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Patient reported quality of life in limb girdle muscular dystrophy

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Dr. Mozaffar has received honoraria and travel reimbursement for serving on advisory boards for Abbvie, Alexion, Amicus, Argenx, Audentes, Modis, Momenta, Ra Pharmaceuticals, Sanofi-Genzyme, Sarepta, Spark Therapeutics, UCB, and Ultragenyx. He has also served on the speaker's bureau for Alexion, CSL, Grifols, and Sanofi-Genzyme. Dr. Mozaffar serves on the medical advisory board for the Myositis Association, Neuromuscular Disease Foundation, Myasthenia Gravis Foundation of California and Myasthenia Gravis Foundation of America and has received travel funding from the Myositis Association and the Neuromuscular Disease Foundation. Dr. Mozaffar receives research funding from the Myositis Association, the Muscular Dystrophy Association, the National Institutes for Health and from the following sponsors: Alexion, Amicus, Argenx, Audentes, Bristol-Myers-Squib, Cartesian Therapeutics, Grifols, Momenta, Ra Pharmaceuticals, Sanofi-Genzyme, Spark Therapeutics, UCB, and Valerion. He has served on the data safety monitoring board for Acceleron, Avexis, and NIH.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.nmd.2021.11.002.

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Abstract

This study determined the frequency and impact of symptoms on quality of life in patients diagnosed with limb girdle muscular dystrophy (LGMD). Participants with a diagnosis of LGMD in registries based at the Coalition to Cure Calpain-3, the Jain foundation, and the Global FKRP Registry competed a survey to report the frequency and relative impact of themes and symptoms of LGMD. Frequency, mean impact, and population impact scores were calculated, and responses were categorized by age, symptom duration, gender, employment status, use of assistive devices, and LGMD subtypes. 134 participants completed the survey. The most prevalent themes included an inability to do activities (100%), limitation with mobility (99.3%), and lower extremity weakness (97.0%). Themes with the greatest impact were: limitations with mobility, lower extremity weakness, and an inability to do activities. Symptom duration and the use of assistive devices were associated with the presence of multiple themes. Employment was associated with the impact of several themes with no differences in frequency. The prevalence and impact of these themes vary in the LMGD population. The most prevalent and impactful themes were related to weakness, but additional concerns related to emotional challenges should also be considered in clinical and research settings.

Keywords

Quality of life; Limb girdle muscular dystrophy; Patient report; Dysferlin; Calpain-3; FKRP

1. Introduction

The limb girdle muscular dystrophies (LGMDs) are a group of over 30 inherited myopathies characterized by progressive hip and shoulder girdle weakness [1]. The combined prevalence is 1.6–2.27 per 100,000[2,3]. The clinical course and impact on quality of life (QoL) are variable, with patients experiencing different ages of onset, degrees of impairment, and patterns of weakness. Some LGMD subtypes are associated with cardiac and pulmonary complications, which may limit life expectancy for some affected individuals [4]. Recent

medical and scientific advances raise the prospect of improved supportive care and novel molecular therapies. Understanding the patient reported symptom themes and impact on QoL will be a key component of determining whether treatments are effective and appropriate for LGMD.

QoL has previously been studied in patients diagnosed with LGMD. One study utilized the Short-Form-36 (SF-36) and The Individualized Neuromuscular Quality of Life questionnaire (INQoL) to quantify changes in the quality of life in 46 patients with LGMD [5]. Worse SF-36 and INQoL scores were associated with later disease onset and older age, though not increased duration of disease. Decreased hip flexor strength, use of assistive walking devices, and greater fatigue were also associated with a lower QoL [5]. We recently conducted qualitative interviews and collected 1385 direct quotes from 20 patients diagnosed with LGMD to determine symptom themes important for LGMD. Patients most frequently reported limitations with mobility, difficulty performing activities, social role limitations, and emotional distress [6].

Knowledge of symptoms and issues with the greatest impact is essential in guiding the development of novel therapeutics and improvement of clinical care [7,8], but quantitative patient-reported data on symptom impact and QoL are scarce for individuals with LGMD. This study aims to determine the patient-reported frequency and impact of symptoms in patients diagnosed with LGMD.

2. Methods

2.1. Study participants

Participants were eligible for this study if they carried a diagnosis of LGMD and were registered with either the Coalition to Cure Calpain-3 registry (https://www.curecalpain3.org/registry/), the Jain foundation registry (https://dysferlinregistry.jain-foundation.org/), or the Global FKRP Registry (https://www.fkrp-registry.org/). These registries include a mix of both genetically confirmed and clinically diagnosed patients with LGMD, and patients were eligible for this study if they self-reported any diagnosis of LGMD. Participants meeting inclusion criteria were sent an email and letter announcing the survey which included a weblink to an online survey. Participants were instructed to complete only one survey if they received invitations through multiple registries, and results were screened for duplicate responses. Survey responses were collected for a period of six months during 2019. All study activities were fully approved by the University of Utah institutional review board.

2.2. Survey development

Themes and symptoms for the survey were identified using data collected through qualitative interviews with 20 LGMD participants diagnosed with six different subtypes [6]. These interviews identified 165 different symptoms of potential importance in LGMD and were used to construct a survey to assess the presence and impact of these themes and symptoms on QoL. Similar symptoms were categorized into 15 symptomatic themes which were further organized into physical health themes and social and cognitive themes

[6]. Questions regarding demographic data and disease characteristics including subtype, if known, were also included in the survey. Patients rated the severity of the impact of these potential symptoms with a 6-point Likert scale with the following options: 1 = I don't experience this; 2 = I experience this but it does not affect my life; 3 = It affects my life a little; 4 = It affects my life moderately; 5 = It affects my life very much; 6 = It affects my life severely. After ranking the importance of the listed symptoms, the participants could list and rank any additional symptoms not included in the survey. This methodology has been previously used to determine frequency and relative importance of symptoms in numerous other neurological diseases including Myotonic Dystrophy 1 and 2, spinal muscular atrophy, facioscapulohumeral dystrophy, Huntington's Disease, Charcot Marie Tooth, and pediatric onset myotonic dystrophy [9–15].

2.3. Statistical analysis

The frequency of the themes and symptoms was calculated. To calculate mean impact and population impact scores, responses of participants who reported symptoms (i.e., 2–6 in the Likert scale) were adjusted to range from 0 to 4, with 4 indicated the most severe impact on life: 0 = I experience this but it does not affect my life; 1 = It affects my life a little; 2 = It affects my life moderately; 3 = It affects my life very much; 4 = It affects my life severely. The mean impact scores were calculated by averaging all Likert responses of those who reported symptoms. The population impact score was calculated by multiplying the frequency by the mean impact score of the participants reporting symptoms or themes, and the score ranges from 0 to 4 with 4 indicating that the item affects all patients to the greatest degree.

Responses were categorized by age (0–20, 21–30, 31–40, 41–50, 51–60, ≥61 + years), symptom duration (0–10, 11–20, 21–30, 31–40, ≥41 + years), gender (male, female), employment status (employed, unemployed), ambulatory status (no assistive device use, use of a brace, cane, or walker, or use of a wheelchair, motorized chair, or multiple devices), and LGMD subtype. Symptom duration was defined as the number of years between the time since the patient first identified any symptoms of LGMD and their current age. The subtypes selected for analysis were limited to LGMDR1 (formerly known as LGMD2A, *CAPN3* gene), LGMDR2 (also known as LGMD2B, *DYSF* gene), LGMDR9 (also known as 2I, *FKRP* gene), LGMDR12 (also known as LGMD2L, *ANO5* gene), and LGMDR22 (formerly known as Bethlem or collagen 6 related disorders, *COL6* genes) due to a low number of participants with other subtypes (< 5). The frequency of the themes across the groups was compared using Fisher exact tests, and the distribution of mean Likert scores across groups was compared using Kruskal-Wallis tests with a two-tailed p value < 0.05 considered significant. Multiple comparison adjustment was not used in this study because it was considered exploratory [16,17].

2.4. Data availability

Anonymized data will be shared by request from any qualified investigator.

3. Results

134 participants completed the survey. Demographic information of the participants is summarized in Table 1, and the frequency and impact of the themes are summarized in Table A.1.

3.1. Frequency of themes and symptoms

100% of participants reported an inability to do activities due to their symptoms. Other prevalent themes included limitation with mobility (99.3%), hip, thigh, or knee weakness (97.0%), fatigue (94.7%), and problems with shoulders or arms (90.3%).

The frequency of hand or finger weakness ($p < 0.05$) and changed body image ($p < 0.05$) increased with age (Fig. 1). Problems with shoulders or arms ($p < 0.05$), respiratory problems ($p < 0.001$), and changed body image due to disease ($p < 0.05$) increased in frequency with increasing symptom duration (Fig. 2). There were no differences in the frequency of any theme between men and women or between the employed and unemployed. Problems with hands or fingers ($p < 0.001$), problems with shoulders or arms ($p < 0.001$), problems with breathing ($p < 0.05$), gastrointestinal issues ($p < 0.05$) and changed body image due to disease ($p < 0.001$) were more prevalent with the use of wheelchairs, motorized chairs, or multiple mobility devices (Fig. 3). The frequency of hand and finger problems differed among LGMD types with the highest frequency in type LGMDR2 ($p < 0.05$). Breathing or respiratory problems ($p < 0.001$) and heart arrhythmias or cardiac issues ($p < 0.05$) also differed among LGMD types with the greatest frequency in those with LGMDR9 and LGMDR22.

Among individual symptoms, difficulty going up stairs, walking long distances, running, and leg weakness were all reported by 100% of patients. Seven other symptoms had a frequency over 98%; the inability to do things a patient was previously able to do (99.25%), muscle fatigue (98.50%), impaired walking (98.49%), difficulty getting around when ambulating on rough ground (98.46%), decreased mobility (98.5%), difficulty getting up quickly (98.45%), difficulty ambulating in the sand (98.44%).

3.2. Impact of themes and symptoms

Hip, thigh, or knee weakness (2.91; SD 1.12), limitations with mobility (2.86; SD 1.13), and inability to do activities (2.52; SD 1.21) were the themes that had the greatest overall mean impact.

Problems with shoulders or arms were more frequent with increasing age ($p < 0.05$) (Fig. 1). Limitations with mobility ($p < 0.001$), inability to do activities ($p < 0.05$), problems with hands or fingers ($p < 0.05$), problems with shoulders or arms ($p < 0.001$), hip, thigh or knee weakness ($p < 0.001$), and decreased satisfaction in social situations ($p < 0.05$) all became more prominent with increasing duration of illness (Fig. 2). There were no differences in the impact of these themes between men and women. Unemployed patients reported a greater impact of inability to do activities ($p < 0.05$), problems with shoulders or arms ($p < 0.05$), problems with breathing or lungs ($p < 0.05$), changed body image due to disease ($p < 0.05$), and fatigue ($p < 0.05$) compared to employed patients (Fig. 4). The reported impact

of limitation with mobility ($p < 0.001$), inability to do activities ($p < 0.05$), problems with shoulders or arms ($p < 0.001$), hip, thigh, and knee weakness ($p < 0.001$), and changed body image due to disease ($p < 0.001$) increased as more assistance was reported (Fig. 3). There were no differences in the impact of themes between LGMD subtypes.

Individual symptoms with a mean impact greater than 3 included difficulty going up stairs (3.35; SD 1.09), an inability to run (3.24; SD 1.16), difficulty running (3.17; SD 1.19), the need to use a railing when going up or down stairs (3.15; SD 1.2), leg weakness (3.11; SD 1.12), difficulty transferring from a wheelchair (3.09; SD 1.2), difficulties getting around when ambulating on slippery surfaces (3.08; SD 1.25), difficulty ambulating up or down hills (3.06; SD 1.22), difficulty walking long distances (3.02; SD 1.23), the need for assistive devices for ambulation (3.02; SD 1.2), and difficulty getting up quickly (3.02; SD 1.21).

3.3. Population impact

Themes with the greatest population impact include limitations with mobility (2.84), hips, thigh, or knee weakness (2.82), and inability to do activities (2.52). Individual symptoms with a population score greater than three include difficulty going up stairs (3.35), difficulty running (3.17), inability to run (3.16), leg weakness (3.11), difficulty walking long distances (3.02), and difficulties getting around when ambulating on slippery surfaces (3.01).

4. Discussion

Our study describes the themes and issues related to LGMD that contribute to disease burden and negatively impact quality of life in patients. This patient-centered study design identifies the manifestations of disease with the greatest burden, helping providers better understand how these symptoms affect their patients' lives. This approach also draws attention to psychological distress that patients experience, like changed body image and fatigue.

Several symptomatic themes reduce the QoL in patients with LGMD with most of these themes related to physical symptoms and problems related to the hip or shoulder girdle muscles. Notably, an inability to do activities was experienced by all the respondents. While physical themes are most prominent, patients also reported a high frequency of social limitations and cognitive difficulties, including emotional distress, impaired body image, and social role dissatisfaction, with these themes being present in over two-thirds of the respondents. Although LGMD is a peripheral disorder, and the physical symptoms are the most prominent, the high frequency of psychological themes may warrant additional screening for patients with muscular dystrophies and a multidisciplinary approach to treatment with counseling and social work. These data remind clinicians of the importance of addressing the social and emotional difficulties that arise with progressive loss of function.

Analysis of the themes across age and symptom duration demonstrated that symptom duration may be a better predictor of disease state than age. Disease onset can occur at various ages in LGMD. Excluding the frequency of hands and finger problems, changed body image, and impact of problems with shoulders and arms, the frequency and impact of

themes was not different based on age categorization but was different based on symptom duration. The frequency and impact of shoulder and arm weakness and the impact of hand and finger weakness was associated with increasing symptom duration, which is an expected finding as upper extremity involvement becomes more common in the later stages of LGMD [18]. Disease duration is a major determinant of symptom burden and may be more meaningful than current age alone for clinical trial design as well as for counseling patients about expected disease progression over time.

While there were no differences in the frequency of symptoms between employed and unemployed patients, unemployed patients perceived a greater impact of several themes on QoL which may suggest functional disability with disease progression that prevents employment. The mean age of employed was 39.62 (SD 12.66) and the unemployed was 45.95 (SD 19.45). These differences may be attributed to a greater average age in the unemployed compared to the employed; however, with only a modest difference in age between these two groups, it is unlikely that age is the predominant factor driving the change in QoL. In similar studies, problems with shoulders and arms and fatigue have been associated with employment status in CMT, DM2, and FSHD [11–13], and the frequency of breathing difficulties has been associated with employment status in SMA [10]. Fatigue and an inability to do activities have previously been identified as influencing themes in employment in people with progressive neurological diseases including CMT, DM2, FSHD, and Huntington Disease [11–14]. Upper extremity weakness, respiratory issues, and fatigue may play and important a role in whether individuals maintain employment. For many, employment is an important part of life which brings meaning through self-realization along with economic benefits. Disease disclosure is often delayed due to fears of financial instability, dismissal, or loss of self-worth, and it can be difficult for many individuals to accept when they are no longer able to work due to their chronic, progressive disease [19]. Patients with degenerative neuromuscular diseases like LGMD may benefit from consultations with occupational therapists to identify potential work-related difficulties and to find solutions to maintain employment.

As a disability worsens and ambulation becomes increasingly difficult, patients may rely on assistive devices eventually requiring a wheelchair or motorized device. Additionally, patients using wheelchairs, motorized chairs, or multiple devices reported a greater impact of changed body image on quality of life than those using no devices or a cane or brace. Changed perception of body image is a form of psychological distress that often accompanies physical disability along with decreased self-esteem [20], and patients may experience distress as they adapt to their disability and require more assistance. Additionally, the use of assistive mobility devices was associated with the frequency of 5 themes and the impact of 6 themes. The association of ambulation status with several important symptomatic themes and perceived impact on quality of life has also been found in patients with SMA [10]. Interventions that address difficulties with ambulation and the need for assistance may have a large effect on disease burden and perceived quality of life.

Despite their different genetic mutations, LGMD subtypes share a similar profile of progressive symptoms, mainly proximal muscle weakness, with a similar impact on quality of life. Beyond the themes that are common across all subtypes, there is phenotypic

heterogeneity and notable differences between subtypes [21]. LGMDR9 and LGMDR22 may experience additional symptoms related to respiratory or cardiac function, and LGMDR2 may experience distal muscle weakness. While a high percentage of our participants with LGMDR22 experiences cardiac and respiratory problems, because there were only 5 participants with LGMDR22 additional data is needed to explore the effects of symptoms in this subtype.

There are several potential limitations to this study. Participants were recruited through patient-based registries, and it is possible that members of a registry have a different profile of symptoms than those who are not in a registry. It is also possible that some responses were influenced by unreported or superimposed diseases experienced by LGMD participants. Diagnoses of LGMD were self-reported by patients in the patient-based registries who may or may not have received formal diagnoses by clinicians, and our results may reflect a broader population than those previously genetically confirmed or individual subtypes. Due to the low sample size of several LGMD subtypes, comparisons between subtypes were limited. Additionally, because participants were divided into employed and unemployed groups, the unemployed group may include participants who are students, stay at home parents, retirees, and other individuals who are unemployed for reasons other than disability. Further research on employment in LGMD may help clarify the impact of LGMD symptoms on employment and

This study builds upon the existing research of the symptomatic burden of LGMDs with an emphasis on the patient viewpoint. Knowledge of these symptoms and the way they may influence patients' lives is valuable to providers who care for this population, as well as to those who work on the research and development of new therapeutics. Patient reported data will improve patient lives by highlighting unique needs and relevant outcome measures of research and clinical trials by providing information on not only the most common symptoms but also those that are the most impactful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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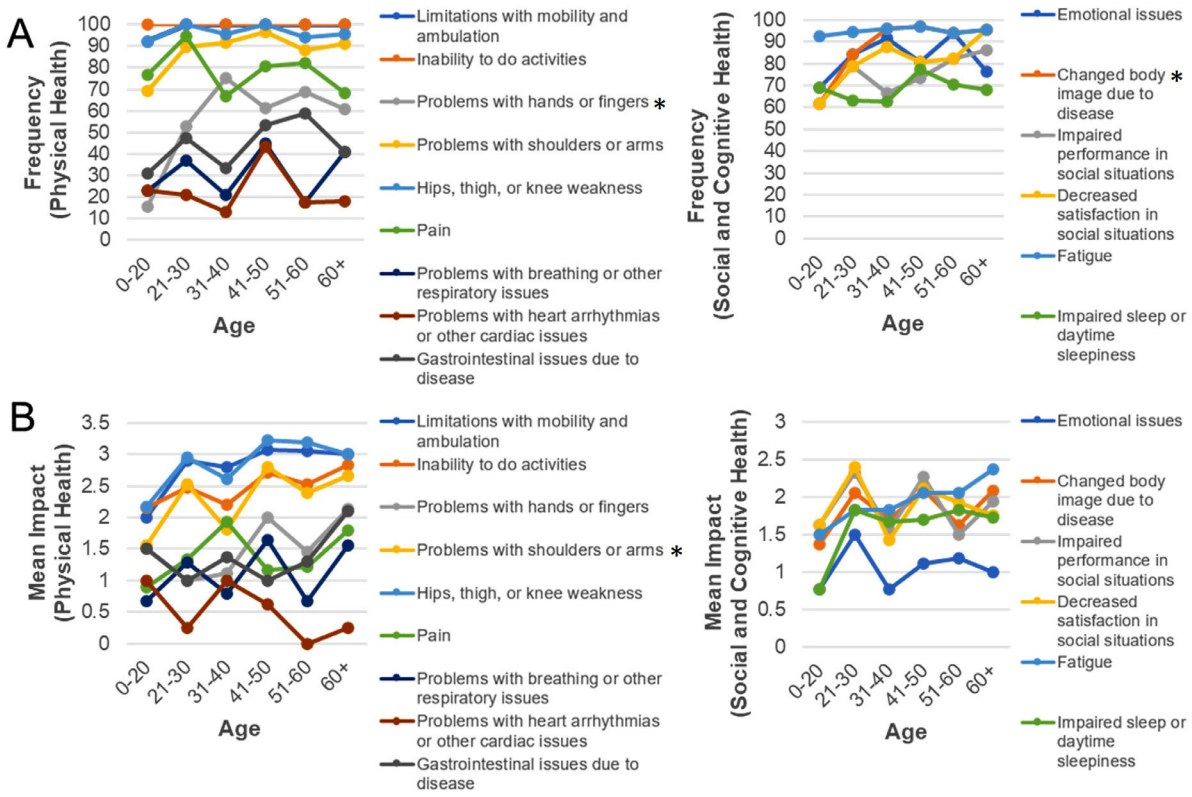

Fig. 1. The impact of LGMD by age.

A. Frequency of themes by age; B. Mean Likert response of themes by age. (*) indicates a *p* -value < 0.05.

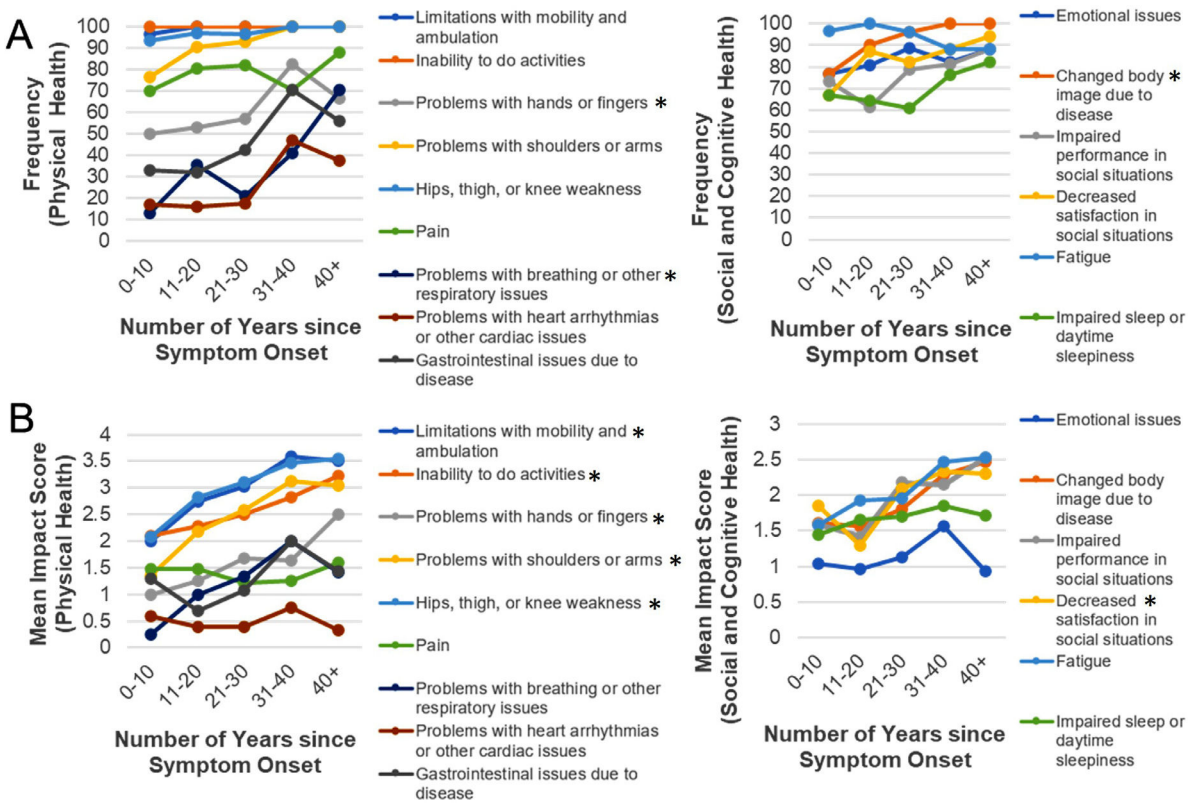

Fig. 2. The impact of LGMD by symptom duration.

A. Frequency of themes by symptom duration; B. Mean Likert response of themes by symptom duration. (*) indicates a p-value < 0.05.

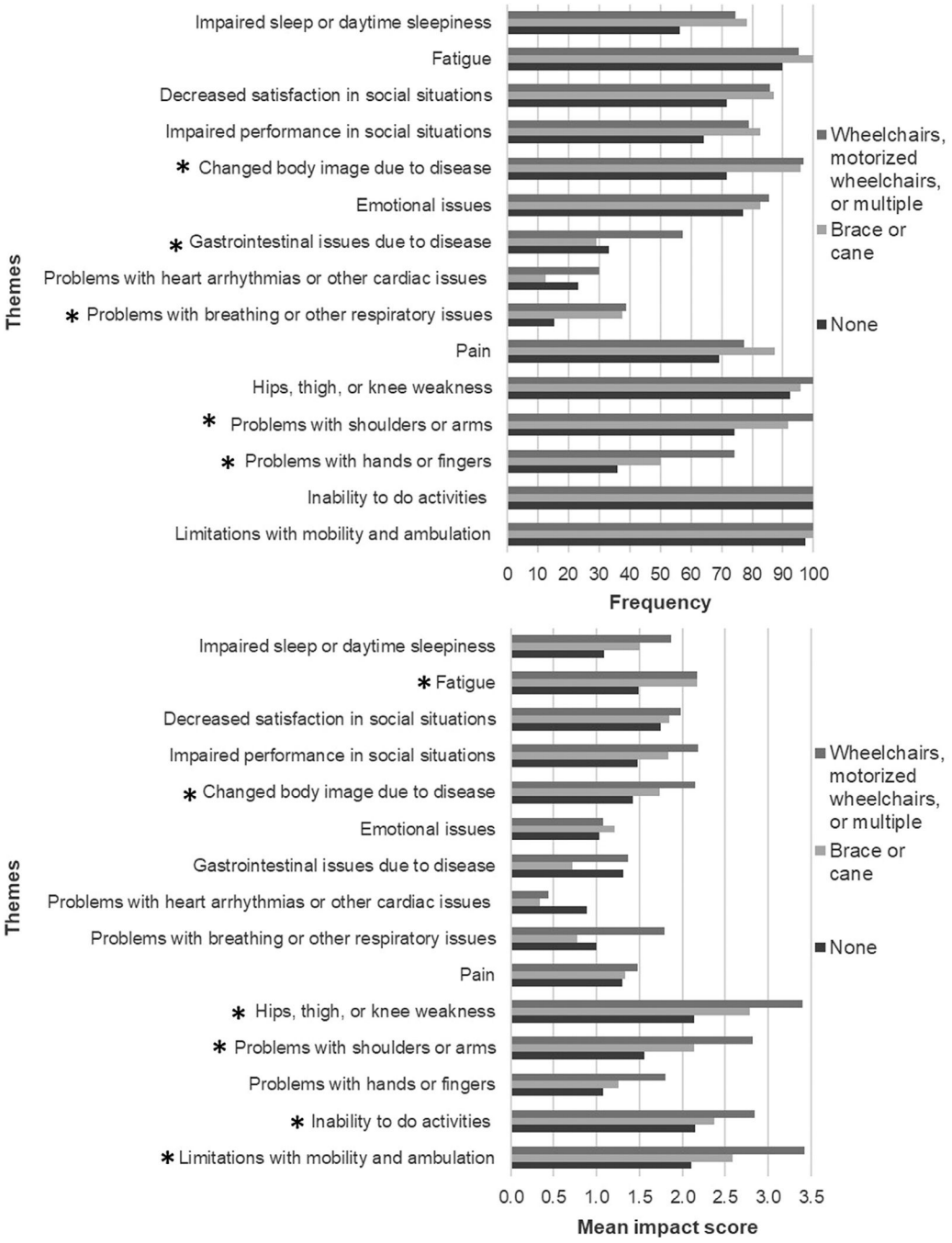

Fig. 3. The impact of LGMD by assistive device use.

A. Frequency of themes by assistive device use; B. Mean Likert response of themes by assistive device use. (*) indicates a p-value < 0.05.

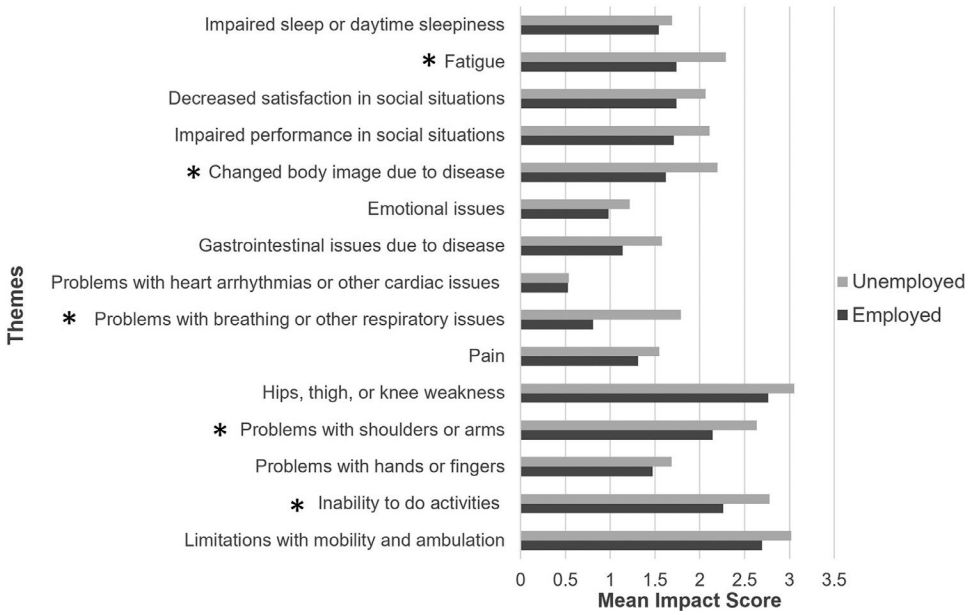

Fig. 4. The impact of LGMD by employment status.

Mean Likert response of themes by employment status. (*) indicates a p-value < 0.05.

Table 1.

Demographics and clinical characteristics (n = 134).

Age (years)	
Mean (SD)	43.69 (SD 16.44)
Range	13–88
Age at onset of LGMD symptoms (years)	19.68 (SD 13.36)
Duration of Symptoms	23.04 (15.13)
Sex (%)	
Male	61 (45.52)
Female	69 (51.49)
Omitted	4 (2.99)
Employment (%)	
Employed	69 (51.49)
Unemployed	59 (44.03)
Omitted	6 (4.48)
Use of Assistive Mobility Devices (%)	
None	29 (21.64)
Brace	4 (2.99)
Cane	20 (14.93)
Wheelchair	7 (5.22)
Motorized Wheelchair	27 (20.15)
Multiple	29 (21.64)
Other	3 (2.24)
Omitted	5 (3.73)
Type of LGMD (%)	
Myofibrillar myopathy	3 (2.24)
Rippling muscle disease	1 (0.75)
LGMDD1	2 (1.49)
LGMDR1	36 (26.87)
LGMDR2	37 (27.61)
LGMDR3	3 (2.24)
LGMDR4	1 (0.75)
LGMDR8	1 (0.75)
LGMDR9	28 (20.90)
LGMDR12	8 (5.97)
LGMDR22	5 (3.73)
Omitted	9 (6.72)