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Sarcopenic Obesity in Facioscapulohumeral Muscular Dystrophy

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ABSTRACT

Background: Sarcopenic obesity has been observed in people with neuromuscular impairment, and is linked to adverse health outcomes. It is unclear however, if sarcopenic obesity develops in adults with facioscapulohumeral muscular dystrophy (FSHD).

Methods: This research was designed to determine if adults with FSHD meet criteria for sarcopenic obesity (appendicular lean mass index (ALMI) scores of <7.26 kg/m^2 or 5.45 kg/m^2; % body fat of ≥28% or 40% in men/women). Ten people with FSHD (50±11 years, 2 females) and ten age/sex-matched controls (47±13 years, 2 females) completed one visit, which included a full-body dual-energy x-ray absorptiometry (DXA) scan. Regional and whole body total mass (g), fat mass (FM, (g, %)), and lean mass (LM, (g, %)) were collected; body mass index (BMI, kg/m^2) and sarcopenia measures (appendicular lean mass (sum of arm/leg lean mass, ALM (kg)), ALMI (kg/m^2)) were computed.

Results: Although total body mass was similar between adults with FSHD and controls (84.5±12.9 vs. 81.8±13.5 kg, respectively; p=0.65), the proportion of mass due to fat was much higher in FSHD, with many individuals having >50% mass due to fat (means: 40.8±7.0 vs. 27.9±7.5%; p=0.001). ALM volume was 23% lower and ALMI was 27% lower in FSHD (p<0.01). Whole body LM trended to be lower in FSHD vs. controls (p=0.05) and arm and leg LM were both lower in FSHD compared with controls (p<0.05). Furthermore, the % LM was 18% lower in FSHD vs. controls (p=0.001). FSHD participants exhibited greater total body FM (p<0.01), total leg fat mass (p<0.001), and but similar total arm fat mass (p=0.09).

Conclusions: These data demonstrate that people with FSHD, although similar in total body mass to controls, commonly meet the definition of sarcopenic obesity, with significant consequences for quality of life, and implications for disease management.

Key Words: FSHD, sarcopenia, obesity, lean mass, fat mass

BACKGROUND

Facioscapulohumeral muscular dystrophy (FSHD) is a dominantly-inherited myopathy, characterized by progressive, frequently asymmetrical, muscular weakness, most prominently in the face, shoulder girdle, and upper-arm region (1, 2). While life expectancy among individuals with FSHD appears to be preserved (2), impairments in functional capacity, as measured by a decreased capacity for independent ambulation (1), and a greater reliance on assistive devices among older adults with FSHD (>50 years), have been reported (3). It is speculated that this functional impairment may be partially driven by alterations in body composition, which likewise have been linked to high rates of skeletal muscle atrophy (1, 2) and corresponding increases in fatty tissue infiltration of the muscular compartments (4). For example, Janssen et al. demonstrated that up to 26% of individuals with FSHD may experience severe rates of fatty infiltration, whereby as much as 75% of lean tissue in the certain muscular compartments is replaced by fat mass (4), an observation that is likely to have clinical and functional implications for people with FSHD.

With the manifestation of muscular atrophy and increased proportion of fat mass, it is likely that people with FSHD exhibit a medical condition known as sarcopenic obesity. Sarcopenic obesity combines the key features of sarcopenia (losses in muscle mass, declining strength, and/or impairments in physical performance (5)) with an increased presence of adiposity (6). The presence of sarcopenic obesity is linked to high mortality rates (7), and a greater propensity towards physical disability (8). While sarcopenic obesity has been noted among individuals with various types of muscular dystrophy (i.e., Duchenne, Becker, and Ullrich congenital muscular dystrophies (9)), it is unclear if people with FSHD exhibit this condition. By identifying sarcopenic obesity as a potential comorbidity of FSHD, the development of effective preventative and therapeutic strategies designed to address the condition may be incorporated as part of the medical treatment plan, thereby leading to gains in functional capacity, a greater ability to perform activities of daily living (ADLs), and an overall improvement in quality of life. Therefore, the purpose of this study was to determine if there was a difference in the number of cases of sarcopenic obesity, between individuals with FSHD, and age- and sex-matched controls.

METHODS

Subjects

Ten adults with genetically-confirmed FSHD (50±11 years, average±SD) and ten age-, sex-, and BMI-matched healthy control participants (47±13 years) (n=20 combined; men: 16, women: 4) completed the study. Inclusion criteria consisted of an age of ≥18 years, and no prior history of cardiovascular, pulmonary, orthopedic, or neuromuscular disorders other than FSHD; female participants were excluded if they were currently pregnant or breastfeeding (10, 11). Physical activity levels were assessed via the Modified Minnesota Leisure Time Physical Activity Questionnaire, and reported as an activity metabolic index score (12). Severity of disease burden among individuals with FSHD was evaluated through completion of the FSHD Health Index survey, whereby a score of 100 reflects the highest disease, and 0 reflects no disease burden (13, 14). The study was approved by the University of Minnesota Institutional Review Board, and conducted in accordance with the Declaration of Helsinki.

Experimental Protocol

Study participants attended one study session, which included a written informed consent following a description of the study design and a total-body dual-energy x-ray absorptiometry (DXA) scan (Lunar iDXA, GE Healthcare, Chicago, IL, USA); female participants took a urine human chorionic gonadotropin (hCG) test (Clinical Guard, Atlanta, GA, USA) to confirm the absence of pregnancy.

Data Collection Techniques

Body composition was obtained from the DXA scan; an estimation of regional and whole body total mass (grams (g)), fat mass (FM (g, %)), lean mass (LM (g, %)), and bone mineral content (g) was provided by enCORE v16 (GE Healthcare, Chicago, IL, USA). As FSHD is primarily a disease that affects the upper extremity, differences between upper and lower lean and fat mass were also obtained. Appendicular lean mass (ALM) was quantified as the sum of fat- and bone-free tissue in the arms and legs, and was normalized to height to control for fluctuations in body size (9). An appendicular lean mass index [ALMI, ALM weight (kilograms (kg))/height^2 (meters (m), m^2)] was utilized as an index of sarcopenia (9), whereby the presence of sarcopenia was defined by an ALMI that is two standard-deviations lower than ALMI from the means observed in sex-specific reference groups (15). Sarcopenic obesity was defined by the combined presentation of an ALMI of <7.26 kg/m^2 and body fat percentage of >27%, or an ALMI of <5.45 kg/m^2 and body fat percentage of >38%, in men and women, respectively (8). Body mass index (BMI) was calculated from manual measurements of height (m) and weight (kg); study participants were categorized by BMI status into standard body composition categories (16).

Statistical Analysis

Data is reported as group averages (mean ± standard deviation), distribution normality was assessed and parametric vs. non-parametric methods were used as appropriate. Independent samples t-tests were used to compare differences in body composition between FSHD and control participants. Pearson product moment correlation was used to determine relationships between continuous variables. Statistical analyses were performed using SPSS v24.0 (SPSS, Inc., Chicago, IL, USA) with significance defined as an α-level of $p<0.05$ for all comparisons.

RESULTS

Subject Characteristics

FSHD and control study participants were similar in age (50±11 vs. 47±14 years, p=0.60), weight (85.4±12.9 vs. 81.8±13.4 kg, p=0.55), height (1.80±0.07 vs. 1.74±0.08, p=0.09), and BMI (26.1±4.4 vs. 26.7±3.6, p=0.77). In the FSHD group, all 10 participants self-reported as non-Hispanic (NH) white; among controls, self-reported race was as follows: NH white: 7 (5 men, 2 women), African-American: 1, Asian: 1, Hispanic: 1. Overall, the whole body total mass [calculated as sum of whole body fat mass (g), whole body lean mass (g), and bone mineral content (g)] of individuals with FSHD was similar to that of healthy controls (84.5 ± 12.9 vs 81.8 ± 13.5, respectively, p=0.65, **Table 1**).

Measures of Sarcopenic Obesity

Adults with FSHD were found to have an ALM that was 23% lower, as compared to the control group (p=0.02, **Table 1**). This observation was further accompanied by an ALMI score that was 27% lower among individuals with FSHD, as compared to healthy controls (p<0.001, **Figure 1**). Furthermore, the relative proportion of whole body fat mass to whole body total mass (% body fat) was 46% greater in FSHD, compared with controls (p<0.001, **Figure 2**). Mean alterations in ALMI (6.3 ±1.3 kg/m^2) and % body fat (40.0 ± 6.4%) among men with FSHD were sufficient to meet the diagnostic criteria for sarcopenic obesity; furthermore, six of eight men with FSHD were individually found to meet compositional requirements for the condition. Conversely, the same criteria were not met in female FSHD counterparts (ALMI: 6.2 ±1.0 kg/m^2, % body fat: 44.1 ±11.4%), and neither of the two FSHD females individually met the diagnostic requirements. Sarcopenic obesity was not observed in any of the control participants.

Additional Measures of Lean Mass

Additional measures of lean mass are located in **Table 1**. The absolute volume of whole body lean mass was 15% lower in FSHD, compared with controls, trending towards significance (p=0.05). In addition, individuals with FSHD demonstrated a relative proportion of whole body lean mass to whole body total mass (% lean mass) that was 18% lower, compared with controls (p=0.001, **Figure 3**). Furthermore, both the absolute volume of total arm (p<0.01) and total leg (p=0.03) lean mass were lower in FSHD by 29% and 21%, respectively, as compared with controls.

Additional Measures of Adiposity

Additional measures of adiposity are located in **Table 1.** Absolute volume of whole body fat mass was 53% greater in FSHD compared with controls (p<0.01). While the absolute volume of total leg fat mass among individuals with FSHD was 78% greater (p<0.001), the arms were somewhat less affected, with mean total arm fat mass only 28% greater in the FSHD group, not rising to statistical significance (p=0.09).

Self-Reported Measures of Functional Ability and Severity of Disease

Self-reported comorbidities are located in **Table 2**. While the control group did exhibit a greater frequency of back problems than counterparts with FSHD (p=0.04), differences in the reporting rate of other comorbidities between FSHD and control groups were not observed (p>0.05 for all). Other self-reported measures included an attenuated amount of physical activity completed each day among individuals with FSHD (activity metabolic index score; FSHD: 28.0±33.6 kcal/day, control: 184.3±152.7 kcal/day; p=0.005). Analysis of FSHD Health Index (HI) results yielded scores ranging from 8.0 to 53.4 a.u. **Table 3**). Total FSHD-HI (r=-0.60), mobility and ambulation (r=-0.50), and activity limitation (r=-0.62) trended to be significantly correlated with ALMI (p=0.07). Activity limitation also trended to be significantly correlated with age (r=0.62, p=0.06).

DISCUSSION

This study is the first to confirm the presence of sarcopenic obesity among individuals with FSHD, as reflected by a mean ALMI and % body fat of <7.26 kg/m^2 and >27% (8); furthermore, we are the first to show that the individuals with FSHD exhibit the signs of sarcopenic obesity more often than age- and sex-matched controls. These observations are consistent with previous reports of significant alterations in body composition in the FSHD population, including widespread increases in measures of adiposity and reductions in lean mass (4, 17, 18). It is worthwhile to note that while individuals with FSHD exhibited a % body fat that was significantly higher than controls, estimated measures of adiposity, as reflected by BMI, did not differ between groups. Because only two

women in each group were tested, the lack of differences in body composition between females with FSHD and controls may be due to sample size, and thus bares further investigation.

Sarcopenic obesity is commonly found in other forms of muscular dystrophy, but has yet to be observed in FSHD. In fact, previous research has confirmed the presence of sarcopenic obesity among individuals with Bethlem myopathy, Ullrich congenital muscular dystrophy, rigid spine syndrome, limb girdle MD type 2d, Duchenne MD, and Becker MD (9, 19, 20). Consistent with our findings, Skalsky et al. demonstrated alterations in body composition – including greater fat mass and lower muscle mass—among individuals with FSHD as compared to controls (18), but did not assess ALM, ALMI, and sarcopenic obesity.

Clinical relevance of sarcopenic obesity

Identifying the presence of sarcopenic obesity is of high significance, as it may indicate an increased propensity towards impairments in functional capacity, and a greater risk for morbidity and mortality. According to the Concord Health and Aging Project, sarcopenic obesity is linked to an increased risk of frailty and instrumental activity of daily living disability (IADL), a measure that is characterized by an inability to perform tasks for independent living (21). Similarly, the Osteoarthritis Initiative reported reductions in gait speed, physical function, and self-reported health status, which were associated with a combination of high BMI (22), a frequently used surrogate measure of body fat in community settings, and low knee extensor strength (23). Finally, research by Baumgartner noted that older men (>60 years of age) with sarcopenic obesity were eight times more likely to develop three or more disabilities than age- and sex-matched controls (8). This observation was even more striking among older women with sarcopenic obesity, in which the risk for multiple disabilities was increased by a factor of 11 (8). In addition, the association between impaired physical function and sarcopenic obesity was stronger than an association with either obesity or sarcopenia alone (8), thereby highlighting the cumulative effect of these factors on functionality in an aging population. Together, these observations suggest that the presence of sarcopenic obesity may compound the physical disability that individuals with FSHD already experience (24). Despite the absence of statistical significance, these reports are in line with our own findings, in which a trending relationship between markers of sarcopenic obesity and self-reported impairments in mobility and ambulation or activity limitation were observed. We hypothesize that, given a larger sample size, our study would have further confirmed this trending relationship.

Since individuals with FSHD are reportedly spared from certain types of cardiovascular disease – including cardiomyopathy (25) – it is possible that any reduction in life span in this group may be driven not by the disease itself, but rather by the influence of sarcopenic obesity. In fact, along with impairments in functional capacity, individuals with sarcopenic obesity are reportedly at an increased risk for various comorbidities, including dyslipidemia (26), insulin resistance (27), osteoarthritis (28), and depression (29), among others (30). Furthermore, adults who meet diagnostic criteria for sarcopenic obesity have also been reported to exhibit an increased risk of mortality (hazard ratio: 1.44) as compared to control counterparts (30); an observation that has been made in both healthy and patient populations. It is worthwhile to note that differences in the prevalence of these measures between individuals with FSHD and controls in our study were not observed, thereby suggesting that groups were well matched in terms of underlying health status.

Whether the presentation of sarcopenic obesity is driven by sex is highly equivocal. Disparities in the prevalence of sarcopenic obesity among men and women are related primarily to ethnicity, whereby women may be more, less, or as equally effected as their male counterparts (31). Among NH whites, which formed the majority of our study (85%), rates of sarcopenic obesity are similar between age-matched men and women (31). Conversely, sex-specific differences in FSHD phenotype presentation, in which women appear to be affected to a lesser degree than their male counterparts, have been reported (32, 33). Although neither of the two women reached the diagnostic criteria for sarcopenic obesity, the small sample size in this study precludes any speculation regarding sex differences in sarcopenic obesity in adults with FSHD. In fact, while an elevated mean % body fat of 44.1±1.0% in the female FSHD group did result in the partial fulfillment of objective requirements (% body fat: >38%), a mean ALMI of 6.2±1.0 kg/m^2 exceeded the limitations associated with presentation of the condition (ALMI: <5.45 kg/m^2). Together, these findings suggest that the alterations in body composition may be related to the intrinsic effects of FSHD, and not to sex differences in the presentation of sarcopenic obesity.

Mechanisms contributing to sarcopenic obesity

Though complex in nature, sarcopenic obesity is believed to be driven by a synergistic combination of biologic, hormonal, and behavioral influences. In fact, the atrophy and loss of type II muscle fibers – a phenomenon that is theorized to be predominantly responsible for the presentation of sarcopenia (34)—is reportedly caused by an amalgamation of factors, including neurodegenerative processes within spinal α-motor neurons, dysregulation of anabolic hormone production (insulin, growth, and sex hormones), and inadequate nutritional intake (34).

Furthermore, sarcopenia is believed to be mediated by a deconditioned state (34), and the presence of a significantly reduced physical activity score in the FSHD cohort suggests that deconditioning was likely a participating factor in the manifestation of sarcopenic obesity. It is worthwhile to note that while individuals with FSHD have been reported to exhibit reductions in both type IIa and IIb muscle fibers (35), it is unclear whether this phenomenon is caused by the factors described above, or is purely an intrinsic result of the disease itself.

Alternatively, sarcopenic obesity may be a result of the inherent genetic condition of FSHD. Individuals with FSHD exhibit indirect evidence of expression of the DUX4 protein in muscle biopsies (36), although the levels must be exceptionally low because immunological detection of DUX4 in muscle sections still eludes the field. Interestingly, low non-cytotoxic levels of DUX4 expression in mouse (37, 38) and human (39) myoblasts impairs their differentiation into multinucleated myotubes, thus an inability to properly replace diseased or damaged muscle tissue with new myofibers may lead to a pro-adipogenic state within muscle of FSHD patients.

As with sarcopenia, the development of obesity is multifocal in nature, and may be founded in environmental, genetic, or energy-balance dysregulation origins (40). In fact, along with possessing greater stores of body fat, older adults with sarcopenic obesity exhibit an increased propensity towards fatty infiltration into the muscle (41). This anatomic alteration has also been observed among individuals with FSHD (4), and is theorized to lead to impairments in the contractile properties of both type I and II muscle fibers (42) and losses in muscular power. Together, this evidence suggests that while sarcopenic obesity in the FSHD population may be initiated by genetic factors, a widespread, multifactorial process also likely contributes to this condition.

Limitations

Limitations of this study should be considered when interpreting the data. The small sample size in female participants, likely contributed to an inability for them to meet the diagnostic criteria for sarcopenic obesity, as previous research by Merlini et al. has confirmed the presence of sarcopenic obesity in both male and female dystrophic groups, but not specifically FSHD (9). Furthermore, as we did not control for clinical severity within the FSHD group, it is possible that our female FSHD participants exhibited a lesser-degree of disease than their male counterparts, whereby the presence of anatomic alterations in body composition were not yet manifest, a theory which has been supported by previous research (32, 33). Since our study used a DXA scan and not MRI imaging to assess body composition, we were unable to assess whether differences in % body fat between FSHD and control groups were driven by general increases in adiposity, or by intramuscular fat infiltration, a finding which has been

previously reported (4), and which is believed to be a hallmark characteristic of FSHD. Finally, while all FSHD study members were Caucasian, 3 of 10 control participants (all men) were of differing races, a factor that may have a confounding effect on study outcomes. Though alterations in body composition between races have been widely reported (43), it appears that these differences may be driven by sex, whereby variances are noted primarily among differing female racial groups (44). According to research by Gerace et al., measures of total body fat and fat-free mass are similar between black and white men (45), though whether the same is true between Caucasian and Hispanic or Asian men remains to be elucidated.

CONCLUSIONS

Sarcopenic obesity is a complex medical condition, which manifests as a number of both acute and long-term implications. Identifying individuals that may be at an increased risk for sarcopenic obesity, will lead to preventative rehabilitative strategies to reduce the prevalence of sarcopenic obesity, among individuals of all ages and health statuses. Furthermore, by identifying sarcopenic obesity as a comorbidity of FSHD, we have taken a major step forward in understanding the anatomic and physiologic contributions to impaired health and physical function in this genetic disease. Future research in this area should focus on strategies (i.e. exercise) to address the sarcopenic obesity-driven losses in functionality, and improve quality of life among individuals with neuromuscular impairment. With strategies to prevent sarcopenic obesity in individuals with FSHD, it may be possible to significantly improve their functional ability, quality of life and longevity by impeding their progression of disability.

LIST OF ABBREVIATIONS

ALM—appendicular lean mass

ALMI—appendicular lean mass index

BMI—body mass index

DXA—dual-energy x-ray absorptiometry

FM—fat mass

FSHD—facioscapulohumeral muscular dystrophy

FSHD-HI—facioscapulohumeral muscular dystrophy health index

LM—lean mass

DECLARATIONS

Ethics approval and consent to participate

The study was approved by the University of Minnesota Institutional Review Board, and conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

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Authors' contributions

KV analyzed and interpreted study participant data, and was the primary contributor in writing the manuscript. MM participated in data collection and organization. MK provided editorial oversight, particularly in regards to the genetic contributions of FSHD. MK-R developed the study design, assisted with data collection, provided editorial oversight, and was involved in creating the theoretic framework of the manuscript.

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FIGURE LEGENDS

Figure 1: Appendicular lean mass index (ALMI, kg/m^2) in FSHD and Controls. Individuals with FSHD had lower lean mass as compared to controls.*p<0.001

Figure 2: % Body fat in FSHD and Controls. Individuals with FSHD had a higher % body fat, as compared to controls.*p<0.001

Figure 3: % Lean mass in FSHD and Controls. Individuals with FSHD had a lower % lean mass, as compared to controls.*p<0.001

Figures

Figure 1

Appendicular lean mass index (ALMI, kg/m2) in FSHD and Controls. Individuals with FSHD had lower lean mass as compared to controls.*p<0.001

Figure 2

% Body fat in FSHD and Controls. Individuals with FSHD had a higher % body fat, as compared to controls.*p<0.001

Figure 3

% Lean mass in FSHD and Controls. Individuals with FSHD had a lower % lean mass, as compared to controls.*p<0.001