



Original Article

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Abstract

Background: Cardiomyopathy is the leading cause of death in patients with Duchenne muscular dystrophy. The relationship between cardiac and skeletal muscle progression is unclear. The objective of this study was to evaluate the correlation between muscle activity and cardiomyopathy. We hypothesised that cardiomyopathy and skeletal muscle activity are directly related. **Methods:** Physical activity was assessed with accelerometers worn for 7 days. Average activity (vector magnitude/min) and percentage of time in different activities were reported. Cardiac MRI was used to assess left ventricular ejection fraction, global circumferential strain (Ecc), late gadolinium enhancement, and cardiac index. Associations were assessed between physical activity and cardiac variables using a Spearman correlation. **Results:** Duchenne muscular dystrophy subjects ($n = 46$) with an average age of 13 ± 4 years had a mean left ventricular ejection fraction of $57 \pm 8\%$. All physical activity measures showed significant correlations with left ventricular ejection fraction ($\rho = 0.38$, $p = 0.01$) and left ventricular cardiac index ($\rho = 0.51$, $p < 0.001$). Less active subjects had lower left ventricular ejection fraction ($p = 0.10$) and left ventricular cardiac index ($p < 0.01$). Non-ambulatory patients ($n = 29$) demonstrated a stronger association between physical activity and left ventricular ejection fraction ($\rho = 0.40$, $p = 0.03$) while ambulatory patients demonstrated a stronger association between physical activity and left ventricular cardiac index ($\rho = 0.53$, $p = 0.03$). Ecc did not associate with physical activity in either cohort. **Conclusion:** Physical activity correlates with left ventricular ejection fraction and left ventricular cardiac index and is modified by ambulation. Future analysis should assess the temporal relationship between physical activity and cardiomyopathy.

Introduction

Duchenne muscular dystrophy is the most severe form of muscular dystrophy and affects approximately 1 in 5000 live male births in the US.¹ It is an X-linked recessive disorder caused by pathogenic variants in the dystrophin gene, resulting in absent or dysfunctional dystrophin protein.² Dystrophin plays a role in the membrane integrity of striated muscle cells, loss of which causes a cascade of events leading to myocyte and myocardial cell death and fibrosis.³ Duchenne muscular dystrophy is, therefore, a progressive muscle wasting disease with patients losing the ability to ambulate at a median of twelve years of age. Non-invasive ventilatory support, corticosteroids, and proactive multidisciplinary care have improved survival for patients with Duchenne muscular dystrophy, with a current mean survival of around 30 years.^{5,6} The leading cause of death in these patients is now cardiomyopathy,⁷ making early diagnosis and treatment of cardiac dysfunction essential.

The aim of this study was to assess the connection between cardiac and skeletal muscle progression in patients with Duchenne muscular dystrophy. The relationship is currently unclear, but understanding this relationship could help elucidate cardiomyopathy pathogenesis. In the era of Duchenne muscular dystrophy gene therapy, especially given the unclear penetration of this therapy to the heart, a better understanding of this relationship is critical. Several studies have claimed the two are unrelated,³ while others looking at Becker muscular dystrophy have suggested there is an inverse relationship with elevated skeletal muscle strength increasing the workload on the heart and therefore leading to earlier onset of cardiomyopathy.⁸ However, researchers focusing on Duchenne muscular dystrophy have also found direct correlations between the two.^{9,10} Many of the traditional methods for assessing skeletal muscle

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function in patients with Duchenne muscular dystrophy are limited to ambulatory patients or may be influenced by a patient's effort or familiarity with the test.^{11,12}

Physical activity assessment by wrist-worn accelerometers is a novel Duchenne muscular dystrophy skeletal muscle outcome measure. Previous research has shown that physical activity correlates well with other methods for assessing skeletal muscle function in Duchenne muscular dystrophy cohorts, such as the 6 minute walk test (6MWT) and quantitative muscle testing (QMT).^{13,14} Stride velocity 95th centile is now accepted as an outcome measure by the European Medicines Agency. Accelerometers are well tolerated and have the benefit of providing a continuous assessment over several days in a non-clinical environment. They offer an objective measure of skeletal muscle activity and can be used on both ambulatory and non-ambulatory patients. The Food and Drug Administration (FDA) has focused on the importance of clinical outcome assessments – how a patient feels, functions, and survives.¹⁵ While biomarkers (imaging and blood tests) are not felt to qualify as clinical outcome measures by themselves, accelerometry is a direct measurement of a patient's function and would qualify. Therefore, a better understanding of accelerometry and its association with cardiac biomarkers is critical.

The primary objective of this study was to assess the average amount and patterns of physical activity in Duchenne muscular dystrophy patients using accelerometers, worn on the wrist for 7 days, and to compare this assessment to measures of cardiac function taken from cardiac MRI. We hypothesised that cardiac muscle progression is directly related to skeletal muscle progression in Duchenne muscular dystrophy patients.

Methods

Participants

The Vanderbilt Institutional Review Board approved this prospective study. All patients underwent appropriate consent or assent. Patients were recruited from the neuromuscular clinics. Duchenne muscular dystrophy diagnosis was confirmed by phenotype and genetic testing or muscle biopsy. Patients for this study were taken from a cohort of patients enrolled in a natural history study that consisted of a baseline visit and two subsequent annual visits (visits 2 and 3), with each visit including a cardiac MRI study and accelerometry. For some patients, accelerometry data were not available at baseline (either because the device malfunctioned or was not returned) and for others, wear times were not sufficient for analysis (required ≥ 3 days of data). The majority of cardiac MRI/accelerometry data pairings for this study were taken from the baseline visit; if baseline data were missing or insufficient, cardiac MRI/accelerometry data pairings were taken from visit 2. If visit 2 data were also insufficient, the subject was removed from the study. Demographics, previous medical history, and medication use were all obtained from the patient's electronic medical records at each visit. Ambulatory status was determined by the treating neurologist.

Cardiovascular measurements

Cardiac MRI was performed on a 1.5 T Siemens Avanto or Avanto Fit (Siemens Healthcare Sector, Erlangen, Germany). Functional imaging was performed as previously described using balanced steady-state free precession imaging.¹⁶ Breath-held, T2-weighted (effective TE 60 ms) double inversion turbo spin-echo was

performed prior to contrast administration. Myocardial grid tagging was performed in the short axis at the base, level of the papillary muscles, and apex using a segmented k-space fast gradient echo sequence with electrocardiogram-triggering with 9–13 phases. Typical imaging parameters included: slice thickness 6–8 mm, field of view 340 mm x 340 mm, matrix size 256 x 192, and minimum echo and repetition times. The sequences were breath-holds and parallel imaging with Generalized Autocalibrating Partial Parallel Acquisition (GRAPPA) and an acceleration factor of two was used.

Intravenous Gadolinium contrast was administered through a peripheral intravenous line at a dose of 0.15 mmol/kg gadobutrol or 0.2 mmol/kg gadopentate dimeglumine (both Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA) as the standard contrast agent changed early in the study period. Late gadolinium enhancement was performed using single-shot inversion recovery (optimized inversion time to null myocardium) and phase-sensitive inversion recovery (inversion time of 300 ms) imaging in the 4-chamber, 3-chamber, and 2-chamber planes as well as the short axis stack. Segmented inversion recovery (optimized inversion time to null myocardium) was also performed in the same slices as the myocardial tagging.

All post-processing was performed blinded to clinical data. Ventricular volumes and function were calculated using Medis QMass (MedisSuite 2.1, Medis, Leiden, The Netherlands). Myocardial tagged images were analysed using harmonic phase methodology (Myocardial Solutions, Morrisville, NC) as previously described.¹⁷ The endocardial and epicardial borders were contoured at end-systole, creating a mesh. The software calculated the peak global circumferential strain values. Global tagged circumferential strain was calculated as the average of the basal, mid, and apical slices. Percent late gadolinium enhancement was calculated using the full width half maximum technique using QMass on the phase-sensitive inversion recovery images.

Physical activity

At each visit, the patients were instructed to wear a triaxial accelerometer (GT3X+, Actigraph, Pensacola, FL) on their dominant wrist continuously for seven consecutive days, including when sleeping, napping, and during water-related activities such as bathing and showering. Raw accelerometry data collected at a sampling frequency of 30 Hz (30 observations per second for each axis) were integrated into 15-s epochs and converted to vector magnitude counts (calculated as the square root of the sum of the squares of each axial measurement) using ActiLife software (Actigraph, Pensacola, FL, version 6.13.3). Non-wear periods were determined using Choi's algorithm¹⁸ and were removed from the analysis. A subject's physical activity data were valid if they contained ≥ 3 days with ≥ 10 hours of daytime wearing between the hours of 7 a.m. and 10 p.m.

The average amount of physical activity was calculated by dividing the total vector magnitudes generated while wearing by the number of minutes wearing during the daytime period (vector magnitude/min). Patterns of physical activity were also assessed by classifying each epoch as Sedentary, Low-intensity, or Moderate-to-vigorous physical activity and calculating the percentage of time spent in each category (Table 1). The values used to categorise each epoch were previously determined in healthy children and adolescents.¹⁹ On average subjects in our prior study spent > 98% of their daytime wearing period in the Sedentary or Low-intensity physical activity categories.¹² While the prior study

Table 1. Physical activity category cut-points (vector magnitude/min)

Physical Activity Category	Cut-points (VM/min)
Sedentary	0-3660
<i>Sedentary-1</i>	0-481
<i>Sedentary-2</i>	482-3660
Low-intensity	3661-9804
<i>Low-intensity-1</i>	3661-5154
<i>Low-intensity-2</i>	5155-9804
Moderate-to-vigorous	>9804

demonstrated the utility of dividing Sedentary into three categories and Low-intensity into two categories, subsequent analysis demonstrated that two Sedentary categories were equally effective. Therefore, the Sedentary and Low-intensity categories were subdivided into two groups (Sedentary-1, Sedentary-2, Low-intensity-1, and Low-intensity-2). The median value of vector magnitudes from this study in each category generated by all subjects was used to create the subdivided categories (Table 1).

Statistical analysis

Welch two-sample t-tests were used to compare ambulatory and non-ambulatory groups for each measure. Associations between all measures of physical activity and all measures of cardiac function were assessed using a Spearman correlation. A Spearman correlation was also used to assess these relationships for ambulatory and non-ambulatory subjects. For these tests, a

p -value < 0.05 was considered significant. All analyses were performed using the programming language R version 3.6.1.

Results

Of the 49 subjects in this study, one participant was excluded because cardiac MRI was not performed and two others were excluded due to a lack of recorded physical activity data. In the 46 remaining subjects, baseline data were taken from 40 subjects and visit 2 data were used for 6 subjects. Demographics are shown in Table 2. Non-ambulatory subjects were significantly older, taller, heavier, and had a larger body surface area than ambulatory subjects. In total, 72% of subjects were currently on corticosteroids, and nearly all had been on steroids at some point in their course. Significantly more non-ambulatory patients were on beta-blocker therapy than ambulatory patients. Three patients did not have available genetic testing and either had testing performed at an outside facility or were diagnosed with a muscle biopsy; 33 (72%) patients had a deletion in the Duchenne muscular dystrophy gene, with the most common being a deletion of exons 45–52 (13%).

Relationship between cardiac biomarkers and physical activity

The relationships between physical activity measures (average activity and the percentage of time spent in the Sedentary-1 and Sedentary-2 categories) and cardiac biomarkers are shown in Table 3. The percentage of time spent in the Sedentary-1 category showed the strongest correlation with both left ventricular ejection fraction and left ventricular cardiac index when evaluating the

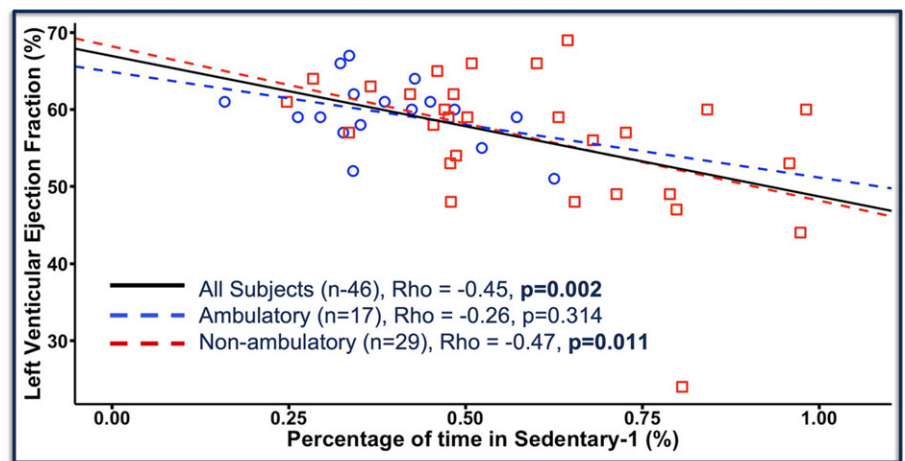
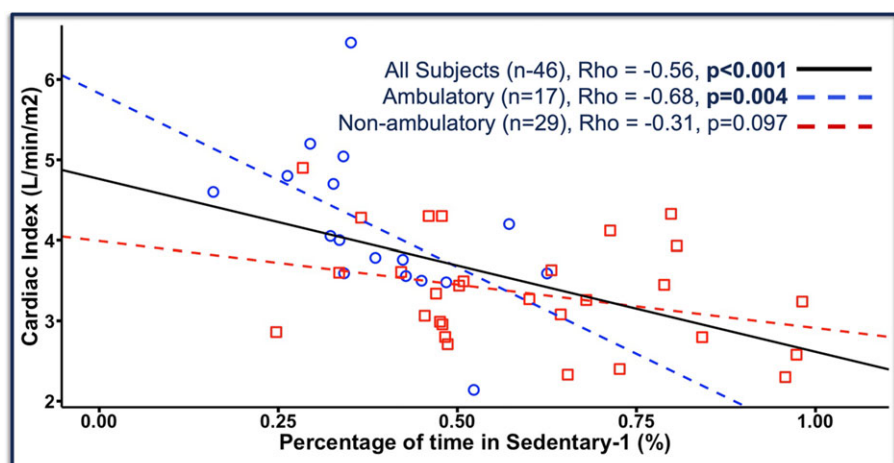
Table 2. Demographics

Anthropometric Measure	All Subjects (n = 46)	Ambulatory (n = 17)	Non-ambulatory (n = 29)	p-value
	Mean ± SD [Range] or n (%)			
Age (years)	13.3 ± 4.2 [8.0, 24.3]	10.4 ± 2.0 [8.0, 14.4]	15.0 ± 4.3 [8.5, 24.3]	<0.001
Height (cm)	145 ± 17 [112, 180]	134 ± 13 [112, 152]	152 ± 16 [117, 180]	<0.001
Weight (kg)	50.5 ± 19.6 [18.9, 103.2]	37.5 ± 13.1 [18.9, 68.2]	58.1 ± 18.8 [24.1, 103.2]	<0.001
Body Surface Area (m²)	1.42 ± 0.34 [0.80, 2.10]	1.17 ± 0.26 [0.80, 1.69]	1.55 ± 0.31 [0.90, 2.10]	<0.001
Race				
White	42 (91%)	16 (94%)	26 (90%)	0.5906
Black	3 (7%)	2 (12%)	1 (3%)	0.3529
Asian	2 (4%)	0 (0%)	2 (7%)	0.1609
Hispanic	7 (15%)	0 (0%)	7 (24%)	0.0058
Corticosteroids (current)	33 (72%)	14 (82%)	19 (66%)	0.2061
Corticosteroids (current or prior)	44 (96%)	16 (94%)	28 (97%)	0.7239
Cardiac meds				
Angiotensin converting enzyme inhibitor	24 (52%)	7 (41%)	17 (59%)	0.2663
Angiotensin receptor blocker	3 (7%)	0 (0%)	3 (10%)	0.0831
Beta blocker	13 (28%)	1 (6%)	12 (41%)	0.0024
Aldosterone inhibitor	3 (7%)	2 (12%)	1 (3%)	0.3529

Table 3. Correlation between physical activity and cardiac biomarkers

Cardiac Biomarker	All Subjects (n = 46)			Ambulatory (n = 17)			Non-Ambulatory (n = 29)		
				rho (p-value)					
	VM/min	Sed-1	Sed-2	VM/min	Sed-1	Sed-2	VM/min	Sed-1	Sed-2
Left ventricular ejection fraction	0.375 (0.010)	-0.446 (0.002)	0.391 (0.007)	0.309 (0.227)	-0.260 (0.314)	0.106 (0.686)	0.398 (0.032)	-0.467 (0.011)	0.466 (0.011)
Left ventricular cardiac index	0.511 (<0.001)	-0.555 (<0.001)	0.314 (0.036)	0.534 (0.029)	-0.676 (0.004)	0.343 (0.178)	0.245 (0.200)	-0.314 (0.097)	0.307 (0.105)
Late gadolinium enhancement ^a	-0.016 (0.929)	0.073 (0.686)	-0.220 (0.219)	0.143 (0.752)	-0.024 (0.977)	-0.310 (0.486)	-0.144 (0.493)	0.168 (0.422)	-0.240 (0.248)
Circumferential strain (global) ^b	-0.394 (0.007)	0.309 (0.039)	-0.162 (0.288)	-0.075 (0.782)	-0.106 (0.696)	-0.054 (0.841)	-0.210 (0.275)	0.215 (0.263)	-0.225 (0.240)

^aLate gadolinium enhancement was not assessed in all patients (n = 33, 8 ambulatory and 25 non-ambulatory). ^bCircumferential strain was not assessed in all patients (n = 45, 16 ambulatory and 29 non-ambulatory).

**Figure 1.** Sedentary time and left ventricular ejection fraction.**Figure 2.** Sedentary time and cardiac index.

entire cohort. There was also a weak correlation with circumferential strain.

Ambulation status appears to modify the relationship between physical activity and cardiac biomarkers. There were no significant correlations between any physical activity measure and left

ventricular ejection fraction in ambulatory subjects, but four of the nine physical activity measures showed significant correlations with left ventricular ejection fraction in non-ambulatory subjects (Figure 1). Conversely, there were no significant relationships between left ventricular cardiac index and physical activity in non-

Table 4. Cardiac biomarkers

	All Subjects (n = 46)	Ambulatory (n = 17)	Non-ambulatory (n = 29)	
Cardiac Biomarker	Mean ± SD [Range]			p-value
Left Ventricular Ejection Fraction (%)	57.5 ± 7.7 [24.0, 69.0]	59.5 ± 4.3 [51.0, 67.0]	56.3 ± 8.9 [24.0, 69.0]	0.103
Cardiac Index (L/min/m ²)	3.65 ± 0.86 [2.14, 6.46]	4.15 ± 0.95 [2.14, 6.46]	3.36 ± 0.67 [2.30, 4.90]	0.006
Late Gadolinium Enhancement (%) ^a	25.7 ± 14.9 [0.0, 61.4]	26.9 ± 15.9 [0.0, 48.0]	25.4 ± 15.0 [0.0, 61.4]	0.810
Circumferential Strain ^b	-15.1 ± 3.2 [-20.0, -3.9]	-16.7 ± 2.4 [-20.0, -11.5]	-14.2 ± 3.2 [-18.8, -3.9]	0.005

^aLate gadolinium enhancement was not assessed in all patients (n = 33, 8 ambulatory and 25 non-ambulatory). ^bCircumferential strain was not assessed in all patients (n = 45, 16 ambulatory and 29 non-ambulatory).

Table 5. Average physical activity^a

	All Subjects (n = 46)	Ambulatory (n = 17)	Non-ambulatory (n = 29)	
Physical Activity	Mean ± SD [Range]			p-value
Average Physical Activity (VM/min)	1524 ± 940 [54, 3699]	2353 ± 713 [1248, 3699]	1039 ± 684 [54, 2417]	<0.001
Sedentary (%)	85.5 ± 11.6 [56.6, 99.9]	75.1 ± 9.4 [56.6, 89.7]	91.7 ± 7.8 [74.0, 99.9]	<0.001
Sedentary-1 (%)	51.9 ± 20.1 [15.9, 98.2]	39.0 ± 11.7 [15.9, 62.5]	59.5 ± 20.3 [24.7, 98.2]	<0.001
Sedentary-2 (%)	33.6 ± 12.2 [1.7, 55.3]	36.1 ± 6.9 [23.5, 48.9]	32.2 ± 14.4 [1.7, 55.3]	0.218
Low-intensity (%)	13.2 ± 10.2 [0.1, 38.8]	22.0 ± 8.1 [10.1, 38.8]	8.1 ± 7.4 [0.1, 25.6]	<0.001
Low-intensity-1 (%)	6.3 ± 4.1 [0.1, 15.3]	9.1 ± 2.9 [4.9, 15.3]	4.7 ± 3.9 [0.1, 14.1]	<0.001
Low-intensity-2 (%)	6.9 ± 6.3 [0.0, 23.4]	12.8 ± 5.4 [4.1, 23.4]	3.4 ± 3.7 [0.0, 12.1]	<0.001
Moderate-to-vigorous (%)	1.3 ± 1.7 [0.0, 7.1]	2.9 ± 1.8 [0.2, 7.1]	0.3 ± 0.6 [0.0, 2.0]	<0.001

^aWelch two sample t-test between ambulatory and non-ambulatory groups.

ambulatory subjects, but all except the Sedentary-2 and Moderate-to-vigorous categories correlated with left ventricular cardiac index in ambulatory subjects (Figure 2). Ecc did not correlate with physical activity in the ambulatory or non-ambulatory subgroups. Late gadolinium enhancement had no significant relationship with any physical activity measure.

Cardiovascular measurements

Measurement of cardiac biomarkers from cardiac MRI is shown in Table 4. There was no significant difference between ambulatory and non-ambulatory groups for both left ventricular ejection fraction and late gadolinium enhancement. However, left ventricular cardiac index and circumferential strain were both significantly better in the ambulatory group.

Physical activity

Physical activity measurements are shown in Table 5. Ambulatory subjects had significantly higher average activity levels and spent

more time in the low-intensity and moderate-to-vigorous physical activity categories than non-ambulatory subjects. Non-ambulatory subjects spent significantly more time in the Sedentary category than ambulatory subjects; however, this difference was mainly caused by non-ambulatory subjects spending more time in the Sedentary-1 category as there was no significant difference in the time spent in the Sedentary-2 category. In a sub-analysis looking at steroid use and physical activity, non-ambulatory subjects on steroids spent more time in moderate-to-vigorous activity than those who were not on steroids (supplementary table).

Discussion

Within this cohort of Duchenne muscular dystrophy patients, physical activity and measures of cardiovascular function at a single time point (specifically left ventricular ejection fraction, left ventricular cardiac index, and Ecc) are directly related. The study showed that patients who were less active, spending more time in the Sedentary-1 category, had decreased left ventricular ejection

fraction and left ventricular cardiac index and had increased myocardial strain. This finding is important because it could potentially allow for physical activity measures to be used for earlier detection of cardiomyopathy. However, while the study has shown a correlation, it does not prove causation. The progressive nature of Duchenne muscular dystrophy may be responsible for the correlation between cardiac biomarkers and physical activity, with age being the confounding factor. Future analysis should focus on this relationship over time to evaluate whether levels of physical activity at baseline are predictive of cardiovascular function in subsequent visits.

Ambulation has an effect on the correlations of both left ventricular ejection fraction and left ventricular cardiac index with physical activity. The lack of correlation between physical activity and left ventricular ejection fraction in ambulatory subjects could be explained by the smaller sample size of the ambulatory group or the inability of wrist-worn accelerometers to capture the full range of activity experienced by patients who still have use of their lower extremities. It is also possible that, since left ventricular dysfunction is a later finding, the correlation with left ventricular ejection fraction only occurs in non-ambulatory patients. Interestingly, there was a relationship between left ventricular cardiac index and ambulation. The stronger correlation in ambulatory patients may suggest that the increased physical activity of ambulation supports cardiac function. When patients become non-ambulatory, they spend significantly more time in sedentary activities and this low-level activity does not have as much of a positive effect on cardiac function. This phenomenon has recently been described in healthy individuals by Owen *et al.*²¹ It is also possible that the correlation of actigraphy with left ventricular cardiac index in ambulatory patients and left ventricular ejection fraction in non-ambulatory patients represents parallel progression of skeletal muscle and cardiac disease. Future research should evaluate this relationship over time to assess if increased activity can maintain left ventricular cardiac index.

Data in other patients with heart failure support a relationship between activity levels and cardiomyopathy. In a study comparing accelerometry and invasive haemodynamic pressures in adult patients with heart failure with reduced ejection fraction, older patients were less active and had lower cardiac index and stroke volume than younger and more active patients.²⁰ Given the significant skeletal muscle weakness in Duchenne muscular dystrophy, comparisons with other types of cardiomyopathy should be performed cautiously. The relationship between activity data and cardiomyopathy progression should be evaluated in a Duchenne muscular dystrophy cohort and not extrapolated from other studies.

The effects of medications on these findings are difficult to ascertain given the small sample size. A higher percentage of the non-ambulatory patients was on beta blockade, which is not surprising given that non-ambulatory patients are more likely to have cardiac dysfunction. It is possible that the beta blockade affected the cardiac index, which is likely dependent on heart rate in Duchenne muscular dystrophy, thus leading to decreased activity levels. Again, this illustrates the difficulty in separating parallel progression of disease from a true relationship. We also found that patients on corticosteroids had slightly increased moderate-to-vigorous activity. This is certainly biologically plausible, but the small percentage of time in both groups suggests that this difference is not clinically meaningful.

Of note, there was no significant difference between late gadolinium enhancement in ambulatory and non-ambulatory

patients in this cohort. It is unclear if this represents a slowing of late gadolinium enhancement progression after loss of ambulation or is related to the small sample size or the subjectivity in the semi-quantitative analysis of late gadolinium enhancement. Our prior work demonstrated a direct correlation between QMT and ventricular function, but only in non-ambulatory patients.¹⁰ While these findings could support the idea that ambulation abrogates any protective effects of activity, given the small sample sizes, larger studies are necessary.

Limitations

The study is limited by its relatively small sample size, but it is one of the largest studies of which we are aware to evaluate accelerometry in Duchenne muscular dystrophy patients. The discrepant sample sizes ($n = 17$ ambulatory vs. $n = 29$ non-ambulatory) may also limit the statistical power of that subgroup analysis. It is a single centre study, which may make results less generalisable, but the catchment area for our clinics is large. We included both ambulatory and non-ambulatory patients in order to capture a broader patient population for baseline accelerometry measures. Further studies should include a larger patient population and multiple centres to further define the role of accelerometry in Duchenne muscular dystrophy care.

Conclusion

Physical activity as measured by accelerometry correlates with cardiac MRI biomarkers and is modified by ambulation. These findings could represent parallel progression of disease and should be validated with larger studies.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S1047951125000162>.

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