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BRIEF COMMUNICATION

Prevalence of Subclinical Left Ventricular Dysfunction Evaluated by Global Longitudinal Strain in Female Carriers of Duchenne Muscular Dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) is a muscular disease genetically linked to the *DMD* gene, which encodes dystrophin, a protein that is crucial for the integrity of skeletal muscle and myocytes. This condition follows an X-linked inheritance pattern. Female carriers are typically asymptomatic; however, they may develop cardiomyopathy, making screening for structural heart disease advisable. We conducted a cross-sectional study to assess the prevalence of subclinical left ventricular (LV) dysfunction, defined by reduced global longitudinal strain (GLS), in asymptomatic female *DMD* carriers. Participants underwent 2-dimensional speckle tracking echocardiography following a standardized protocol, with GLS values ≤ 18% classified as reduced. Continuous variables were described as mean ± standard deviation and categorical variables as percentages. The association between left ventricular ejection fraction (LVEF) and GLS was assessed using Pearson's correlation coefficient. The significance level adopted was 5%. Using a convenience sample, 17 participants (mean age 39 ± 5 years) were enrolled. No significant changes were observed in LV diameters, and the mean LVEF was 62% ± 5%. Reduced GLS was identified in 3 participants, indicating a prevalence of 17.6% for subclinical LV dysfunction. A weak correlation was found between GLS and LVEF (r = 0.366). Our findings indicate that approximately 1 in 6 female *DMD* carriers had subclinical LV dysfunction. These results highlight the need for genetic counseling for mothers of patients with DMD, as well as early screening with sensitive methods to detect heart disease in female *DMD* carriers.

Keywords

Duchenne Muscular Dystrophy; X-Linked Genetic Diseases; Left Ventricular Dysfunction; Global Longitudinal Strain; Women's Health.

Introduction

Duchenne muscular dystrophy (DMD) is caused by pathogenic variants in the dystrophin gene. It exhibits an X-linked inheritance pattern, affecting approximately 1 in 3,500 to 5,000 liveborn boys. The absence of a functional dystrophin protein causes progressive skeletal muscle weakness and cardiomyopathy.[1]

Pathogenic variants can be found in children (*de novo*) or inherited from the mother, which occurs in 70% of cases. Due to skewed X inactivation, most women remain clinically asymptomatic; however, manifesting female carriers were reported in a prevalence of 0.35 to 0.8 per 100,000 person-years.[2]

The incidence of cardiomyopathy in male *DMD* carriers increases with age, as more than 90% of these males over 18 years of age exhibit cardiac dysfunction, which leads to death by age of 30.[3] Cardiac disease has also been reported in women, with prevalence rates varying between less than 10% and more than 60% among carriers. [4-6] The severity of cardiac disease is heterogeneous, and few studies have investigated the early signs of cardiac involvement in this group.[6, 7] Global longitudinal strain (GLS) derived from speckle tracking echocardiography (STE) is recognized as a

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valuable tool for the early detection of subtle systolic function impairment from various etiologies.[8] In this context, this study aimed to assess the prevalence of subclinical left ventricular (LV) dysfunction, evaluated by GLS using STE, in a group of female *DMD* carriers.

Methods

A cross-sectional observational study was conducted from August 2021 to December 2022, using a convenience sample of asymptomatic women over 18 years of age with pathogenic variants in the *DMD* gene, who were followed at the cardiology outpatient clinic of a university hospital. Only biological mothers of patients with DMD and prior genetic testing confirming their carrier status were included. Exclusion criteria included any history of structural heart disease, such as valvar heart disease, as well as signs or symptoms of coronary disease, diabetes mellitus, and/or uncontrolled arterial hypertension.

All enrolled patients were evaluated with STE, using Philips® Epiq CVx AutoStrain software. Standard parasternal long-axis views were acquired to measure LV dimensions and wall thickness. Three consecutive cardiac cycles of apical views (4 and 2 chambers and long axis) were obtained for both STE-based strain analysis and conventional LV ejection fraction (LVEF) measurements using Simpson's method.[9] Longitudinal strain was measured at the LV endocardial border, as identified in the selected images. Subclinical LV systolic dysfunction was defined as an absolute GLS value ≤ 18%.[10] All GLS measurements were performed by 2 independent observers using the post-processing software package, with the images stored in Digital Imaging and Communications in Medicine (DICOM) format, acquired using the Philips system.

Statistical analysis

Continuous variables were described as mean ± standard deviation, and categorical variables were described as percentages. Intraclass correlation coefficient (ICC) was used to compare GLS results from both observers. In cases of discordant measurements, the lowest value was disregarded. The association between LVEF and GLS, both normally distributed as confirmed by the Kolmogorov-Smirnov test, was assessed using Pearson's correlation coefficient. All analyses were carried out using SPSS software, version 29.0, with a significance level set at 5%. The study was approved by the local ethics committee, and all participants provided informed consent.

Results

The study included 17 women with a mean age of 39 ± 5 years. Nine participants (53%) had no previous cardiological evaluation.

Echocardiographic parameters are described in Table 1. No alterations were found in LV diameters or diastolic function. All participants had LVEF values > 50% with a mean of 62% ± 5%. The GLS was 20.9% ± 3.1%, based on measurements assessed by 2 observers (ICC = 0.81).

Subclinical LV dysfunction was found in 3 of the 17 female *DMD* carriers, representing 17.6% of the study sample. Results representing GLS and LVEF values are shown in Figure 1, and the results indicate a weak correlation between them (r = 0.366).

Table 1 – Echocardiographic parameters of female *DMD* carriers

Parameters	Total participants (n =17)
Aorta, mm	28.8 ± 2.9
LA, mm	31.5 ± 4.4
LA volume, ml/m²	25 ± 10
LVEDD, mm	46.8 ± 3.3
LVESD, mm	30.7 ± 3.1
LVPW, mm	7.5 ± 0.9
IVS, mm	7.5 ± 0.9
TAPSE, mm	21.3 ± 3.3
E-wave velocity, cm/s	84.8 ± 14.0
Lateral e' wave velocity, cm/s	12.9 ± 2.9
Septal e' wave velocity, cm/s	9.6 ± 1.5
PASP, mmHg	21.7 ± 4.4
LVEF (Simpson), %	61.9 ± 5.2
GLS, %	20.9 ± 3.1

Values represent mean ± standard deviation. GLS: global longitudinal strain; IVS: diastolic interventricular septum; LA: left atrium; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVPW: left ventricular posterior wall; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion.

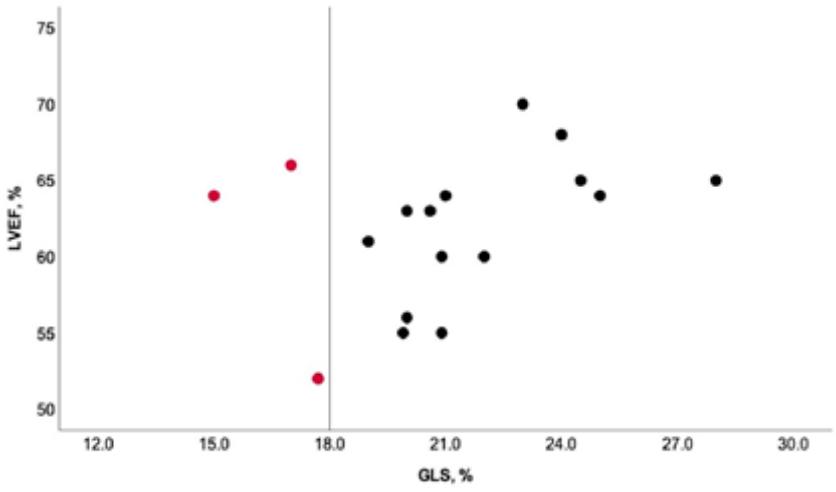

Figure 1 – Correlation between GLS and LVEF
Pearson's coefficient (r) = 0.366; red dots represent participants with reduced GLS (reference line = 18%). GLS: global longitudinal strain; LVEF: left ventricular ejection fraction.

Discussion

Our results demonstrated a 17.6% prevalence of subclinical LV dysfunction in a group of asymptomatic female *DMD* carriers, based on the criterion of GLS ≤ 18%.

In a cross-sectional study involving female *DMD* carriers with a mean age of 49.6 years, 63% exhibited LV dysfunction based on low LVEF and/or reduced GLS by STE (< 20%). In the same study, the authors reported some degree of myocardial fibrosis in 49% of participants when evaluated with cardiac magnetic resonance (CMR).[6] In contrast, our findings revealed a lower prevalence of reduced GLS; however, we assessed a younger group of completely asymptomatic women using a more stringent criterion (GLS < 18%), thereby minimizing borderline results. Additionally, all women evaluated in our protocol had LVEF > 50%.

Another recent study reported subclinical cardiac dysfunction in asymptomatic female *DMD* carriers (mean of age 39 years; LVEF > 50%). GLS assessed by CMR was 19.4% ± 2.4% in carriers versus 22.3% ± 2.2% in controls (p = 0.001).[7] Despite using CMR, these results are similar to ours, where mean GLS was 20.9% ± 3.1% (Table 1); however, we did not include a control group.

We observed only a weak correlation between LVEF and GLS (Figure 1). This finding reinforces the notion that, while LVEF is considered a primary indicator in assessing LV function, it may remain normal in the early stages of cardiac involvement.[8, 11]

This study has several important limitations. First, it involved a small number of participants. However, given that DMD is a rare disease, we believe our results are still relevant. Secondly, GLS by STE are both operator- and software-dependent.[10] To minimize potential bias, we utilized the same software and involved 2 independent examiners in the evaluation. Additionally, this study was cross-sectional and did not include a control group; therefore, prospective studies with long-term follow-up are needed to confirm the significance and prognostic value of these findings.

Conclusion

One in 6 female *DMD* carriers exhibited subclinical LV dysfunction, which may indicate the onset of the cardiomyopathy process. These results underscore the importance of genetic counseling for mothers of patients with DMD and highlight the need for early cardiological screening using sensitive methods to detect heart disease in female *DMD* carriers.

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Author Contributions

Conception and design of the research and statistical analysis: Rodrigues EV, Souza F; acquisition of data and writing of the manuscript: Rodrigues EV, Pereira APLC, Correa Filho WB, Souza F; analysis and interpretation of the data: Rodrigues EV, Pereira APLC, Correa Filho WB, Lima MAFD, Siqueira Junior MAF, Nucera APCS, Souza F; critical revision of the manuscript for intellectual content: Rodrigues EV, Lima MAFD, Siqueira Junior MAF, Nucera APCS, Souza F.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the HUGG-UNIRIO/EBSERH o under the protocol number 4.464.928. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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