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Duchenne and Becker muscular dystrophy carriers: Evidence of cardiomyopathy by exercise and cardiac MRI testing

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ABSTRACT

Background: Varied detection methods have resulted in conflicting reports on the prevalence of cardiac disease in Duchenne and Becker muscular dystrophy carriers (MDC).
Methods: We performed a prospective cohort study of 77 genetically-confirmed MDC mothers, 22 non-carrier mothers, and 25 controls. All participants underwent Cardiopulmonary Exercise Testing (CPET) and Cardiac Magnetic Resonance imaging (CMR).
Results: 25% of carriers had ventricular ectopy in recovery of exercise (RecVE) as compared to 1 non-carrier and no controls ($p = .003$). No difference in age or maximal oxygen consumption was noted. 11 carriers had abnormal (<55%) left ventricular ejection fraction by CMR. Evidence of late gadolinium enhancement (LGE) was noted in 48% of MDC, 1 non-carrier patient and no control subjects ($p < .0001$). Subset analysis of LGE+ and LGE- subjects revealed differences in age (44.1 v 38.6 yrs.; $p = .005$), presence of RecVE, (38.9% v 10.5%, $p = .004$), and high serum creatine kinase (CK) (> 289 U/l; 52.8% v 31.6%, $p = .065$).
Conclusion: We describe the prevalence of disease using CPET and CMR in genetically-proven MDC. 49% of carriers had fibrosis, opposed to 5% of non-carriers, highlighting the importance of genetic testing in this population. Despite cardiomyopathy, functional assessment by treadmill was normal, illustrating the discrepancy in cardiac and skeletal muscle impacts. Age, RecVE and serum CK appear to have an important role in predicting cardiomyopathy. Serum CK levels suggest that a systemic higher global disease severity and not tissue heterogeneity may be the etiology for greater cardiac disease and relatively spared skeletal muscle disease in this population.
Clinical Trial Registration
https://clinicaltrials.gov/ct2/show/NCT02972580?term=mendell&cond=Duchenne+Muscular+Dystrophy&rank=5; ClinicalTrials.gov Identifier: NCT02972580

1. Introduction

Duchenne and Becker muscular dystrophy are progressive neuromuscular diseases caused by mutations in the DMD gene, which encodes dystrophin [1]. Duchenne muscular dystrophy (DMD) is the most common childhood muscular dystrophy, seen in 1/5000 live births [2,3]. Manifestations of DMD in affected boys include profound progressive muscle weakness with loss of ambulation and the development of cardiomyopathy in early adolescence [4,5]. Becker muscular dystrophy (BMD) is less common, presenting in 1/19,000 live births. Dystrophic degeneration of muscle cells, reflected in serum creatine kinase (CK) levels, peak by age 6 years in DMD and 10–15 years in BMD patients [6,7]. BMD subjects generally have less severe disease, although the clinical spectrum of BMD is broad [8,9]. At present, boys with DMD have life expectances on average in their 20's. With improvements in respiratory support, steroid therapy, and respiratory care, cardiomyopathy is now the leading cause of death [10–15].

In 70% of subjects with DMD, an identified DMD gene mutation is causative. In-frame mutations result in the BMD phenotype. The mutation is inherited in an X-linked recessive pattern from a maternal carrier. Fifty percent of the male offspring of female DMD mutation carriers will manifest a DMD phenotype while 50% of female offspring will be carriers. In 30% of DMD boys, the mutation is a de novo occurrence [16,17]. Female carriers should theoretically be spared from phenotypic disease given the presence of a normal DMD gene on their second X-chromosome; however, they have long been reported to demonstrate some manifestations of similar dystrophin-deficient disease. Muscle weakness, abnormal gait, fatigue and cardiac involvement have all

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been reported [18]. Additionally, there are overtly manifesting young female carriers who present with onset and progression of disease like affected boys that offer evidence of clinical impacts of having one abnormal gene [19]. Many studies describe a non-random X-chromosome inactivation pattern in some manifesting patients, which offers a genetic basis for this varied expression [20].

The mechanism of cardiomyopathy is an absence of functional dystrophin protein (DMD) or deficient levels of dystrophin (BMD). Dystrophin is a large protein, binding actin on the N-terminus and the extracellular matrix of the cell at the C-terminus. It functions to stabilize the plasma membrane by transmitting forces from the sarcomeric contraction to the extra-cellular matrix [21,22]. Without dystrophin, myocyte contraction results in membrane damage and fibrofatty replacement, resulting in cardiomyopathy [23,24]. This cardiomyopathy has been increasingly well-described by cardiac magnetic resonance imaging (CMR) for affected boys as a predictable pattern of subepicardial fibrosis [5,25–27] preceding a decrease in left ventricular ejection fraction (LVEF) [28–30]. However, prevalence and characterization of cardiomyopathy in female muscular dystrophy carriers (MDC) has thus far been incomplete. Few have included evaluation by CMR and varied detection methods have resulted in conflicting reports on the prevalence of cardiomyopathy in MDC [31–33]. Lang et al., reported a retrospective study on 22 genetically-confirmed DMD carriers (ages 13.2–60.0 years) utilizing traditional CMR measures, including LVEF and LGE status. They noted that 7/22 patients had LGE and 4/22 (18%) had LV dysfunction (LVEF <55%) [34]. CMR Native T1 mapping is a relatively novel technique to detect myocardial edema and diffuse fibrosis as evidence of occult cardiomyopathy [35–39]. Pre-contrast native T1 mapping for diffuse myocardial fibrosis in DMD boys has been reported to be abnormal and precedes LGE as well as global functional decline.[40] T1 mapping has not been reported in DMD carriers.

In addition, studies thus far on the cardiac status of carriers have rested entirely on traditional imaging assessments, with reports of a dilated cardiomyopathy phenotype in a small fraction of patients. Interestingly, exercise stress testing has not been utilized in this population, despite evidence in large scale ischemic and non-ischemic heart failure studies that cardiopulmonary exercise testing (CPET) offers a robust method of prognostication for disease severity in heart failure. Measures of oxygen consumption (peak VO2) and regression slope relating minute ventilation to carbon dioxide output (VE/VCO2 slope) are metrics which are most directly related to outcomes in heart failure [41,42]. We sought to evaluate the prevalence of occult cardiomyopathy in genetically-confirmed MDC subjects using CPET and CMR, including native T1 mapping.

2. Methods

2.1. Subjects

Potential MDC subjects were prospectively recruited from a tertiary care muscular dystrophy clinic where their family member was clinically evaluated and from postings at ClinicalTrials.Gov and Parent Project Muscular Dystrophy's website. The study was approved by our institutional review board. Subjects could have no contraindication to CMR or CPET. Control patients were age-matched women from a volunteering cohort responding to an email solicitation sent to the employees at the same hospital. Subjects signed informed consent to participate in a longitudinal study over three years. Inclusion in the MDC cohort required confirmation of a validated DMD gene mutation from a Clinical Laboratory Improvement Amendments approved laboratory. Other potential carriers were genetically tested (Emory Genetics Laboratory) and categorized as a MDC (genetically positive testing) or non-carrier (genetically negative testing). Genetic testing was repeated when review required additional determination of the validity of the results. A total of 77 DMD mutations were found (6 were in-frame, predicting a BMD phenotype).

2.2. Investigation protocol

Medical history, physical, neuromuscular examination (strength and timed functional tests), cognitive and neuropsychological evaluation were obtained on all subjects by neuromuscular experts (JRM, KJL, SAA). Control subjects underwent identical screening other than genetic testing. Assessment of the CMR and CPET was blinded to genetic test results and made available only during statistical analysis. CK levels were drawn prior to cardiac testing. This report will only address the baseline cardiac findings; skeletal muscle assessments and cognitive assessments, along with three-year longitudinal data, will be reported separately with correlations between cardiac and skeletal muscle results.

2.3. Cardiopulmonary exercise testing (CPET)

Treadmill CPET was performed at a single site by certified exercise physiologists and interpreted by a single investigator (MLM). The American Heart Association/American College of Sports Medicine's Preparticipation Questionnaire survey was reviewed prior to all testing [43]. All subjects performed treadmill peak VO_2 test using either a Standard or Modified Bruce protocol with protocol selection determined by subjects anticipated peak VO_2. 12-lead EKG was continuously monitored (GE Cardiosoft, 2017) for ST depression and arrhythmia at baseline, with exercise, and for 10 min of recovery. Blood pressure was manually obtained at baseline, with each exercise stage, immediately following peak exercise and during recovery until blood pressure returned to baseline values. Subjects were encouraged to exercise to exhaustion and achieve a Respiratory Exchange Ratio (RER) >1.1. Breath-by-breath VO_2 data was analyzed by a single exercise physiologist for VO_2 peak, RER, VE/VCO_2 slope, and AT using an 8-breath rolling average (CareFusion Vyntus CPX, 2017). Peak VO_2 was determined as the highest VO_2 recorded at the end of exercise with RER >1.1. VE/VCO_2 slope was calculated from exercise onset to AT. AT was detected using the plot of ventilatory equivalents and when unclear, the V-slope plot was utilized.

2.4. Cardiac magnetic resonance (CMR) imaging & analysis

CMR studies were conducted on a Siemens 3-Tesla Prisma or Skyra with a multi-channel MR coil (Siemens Medical Solutions, Malvern, PA/Erlangen, Germany). Cardiac functional imaging was performed using breath-held retrospective ECG-gating, segmented Steady State Free Precession technique. Standard imaging included a short axis stack of cine images from cardiac base to apex. Pre-contrast T1 mapping in a mid-short axis plane was performed for native T1 values [44–46]. LGE using inversion-recovery gradient echo acquisitions were obtained in the identical long axis and short axis planes, with inversion time optimized to null normal myocardium. Images were acquired 10 min post intravenous administration of 0.2 mmol/kg Gadavist (Gadobutrol, Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA) via a peripheral intravenous line [28–30,47]. Ventricular volumes and function were assessed via standard planimetry techniques using semi-automated computer software (QMASS v.7.6., Medis Medical Imaging Systems, Netherlands) by a single investigator as previously described [48,49]. Native T1 mapping techniques as described by Messroghli et al., were used to assess diffuse myocardial fibrosis [38]. Data on pre-contrast T1 mapping was analyzed using Centricity PACS (GE Healthcare, Barrington, IL) in the acquired mid-ventricular short axis slice as reported by Goebel et al. [39] The region of interest included only the myocardium with avoidance of subendocardial trabeculations and epicardial fat as previously described to eliminate partial volume artifacts [35,39]. Mid-ventricular slice average native T1 was recorded blinded to the subject's disease status. For the purposes of consistency, all CMR studies were analyzed by a single observer (KNH) with >10 years CMR experience. Native T1 mapping was repeated at an interval of >6 months later in a blinded fashion.

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2.5. Statistical analysis

Data were collected utilizing REDCap (Research Electronic Data Capture) hosted at the study hospital [50]. Group comparisons were assessed using two-sample *t*-tests or Wilcoxon rank sum tests and Chi-square/Fisher exact tests or by using one-way ANOVA tests as well as post hoc comparisons with Tukey adjustments for continuous data and Chi-square/Fisher Exact tests for categorical data. All analyses were conducted using two-sided *p*-values <.05 considered statistically significant. Receiver operating characteristic (ROC) analysis was used to test whether the native T1 value was able to distinguished MDC from the non-carrier and control cohorts. Within the MDC group, ROC analysis was used to assess whether T1 durations could also predict LGE positivity. Intra-observer for the native T1 mapping analysis was repeated at a >6 month interval in a blinded fashion. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Subject characteristics

Of the 77 carriers of a DMD mutation, the average age was 41.3 ± 8.5 years and did not differ from the non-carrier (40.6 ± 10.3 years) or control groups (42.9 ± 7.2 years). There were 117 Caucasian, 6 Asian, 1 Hispanic and 1 Middle Eastern subjects in the study. Of MDC subjects, 49% self-identified as having a "musculoskeletal disorder" along with 50% of non-carrier mothers (Table 1). Despite this, only 4 MDC and 1 non-carrier mom reported that exercise was limited by musculoskeletal complaints on CPET. A higher incidence of prescription medication use was noted in MDC group ($p = .015$), although there was no difference in cardiac or hypertension-specific prescriptions (Supplemental Table I).

3.2. Cardiopulmonary exercise testing (CPET)

We found that control subjects and non-carriers were more likely to be asymptomatic during exercise testing compared to the MDC ($p = .014$). There were no significant differences in termination of testing due to muscle pain or weakness between MDC compared to control or non-carriers. No terminations were due to arrhythmia, elevated blood pressure, a desire to stop or gait problems (Supplemental Table II). All participants were able to achieve a maximal test with and RER of >1.1. The majority of participants in all three cohorts had a normal EKG at baseline and throughout the testing ($p = .86$).

When assessing the exercise capacity, there was no difference peak VO2, VE/VCO2 slope, anaerobic threshold or blood pressure response and no patient in any cohort had sustained arrhythmia during testing (Table 2). A statistical difference in the occurrence of any ventricular ectopy in recovery (RecVE) was noted in the MDC ($n = 19$; 25%) compared to non-carrier (n = 1; 4.5%) and the control (0%) subjects ($p = .003$). Mean number of ectopic beats in the MDC cohort was 3.5 beats in the 10 min recovery period (range of 1–12). Baseline VE was present in 17 (25%) MDC, 1 (4.5%) non-carriers and 2 (8%) controls but did not meet statistical significance ($p = .08$). Of the 17 carriers who had VE during baseline testing, 10 of those suppressed normally at peak exercise. Five subjects had non-suppression at peak and continued to have RecVE and all had LGE on CMR.

Table 1
Cohorts characteristics.

	MDC ($n = 77$)	Non-Carrier ($n = 22$)	Control ($n = 25$)	*p*-Value
Age (years)	41.3 ± 8.5	40.6 ± 10.3	42.9 ± 7.2	0.62
Height (cm)	164.1 ± 6.0	162.7 ± 4.0	164.1 ± 6.7	0.61
Weight (kg)	76.6 ± 17.9	82.4 ± 20.6	69.9 ± 14.9	0.07
BMI (kg/m2)	27.9 ± 6.0	30.9 ± 7.5	26.2 ± 6.0	**0.04**
Serum CK (U/l)	487.2 ± 977.4	115.3 ± 133.8	75.5 ± 17.8	**0.026**

p-values < .05 noted in bold.

Table 2
Treadmill & CMR results.

	MDC ($n = 76$)	Non-Carriers (n = 22)	Controls (n = 25)	p-Value
Treadmill variables				
Peak VO2 (ml/min/kg)	28.6 ± 7.0	28.7 ± 7.8	31.3 ± 5.7	0.22
RER peak	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.39
VE/VCO2 slope	25.2 ± 2.6	23.9 ± 2.7	25.2 ± 2.5	**0.05**
VO2 at AT (ml/min/kg)	18.2 ± 4.3	18.6 ± 4.8	19.6 ± 3.3	0.32
Heart rate baseline (bpm)	72.1 ± 10.2	72.4 ± 8.4	70.6 ± 10.5	0.8
BP baseline systolic (mmHg)	118.8 ± 13.3	121.1 ± 18.8	126.3 ± 16.8	0.13
BP baseline diastolic (mmHg)	73.6 ± 10.8	77.5 ± 12.6	81.5 ± 11.2	**0.02**
Heart rate peak (bpm)	171.6 ± 15.9	177.5 ± 15.3	176.4 ± 11.8	0.17
Heart rate % predicted	95.0 ± 7.6	97.9 ± 5.9	98.9 ± 5.8	**0.03**
BP peak systolic (mmHg)	159.3 ± 22.7	168.0 ± 29.2	162.4 ± 22.6	0.35
ST depression	2 (2.6%)	0	1 (4%)	0.66
Atrial ectopy at baseline	2 (2.6%)	0	0	0.53
Atrial ectopy at peak	6 (7.9%)	0	2 (8%)	0.39
Atrial ectopy in recovery	10 (13.2%)	4 (18.2%)	0	0.11
Ventricular ectopy at baseline	17 (22.4%)	1 (4.5%)	2 (8%)	0.06
Ventricular ectopy at peak	18 (23.7%)	4 (18.1%)	8 (32%)	0.53
Ventricular ectopy in recovery	19 (25%)	1 (4.5%)	0	**0.003**
LGE positive	36 (49%)	1 (2.7%)	0	<**0.0001**
CMR variables				
T1 (ms)	1266 ± 33	1243 ± 30	1235 ± 31	<**0.0001**
LVESVi (ml/m2)	33.9 ± 8.1	28.6 ± 7.6	28.0 ± 7.2	**0.001**
LVEDVi (ml/m2)	80.7 ± 13.4	75.0 ± 11.6	73.3 ± 12.2	**0.024**
LVEF (%)	59.2 ± 5.0	62.5 ± 5.2	62.3 ± 4.9	**0.004**

Peak VO2 = maximal oxygen consumption, RER peak = respiratory exchange ratio at peak, VE/VCO2 slope = regression slope of minute ventilation to carbon dioxide output, VO2 at AT = oxygen consumption at anaerobic threshold, BP = blood pressure. Baseline refers to pre-exercise 12-leak electrocardiogram, peak is the stage in which they reached highest VO2 in exercise, and recovery for 10 min post exercise. BMI = body mass index, LGE = late gadolinium enhancement by CMR, LVESVi = left ventricular end-systolic volume indexed to body surface area, LVEDVi = left ventricular end-diastolic volume indexed to body surface area, LVEF = left ventricular ejection fraction.
p-values < .05 noted in bold.

3.3. Cardiac magnetic resonance volumetric and LVEF

We performed CMR on all but 2 (unable to tolerate CMR) recruited subjects (Table 2). The mean left ventricular end-diastolic volume indexed (LVEDVi) was normal in all groups with slightly higher LVEDVi in the MDC. The mean LVEF was normal in all groups with slightly lower LVEF in the MDC group. Mild left ventricular dysfunction (LVEF <55%) was present in 11/77 (14.2%) of MDC, 1/20 (4.5%, the subject with LGE) of non-carriers and 2/25 (8%) of control subjects. There was no difference for right ventricular size or EF.

3.4. Myocardial tissue characteristics (LGE and Native T1 Mapping)

Native T1 analysis demonstrated excellent intra-observer agreement (ICC = 0.962 for intra-observer, $p < .0001$ for both) similar to prior reports [40]. The native T1 values were higher in MDC (1266 ± 33 ms) than non-carrier (1243 ± 30 ms) and control (1235 ± 31 ms) groups (p < .0001), as illustrated in representative cases shown in Fig. 1. There was no difference between the non-carrier or control group ($p = .50$). The MDC group had significantly more subjects with positive LGE findings 36/77 (48%) compared to 1/22 (4.5%) in the non-carriers and 0/25 (0%) in the control group (p < .0001). Of note,

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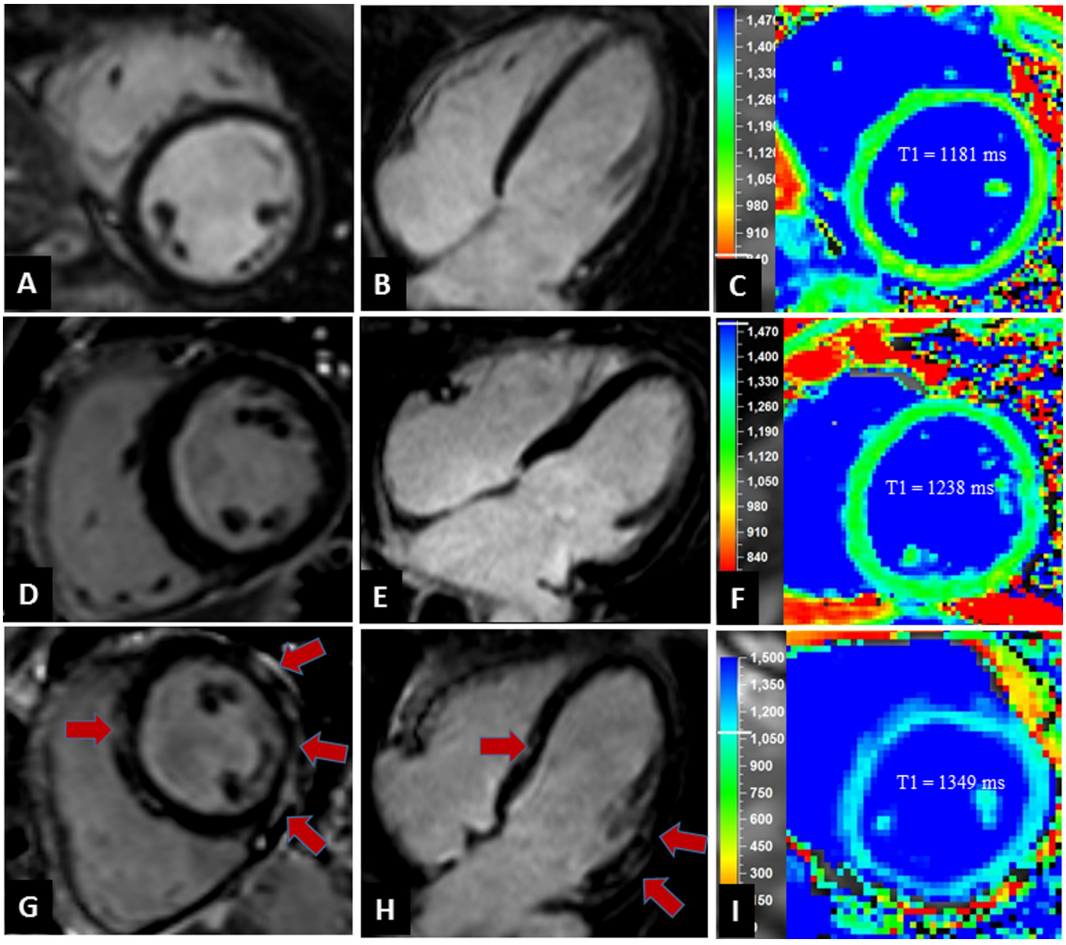

Fig. 1. LGE and Native T1 Imaging. (A-C) Control subject with no LGE and normal T1 value (1181 ms); (D-F) non-carrier subject with no LGE and normal T1 value (1238 ms); (G-H) MDC subject positive for LGE (red arrows) and higher T1 value (1349 ms). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the single non-carrier subject with LGE had mild left ventricular dysfunction (LVEF = 48%) and elevated native T1 of 1267 ms, which was similar to the mean T1 value of the carrier group. The MDC group ($n = 75$) was then dichotomized to LGE positive ($n = 36$) or LGE negative ($n = 39$). The MDC subjects with LGE+ findings were significantly older than who were LGE-, (44.1 ± 8.5 vs. 38.8 ± 7.7 yrs.; $p = .006$). The average LVEF was normal for both groups; however, 8/36 (22.2%) of the LGE+ carrier group had an LVEF<55% compared to only 3/39 (7.6%) of the LGE- MDC subjects.

3.5. Native T1 mapping

Overall, data analysis revealed no outliers in the control group and 2 outliers (outside of 1.5× the interquartile range) in the non-carrier group (T1 = 1305 and 1320 msec). However, as outlier exclusion did not lead to a relevant change in statistical results (native T1 value differences between MDC, non-carrier and control group), these outliers were included in the statistical analysis. When considering the ability to discriminate a non-carrier mom from a MDC, we found a significant inter-individual variance of the average native T1, as well as a substantial overlap between the observed groups (Fig. 2; Table 2) ($p = .478$). ROC analysis of T1 values resulted in an area under the curve (AUC) of 0.744 ($p = .0001$) (Fig. 2). In an analysis of the utility of T1 values in detecting LGE in the MDC group alone, the AUC was 0.801 ($p = .0001$). To reach a specificity of 81% for LGE positivity in the MDC group, the slice-averaged native T1 cut-off value was >1270 ms with a sensitivity of 62% (Fig. 3).

3.6. Combined CPET and CMR evaluation

We next attempted to determine if findings on CPET correlated with CMR (Table 3). Of the 9 subjects with ventricular ectopy at both baseline and in recovery, all but one had LGE on CMR. Peak VO2 values were not different between LGE+ (28.8 ± 7.0 ml/min/kg) and LGE- (28.4 ± 7.1 ml/min/kg; $p = .39$) groups in a sub-analysis of MDC subjects. The same was true for VE/VCO2 (25.2 ± 2.5 v. 25.4 ± 2.6 ml/min/kg). Peak heart rates were slightly different, with peak exercise HR of 166.0 ± 18.3 bpm in those subjects with LGE versus 176.8 ± 11.6 bpm with no LGE ($p = .003$). However, all subjects achieved >90% target heart rate.

Subset analysis of LGE+ and LGE- subjects (Table 3) additionally revealed a higher proportion of those with RecVE, (38.9% v. 10.5%, $p = .004$), and high serum CK, defined as a value higher than our institution's upper limit of normal of 289 U/l (52.8% v. 31.6%, $p = .065$). Mean values for MDC were 487.2 ± 977.4 U/l, for non-carrier moms 115.3 ± 133.8 U/l and controls 75.5 ± 17.8 U/l ($p = .026$). Additionally, comparing those with high CK to low CK, T1 times were longer at 1284.0 msec versus 1259.5 msec ($p = .004$). The youngest MDC subject manifesting LGE was 31 years. Independent predictors of LGE+ included age (odds ratio [OR] of 10.9 per decade), presence of RecVE (OR

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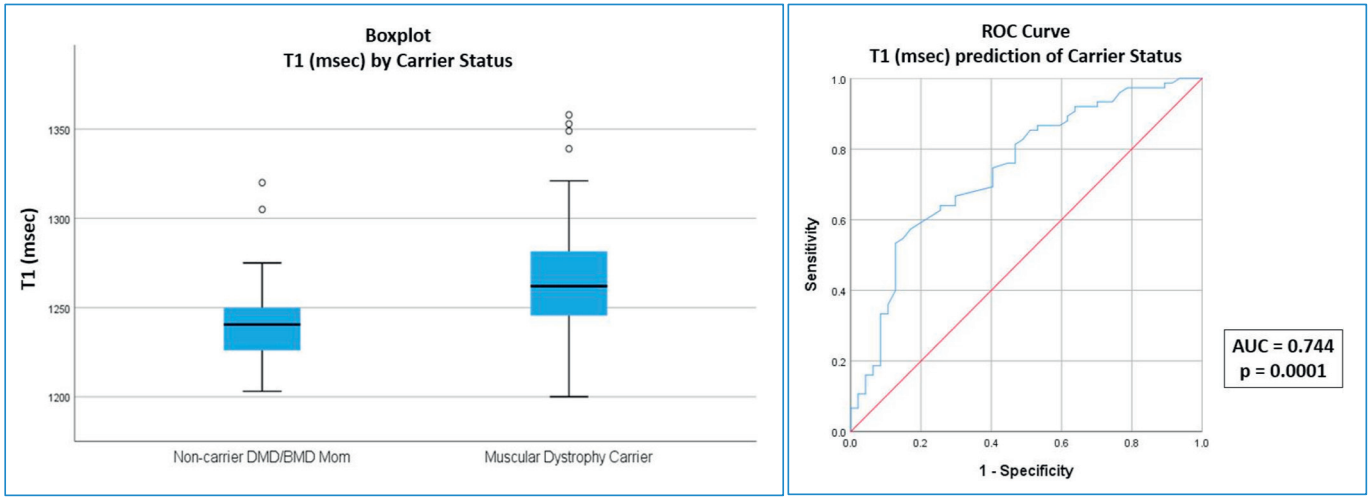

Fig. 2. Comparison of T1 values between non-carrier and MDC subjects. Boxplot and receiver operating characteristic (ROC) curves, comparing slice-averaged native T1 times between non-carrier and MDC cohorts. High inter-individual variability results in substantial overlap in group ranges. ROC curve demonstrates a significant AUC without evident high sensitivity and specificity cut-point. DMD = Duchenne muscular dystrophy BMB = Becker muscular dystrophy; AUC = area under the curve. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

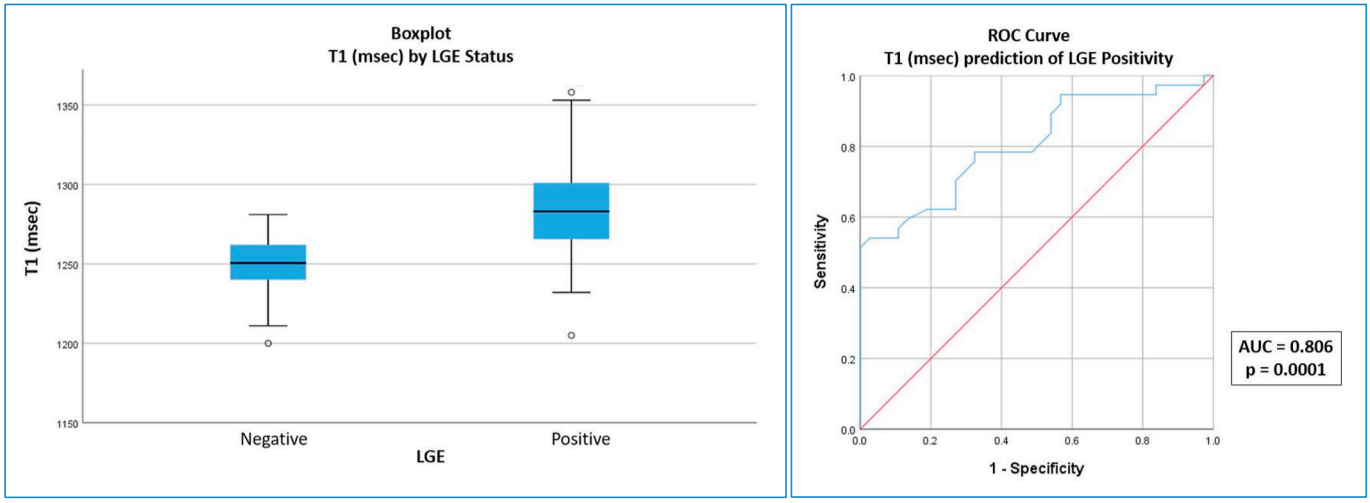

Fig. 3. Comparison of T1 values between LGE negative and LGE positive MDC subjects. Boxplot and receiver operating characteristic (ROC) curves, comparing slice-averaged native T1 times between MDC cohorts by their LGE status. A specificity of 81% for LGE positivity in the MDC group was achieved at a slice-averaged native T1 cut-off value of >1270 ms at a sensitivity of 62%. AUC = area under the curve. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4.0), and a CK >289 U/L (OR 2.4). Multivariate analysis with the three predictors did not substantially change ORs.

4. Discussion

This study highlights the importance of genetic testing for mothers of boys with DMD/BMD as our data support that heterozygote DMD mutation conveys a risk for cardiac disease manifestations with 48% of MDC showing subepicardial LGE patterns. The decline in LVEF appears to trail the LGE findings, which is similar to affected males. The use of CMR allows early detection of fibrofatty replacement of myocardium, a pathognomonic finding of dystrophin-associated cardiomyopathy that occurs prior to ventricular dysfunction. We found that genetically-proven carriers in comparison to non-carriers and control subjects had a substantially higher prevalence of cardiac disease when using a combination of CPET and CMR. Our discovery that RecVE correlated with findings of LGE on CMR was unexpected and suggests that CPET in addition to CMR should be performed to monitor the cardiac status in the genetically susceptible population.

4.1. Exercise in MDC

There are no current exercise guidelines for MDC subjects. This is the first study to evaluate the functional status of women who are carriers of dystrophin mutations with standardized exercise testing. Our study allays any feasibility concerns in regards to CPET in this population. Given the higher rate of reported musculoskeletal symptoms in subjects with MDC (as well as in the non-carriers), there were initial concerns that study subjects would not be able to participate in a maximal exercise testing format. In fact, this modality is not used in DMD/BMD boys due to muscle weakness resulting in gait and balance issues. While a small percentage of carriers did have musculoskeletal complaints during testing, none requested early termination on the basis of muscle fatigue and all were able to provide a maximal exertion as measured by RER. Additionally, no subjects were found to be unsafe during CPET

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Table 3
Comparison of Carriers with and without fibrosis. BMI = body mass index, Peak VO2 = maximal oxygen consumption, RER peak = respiratory exchange ratio at peak, VE/VCO2 slope = regression slope of minute ventilation to carbon dioxide output, VO2 at AT = oxygen consumption at anaerobic threshold. Recovery electrocardiogram was monitored for 10 min post exercise. LVESVi = left ventricular end-systolic volume indexed to body surface area, LVEDVi = left ventricular end-diastolic volume indexed to body surface area, LVEF = left ventricular ejection fraction.

	LGE + (n = 36)	LGE − (n = 39)	p-Value
Age (years)	44.1 ± 8.5	38.8.0 ± 7.7	**0.006**
Height (cm)	163.6 ± 6.1	164.5 ± 6.1	0.53
BMI (kg/m2)	27.5 ± 5.5	28.0 ± 6.2	0.69
Weight (kg)	76.2 ± 17.7	76.7 ± 19.1	0.91
Peak VO2 (ml/min/kg)	28.0 ± 7.0	29.4 ± 7.1	0.39
RER peak	1.2 ± 0.1	1.2 ± 0.1	0.43
VE/VCO2 slope	25.2 ± 2.5	25.4 ± 2.6	0.85
VO2 at AT (ml/min/kg)	18.1 ± 4.3	18.4 ± 3.1	0.78
Heart rate peak (bpm)	166.0 ± 18.3	176.8 ± 11.6	**0.003**
Heart rate % predicted	93.4 ± 9.1	96.4 ± 5.4	0.09
Ventricular ectopy in recovery	13 (37.1%)	5 (12.8%)	**0.03**
LVESVi (ml/m2)	36.0 ± 9.4	32.1 ± 6.4	**0.04**
LVEDVi (ml/m2)	81.4 ± 15.4	80.2 ± 11.4	0.70
LVEF (%)	58.1 ± 5.1	60.1 ± 4.7	0.08

p-values < .05 noted in bold.

either by ischemic or arrhythmic finding. While there was a higher ventricular ectopy burden, there were no malignant arrhythmias or evidence of cardiac compromise limiting any subject's ability to exercise maximally.

Peak VO2 has been demonstrated to be a reliable assessment of functional capacity, and the prognostic value of peak VO2 and VE/VCO2 have previously been established in non-ischemic cardiomyopathy subjects [51]. A lower risk of cardiac event is seen in non-ischemic cardiomyopathy subjects with higher peak VO2 and/or lower VE/VCOs slopes. Our results demonstrate that there is no difference in functional capacity between MDC and non-carriers or control subjects. Given the self-identification of having a "musculoskeletal disorder," reports of skeletal muscle symptoms, and the burdens of caregiving for their sons with DMD/BMD, the normal functional capacities in MDC and non-carrier moms was surprising. Of future interest is the longer-term implications of a combined assessment of LGE by CMR and peak VO2 by CPET.

4.2. Exercise-induced ventricular ectopy

Baseline ECG abnormalities have been reported in MDC, but without demonstration that there was a predictive quality to the abnormalities reported. In our study, ectopy during CPET were more prevalent than expected. No difference in atrial arrhythmia burden was demonstrated between the three groups. Premature ventricular contractions were seen at baseline in all three cohorts. RecVE as a single, binary factor stood out as a predictive finding for the presence of fibrosis by CMR, and this was supported in our analysis. Our data suggests that any ventricular ectopy in the recovery phase of exercise conveyed a higher risk of having fibrosis. In fact, the patient with the highest number of ectopic beats additionally had the highest T1 time recorded in the cohort (1358 msec). None of the study participants had sustain ventricular tachycardia.

The finding of RecVE as a predictive factor was unexpected, and we were surprised to find that a prior meta-analysis of 5 studies on asymptomatic subjects without clinical heart disease also reported isolated premature ventricular contractions in recovery, and not exercise. While these studies were a male-predominant cohort being screened for acquired heart disease, this meta-analysis is interesting, in that RecVE were found to be an independent risk factor for an aggregate cardiac event outcome (MI, hospitalization, all-cause mortality) with a pooled risk ratio of 1.8 (95% CI 1.4–2.3). While the pathophysiologic basis for RecVE is not clear, a weak post-exercise vagal tone response/autonomic dysfunction etiology has been suggested as related to a pro-arrhythmic substrate [51]. Implications for this in a population of MDC deserves further investigation.

4.3. LGE a surrogate of fibrosis by CMR

Of the existing studies, the vast majority utilize echocardiogram. In one study, 56 adult carriers were compared with 35 normal controls [52]. Genetic status of the carriers was confirmed and abnormalities were reported on echocardiogram and electrocardiogram in 18% (10/56) of carriers. Seven percent (4/56) had cardiomyopathy defined as significant left ventricular dilation and decreased shortening fraction. In another study of 129 adult carriers by echocardiogram [53], dilated cardiomyopathy was found in seven DMD carriers (8%), and in none of the BMD carriers. In addition, 18% had left ventricle dilation (DMD 19%, BMD 16%). Politano et al., also reports a similar dilated cardiomyopathy incidence of 8.6% in DMD carriers and 13.3% in BMD carriers [54].

At present, few carrier studies exist utilizing CMR to assess disease in carriers. A recent literature review detailing current knowledge in dystrophin disease in carriers highlighted CMR as one area in which little is known [55]. In the largest study, DMD carriers and some first-degree male relatives were studied utilizing CMR with LGE imaging. Thirty-six carriers (20 DMD, 16 BMD) carriers were tested, and 44% had non-ischemic subepicardial gadolinium enhancement in the free wall of the left ventricle associated with varying degrees of myocardial fibrosis. There were 22 mother and first-degree affected male pairs, and the carriers had an LGE fibrosis pattern that mirrored that which was found in the DMD boys [56].

Our findings demonstrate that a clinical picture of dilation and dysfunction are not early features of the cardiac disease in MDC subjects. Fibrosis clearly precedes the decrease in LVEF mirroring the findings in the boys. This non-coincident change supports the assertion that CMR is the diagnostic modality of choice, as echocardiogram will underestimate the presence of disease.

4.4. High serum CK

Serum CK levels were found to be significantly elevated in the MDC group. The level of serum CK in DMD carriers is dependent on X-inactivation and distribution of the DMD (dystrophin) gene mutation. Normally, this would be equally distributed so that 50% of the nuclei of muscle fibers express dystrophin and this is sufficient to protect the muscle fiber from breakdown. When this ratio changes, as seen in manifesting carriers, a higher percent of muscle fibers lose dystrophin, this appears to result in muscle fragility and scattered in muscle breakdown and elevated CK levels. We feel that this accounts for the difference in serum CK between MDC. Therefore, a higher serum CK suggests reduced dystrophin expression and more disease burden. Univariate analysis of serum CK as a predictor of cardiac fibrosis was revealing, as discussed in detail below.

4.5. Predictors of cardiac fibrosis

Univariate analysis revealed that age, RecVE and high CK levels were independent predictors of fibrosis. Per decade of age, an odds ratio (OR) for LGE positivity was 10.9. OR for the presence of RecVE was 4.0 and for a CK level of greater than the upper limit of normal of 289 U/l was 2.4. This suggests that a 45 year-old MDC patient has a 1 in 2 chance of having fibrosis by CMR. A multivariate analysis including the same three variables revealed an OR of 10.8 per decade of age, 4.3 for RecVE and 2.5 for a high CK, suggesting that confounding was not problematic. High CK association may offer evidence that global dystrophin levels, and not mosaicism of X-inactivation, account for the asymmetric presentation of cardiac disease in the absence of musculoskeletal manifestations in MDC.

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4.6. Diagnostic value of native T1 mapping

Native T1 has been used to detect diseased myocardium in healthy subjects and in BMD/DMDboys [39,40,57]. Native T1 values can potentially be used to detect occult disease prior to the development of LGE or decline in LVEF. In our study, mean native T1 values were significantly higher in the MDC group compared to control or non-carrier subjects. Within the MDC group, those with LGE have higher T1 values compared to those without LGE and the native T1 value increases with age. However, given significant inter-individual variance of the average native T1 values, a specific T1 value cut-off in discriminating MDC versus non-carriers or which MDCs have LGE is challenging. As suggested by the characteristics of our ROC curve, an optimal high sensitivity and specificity value is not clearly evident. Given the impact of a false positive or negative for either carrier status or LGE positivity, we would hesitate to use this as a diagnostic marker alone. The findings indicate that without the use of contrast, T1 has utility as it clearly suggests the presence of a cardiomyopathy phenotype, but does not replace genetic testing. Additionally, native T1 relaxation time (and hence native T1 values) are dependent on the individual institution and scanner field strength. CMR guidelines note that reference values should be validated by individual institutions and scanners with different field strengths [35,58].

4.7. Limitations

This study is a single center study, although the subjects were recruited from all over the country with access to the study coordinator through postings on ClinicalTrials.Gov and the Parent Project Muscular Dystrophy website. The control sample recruited for the current study were hospital employees, which may not be representative of women from the general public (e.g., more likely to have an advanced degree, higher socioeconomic status, etc.). However, hospital employees may better match the education level, socioeconomic status, and exposure to stress of the mothers than a sample of control recruited from the general population. T1 values vary with field strength and still not well standardized. Results of one study cannot be broadly applied to different field strengths and vendors. Other centers wishing to reproduce the findings of this study may need to repeat validation of thresholds using their local set-up. Our current study does not report segmental T1, post-contrast T1 mapping or extracellular volume (ECV) estimation, which can be derived from pre- and post-contrast T1 maps. However, the power of native T1 mapping is that it can be done without contrast, avoiding the risk of gadolinium deposition.

5. Conclusion

Based upon our work, we would advocate for genetic testing of all potential carriers of *DMD* mutations and for CMR in the cardiac evaluation of proven carriers of dystrophin mutations. Additional longitudinal studies are required to determine the predictive quality of cardiac fibrosis in this unique population. Of particular interest in our longitudinal assessments will be the false-positive subjects with RecVE but without fibrosis in our baseline CMR, in particular given evidence of diffuse fibrosis by T1 measures. CMR should be considered in genetically confirmed subjects beginning in the 3rd decade and for those with high CK levels given the prevalence of occult cardiomyopathy. For DMD/BMD mothers with negative genetic testing, the risk of cardiomyopathy is similar to the general population and should be managed expectantly. The frequency of CMR evaluations are unclear at this time but our ongoing longitudinal study may offer some insight.

The discrepancy between functional testing by treadmill and the findings of cardiac disease by CMR also deserves further investigation. Our findings suggest that MDC manifest predominantly cardiac muscle and not skeletal muscle disease, as VO2max measures were no different than the non-carrier moms and controls. These findings, along with this association with higher serum CK measures in MDC with fibrosis by CMR, suggest that a global disease severity, and not tissue-specific effect, is at play in the discrepancy between cardiac and skeletal muscle manifestations of disease.

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Dr. Mah is an Advisory Board Member for Catabasis. Dr. Mendell is a consultant for AveXis, Inc. Sarepta Therapeutics, Exonics Therapeutics, and Myonexus Therapeutics. He has no investments in products that are under study. Dr. Al-Zaidy is a paid consultant for AveXis, Inc. Dr. Camino was employed at Nationwide Children's Hospital during collection of this data but now is an employee of Parent Project Muscular Dystrophy. Dr. Hor is a consultant for Medtronics and Catabasis as well as an Advisory Board Member for Capricor Inc. None of our disclosure relationships directly relate to care of carrier cardiomyopathy.

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Appendix A. Supplementary data

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