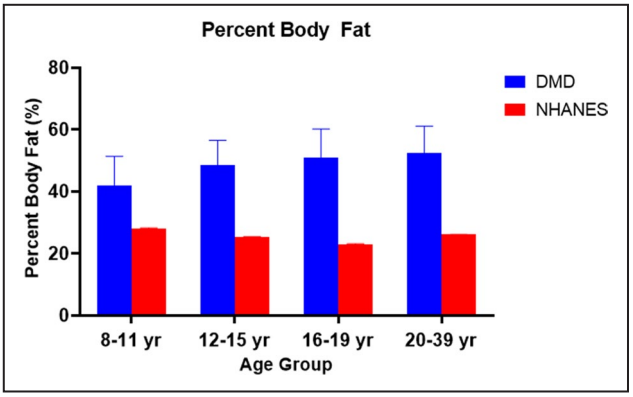

Figure 1. Comparison of percentage of body fat in patients with and without Duchenne muscular dystrophy.
The *P* values are <0.0001 for each age group. DMD indicates Duchenne muscular dystrophy; and NHANES, National Health and Nutrition Examination Survey.

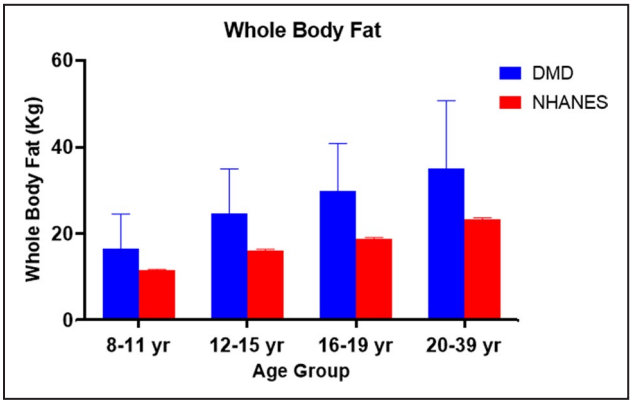

Figure 2. Comparison of whole body fat in patients with and without Duchenne muscular dystrophy.
The *P* values are <0.0001 for each age group. DMD indicates Duchenne muscular dystrophy; and NHANES, National Health and Nutrition Examination Survey.

analysis, only PBF remained independently associated with LGE+ after adjusting for age and corticosteroid duration (Table 6). Of note, corticosteroid duration was not associated with the development of LGE+ on multivariable analysis.

DISCUSSION

In this study, we sought to evaluate the association of adiposity with cardiac dysfunction and structure in patients with DMD. The study found that patients with DMD had significantly higher adiposity indices compared with the US general population. We demonstrated that WBF and PBF were independently associated with cardiac dysfunction after adjusting for age, LGE+, and corticosteroid duration. We also found that higher PBF was independently associated with LGE+. These results suggest that patients with DMD who have higher adiposity indices are at increased risk of developing cardiac dysfunction and LGE+.

There have been several studies in adults looking at the effects of obesity and adiposity on the presence of LGE and adverse cardiac events.[25–29] To our knowledge, our study is the first to look specifically at measures of adiposity and their relation to cardiac function and LGE+ in patients with DMD. In DMD, cardiomyocytes are vulnerable to injury caused by a deficiency in dystrophin, which in turn leads to fibrofatty infiltration.[30] Our study suggests that in patients with DMD, increased adiposity indices measured by DXA are associated with LGE+, which typically precedes cardiac dysfunction. Additionally, our study shows an association between adiposity indices and cardiac dysfunction. Our patient population had higher adiposity indices when compared with the NHANES participants. Previous pediatric studies have shown that increased adiposity in childhood is associated with atherosclerotic lesions and arterial stiffness in adulthood.[31,32] Arterial stiffness has been shown by our group to be abnormal in patients with DMD, however, the cause and long-term effects have yet to be determined.[33] It is also possible that adiposity accelerates the development of LGE+ and thus enhances cardiac dysfunction in DMD.

Both age and adiposity were independently associated with LGE+ and cardiac dysfunction. Adiposity is of particular clinical relevance, as it is a potentially modifiable variable in this population (Figure 3). Focus

Table 4. Bivariate Analysis of Adiposity Indices, Cardiac Function, Corticosteroid Duration, LGE, and Age at the Last CMR Visit

	Whole body fat index (kg/m)		Percentage of body fat (%)		BMI (kg/m^2)	
	R or mean difference	*P* value	*R* or mean difference	*P* value	*R* or mean difference	*P* value
LVEF <55%	+2.9*	0.001	+0.1*	0.06	+1.5*	0.03
LGE+	+2.0*	0.02	+2.4*	0.02	+0.8*	0.20
Corticosteroid duration, y	0.1†	0.02	0.3†	<0.0001	0.3†	<0.0001
Age, y	0.2†	0.01	0.4†	<0.0001	0.2†	<0.0001

BMI indicates body mass index; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; and LVEF, left ventricular ejection fraction.
*Mean difference between groups from 1-way ANOVA analysis.
†*R* for continuous variables from bivariate analysis.

Table 5. Characteristics of Patients With and Without Cardiomyopathy (LVEF ≥55 and <55) at Their Last CMR Visit Adjusted for Age

	All patients (n=324)	Cardiomyopathy		*P* value
		With (n=116)	Without (n=208)	
Age at MRI, y	15.2±3.6	16.8±0.3	14.3±0.3	<0.0001
PBF (%)	48±8.9	49.4±0.9	47.3±0.6	0.06
WBF, kg/m	17.4±7.3	19.2±0.7	16.5±0.5	0.001
BMI, kg/m^2	25±6.4	26.1±0.6	24.4±0.5	0.03
BMI percentile, %	74.5±29	74.7±2.7	74.4±2	0.96
LGE+	175 (54.0)*	94 (53.7)	81 (46.3)	<0.0001
Corticosteroid duration, y	9±2.2	10.1±0.3	8.3±0.3	<0.0001

The values presented are the mean±root mean square error for all patients and mean±standard error for those with and without cardiomyopathy. The *P* values were calculated after adjusting for age at the patient's last CMR visit. BMI indicates body mass index; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; PBF, percentage of body fat; and WBF, whole body fat mass indexed to height.

*Percentage of the sample.

on nutrition, activity, and healthy weight gain early in this disease process may help preserve cardiac function over time. Multidisciplinary teams, including physical therapists, occupational therapists, and registered dietitians have been recommended as part of routine care for patients with DMD.[14] Rehabilitation interventions should target prevention of contractures and deformities with stretching and orthotics to maintain physical activity. Aerobic exercise and activity are also recommended at submaximal effort to prevent muscle injury, as eccentric and high-resistance exercise have been shown to increase risk of muscle damage.[5] Various exercise modalities have been studied in this population, but there are still gaps in the understanding of the amount and type of exercise to optimize cardiorespiratory health and quality of life.[34–37] Nutritional management is focused on optimizing dietary requirements based on daily nutritional needs and energy expenditure. The risk of obesity is high during childhood and adolescence, and addressing excessive weight gain early on with adjustment in dietary intake, as well as judicious titration of corticosteroid dosing, are essential.[5]

Despite our findings that corticosteroid duration was independently associated with adiposity measures, corticosteroid duration was not associated with cardiac dysfunction or LGE+. This is not surprising given that previous studies have shown preserved cardiac function with corticosteroid use in patients with DMD.[12,13] Novel genetic therapies have been developed, and several are currently in clinical trials. These therapies include exon skipping, clustered regularly interspaced short palindromic repeats, RNA editing, and surrogate gene therapy. Exon skipping, clustered regularly interspaced short palindromic repeats and RNA editing all involve restoring the transcription or expression of dystrophin, but have limitations including unwanted involvement of other genes and immune responses. Surrogate gene therapy involves direct delivery of dystrophin alternatives to tissue or the use of other cytoskeletal binding proteins as dystrophin surrogates. These therapies are delivered with viral vectors which can cause dose-related liver toxicity and immune responses. Clustered regularly interspaced short palindromic repeats–Cas9 research have shown dystrophin expression in the hearts of mouse models and surrogate gene therapy, specifically GALGT2 gene overexpression, has prevented ventricular remodeling and fibrosis in animal models.[38,39] These novel therapies may make treatment with corticosteroids

Table 6. Multivariable Analysis of Adiposity Indices, Cardiac Dysfunction, and LGE

	Dependent variable			
	LVEF <55%		LGE+	
Independent variable	OR (95% CI)*	*P* value	OR (95% CI)	*P* value
WBF (per 1 kg/m)	1.07 (1.03–1.11)	0.0008	…	…
PBF (per 1%)	1.04 (1.01–1.07)	0.003	1.04 (1.002–1.07)	0.04
Age at last CMR (per 1 y)	1.13 (1.05–1.22)	0.001	1.24 (1.15–1.34)	<0.0001
LGE at last CMR	5.1 (2.9–9.0)	<0.0001	…	…

CMR indicates cardiac MRI; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; OR, odds ratio; PBF, percentage of body fat; and WBF, whole body fat mass indexed to height.

*Odds ratio (95% CI).

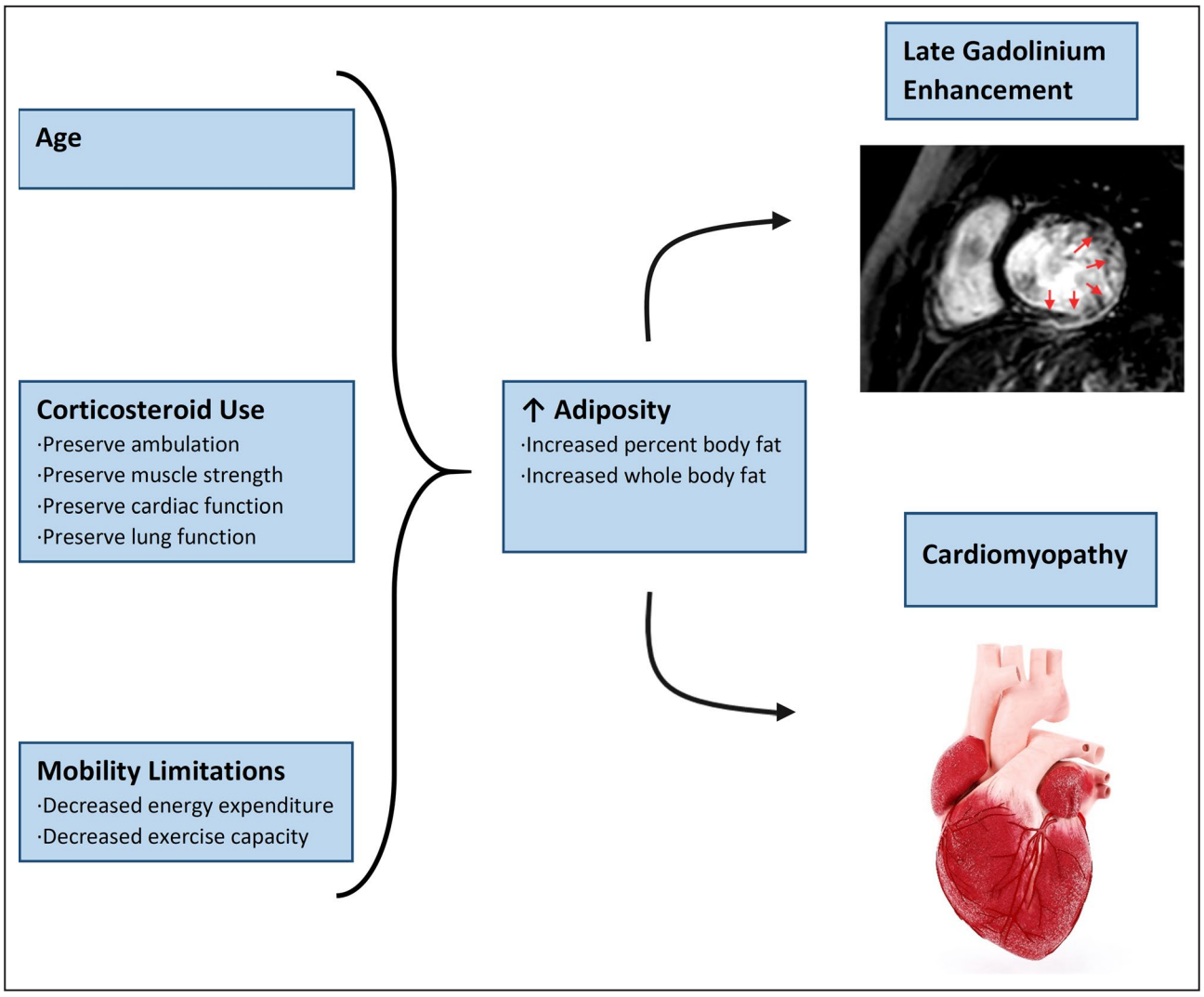

Figure 3. The relationship between adiposity and the heart in patients with Duchenne muscular dystrophy.
Risk factors associated with increased adiposity are listed on the left side of the diagram. Measurements of adiposity are listed in the center and the effects of adiposity on the heart are depicted on the right. The red arrows point to full thickness late gadolinium enhancement of the mid inferior, inferolateral, and anterolateral segments of the left ventricular myocardium in a patient with Duchenne muscular dystrophy.

unnecessary and thus may improve adiposity, but for now corticosteroids are an important treatment modality to preserve mobility and cardiac and pulmonary function.[5,12,13,40] Our study suggests that avoiding excess weight gain in patients with DMD after starting corticosteroids may contribute to preserved cardiac function.

While BMI is routinely used to screen for obesity in both patients with DMD and pediatric patients,[5,32] we did not observe an association between BMI and LGE+ or cardiac dysfunction upon multivariable analysis. Our cohort had higher BMIs when compared with the NHANES participants, but only 36% were considered obese. Only 3.1% of our cohort were deceased at the end of the study period. It is possible that obese patients with DMD have higher mortality secondary to complications from obesity, including cardiomyopathy, and thus our proportion of adult patients with obesity is lower than expected. However, because of the small number of events, we could not investigate this further. BMI does not distinguish between lean and fat mass, and is also influenced by height measures. The median age and functional mobility scores of the patients in our study indicated that most were nonambulatory at the time of their CMR and DXA scans. Surrogate measures of height, such as ulnar length, may overestimate height and result in an underestimation of BMI. DXA-derived adiposity indices allow additional measures of adiposity beyond the use of BMI and may help in nutritional and physical treatment plans for patients with DMD.

Limitations

This is a retrospective study and thus susceptible to inherent limitations of a retrospective data collection. In addition, a number of patients were on beta blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers, with some heterogeneity between patients and between providers in prescription patterns. Thus, we could not adjust for the potential effects of cardiac medication use and duration in our multivariable analysis. Our study did not account for cumulative corticosteroid dosing or use of noncardiac medications, which were outside the scope of the retrospective analyses here. Different DMD genotypes were also not accounted for in this study. Nonetheless, our patients comprised a sizeable cohort who were monitored and treated in a consistent manner with a proactive interdisciplinary team approach at a single center.

CONCLUSIONS

This is the first study to evaluate the association of adiposity on cardiac function and structure in patients with DMD. We demonstrated an independent association of adiposity with left ventricular dysfunction and LGE+ in patients with DMD. BMI did not correlate with either cardiac dysfunction or LGE+ and is unlikely to be helpful in assessing adiposity in patients with DMD once ambulation is lost. Careful management to prevent obesity and excessive adiposity may preserve cardiac function in this patient population.

ARTICLE INFORMATION

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Affiliations

Heart Institute (S.E.H., S.M.L., P.R.K., E.M.U., T.D.R., M.D.T.), Heart Institute Research Core (P.R.K.), Neurology (C.T.) and Endocrinology (M.M.R.), Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH (S.M.L., C.T., M.M.R., E.M.U., T.D.R., M.D.T.); and Pediatric Cardiology and Heart Institute, University of Pittsburgh Medical Center Children's Hospital of Pittsburgh, Pittsburgh, PA (T.A.).

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Disclosures

None.

Supplementary Material

Tables S1–S2

REFERENCES

1. Connuck DM, Sleeper LA, Colan SD, Cox GF, Towbin JA, Lowe AM, Wilkinson JD, Orav EJ, Cuniberti L, Salbert BA, et al. Characteristics and outcomes of cardiomyopathy in children with Duchenne or Becker muscular dystrophy: a comparative study from the Pediatric Cardiomyopathy Registry. *Am Heart J*. 2008;155:998–1005. doi: 10.1016/j.ahj.2008.01.018
2. Ong KS, Kinnett K, Soelaeman R, Webb L, Bain JS, Martin AS, Westfield C, Bolen J, Street N. Evaluating implementation of the updated care considerations for Duchenne muscular dystrophy. *Pediatrics*. 2018;142:S118–S128. doi: 10.1542/peds.2018-0333N
3. Feingold B, Mahle WT, Auerbach S, Clemens P, Domenighetti AA, Jefferies JL, Judge DP, Lal AK, Markham LW, Parks WJ, et al. Management of cardiac involvement associated with neuromuscular diseases: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e200–e231. doi: 10.1161/CIR.0000000000000526
4. American Academy of Pediatrics Section on Cardiology and Cardiac Surgery. Cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy. *Pediatrics*. 2005;116: 1569–1573.
5. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, Case LE, Cripe L, Hadjiyannakis S, Olson AK, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17:347–361. doi: 10.1016/S1474-4422(18)30025-5
6. Hor KN, Taylor MD, Al-Khalidi HR, Cripe LH, Raman SV, Jefferies JL, O'Donnell R, Benson DW, Mazur W. Prevalence and distribution of late gadolinium enhancement in a large population of patients with Duchenne muscular dystrophy: effect of age and left ventricular systolic function. *J Cardiovasc Magn Reson*. 2013;15:107. doi: 10.1186/1532-429X-15-107
7. Tandon A, Villa CR, Hor KN, Jefferies JL, Gao Z, Towbin JA, Wong BL, Mazur W, Fleck RJ, Sticka JJ, et al. Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in Duchenne muscular dystrophy. *J Am Heart Assoc*. 2015;4:e001338. doi: 10.1161/JAHA.114.001338
8. Silva MC, Meira ZM, Gurgel Giannetti J, da Silva MM, Campos AF, Barbosa Mde M, Starling Filho GM, Ferreira Rde A, Zatz M, Rochitte CE. Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. *J Am Coll Cardiol*. 2007;49:1874–1879. doi: 10.1016/j.jacc.2006.10.078
9. Puchalski MD, Williams RV, Askovich B, Sower CT, Hor KH, Su JT, Pack N, Dibella E, Gottliebson WM. Late gadolinium enhancement: precursor to cardiomyopathy in Duchenne muscular dystrophy? *Int J Cardiovasc Imaging*. 2009;25:57–63. doi: 10.1007/s10554-008-9352-y
10. Cote AT, Harris KC, Panagiotopoulos C, Sandor GG, Devlin AM. Childhood obesity and cardiovascular dysfunction. *J Am Coll Cardiol*. 2013;62:1309–1319.
11. Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2016:CD003725. doi: 10.1002/14651858.CD003725.pub4
12. Schram G, Fournier A, Leduc H, Dahdah N, Therien J, Vanasse M, Khairy P. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. *J Am Coll Cardiol*. 2013;61:948–954. doi: 10.1016/j.jacc.2012.12.008
13. Markham LW, Spicer RL, Khoury PR, Wong BL, Mathews KD, Cripe LH. Steroid therapy and cardiac function in Duchenne muscular dystrophy. *Pediatr Cardiol*. 2005;26:768–771. doi: 10.1007/s00246-005-0909-4
14. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, Case LE, Clemens PR, Hadjiyannakis S, Pandya S, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018;17:251–267. doi: 10.1016/S1474-4422(18)30024-3
15. 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;105:1486–1491. doi: 10.1017/S0007114510005180
16. Weber DR, Hadjiyannakis S, McMillan HJ, Noritz G, Ward LM. Obesity and endocrine management of the patient with Duchenne muscular dystrophy. *Pediatrics*. 2018;142:S43–S52. doi: 10.1542/peds.2018-0333F
17. Kim J, Jung IY, Kim SJ, Lee JY, Park SK, Shin HI, Bang MS. A new functional scale and ambulatory functional classification of Duchenne muscular dystrophy: scale development and preliminary analyses of reliability and validity. *Ann Rehabil Med*. 2018;42:690–701. doi: 10.5535/arm.2018.42.5.690
18. Peltz G, Aguirre MT, Sanderson M, Fadden MK. The role of fat mass index in determining obesity. *Am J Hum Biol*. 2010;22:639–647. doi: 10.1002/ajhb.21056

19. Gauld LM, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. *Dev Med Child Neurol*. 2004;46:475–480. doi: 10.1111/j.1469-8749.2004.tb00508.x
20. Borrud LG, Flegal KM, Looker AC, Everhart JE, Harris TB, Shepherd JA. Body composition data for individuals 8 years of age and older: U.S. population, 1999-2004. *Vital Health Stat 11*. 2010;250:1–87.
21. Weber DR, Moore RH, Leonard MB, Zemel BS. Fat and lean BMI reference curves in children and adolescents and their utility in identifying excess adiposity compared with BMI and percentage body fat. *Am J Clin Nutr*. 2013;98:49–56. doi: 10.3945/ajcn.112.053611
22. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006;295:1549–1555. doi: 10.1001/jama.295.13.1549
23. Yeboah J, Rodriguez CJ, Qureshi W, Liu S, Carr JJ, Lima JA, Hundley WG, Herrington DM. Prognosis of low normal left ventricular ejection fraction in an asymptomatic population-based adult cohort: the Multiethnic Study of Atherosclerosis. *J Card Fail*. 2016;22:763–768. doi: 10.1016/j.cardfail.2016.03.013
24. Ueda T, Kawakami R, Nishida T, Onoue K, Soeda T, Okayama S, Takeda Y, Watanabe M, Kawata H, Uemura S, et al. Left ventricular ejection fraction (EF) of 55% as cutoff for late transition from heart failure (HF) with preserved EF to HF with mildly reduced EF. *Circ J*. 2015;79:2209–2215. doi: 10.1253/circj.CJ-15-0425
25. Makowski MR, Jansen CHP, Ebersberger U, Schaeffter T, Razavi R, Mangino M, Spector TD, Botnar RM, Greil GF. Influence of acquired obesity on coronary vessel wall late gadolinium enhancement in discordant monozygote twins. *Eur Radiol*. 2017;27:4612–4618. doi: 10.1007/s00330-016-4616-8
26. Wu CK, Tsai HY, Su MM, Wu YF, Hwang JJ, Lin JL, Lin LY, Chen JJ. Evolutional change in epicardial fat and its correlation with myocardial diffuse fibrosis in heart failure patients. *J Clin Lipidol*. 2017;11:1421–1431. doi: 10.1016/j.jacl.2017.08.018
27. Shah RV, Heydari B, Coelho-Filho O, Abbasi SA, Feng JH, Neilan TG, Francis S, Blankstein R, Steigner M, Jerosch-Herold M, et al. Vasodilator stress perfusion CMR imaging is feasible and prognostic in obese patients. *JACC Cardiovasc Imaging*. 2014;7:462–472.
28. Antonopoulos AS, Antoniades C. Cardiac magnetic resonance imaging of epicardial and intramyocardial adiposity as an early sign of myocardial disease. *Circ Cardiovasc Imaging*. 2018;11:e008083. doi: 10.1161/CIRCIMAGING.118.008083
29. Cannavale G, Francone M, Galea N, Vullo F, Molisso A, Carbone I, Catalano C. Fatty images of the heart: spectrum of normal and pathological findings by computed tomography and cardiac magnetic resonance imaging. *Biomed Res Int*. 2018;2018:5610347. doi: 10.1155/2018/5610347
30. Kamdar F, Garry DJ. Dystrophin-deficient cardiomyopathy. *J Am Coll Cardiol*. 2016;67:2533–2546. doi: 10.1016/j.jacc.2016.02.081
31. Alpert MA, Omran J, Bostick BP. Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. *Curr Obes Rep*. 2016;5:424–434. doi: 10.1007/s13679-016-0235-6
32. Chung ST, Onuzuruike AU, Magge SN. Cardiometabolic risk in obese children. *Ann N Y Acad Sci*. 2018;1411:166–183.
33. Ryan TD, Parent JJ, Gao Z, Khoury PR, Dupont E, Smith JN, Wong B, Urbina EM, Jefferies JL. Central arterial function measured by noninvasive pulse wave analysis is abnormal in patients with Duchenne muscular dystrophy. *Pediatr Cardiol*. 2017;38:1269–1276. doi: 10.1007/s00246-017-1657-y
34. Markert CD, Case LE, Carter GT, Furlong PA, Grange RW. Exercise and Duchenne muscular dystrophy: where we have been and where we need to go. *Muscle Nerve*. 2012;45:746–751. doi: 10.1002/mus.23244
35. Markert CD, Ambrosio F, Call JA, Grange RW. Exercise and Duchenne muscular dystrophy: toward evidence-based exercise prescription. *Muscle Nerve*. 2011;43:464–478. doi: 10.1002/mus.21987
36. Jansen M, van Alfen N, Geurts AC, de Groot IJ. Assisted bicycle training delays functional deterioration in boys with Duchenne muscular dystrophy: the randomized controlled trial "no use is disuse." *Neurorehabil Neural Repair*. 2013;27:816–827. doi: 10.1177/1545968313496326
37. Moreira-Marconi E, Sa-Caputo DC, Dionello CF, Guedes-Aguiar EO, Sousa-Goncalves CR, Morel DS, Paineiras-Domingos LL, Souza PL, Kutter CR, Costa-Cavalcanti RG, et al. Whole-body vibration exercise is well tolerated in patients with Duchenne muscular dystrophy: a systematic review. *Afr J Tradit Complement Altern Med*. 2017;14:2–10. doi: 10.21010/ajtcam.v14i4S.1
38. Sheikh O, Yokota T. Developing DMD therapeutics: a review of the effectiveness of small molecules, stop-codon readthrough, dystrophin gene replacement, and exon-skipping therapies. *Expert Opin Investig Drugs*. 2021;30:167–176. doi: 10.1080/13543784.2021.1868434
39. Himic V, Davies KE. Evaluating the potential of novel genetic approaches for the treatment of Duchenne muscular dystrophy. *Eur J Hum Genet*. 2021;29:1369–1376. doi: 10.1038/s41431-021-00811-2
40. Gloss D, Moxley RT III, Ashwal S, Oskoui M. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy: report of the guideline development subcommittee of the American Academy of Neurology. *Neurology*. 2016;86:465–472. doi: 10.1212/WNL.0000000000002337

SUPPLEMENTAL MATERIAL

Table S1. Patient Characteristics at Their Last CMR Visit.

	LVEF < 55	LVEF ≥ 55	*p* value	LGE +	LGE -	*p* value
Total (n=324)	116	208	-	175	149	-
Age at CMR (years)	16.7 (4)	14.3 (3.3)	<.0001	16.3 (3.8)	13.8 (3.2)	<.0001
Height (cm)	142.3 (14.3)	140.4 (13.3)	0.2	142.2 (13.6)	139.8 (13.6)	0.1
Weight (kg)	55.5 (18.5)	47.6 (15.3)	<.0001	54.7 (16.8)	45.4 (15.6)	<.0001
BMI (kg/m2)	27.9 (10.5)	24.5 (8.4)	0.002	27.6 (9.9)	23.5 (8.2)	<.0001
Systolic blood pressure (mmHg)	108.5 (11.7)	110.7 (10.2)	0.08	109.4 (11.3)	110.6 (10.2)	0.3
Functional Mobility Score	4.3 (2)	3.8 (2.1)	0.04	4.4 (2)	3.6 (2.1)	0.001
LV end-diastolic volume index, mL/m^2	85.3 (21.9)	69.8 (14.4)	<.0001	82.1 (20.8)	68 (13.4)	<.0001
LV end-systolic volume index, mL/m^2	44.2 (16.6)	27.5 (7.5)	<.0001	39.1 (16.2)	27.3 (7.2)	<.0001
LV mass index, g/m^2	41.9 (11.6)	36.9 (8.7)	<.0001	41.5 (10.9)	35.5 (8.2)	<.0001
LV ejection fraction (%)	59.1 (6.9)	61 (4.4)	0.003	53.6 (8.4)	60.4 (5.2)	<.0001
LV ejection fraction <55%, n (%)	-	-	-	94 (54)	22 (15)	<.0001
WBF (kg/m)	19.2 (8.1)	16.3 (6.8)	0.001	18.3 (7.5)	16.3 (7.2)	0.02
WLM (kg/m)	17.9 (3.2)	17.2 (2.8)	0.04	17.8 (3.1)	17.2 (2.8)	0.07
PBF (%)	49.4 (9.4)	47.2 (9.6)	0.05	49.1 (9)	46.7 (10)	0.02
Number of patients on corticosteroids, n (%)	115 (99)	201 (96)	0.1	170 (97)	146 (98)	0.6
Corticosteroid duration (years)	10.1 (3.9)	8 (3.7)	<.0001	9.6 (3.9)	7.8 (3.7)	<.0001
Age at start of corticosteroids (years)	6.7 (2.8)	6.1 (2.1)	0.03	6.6 (2.5)	5.9 (2.1)	0.001
Treated with an ACE Inhibitor, n (%)	50 (43)	71 (34)	0.1	73 (42)	48 (32)	0.06
Treated with a Beta Blocker, n (%)	73 (62)	37 (18)	<.0001	93 (53)	17 (11)	<.0001
Treated with an ARB, n (%)	6 (5)	21 (10)	0.1	14 (8)	13 (9)	0.8
Treated with Spironolactone, n (%)	33 (28)	42 (20)	0.1	63 (36)	12 (8)	<.0001
Number of CMRs per patient	3.9 (2.1)	3.1 (2)	0.001	3.9 (2.1)	2.8 (1.8)	<.0001
Age at first CMR (years)	11.3(3.2)	10.2 (2.4)	0.001	11 (3)	10 (2.4)	0.001
Number of patients with LGE+	94 (81)*	79 (38)*	<.0001	-	-	-
Number of DXA scans per patient	6.7 (2.9)	6.2 (2.9)	0.1	6.8 (3)	5.8 (2.7)	0.002

Data are presented as mean (± standard deviation) or total number (percent of total). P values derived by comparison of means or comparison of proportions. CMR indicates cardiac MRI; LV, left ventricular; BMI, body mass index; WBF, whole body fat indexed; WLM, whole body lean mass indexed; PBF, percentage of body fat; LGE, late gadolinium enhancement; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; and DXA, dual-energy X-ray absorptiometry. *total number (percent of total)

Table S2. Whole Body Fat in Patients with Duchenne Muscular Dystrophy.

	Whole Body Total Fat index (kg/m)
Age (Years)	DMD Mean ±SD
8-11	15.9 ± 6.5
n	73
12-15	17.6 ± 7.8
n	132
16-19	17.5 ± 7.3
n	86
20-39	19.4 ± 7.6
n	33

DMD indicates Duchenne muscular dystrophy.