Prevalence and Characteristics of Sarcopenic Obesity in Adults with Class II/III Obesity

by

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Abstract

Adults with class II/III obesity (BMI ≥35 kg/m^2) are at increased health risk, and may also present with lower lean mass in relation to excess adiposity, a condition termed sarcopenic obesity. A variety of body composition indices and cutpoints have been used to define this condition, mostly in older adults (>65 years), leading to conflicting prevalence and risk prediction. Sarcopenia is associated with increased morbidity and mortality in the elderly, but the clinical implications in adults with class II/III obesity are unknown. The objective of this thesis was two-fold. First, to explore the prevalence of sarcopenia in a sample of adults with class II/III obesity using different diagnostic criteria, and second, to describe the clinical characteristics of participants with sarcopenic obesity, compared to their counterparts (non-sarcopenic obese).

Eighteen definitions for sarcopenic obesity were initially identified from a literature review of studies using dual-energy X-ray absorptiometry (DXA) to assess lean mass, and applied to a sample of patients from an obesity specialty clinic. In this cross-sectional analysis, baseline data on demographic, anthropometric, biochemical, comorbidity, and activity variables were collected. Body composition was assessed by DXA. Self-reported difficulties with activities of daily living (ADL) were evaluated from 11 items on a questionnaire. A total of 120 participants (86 % female) aged 46 ± 11 years were included. Lean mass was extremely variable in individuals, even with similar body sizes, and across the age spectrum. The prevalence of sarcopenic obesity ranged from 0 – 84.5 % in females and 0 – 100 % in males, depending upon the diagnostic criteria applied, with higher prevalence among definitions accounting for measures of body size or fat mass.

In order to select a cohort-specific definition of sarcopenic obesity for this young-to-middle aged cohort, we explored five criteria, which were tested in relation to self-reported ADL using

receiver operating characteristic analysis. The appendicular skeletal mass by weight x 100 (%) definition was the best correlate for both sexes [females (r= -0.232, p=.024); males (r_s =-0.510, p=.037)], and therefore chosen as the method to define sarcopenia in this cohort. Sex-specific cutpoints of appendicular skeletal mass/weight x 100 (%) were <19.35 % for females and < 24.33 % for males, which resulted in a prevalence of sarcopenic obesity of 25% (females 22.3 %, males 41.2 %). Sarcopenic obesity was significantly associated with older age (50.7 ± 12.7 vs. 45.7 ± 10.3 years for non-sarcopenic, p=.033), higher waist circumference (130.2 ± 21.1 vs. 121.1 ± 11.7 cm for non-sarcopenic, p=.004), and higher triglycerides (2.06 ± 1.00 vs. 1.62 ± 0.73 mmol/L, p=.040). Only two participants had hypoalbuminemia and both were identified with sarcopenia. The use of anti-hypertensive medications was greater among individuals with sarcopenic obesity, compared to their counterparts (50 vs. 28.9%, respectively, p=0.035). Individuals with sarcopenic obesity were less likely to meet physical activity guidelines (3.3 vs. 25.6 % of participants without sarcopenia, p=0.007). In participants who met guidelines, 95.8 % were identified as non-sarcopenic. Nearly three-quarters of participants with sarcopenic obesity reported difficulty with ≥3 ADL items compared to less than half (44 %) of the non-sarcopenic obese group. (p=0.08). Individuals with sarcopenic obesity were 5.4 times more likely to report ≥ 3 items for difficulty with ADL, independent of age, sex and multimorbidity.

In summary, sarcopenic obesity was present in a sample of young-to-middle aged adults with class II/III obesity and associated with poorer clinical characteristics, when compared the non-sarcopenic obese group. Investigating the prevalence and clinical characteristics of sarcopenic obesity is an important step towards recognition of this condition as a significant health problem, and for the establishment of adequate prevention and treatment strategies.

Preface

This thesis is an original work by Carlene A. Johnson Stoklossa. The research project, of which this thesis is a part, received ethics approval from the University of Alberta Research Ethics Board, "Prevalence and Characteristics of Sarcopenic Obesity in a Bariatric Population: a Chart Review Study", No.00008163, 20 Aug 2009.

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Etched in glass in the lobby of the Li Ka Shing building, in the stairwell to the Human Nutrition Research Unit, is an excerpt of one of my favourite poems by Robert Frost:

Two roads diverged in a wood, and I—
I took the one less traveled by,
and that has made all the difference.

Every day I would read this poem. Returning to school after 16 years was certainly a road less travelled. Along this path, many people have provided me with guidance and mentorship, and without their generosity of time and expertise, I would not have developed professionally as a registered dietitian and been able to pursue this research leading to a graduate degree.

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List of Abbreviations

%FM	percentage of fat mass
%FFM	percentage of fat-free mass
ADL	activities of daily living
ASM	appendicular skeletal mass
ASMI	appendicular skeletal mass index
AUC	area under the curve
BIA	bioelectrical impedance analysis
BMI	body mass index
BP	blood pressure
CI	confidence interval
cm	centimeter
cm^2	centimeters squared
CMOP	Canadian model of occupational performance
CPAG	Canadian physical activity guidelines for adults
CRP	c-reactive protein
DM	diabetes mellitus, also known as type 2 diabetes
DXA	dual-energy X-ray absorptiometry
e-GFR	estimated glomular filtration rate
EABSC	Edmonton Adult Bariatric Specialty Clinic

ECW	extracellular water
EOSS	Edmonton Obesity Staging System
ESPEN	European Society for Parenteral and Enteral Nutrition
F	female
FBG	fasting blood glucose
FFM	fat-free mass
FFMI	fat-free mass index
FM	fat mass
FMI	fat mass index
g	grams
HA-LM	high adiposity and low muscle mass
HbA1c	glycated haemoglobin
HDL	high density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
ICD-10	international classification of diseases, 10^{th} revision, clinical modification
ICW	intracellular water
IFG	impaired fasting glucose
k	kappa
kcal	kilocalorie
kg	kilogram
KHANES	Korean health and nutrition examination survey;

kHz	kilohertz
L	left
LDL	low density lipoprotein
LST	lean soft tissue
M	male
m^2	meters squared
mmHg	millimeters of mercury
NCEP-ATP	national cholesterol education program- adult treatment panel
NHANES	national health and nutrition examination survey
R	right
ROC	receiver operating curve
SD	standard deviation
SPSS	statistical package for the social sciences
TBW	total body water
TChol	total cholesterol
TG	triglycerides
vs.	versus
WC	waist circumference
WHO	World Health Organization

Chapter 1: Introduction

1.1 Thesis organization

This thesis was prepared as a publication-format thesis according to the requirements provided by the Faculty of Graduate Studies and Research, University of Alberta. After the introduction, the literature review is presented in two chapters: Chapter 2 provides a review of the common methods to assess body composition of adults with class II/III obesity; Chapter 3 provides a review of the diagnoses and clinical outcomes associated with sarcopenic obesity. A preface precedes Chapters 2, 4 and 5 with a brief description for each publication contained within the chapter. A version of Chapter 2 was published in *Current Obesity Reports*. A version of Chapter 4 was submitted to *Journal of Nutrition and Metabolism.* A version of Chapter 5 was submitted to *American Journal of Clinical Nutrition.*

1.2 Background/rationale

Sarcopenic obesity is an abnormal body composition phenotype characterized by the concurrent presence of low lean mass and high fat mass. Research on sarcopenic obesity has focused on the elderly population, with little understanding of the prevalence and clinical consequences of this condition among young-to-middle aged adults. However, recent evidence suggests this abnormal body composition phenotype is actually prevalent across the age and body mass index (BMI) spectrum (1).

Individuals with obesity may be at greater risk for sarcopenia. In the context of obesity, weight gain leads to an increase in fat mass that is greater in proportion to the smaller increase in lean mass. These individuals are also at risk for repeated weight loss-gain cycles (2-5) which can lead to similar unfavourable body composition changes with weight regain mostly attributed to increases in fat mass with lean mass remaining lower than baseline (i.e., prior to weight loss) (6). Likewise, obesity treatment is also associated with loss of lean mass and may result in body composition changes where a non-sarcopenic person can become sarcopenic (7). Obesity (BMI $\geq$ 30 kg/m^2) affects 24.5 % of Canadian adults (18 – 64 years) and 29.2 % of those age 65 years and older (8). With the normal aging process, fat mass tends to increase and lean tissue tends to decrease, potentially giving rise to the sarcopenic obesity phenotype (5).

The identification of sarcopenic obesity is a challenge, limited by the availability of accurate body composition techniques and the diversity of proposed diagnostic criteria. A variety of body composition indices and cutoffs have been used to define sarcopenia and obesity, leading to conflicting findings on the prevalence and risk prediction of this combined condition (7, 10). Importantly, the prevalence of sarcopenic obesity in those with more pronounced cases of obesity, such as class II/III obesity (BMI $\geq$35 kg/m^2) is not well understood, as the equipment

capacity is often inadequate to accommodate people with larger body sizes (such as weight and width). This is a significant problem because there is a growing prevalence of class III obesity (9).

Increasing evidence highlights the negative impact of sarcopenic obesity to health. The consequences of excess adiposity with sarcopenia are combined and as such, sarcopenic obesity has been independently associated with worse morbidity and disability than either sarcopenia or obesity alone (1). Other examples of health outcomes associated with this condition include poorer physical function and disability related to activities of daily living (11-14), risk of falls (15), multimorbidity (16), and higher risk of cardiometabolic disease (i.e., inflammation, insulin resistance/abnormal glycemic control, metabolic syndrome and dyslipidemia) (17-19).

Sarcopenic obesity has been primarily studied in the elderly, with limited understanding of its prevalence and significance in younger cohorts. Therefore, there is a lack of diagnostic criteria, and risk assessment for such cohorts, particularly among those with a BMI $\geq$35 kg/m^2. Investigating the prevalence and clinical characteristics of sarcopenic obesity in adults with class II/III obesity is an important step towards recognition of this condition as a significant health problem, and for the establishment of adequate preventive and treatment strategies.

1.3 Study objectives

1. To explore the prevalence of sarcopenia in a sample of adults with class II/III obesity (BMI ≥35 kg/m^2) using different diagnostic criteria (Chapter 4).
2. To compare clinical characteristics between participants with sarcopenic obesity to those participants with obesity but not sarcopenia (Chapter 5).

1.4 Hypotheses

Hypothesis 1:

In a sample of adults with class II/III obesity, sarcopenic obesity will be present, although highly variable (5 – 95 %) depending on the definition used.

Hypothesis 2:

In a sample of adults with class II/III obesity, participants with sarcopenic obesity will present with poorer clinical characteristics compared to their non-sarcopenic obese counterparts, including:

a) higher prevalence of abnormal biochemical variables including:
    i) elevated marker of systemic inflammation, as assessed by c-reactive protein (CRP) levels
    ii) low 25-OH vitamin D_3 levels
    iii) elevated lipid values for total cholesterol, low-density lipoprotein, and triglycerides; lower levels of high-density lipoprotein
b) higher prevalence of comorbid conditions including:
    i) the individual conditions of hypertension, dyslipidemia, metabolic syndrome, diabetes/impaired fasting glucose, chronic kidney disease, mental health, sleep apnea or osteoarthritis
    ii) a composite score of mulitmorbidity, as assessed by 3 or more comorbid conditions
    iii) higher prevalence of the higher stage scores (2 – 4) for comorbidity and function, as assessed by the Edmonton Obesity Staging System

c) higher prevalence of self-reported difficulties with activities of daily living, as assessed by an occupational therapy referral screening questionnaire.

1.5 Research questions

In a sample of adults with class II/III obesity:

1) How variable is the prevalence of sarcopenic obesity using different definitions? (Chapter 4)
2) Which definitions (body composition variable and cutpoint) can identify a greater number of adults with class II/III obesity with sarcopenic obesity? (Chapter 4)
3) Which sarcopenic obesity definition (body composition variable and cutpoint) can best discriminate participants with sarcopenic obesity as having more items of self-reported difficulty with activities of daily living (as a choice of a clinically relevant outcome)? (Chapter 5)
4) What are the clinical characteristics of participants with sarcopenic obesity compared to their non-sarcopenic obese counterparts? (Chapter 5)

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Chapter 2: Practical considerations for body composition assessment of adults with class II/III obesity using bioelectrical impedance analysis or dual-energy X-ray absorptiometry

Preface

Clinicians and researchers are increasingly interested in the assessment of body composition as part of the obesity treatment plan to help inform treatment decisions and optimize patient outcomes. Although alternative methods and tools are available, the two most commonly used tools for body composition analysis in clinical and research settings are BIA and DXA, respectively. The purpose of this review was to explore the practical considerations for body composition assessment in adults with class II/III obesity.

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2.1 Introduction

Obesity defined as a body mass index (BMI) ≥30 kg/m^2 affects one in three adults in the United States of America (USA) (1) and Canada (2). There are three classes of obesity: class I (BMI 30 – 34.9 kg/m^2), class II (BMI 35 – 39.9 kg/m^2) and class III (BMI ≥40 kg/m^2) (3). Class III obesity affects 2.5 % of Canadian and 6.4 % of American adults, impacting more women (3 % Canada, 8.3 % USA) than men (2 % Canada, 4.4 % USA), and is associated with the highest level of health risk (1, 2).

BMI is commonly used to identify those at increased health risk and as referral criteria for obesity treatment, including bariatric surgery (e.g., BMI ≥35 kg/m^2) (4). Although quick and easy to determine, BMI is a proxy measure for adiposity; it cannot estimate or quantify fat mass nor determine the presence of conditions such as sarcopenia (lower muscle mass and function). Sarcopenia is most commonly associated with older adults (5), but it can occur across all age and BMI categories (6) and in healthy middle-aged adults (7). Body composition analysis is needed to quantify fat mass (FM) and fat-free mass (FFM), including the components of FFM, specifically bone, lean soft tissue (LST) and total body water (TBW). Although there is great emphasis on FM in obesity, the amount of FFM is essential to health. A desirable outcome of obesity treatment is to not just reduce total body weight but to achieve a reduction in FM while preserving FFM. Lower FFM combined with higher FM, known as sarcopenic obesity, is linked with increased morbidity and mortality (8).

Validated methods and tools for the assessment of body composition have been developed to objectively quantify FM and FFM. The two most commonly used tools for body composition analysis in clinical and research settings are bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA), respectively. Clinicians and researchers are increasingly

interested in the assessment of body composition as part of the obesity treatment plan to help inform treatment decisions and optimize patient outcomes. To provide some background on these methods in the context of obesity, a brief overview of BIA and DXA is included. Interested readers may want to review the following tutorials: a two-part series on BIA published by Kyle et al. (9, 10), LST imaging including BIA and DXA by Prado & Heymsfield (11), and body composition tools for assessment of adult malnutrition by Earthman (12).

2.2 Bioelectrical impedance analysis

BIA is commonly used in a clinical setting because the equipment is small, portable, affordable, and relatively easy to use requiring minimal training. BIA utilizes a mild electrical current (single or multifrequency waves) to measure differences in resistance and reactance between tissue types based upon water and electrolyte content. Population-specific regression equations are used to estimate FM and FFM, usually based on the relation between TBW and FFM. If normal-weight regression equations are used for participants with obesity, measurement errors from abnormal tissue density and hydration can result.

Foundational to bioelectrical impedance analysis technology, two important assumptions are made: 1) the body is a consistent cylinder (9, 10) and 2) tissue hydration status is constant (73.2 %) (13) and the ratio of extracellular water (ECW) to intracellular water (ICW) is a consistent proportion (1:3). Obesity challenges both of these assumptions. With obesity, there can be variance in FM distribution (e.g., central vs. peripheral, android vs. gynoid (14)), and fluid distribution (e.g., edema, lymphedema) or altered body shape (e.g., shortened limbs or amputations (10), resulting in body segments not shaped as a consistent cylinder. For the second assumption, tissue hydration status is not a constant across BMI categories. Obesity is associated with a state of general “overhydration,” with excess TBW and an increased ratio of ECW relative

to ICW. The hydration status of FFM is elevated; one study measured 75.6 % using isotope dilution (15). Elevated TBW and ECW will result in errors of overestimation of FFM and thereby underestimation of FM, with lower accuracy at higher levels of obesity (14, 16).

Another challenge with BIA and obesity is the fact that single-frequency (50 kHz) waves cannot fully penetrate the cell membrane. Only some of the ICW is included in the TBW values, resulting in an overestimation of TBW and FFM and underestimation of FM (17). Although multiple-frequency waves can improve tissue penetration, the altered ratio of ECW/ICW and increased resistance of ICW still result in overestimation of FFM in participants with obesity (17, 16). A summary of the measurement errors using BIA in participants with obesity is presented in **Table 2.1**. In the 2004 European Society for Parenteral and Enteral Nutrition (ESPEN) Guidelines, BIA assessment was determined to have questionable validity for FFM and FM when BMI >34 kg/m^2 (10).

2.3 Dual-energy X-ray absorptiometry (DXA)

DXA utilizes X-rays (photons with two different energy levels) to measure the attenuation (i.e., energy absorbed) by each tissue type. FM and FFM (which includes separate measures for bone and LST) are measured for the whole body or segments of interest such as appendicular skeletal muscle mass (ASM= sum of the LST from the limbs, a surrogate measurement of total muscle mass). DXA provides an accurate and safe assessment of body composition, with minimal radiation exposure, and provides measurement of more components than BIA. DXA is commonly used in research or clinical diagnostic settings (e.g., bone density), as it requires trained technicians, a large dedicated room space and capital expenditure. The precision and reliability of DXA lead it to be the reference method for body composition analysis (11).

Although BIA and DXA have been extensively used in "healthy" populations (i.e., normal BMI 18.5 – 24.9 kg/m^2) and older adults (e.g., for bone density studies), these tools are less commonly used in adults with class II/III obesity. One of the benefits of DXA over BIA is the ability to assess bone density, which is now recommended for patients after bariatric surgery (4). Measurements of body composition in this cohort can enhance assessment and risk stratification of the complex and diverse chronic disease of obesity, including identification of sarcopenic obesity (i.e., low muscle mass and high adiposity) and osteosarcopenic obesity (6, 18, 7, 19). Understanding the barriers to body composition assessment can support patient care management with evidence-based practice tools and identify opportunities for future research.

2.4 Literature search methodology

The purposes of this review were to identify recent studies assessing body composition in adults (18 – 64 years) with class II /III obesity (BMI ≥35 kg/m^2) and explore practical considerations for use of the two most commonly used body composition methods, BIA and DXA. A literature search was conducted using Medline, Scopus and Web of Science databases for studies published from 01 October 2005 to 31 October 2015 that measured body composition with BIA and/or DXA of adults (18 – 64 years) with a BMI ≥35 kg/m^2. Studies including children (17 years or less), older adults (65 years or more), and participants with a BMI <35 kg/m^2 or cancer were excluded.

Twelve studies published met inclusion criteria; nine studies used a single method, either BIA (five studies) (20-24) or DXA (four studies) (25-28), while three of the 12 studies compared BIA to DXA (29-31). Of the eight BIA studies, five utilized a single frequency wave (50 kHz) (29, 20-23) and three utilized multifrequency waves (30, 24, 31). Of the seven DXA studies, five used the standard DXA technology (29-31, 26, 28) and two studies used newer iDXA technology

(25, 27). In total, there were 920 participants (77.7 % female) and six of the 12 studies included post-bariatric surgery participants (n=500, 69.2 % Roux-en-Y gastric bypass).

2.5 Defining obesity: comparing body mass index to percentage of fat mass

Obesity can be defined by the percentage of fat mass (%FM) based upon body composition analysis. There are several published cutpoints for %FM that are sex-specific (32). Frankenfield et al. (21) used BIA (n=141, BMI 15.9 – 93.4 kg/m^2) to explore the accuracy and specificity of BMI to identify participants that exceed the %FM cutpoints. All participants with obesity (approximately 40 % of the sample) exceeded the %FM cutpoints (>25 % for males and >30 % for females), showing BMI ≥30 kg/m^2 had a high sensitivity and accuracy to identify excess adiposity. For participants with a BMI <30 kg/m^2, 46 % of females and 30 % of males exceeded %FM cut points. The authors noted alterations in FM and FFM were identified across all BMI categories, supporting the notion that BMI alone can misclassify participants at increased health risk due to unfavourable body composition (21).

2.6 Barriers to assessment of adults with class II/III obesity

Methodological and equipment-related limitations for the assessment of adults with class II/III obesity were identified. These barriers to assessment of body composition in this clinical cohort were clustered into five key areas: differences in equipment and technology, equipment weight capacity, participant positioning, total body water, and tissue penetration.

Differences in equipment and technology

In the selected studies, five countries (Brazil, Canada, France, Italy, USA) were represented. Eight different BIA models and four different DXA models from two manufacturers (Hologic, GE Healthcare) were used. The software versions were not often reported, which is important as

software upgrades occur more often than hardware. The difference in equipment is inevitable, considering the number of countries, different manufacturers, product advancements, different times of procurement, and publication. It is important to keep in mind there are differences in technique, measurement, and study samples, impacting the outcome data and comparisons of studies (12).

Equipment weight capacity

Both BIA and DXA require measured total body weight to determine body composition. A weigh scale is often integrated into the equipment, with weight capacity limits set in place by the manufacturer. A summary of weight capacity limits for different full-body DXA models is found in **Table 2.2**. A separate or "stand-alone" scale may also be used to measure body weight. All reviewed studies reported measured weights. Only four of the eight BIA studies indicated the use of a stand-alone weigh scale, and no BIA studies reported the scale weight capacity. Compared to the DXA studies, participants with the highest weights were included in the BIA studies (maximum 214.0 kg) (20). Weight and BMI were used as exclusion criteria from DXA studies due to equipment weight capacity limits. Five of the seven DXA studies reported weight capacities from 120 to 160 kg (29, 30, 26) with the recently commercialized iDXA limits of 182 kg (27) up to 204 kg (25). Two of the seven DXA studies did not report equipment weight capacity, and instead, used BMI > 40 kg/m^2 as a surrogate marker for exclusion (28, 31).

Equipment weight capacity limits the available data on participants with class II/III obesity and may prohibit validation of body composition tools in this cohort. Due to individual variance in height and weight, use of BMI alone may unnecessarily exclude some participants from DXA. Assessment and reporting participant anthropometrics for each limiting factor may improve inclusion criteria and access to those excluded from DXA measurements based upon BMI alone.

In addition, reporting exclusion criteria based upon anthropometrics could help clinicians determine if body composition analysis is feasible for their patient.

Participant positioning

For segmental BIA models, the electrodes are contact points integrated into the standing scale and handgrips. Participants are required to stand with legs separated (45°) and hold the handgrips with arms extended (30°) to ensure limb separation while maintaining adequate skin contact with the electrodes (10). Utilization of the two-point method to measure impedance of the lower (i.e., foot-to-foot) or upper body (i.e., hand-to-hand) segments can produce estimation errors for whole body composition. Four- to eight-point electrode placements are required for whole-body BIA assessment. With this method, individual electrodes are placed directly upon the skin, permitting measurement in either a standing or supine position.

Any skin contact, either between the legs or the arms and torso, results in measurement errors (up to 18%) (33). For some participants with obesity, it may not be possible to achieve leg separation while maintaining foot contact with the electrodes on a narrow standing platform. The reviewed BIA studies provided limited methodology or descriptions for participant positioning, with one exception. Frankenfield et al. provided details to achieve limb separation, including placement of a dry towel to avoid skin-to-skin contact (21). No study reported on the participants' ability to stand or sustain the required body position for the BIA test.

For DXA, participants are required to lie still in a supine position while the scan arm moves across the participant for the length of the instrument bed. The participant's body supine length (height), width, and depth must fit within the DXA scan area limits. Dimension limits of different full body DXA models are summarized in **Table 2.2**. In the reviewed DXA studies,

scan arm height and supine body depth were not reported. Just one study measured body depth, with supine anterior/posterior thickness >25 cm used as exclusion criteria (31). Although waist circumference was reported in one study (29), this measure is taken from a standing position; it could not be substituted for *supine* width or depth. Although the supine length dimension of DXA models (198 cm) is sufficient to accommodate most North American adults (95^{th} percentile, age 20 years and older for females=173.7 cm, males=188.2 cm (34)), some taller participants may still be excluded. Validated techniques for scanning taller participants (e.g., bent knees) within normal BMI ranges could be explored for use with class II/III participants (35).

To assess wider participants, "reflection positioning" has been used (36). The participant is positioned off-center (typically toward the right side of the scan bed) to include the torso and right arm, with the lower portion of the left arm positioned outside of the scan area. Based upon the bilateral symmetry of the human body, the values of the right arm are used to "reflect" the left arm values. This alternative method was validated by Tataranni et al. (n=183, BMI 17.7 – 52.8 kg/m^2) with low predictive errors for %FM [r^2=.90 (standard error of the estimate (SEE)=4.1%)], FFM [r^2=.89 (SEE=3.72 kg)] and FM [r^2=.95 (SEE=3.57 kg)] (37). Similar values were recorded for all three measurements between right and left sides. In the reviewed studies, only one discussed this method. Carver et al. examined 65 participants with class III obesity (BMI 49 ± 6 kg/m^2); 51 % required reflection positioning for whole body composition analysis despite wider scan bed limits with iDXA (25).

Rothney et al. (27) used an alternative method for assessment of wider participants. This study explored measuring either the left or right half of the body (i.e., half-body scans also called hemi-scans) as a proxy for a full body measurement by iDXA. The half-body scans of 52

participants (BMI 30.4 – 41.0 kg/m^2) were validated against their whole-body scans for within-participant (>97 %) and within-group (>99.9 %) variances for total FM, %FM, and LST (all r^2 < 0.033). A small variance with increased bone mass consistent with handedness (+30 g, 1 %) was measured (27). In this study, half-body scans provided a valid method using DXA to assess participants that exceed supine width limits. The maximum BMI in this study was 41 kg/m^2, only representing the lowest range of class III obesity. Both studies utilized iDXA, with larger scan bed area and weight capacity, permitting imaging of participants with wider, thicker, and heavier body dimensions (25, 27). Further validation is required of the half-body scan method with class III participants.

Total body water

Two of the eight BIA studies reviewed reported %TBW. De Freitas et al. compared single-frequency (50 kHz) BIA (Quantum II, RLJ Systems) for 36 patients before and 6 months after bariatric surgery. Before surgery, TBW was 36.1 ± 4.8 % (29 – 48 %) with an increase to 45.0 ± 5.8 % (36 – 58 %) at 6 months after surgery (20). Nicoletti et al. (22) used single-frequency (50 kHz) BIA (101-Q, RLJ Systems) for 43 women before and annually for 4 years after bariatric surgery. The %TBW was 33.1 ± 3.8 % before surgery, with an increase to 48.5 ± 6.7 % at 1 year and 46.6 ± 6.7 % at year 4. Both studies showed a reduced hydration status both before and after bariatric surgery, with trends for %TBW to increase after bariatric surgery. Studies on body composition of adults with class II/III obesity without bariatric surgery are needed.

Tissue penetration

For DXA, the X-ray beams must be able to penetrate (attenuate) the body in order to differentiate the tissues measured. Tissue depth is important; attenuation errors occur when tissue depths exceed 25 cm, resulting in an underestimation of FM. To account for this, some DXA models

can increase scan time (i.e., use "slow" or "thick" mode) to improve attenuation and scan accuracy. No study reviewed specifically discussed wave frequency or attenuation in context of their results. For one iDXA study, longer scan modes (13 vs. 7 minutes) were reported to enhance tissue penetration and reduce measurement errors although the types of errors were not specified (25). Due to increased DXA scan time, participants have a small but increased radiation exposure and may become too uncomfortable to sustain a still, supine position. This may present a barrier for assessment in some participants.

2.7 Comparing bioelectrical impedance analysis to dual-energy X-ray absorptiometry

Three of the reviewed studies completed cross-sectional validations of BIA to DXA measurements (29-31). Bedogni et al. compared measures of FM using single-frequency (50 Hz) BIA to DXA (GE Lunar Prodigy) and utilized an obese-specific regression equation (validated by Jimenez et al. using iDXA n=159, 79 % female) to determine FM from impedance values in women (n= 57, BMI 37.3 – 55.2 kg/m^2) (29).

Comparing the two methods, the measurement of %FM by BIA was determined to be unreliable, based upon Bland-Altman analysis (levels of agreement ranging from -4.9% to 8.2%). Therefore investigators concluded that BIA, even with an obesity-specific equation, was not interchangeable with DXA. The use of a different BIA device from the one used for Jimenez et al. validated equation can justify the lack of accuracy found in the Bedogni et al study.

The second study by Faria et al. compared FM measurements of 73 participants (89% female, BMI 40.17 ± 4.08 kg/m^2) using a multifrequency BIA (InBody 720) with measurements from DXA. Both methods to measure FM produced an "almost perfect correlation"; however BIA significantly underestimated FM (-2.05 kg or -1.16%, $p<.0001$) and overestimated FFM (1.28 kg

(p=0.0007), or 1.61% (p<0.0001)) compared to DXA. These results, in contrast to the authors' conclusions, suggest that BIA was not accurate enough for research or application to clinical practice in an obese cohort or for individual assessment (30).

In the third study, Shafer et al. utilized an eight-point, segmental, multifrequency BIA (InBody 320) to compare %FM measures to those obtained from DXA (Hologic QDR Delphi-W) in 132 participants (n= 42 with BMI 30 – 39 kg/m^2, class III obesity excluded). In participants with class I/II obesity, BIA overestimated %FM (3.40 ± 0.39 %) with increased error as %FM increased (r=0.424, p<0.0001) with limits of agreement ranging from -5.7% to 7.2% FM. This study concluded BIA was not a reliable tool to measure body composition in an adult cohort with class I/II obesity (31).

In all three studies, BIA results were not consistent with DXA with the rate of error increasing with higher adiposity with the maximum BMI studied being 55.2 kg/m^2. Although the Bland-Altman analysis reported for each study demonstrated agreement between BIA and DXA for some individuals, there were overall high variability and estimation bias, making individual measurements unreliable (31, 30, 29). Each study excluded participants due to equipment weight limitations [120 kg (30), 130 kg (29), BMI <40 kg/m^2 (31)], restricting the data available from participants with class III obesity.

2.8 Additional considerations

A few considerations are highlighted to inform future research and clinical practice.

Males are underrepresented. Male participants often represent less than 20 % in both clinical obesity practice and research obesity literature. Compared to females, males have more FFM and potentially are at increased risk of greater FFM loss during weight loss (38). Further research is

required not only for body composition of men with obesity but also for the possible barriers leading to underrepresentation in treatment and research.

Data on participants with higher body mass index in class III obesity is limited or lacking. Many studies either collate results for all class III participants or exclude participants with BMI >40 kg/m^2 or who exceed equipment limits. Our understanding of body composition at higher levels of obesity as a result is very limited. Unlike other BMI categories with a narrow five-point range, class III obesity has the widest range, with no upper limit above 40 kg/m^2. Stratifying results within class III could enhance the understanding of body composition within class III and at extremes of BMI.

The % fat-free mass can increase, despite loss of fat-free mass (kg). Reporting of body composition results can be misleading; for the same participant or group, FFM could be reported as both a loss and a gain. For example, Ciangura et al. examined the body composition of patients before and after bariatric surgery. In the first 3 months post-surgery, participants lost LST mass (a component of FFM) at a rate of -2.3 ± 1.2 kg/month; however when reported as a percentage relative to FM, %FFM increased by 2.8 % (26). This study demonstrated that post-surgical participants lost FFM at a specific rate and the time frame. However, it could be misinterpreted that participants *increased* lean tissue after surgery because %FFM increased. Participants who are actually losing FFM mass may not be identified as at risk, impacting assessment and treatment decisions. The reported preservation or increase in %FFM after weight loss is confounded by a possible elevation in TBW, contributing to a *relative* change compared to %FM (21). The rate of error was proportional to body weight, increasing at higher body weights. When examining the outcome data for body composition during weight loss, the

absolute changes in FFM independent of FM and BMI (e.g., appendicular skeletal muscle by height [m^2], from DXA) may be a better marker of FFM changes (8).

2.9 Conclusion

Although extensive research and reviews on body composition are reported in the literature, few studies using BIA and/or DXA including participants with class II/III obesity were identified. In general, both BIA and DXA can provide relatively safe, quick, and non-invasive measures of body composition.

It is easy to understand the interest of clinicians in BIA; it is inexpensive, portable, low risk, and able to accommodate people with larger body dimensions and requires minimal training or expertise. Anthropometric measures and BMI are important but have limited value for body composition. BIA can estimate adiposity better than BMI when BMI <35 kg/m^2, but there are methodological problems for participants with class II/III obesity limiting the reliability for body composition.

DXA can provide accurate and reliable measures of body composition, yet equipment-related barriers have limited assessment of heavier, taller, and wider participants. As demonstrated with iDXA and half-body scans, advancements with equipment, technology, and methodology permit assessment of more people with class II/III obesity. Accurate and reliable assessments of body composition in this cohort are important to help determine health risk in more adults with class III obesity and contribute to understanding of the longer-term effects of this disease and treatment. Further studies are needed to measure body composition with DXA at initiation and at several points during interventions to support individualized obesity treatment, risk reduction, and outcome optimization. Longitudinal studies of body composition across interventions and

phases of treatment (loss, maintenance, gain/regain) should also be considered, to optimize patient care.

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2.11 Tables

Table 2.1. Summary of errors associated with assessing body composition using bioelectrical impedance analysis (BIA) in participants with class II/III obesity.

Error type	Fat mass	Fat-free mass
Increased TBW (>73.2 %)	Underestimated	Overestimated
Increased ECW	Underestimated	Overestimated
Use of normal-weight regression prediction formulas	Underestimated	Overestimated
Use of two vs. eight electrodes	Underestimated	Overestimated
Use of single (50 kHz) vs. multifrequency waves	Underestimated	Overestimated

TBW: total body water; ECW: extracellular water; kHz: kilohertz

Table 2.2. Scan area dimensions and participant weight capacity of full body dual-energy X-ray absorptiometers (DXA) from two manufacturers.

Scan area	Hologic, Inc.[a] (39-41)		GE Healthcare[a] (42) DPX, Prodigy		Lunar iDXA
Length, cm	All models	195	DPX	195	197.7
			Prodigy	197.7	
Width, cm	All models	65		60	66
Weight capacity, kg	Delphi, QDR, Explorer	136	DPX	136	204
	Discovery A,W:		Prodigy	160	
	Prior to March 2005	159			
	March 2005 to April 2007	182			
	After April 2007	204			
	Horizon	204			

[a]References 39-42. cm: centimeters; DXA: dual energy X-ray absorptiometry; kg: kilograms.

Chapter 3: A review of the literature on sarcopenic obesity

Preface

The human body is a complex system. Our understanding of this system continues to evolve and change as we make advancements with research and technology. As discussed in Chapter 2, with dual-energy X-ray absorptiometry (DXA), the assessment of body composition enables us to identify abnormal body composition phenotypes, such as sarcopenic obesity. The focus of this chapter is to review the recent literature on the prevalence and clinical significance of sarcopenic obesity, defined from DXA-derived body composition variables.

3.1 Introduction

The term *sarcopenic obesity* is a composite of two separate and distinct conditions, sarcopenia and obesity. There are several definitions used for both sarcopenia and obesity, leading to a variety of permutations to define this condition. To understand sarcopenic obesity, it is important to explore its different definitions, comprised of both variables and cutpoints. As discussed in Chapter 2, body composition assessment by DXA is the preferred method for adults with class II/III obesity (body mass index, BMI ≥35 kg/m^2), therefore only definitions using body composition variables determined by DXA to assess lean soft tissue (LST) will be reviewed.

Sarcopenia is a term derived from the Greek for "*sarx-"* meaning "flesh" and "*-penia*" meaning "poverty" (1). The term describes a condition of loss or relatively low muscle mass, which is the major component of LST. The condition is most often associated with aging, where reductions in muscle mass tend to present starting in the 5th decade of life (2). Sarcopenia is more common in older adults and linked to frailty (3). In a recent systematic review by the International Sarcopenia Initiative, the prevalence of sarcopenia (obesity not reported) was identified not only in acute care (10 %) and long-term care settings (14 – 33 %), but in community-dwelling adults 50 years and older (1 – 29 %) (4).

3.2 Body composition terminology

Multiple terms are used in the body composition literature for the same variable, creating confusion and challenges to compare studies. For the purposes of this review, consistent terminology was used that may vary from the terminology used by the original authors but still accurately represent the body composition variables measured. Fat mass (FM) was used instead of body fat or adipose tissue. The term LST was used for studies measuring the non-bone, non-fat body compartment in general from the whole body (i.e. arms, legs, trunk and head). The term

appendicular skeletal mass (ASM) was used for studies measuring LST from the arms and legs (5, 6). To improve consistency and clarity, different phenotype groups were described using the following terms: sarcopenic, non-sarcopenic, obese, non-obese. To describe the body composition phenotype group "non-sarcopenic and non-obese", the more concise term "normal" (in relation to a normal phenotype) was used instead of "healthy" or "ideal".

3.3 Sarcopenia and older adults

It is important to understand that the foundation for the recent research on sarcopenic obesity started with studies of sarcopenia in older adults. Over the years, several working groups have looked into defining sarcopenia in aging (>65 years). In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed a consensus recommendation in which sarcopenia was defined as a measure of low muscle mass, combined with an indication of low function, be it strength or performance (7). No individual definition was proposed, however body composition assessment by DXA was recommended. In 2011, an international consensus paper recommended sarcopenia to be defined as "reduced muscle mass with limited mobility", with body composition calculated as ASM index (ASMI) with cutpoints two standard deviations (SD) below the mean of a healthy young (20 – 30 years) reference population of the same ethnicity and limited mobility assessed by a timed walking test (8). In 2014, the Foundations for the National Institutes of Health (FNIH) Sarcopenia Project published a series of five manuscripts on sarcopenia (9-13). In their recommendations, sarcopenia for adults >65 years was defined as ASMI/BMI (females <0.512, males <0.789). No recommendations were made for adults <65 years or individuals with class II/III obesity.

3.4 Sarcopenic obesity: variables and cutpoints

One of the most commonly used definitions for sarcopenia (and hence sarcopenic obesity in a combination with obesity indexes) resulted from examining body composition of older adults (>64 years, n=883) defined by ASMI (kg/m^2) with cutpoints set at 2 SD below the sex-specific mean of a reference population of young, healthy adults (18 – 40 years) from New Mexico, USA (14). One reason why this definition continued to be widely used was due to its ability to predict health outcomes, particularly physical disability. The authors investigated the relationship between disability and self-reported independent activities of daily living scale (IADL). Moderate disability was defined as difficulty with three or more of the six items. BMI range was not reported, however the mean BMI for females (25.3 ± 3.9 kg/m^2) and males (25.9 ± 3.9 kg/m^2) suggest few (if any) participants with BMI ≥35 kg/m^2 were included. The authors concluded that sarcopenia was an independent predictor of IADL with a 3-4 times increased risk.

Furthering their research with a 2004 study (15), Baumgartner et al. explored sarcopenic obesity and disability in a similar cohort over eight years (>60 years, n=451). The same ASMI cutpoints were used, but obesity was defined at >60th percentile of FM from the study cohort (females 40 %FM, males 28 %FM). With this definition, the prevalence of sarcopenic obesity was 5.8 % at baseline. Compared to their baseline IADL scores, participants with sarcopenic obesity showed worsening of function over the study period and the reduction in function occurred earlier in the study compared to participants in the non-obese and non-sarcopenic obese groups (1.5 years vs. 2.1 – 2.4 years, respectively). The authors concluded sarcopenic obesity preceded participant's IADL disability and was associated with earlier onset (15).

Four other researchers have used the same variable, ASMI, with different cutpoints to define sarcopenia (16-19). In a Canadian study, Bouchard et al. (19) defined sarcopenia as ASMI with

cutpoints (females <6.29 kg/m^2 and males <8.51 kg/m^2) set as two SD below the mean of a young, reference group (20-35 years). Obesity was defined for females ≥35 % FM and males ≥ 28 %FM. In their sample (68 – 82 years, n=894), four body composition phenotypes were defined for each sex for based upon the presence or absence of sarcopenia and obesity. BMI ranged from 17 – 50 kg/m^2, however the proportion of participants with class II/III obesity was not reported. Sarcopenic obesity was identified in 10.8 % of females and 18.8 % of males. Participants with sarcopenic obesity and obesity (without sarcopenia) had the highest total number of chronic conditions compared to participants without obesity. Participants with obesity (both sarcopenic and non-sarcopenic groups) reported multiple comorbidities, with no differences between the groups [females (4.2 ± 0.3 vs. 3.9 ± 0.12, p=.38, respectively), and males (3.2 ± 0.2 vs. 3.3 ± 0.2, p=.67, respectively)] (19). All participants completed four separate assessments for lower body functional capacity, from which a global score was calculated. For the individual tests, there were no differences between participants with sarcopenic obese compared to all non-sarcopenic participants. Lower global scores were calculated for the groups with obesity groups compared to the non-obese groups, but no differences were found based on sarcopenia status (sarcopenic vs. non-sarcopenic) within the group with obesity. In summary, sarcopenic obesity was associated with multimorbidity, but not with poorer performance on tests for lower body physical capacity. As results for participants with class II/III obesity were not reported separately, it was not possible to determine if there were differences for these participants.

Both previous studies (14, 19) used a single sex-specific definition for their cohort. In the following studies, multiple definitions were explored in the same study sample to help identify their predictive value in the identification of sarcopenic obesity. In their study of healthy older

Italian women (67 – 78 years, n=167), Zoico et al. (17), defined sarcopenic obesity by exploring three definitions for sarcopenia concurrent with two definitions of obesity. First, for sarcopenia, ASMI was calculated into two classes: class 1 (4.7 – 5.6 kg/m^2) as 1 SD below the mean; class 2 (<4.7 kg/m^2) as 2 SD below the mean of the distribution for a young reference group. Obesity was defined by two methods; BMI >30 kg/m^2 (15.8 % of sample) and %FM (highest quintile of the study group, >42.9 %FM). The other two methods used total LST indexed to height (LSTI <5.7 kg/m^2) and weight (LST/weight x 100, %). The same approach to define sarcopenia into classes was used for LST/weight x 100 (%): class I = 23.1 – 26.7 % and class II <23.1 %. Sarcopenic obesity was identified for 12.4 % of the sample.

Participants were categorized with disability if they reported any limitations on three scales for activities of daily living (ADL) or impairment of physical function. Limitations with ADL were identified in all phenotype groups (33.9 – 52.2 % of participants). Close to half (47.6 %) of the participants with sarcopenic obesity reported functional limitations, which was similar to the results for participants in the obese (52.2 %) and sarcopenic (42.2 %) groups and higher than reported by the normal phenotype group (33.9 %, $p<.05$) (17). For those with obesity (as defined by BMI <30 kg/m^2 or highest quintile of %FM), a higher prevalence of disability was identified compared to participants with BMI 20 – 24.9 kg/m^2 ($p<.01$) or the lowest quintile of %FM ($p<.05$). Class II sarcopenia (as defined by LST/weight x 100, %) had 3.8 times increased risk of disability, compared to the normal phenotype group. In contrast to the results of Baumgartner et al. (15), sarcopenia defined by ASMI was not associated with disability. The authors concluded indexing lean mass to weight, instead of height to account to the body size, might better identify those at risk for disability within their study sample (17). The amount of LST in proportion to the body mass it is required to move may be more important to perform ADL without difficulty.

Using a similar approach, Kim et al. (18) explored sarcopenic obesity in a sample of older Korean adults (>60 years, n=526), by combining obesity (females >31.71 %FM, males >20.21 %FM) with three methods to define for sarcopenia. The first two definitions used ASMI, with two different methods to define the cutpoints: 1) the lowest two quintiles (females <7.36 kg/m^2, males <8.81 kg/m^2) of the entire study group (20 – 88 years) and 2) two SD below the mean of a young reference group (20 – 40 years) (females <5.14 kg/m^2 and <7.40 kg/m^2). The highest prevalence was reported for ASMI (quintiles method), with 22.5 % of females and 15.4 % of males being identified with sarcopenic obesity, compared to just 0.8 % of females and 1.3 % of males with cutpoints derived by the two SD method. The third definition selected was LST/weight x 100 (%) with cutpoints at two SD below the mean of the reference group (females <30.7 %, males <35.71 %). With this definition, the prevalence of sarcopenic obesity was 12.5 % for females and 5.1 % for males. When each definition was explored in relation to the risk for metabolic syndrome, only the last definition (LST/weight x 100, %) was associated with a three times increased risk for metabolic syndrome, compared to participants with a normal body composition phenotype. (55.6 vs. 21.5 %, p<.001, respectively). As observed in the Zoico et al. study (17), there was variability in the prevalence rates depending upon the definition. As discussed by Kim et al. (18) in their cohort, sarcopenia defined as LST in relation to body weight was better than ASMI alone in identifying sarcopenic obesity and its relationship with metabolic syndrome. In addition, as discussed by the authors, the cutpoints derived from their Korean reference and study groups may not be applicable to a Caucasian cohort.

Another study using ASMI was Newman et al. (16) that explored another definition, ASM adjusted by height and FM. Participants in this study were older American adults, aged 70 – 79 years (n=2984). Sarcopenia was defined as: 1) ASMI (kg/m^2) using the cutpoints proposed by

Baumgartner et al. (14) and 2) residuals (<20th percentile) of ASM adjusted for height and FM. For participants with obesity (BMI ≥30 kg/m^2), none were identified to have sarcopenic obesity using the ASMI cutpoint definition, however 21.0 % of females and 11.5 % of males had sarcopenic obesity using the residual definition. Sarcopenia (by either definition) was associated with a higher prevalence of multimorbidity (3 or more comorbid conditions) in males (but not females) compared to non-sarcopenic participants. Sarcopenia (residual method only) was associated with lower performance scores related to lower extremities, including gait speed, balance while standing, and getting up from a chair. Based upon their results, the authors concluded when considering a definition for sarcopenia, *"fat mass should be considered…in women and in overweight and obese individuals*" (16). The residual definition accounted for ASM relative to body size by adjusting for both height and FM, which may identify more individuals with obesity.

Using the National Health and Examination Survey (NHANES) data, Batsis et al. (20) explored several definitions of sarcopenic obesity in adults >60 years (n=4984). Obesity, defined by BMI ≥30 kg/m^2 and FM (females ≥35 %FM, males ≥25 %FM), was combined with two sarcopenia definitions, ASM (kg) and ASM/BMI (females <0.512, males <0.789), as proposed by the FNIH Sarcopenia Project group (12). Obesity was observed in 33.2 % of females and 29.8 % males, however participants weighing >136.4 kg were excluded due to equipment capacity, limiting the number of participants with class III obesity. The prevalence of sarcopenic obesity was variable depending upon the definition: in females, 2.5 % (ASM, BMI ≥30 kg/m^2), 33.5 % (ASM, %FM), and 19.1 % (ASM/BMI, %FM); in males 0.2 % (ASM, BMI ≥ 30 kg/m^2), 12.6 % (ASM, %FM), and 27.3 % (ASM/BMI, %FM). A greater proportion of females were identified with sarcopenia when defined by ASM (kg) (40 vs. 16 % of males, respectively) but when defined by ASM/BMI,

more males had sarcopenia (27.8 vs. 19.3 % of females). Functional limitations were assessed from self-reported ADL and mobility. With obesity defined by BMI, or sarcopenia defined by ASM (kg), no differences in functional limitations were identified between sarcopenic obese and non-sarcopenic obese groups. With obesity defined by %FM and sarcopenia by ASM/BMI, both sarcopenic obesity and sarcopenia were associated with functional limitations (20).

Two studies defined sarcopenia as ASM/weight x 100 (%) (21, 22), using a similar approach to that described earlier in this chapter. Oh et al. (21) determined cutpoints (females <23.4 %, males <29.6 %) using one SD below the mean of their young reference group (20 – 39 years, Korea) and Levine & Crimmins (22) selected cutpoints (females <19.43 %, males <25.72 %) as two SD below their young reference group (20 – 40 years, USA). In the Oh et al. study (21), older Korean adults (>60 years, n=1433) were compared based on four phenotypes: sarcopenic obese, sarcopenic non-obese, non-sarcopenic obese and normal. Sarcopenic obesity affected more females than males (31.3 vs. 19.6 %, respectively). Compared to non-sarcopenic obese participants, individuals with sarcopenic obesity had higher mean serum triglycerides and more insulin resistance (fasting insulin and homeostasis model of assessment of insulin resistance, HOMA-IR). For females with sarcopenic obesity, mean high-density lipoprotein was lower compared to three other phenotype groups. Vitamin D deficiency (mean serum 25-OH vitamin D_3 <50 nmol/L) was identified in the sarcopenic obese group (lowest values) for both sexes and for all female phenotypes groups (% not reported) (21).

In the study by Levine & Crimmins (22), American adults >60 years (n=2287) were also compared based on four body composition phenotype groups: sarcopenic (obese and non-obese) and non-sarcopenic (obese and normal). The prevalence of sarcopenic obesity was 10.4 % (sex-specific not reported). Participants with sarcopenic obesity had the highest insulin resistance

(HOMA-IR) (mean ratio 6.1), compared to non-sarcopenic obese (mean ratio 4.5), sarcopenic non-obese (mean ratio 3.1) and normal (mean ratio 2.2). Likewise, sarcopenic obese had the highest waist circumference (107.8 ± 11.7 cm), compared to non-sarcopenic obese (102.5 ± 11.2 cm), sarcopenic non-obese (82.2 ± 2.7 cm) and normal (79.9 ± 6.2 cm) groups. Both obese groups (sarcopenic and non-sarcopenic) were not different for mean C-reactive protein (CRP) (6.3 ± 8.2 vs. 5.3 ± 6.3 mg/L, respectively), and the mean CRP for sarcopenic non-obese participants (10.6 ± 20.4 mg/L) were the highest and the most variable. When compared with physical function, participants in both sarcopenic groups and the non-sarcopenic obesity group were associated with more items of self-reported difficulty with six different ADL tasks that involved movement of the lower extremities such as getting up from a chair, kneeling, climbing stairs and standing for a long time. Therefore, compared to normal, the three abnormal phenotypes were associated with problems with physical function (22). For the sarcopenic group, because they had the highest levels of insulin resistance and central obesity, the authors noted these factors might contribute in part to the difficulty with ADL tasks.

In the studies reviewed above, it is clear that the prevalence of sarcopenic obesity is highly variable. This point was well demonstrated in another study by Batsis et al. (23). In their analysis of eight definitions applied to the same large sample of adults from the NHANES data set (age >60 years, n= 4984), the prevalence of sarcopenic obesity ranged from 3.6 – 94 % in females and 4.4 – 84 % in males (23).

Thus far, several different definitions (including cutpoints) have been used to define both sarcopenia and obesity with variable prevalence and health implications. The challenge remains on how to best identify abnormal body composition phenotypes understanding the combined and independent predicted value of sarcopenia and obesity on health. An alternative approach to

define abnormal body composition was proposed by two studies using NHANES data (n=13,236) of adults 18 and older (24, 25). Reference curves developed from DXA analysis were used to define a sarcopenic obese-like phenotype termed high adiposity-low muscle mass (HA-LM) (24). In Prado et al. (24), sex, age and BMI specific reference curves were developed for deciles groups of ASMI and FMI, from which four body composition phenotypes were derived including HA-LM, reported in 10.3 % of females and 15.2 % of males. This study was one of the first to identify that abnormalities in body composition, particularly HA-LM was observed across both the age and BMI spectrum, shining a light on the fact that young-to-middle aged adults are affected (24). Using the same dataset, Siervo et al. (25) developed sex-age-and BMI reference curves for FM and FFM described as the load-capacity model, whereas FM is the load to which FFM must have the capacity to move in order to maintain function (25, 26). Reference curves were also developed for trunk FM and ASM. While the predictive value of both these definitions remains to be investigated, the use of reference curves presents a new approach to identify sarcopenic obesity, while adjusting not just for sex but also for age and BMI (24-26).

In the literature reviewed thus far, sarcopenic obesity has been associated with impairments to the individual's ability to function, with increased difficulties with ADL and disability, (15, 22, 27, 28) including falls (29). Skeletal muscle, the main component of LST, has a critical role on strength, functional mobility and independence (5, 26, 30). LST is also important for immune function and overall health processes (e.g., kidney and hepatic function).

Sarcopenic obesity is additionally associated with cardiometabolic risk factors including metabolic syndrome (31), systemic inflammation, dyslipidemia, hypertension, insulin resistance and diabetes, (31-33) and multimorbidity (34). Sarcopenic obesity has also been previously associated with non-alcoholic fatty liver disease (35).

There are recommendations for potential sarcopenia biomarkers, including some common biochemical values such as CRP, serum albumin, and vitamin D. Although these biomarkers are not specific to LST, they are related and may serve to be clinically relevant (36). In addition to morbidity and disability, sarcopenic obesity was associated with a 24 % increased risk of all-cause mortality in a recent meta-analysis of 12 prospective studies (N= 35,287 participants and 14,306 deaths) (37).

As described above, sarcopenic obesity is associated with several health conditions, yet the lack of consistency in defining this condition precludes an adequate understanding of the risk associated with the complex relationship between FM and FFM and the clinical implications of this combined condition (23, 26, 30). There is a need for a definition that is sensitive enough to detect relatively low lean mass in those with larger body size due to excess adiposity. Anthropometric measurements alone are not sufficient, as they can mask sarcopenia. As such, body composition assessment (by DXA) is required to identify people with this abnormal phenotype. Unfortunately, the prevalence of sarcopenic obesity in adults with class II/III obesity (BMI $\geq$35 kg/m^2) is not well understood, as body composition equipment capacity is often inadequate to accommodate people with larger body sizes (such as weight and width), as discussed in Chapter 2.

3.5 Conclusion

With the increasing prevalence of more pronounced cases of obesity (38) and sarcopenia (4), the prevalence of sarcopenic obesity is likely to increase dramatically. Determining its prevalence is challenging, due to the number of variables, methods and cutpoints to define the condition. The majority of studies focused on older adults >65 years and lower BMI categories, leaving the prevalence and associated clinical risks in adults with class II/III obesity as yet to be determined.

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Chapter 4: Prevalence of sarcopenic obesity in adults with class II/III obesity using different diagnostic criteria

Preface

A variety of body composition indices and cutpoints have been used to define this condition, mostly in older adults (>65 years), leading to conflicting prevalence and risk prediction. The aim of our study discussed in this chapter was to investigate variability in the prevalence of sarcopenic obesity in an adult sample of individuals with class II/III obesity (BMI ≥35 kg/m^2) using different diagnostic criteria.

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4.1 Introduction

Obesity is a complex, chronic global disease affecting people worldwide across all ages, sexes, ethnicities, and nationalities. Indexing weight to height is often done to classify body weight as "healthy" or "abnormal". One of the earliest comparisons, the Quetelet index, was developed in the 19th century to describe body size (1) and later termed body mass index (BMI). This index is still used today, defining obesity as a BMI $\geq$30 kg/m^2 for both females and males. This classification can be further subdivided into class I (BMI 30 – 34.9 kg/m^2), class II (BMI 35 – 39.9 kg/m^2) and class III (BMI $\geq$40 kg/m^2). The prevalence of the highest obesity class is of concern due to its association with poorer health outcomes compared to lower BMI categories. In 2013 – 2014, class III obesity affected 5.5 % of males and 9.9 % of females in the United States, with a linear increase in prevalence for females since 2005 (2).

In addition to BMI, other anthropometric measurements can be used to identify obesity such as waist circumference. These methods provide a surrogate assessment of fat mass (FM) but are poor detectors of lean mass, also called lean soft tissue (LST) and hence body composition. As such, people with obesity can have varying proportions of LST, which can in turn be associated with unique health risks as described below. Therefore, the use of anthropometry to diagnose obesity precludes an assessment of body composition and hence, an accurate characterization of the different proportions of FM versus LST of an individual.

Recent studies have determined that obesity can co-exist with low LST (sarcopenia). The gravity impact of the excess body weight may not be sufficient to promote an adequate quantity of LST; therefore, individuals with obesity may have high FM without a parallel increase in LST (3). Notably, this phenotype termed *sarcopenic obesity* can only be identified using body composition assessment techniques. Low LST is an important prognostic factor in health and

clinical conditions, as its main component is skeletal muscle mass, a tissue of vital importance for strength, functional mobility, immune function and wound healing, among others (4).

Sarcopenia has been primarily studied in older adults and individuals with chronic conditions but emerging evidence suggests that "healthy", younger individuals are also at risk for presenting with this condition (5) (6). Compounded with the consequences of excess FM, the concurrent sarcopenic obesity phenotype has been independently associated with worse morbidity and disability than either sarcopenia or obesity alone (7). In the context of obesity treatment, weight loss results in the loss of both FM and LST. With repeated weight loss-gain cycles combined with age-related body composition changes, developing sarcopenic obesity is possible (7).

The identification of sarcopenic obesity is not only limited due to the availability of accurate body composition techniques but also due to heterogeneity in its diagnostic criteria. A variety of body composition indices and cut-offs have been used to define sarcopenia and obesity, leading to conflicting findings on the prevalence and risk prediction of this condition (7, 8). Additionally, the great majority of studies have focused on identifying sarcopenic obesity in older adults and the prevalence within younger adults and those with class II/III obesity is not well defined. With the increasing prevalence of class III obesity (2) and of sarcopenia (6), the prevalence of sarcopenic obesity in these individuals is likely to increase dramatically. However, as mentioned above, this prevalence is likely to be affected by a lack of consensus and different cutpoints used to categorize individuals into having or not having sarcopenia with obesity. Therefore, the objective of this study is to explore the variability in the prevalence of sarcopenic obesity in an adult sample with class II/III obesity using different diagnostic criteria.

4.2 Methods

The study was a cross-sectional, retrospective analysis of a sample of patients from the Edmonton Adult Bariatric Specialty Clinic (Alberta, Canada). This multidisciplinary clinic provides medical and bariatric surgical interventions for adults (18 – 69 years) with class II/III obesity (BMI ≥35 kg/m^2) with health care services covered under the Alberta Health Care Insurance Plan. Ethics approval was received from the University of Alberta Health Research Ethics Board, with administrative and operational approval by Alberta Health Services.

As part of the initial clinic assessment, a registered nurse gathered demographic and medical history from the medical record and self-report information. Height was measured (without shoes, within 0.1 cm) with a wall-mounted stadiometer. Weight was measured (single layer of clothing, without shoes, within 0.1 kg) with a high-capacity weigh scale (Scale-Tronix 6702W®, WelchAllyn Inc., Skaneateles Falls, New York.). Waist circumference was measured (within 0.1 cm) with a non-stretch tape at the mid-point of the torso (between lowest rib and iliac crest) on the right side using a cross-handed technique, recorded as the average of three consecutive measures.

A requisition for whole body composition analysis by dual-energy X-ray absorptiometry (DXA) was provided to each patient at the initial assessment and completed at a local medical imaging center [Hologic Discovery A (S/N 45026) or W (S/N 83792) scanners, software version 12.7.4.2, Hologic Inc., Bedford MA]. No participants exceeded the DXA weight capacity limit (204 kg) or scan area length (195 cm). Reflection positioning was used for participants with larger supine widths (>65 cm). When required, participants were positioned to center their torso on the scan bed, requiring part of their left arm extended out of scan range. Right-side data was duplicated when values for the left side were either not reliable or available (9-11). Collected values

included whole body and segmental values for FM, lean soft tissue (LST), appendicular skeletal muscle mass (ASM, which is LST from arms and legs) and fat-free mass (FFM = LST + bone), and its derivatives adjusted by height in square meters, also called indexes (e.g., FMI, ASMI). Detailed definitions of each of these body composition variables can be found elsewhere (12).

Participants with complete initial clinic assessments and body composition analysis by DXA were included in the study. DXA scans available for analysis dated from January 2009 to June 2012, after which they were no longer ordered at the initial clinical assessment. All data was collected prior to starting obesity treatment. Participants were excluded from the final analysis if DXA data was unreliable (i.e., segmental measurements were outside of the field of view or due to lack of separation of tissues between the arms and torso). Participants with recent weight changes due to metabolic health conditions (i.e., cancer, thyroid, cachexia) or pregnancy were excluded.

Sarcopenic obesity: definitions and terminology

A literature search was conducted using PubMed, Scopus and Web of Science databases to identify studies using definitions sarcopenic obesity based upon body composition data derived from DXA with or without use of anthropometric variables (e.g., weight, BMI and waist circumference), excluding clinical studies (e.g., cancer). For definitions using ethnic-specific cutpoints, white/Caucasian references were included as the majority of our population (83.9 % Edmonton, 86 % Canada) self-identified as Caucasian (13). Ethnicity was not collected as part of the clinic assessment, in accordance with the Freedom of Information and Protection of Privacy Act (14), therefore unavailable for analysis.

Based on the literature review, ten studies were identified using nine variables based upon LST or ASM to define sarcopenia (**Table 4.1**) and four variables were identified to define obesity (**Table 4.2**, plus FMI phenotype listed in **Table 4.1**) (6, 15-23). With the exception of BMI, each variable for sarcopenia and obesity used sex-specific cutpoints, with more than one cutpoint for some variables. Sixteen unique definitions (composed of a variable and cutpoint for each sarcopenia and obesity) were identified and applied to the sample to explore the prevalence of sarcopenic obesity. Linear regression analysis with ASM, height, and FM (kg) was used to determine prevalence of sarcopenia using the Newman et al. residual method (19). The classification by body composition phenotypes was determined using deciles of population-derived ASMI and FMI cutpoints based on sex, BMI and age, as per the protocol described in Prado et al (6). The classification of abnormal body composition phenotype as a load-capacity model (load being FM and capacity FFM) was calculated as the ratio of FM/FFM (as centiles), as per methodology described in Siervo et al (23).

Additional classifications were derived from our study cohort, using ASMI calculated as the lowest 20^{th} percentile and two standard deviations (SD) below the mean of the distribution, a method commonly reported in the literature when a reference population is not available (25). Definitions of sarcopenic obesity utilizing measures of muscle strength or function were not included, as these data were not available for our cohort.

The use of inconsistent body composition terminology may preclude a clear understanding of sarcopenic obesity's diagnostic criteria in the literature (i.e., authors using different terminology for the same body composition variables). Therefore, in order to improve clarity while still accurately representing the body composition components being measured in each study, we consistently use the terms LST for studies measuring the non-bone, non-fat body compartment in

general from the whole body (i.e., arms, legs, trunk, and head) and ASM for studies measuring LST from the arms and legs (12).

Statistical analysis

The sample was analyzed by sex due to well-known differences in body composition between females and males. Descriptive statistics were used for participant characteristics, anthropometrics and body composition, and reported as mean ± SD and median (range). Normality testing was completed using the Shapiro-Wilk test. Frequencies and proportions were reported for categorical variables. Independent samples t-test for normally distributed data and non-parametric (Mann-Whitney U) independent samples t-test were used to compare variables between sexes. To account for variable with missing data (waist circumference), participants were compared to determine if differences existed between the groups. Correlations were tested using Pearson's r to explore the relationship between variables. Two-tailed tests were used for all the analysis with a p-value of $<.05$ considered for statistical significance. Data was analysed using IBM SPSS Statistics, version 23 (IBM Corp., Armonk, N.Y. USA).

4.3 Results

A total of 167 participants with completed initial assessments and DXA scans were initially reviewed, in which 120 participants (85.8 % female) had DXA data to be included in the final analysis. Mean age of the entire cohort was 46.9 ± 11.1 years. Participant characteristics, anthropometrics and body composition are presented in **Table 4.3**. The sample was community-dwelling (100 %) and predominantly married/common-law (females 68 %, males 65 %), worked outside the home (females 68 %, males 70 %) and 7.8 % of females (no males) were current smokers. The sample was generally well educated (females 98 %, males 94 % completed high school), with more females than males who completed their education at a university/college level (females 57 %, males 35 %). Physical activity guidelines (>150 minutes of moderate intensity activities a week) were met by 20 % of females and 23 % of males.

Due to the positively skewed data for weight in females, some variables were not normally distributed. Independent samples t-tests and non-parametric (Mann-Whitney U) tests results were compared and showed the same results. No significant differences were observed between females and males for age, BMI and FM (kg), **Table 4.3**. Compared to males, females had higher values for FM (%), FMI and FM/FFM ratio and lower values for variables depicting the lean mass compartment. A large variability in LST (kg) was observed for individuals with the same body size, **Figure 4.1 A, B**. The relationship between BMI and LST in females and males was moderate and weak (R=0.41, R=0.20 respectively), **Figure 4.1A**. For example, females with the same BMI (40 kg/m^2) could present with a large difference in LST (33.7 kg) (**Figure 4.1A**).

The entire cohort met the criteria for obesity defined by BMI, waist circumference and FMI cutpoints (Table 4.2). For %FM, all males exceeded the five different cutpoints. One female (BMI 39.7 kg/m^2 and 32.2 %FM) did not meet the criteria for obesity defined by %FM with five

of the six different cutpoints. Ten females (9.7 %) had %FM below the highest cutpoint (42.9 %), therefore would not be identified with obesity despite BMI's ranging from 35.9 – 45.1 kg/m^2. Of note, the highest sex-specific 20th percentile for FMI was >23.8 kg/m^2 for females and >21.5 kg/m^2 for males.

Considering the entire cohort had class II/III obesity as defined by BMI, when each definition of sarcopenia was applied to the current sample, the prevalence of sarcopenic obesity varied from 0 – 84.5 % for females and 0 – 100 % for males (**Table 4.4**). Definitions using unadjusted values for LST, ASM or ASMI, with the exception of the highest ASMI cutpoint, failed to identify any participants with sarcopenic obesity. Notably, a higher prevalence of sarcopenic obesity was identified by definitions combining ASM either with weight, BMI or a measure of FM.

The sex-specific cutpoints developed from the Newman et al. (19) study group was only able to identify males with sarcopenic obesity in our cohort, **Table 4.4**. Applying the Newman et al. (19) residual method to derive cutpoints from the current cohort, sarcopenic obesity was identified in both sexes. For the latter, the cohort-specific cutpoints derived from the 20th percentile of the sex-specific distributions of the residuals were <2.96 for females and <-4.82 for males, identifying 19.4 % of females and 17.6 % of males with sarcopenic obesity. Equivalent cutpoints for ASMI were also derived from the study cohort. The cohort-specific 20th percentile cutpoint to describe sarcopenic obesity by ASMI was <8.21 kg/m^2 for females and <9.44 kg/m^2 for males. Using the lowest 2 SD criteria for ASMI, the cohort-specific cutpoints were <6.79 kg/m^2 for females and <8.62 kg/m^2 for males. Selecting the cohort-specific 20th percentile, low ASMI was observed across the age spectrum, **Figure 4.2**. The age of females below the 20th percentile for ASMI ranged from 24 to 69 years.

Using the phenotype definition proposed by Prado et al. (6) to the entire sample, 16 participants (13.3 %) where classified with high adiposity and low muscularity (sarcopenic obesity–like phenotype), and 95 participants (79.2 %) presented with the high adiposity and high muscularity phenotype (obese non-sarcopenic-like phenotype), **Figure 4.3**. Nine females were classified as having a normal body composition phenotype. Using the load-capacity model to account for the interaction of both body compartments (23), the FM/FFM ratio identified about a third of females and three-quarters of males with moderate and severe body composition phenotype (≥ 85th percentile), respectively (**Table 4.4**).

4.4 Discussion

Several researchers have identified sarcopenic obesity in older adults (26) and groups with certain chronic diseases (12). Although several diagnostic criteria have been used, no one approach has been widely accepted. This is the first study to use state-of-the-art methodology (DXA) to explore the prevalence of sarcopenia in a young-to-middle aged adult cohort with class II/III obesity. LST was extremely variable in individuals with similar BMI, illustrating a wide variability of body composition within similar body sizes. Using 18 previously reported definitions, the prevalence of sarcopenic obesity varied from zero to 100 %. Such variability precludes a comprehensive understanding of the prevalence of sarcopenia in younger individuals with more severe classes of obesity as well as the development of preventive and treatment strategies for this condition in clinical settings. As these individuals are actively seeking obesity treatment, maintaining lean mass should be a co-primary endpoint of the nutrition care plan together with weight management.

Although FM usually varies by BMI and different cutpoints have been used to define obesity, all males and almost all females were classified as obese using diverse %FM cutpoints (30 – 42.9 % for females and 20 – 29 % for males). Most individuals with a BMI ≥35 kg/m^2, excluding extremely muscular individuals, will present with excess adiposity (27) and prevalence will vary only based on the comparison cohort used to identify the cutpoint. For example, 10 females from our cohort would not be considered to have obesity using the Zoico et al. (15) cutpoint based on quintiles of %FM from a sample of healthy elderly females (BMI 26 ±3.8 kg/m^2). Nonetheless, these 10 females were within 0.2 % to 3.7 % below the %FM cutpoint. Interestingly, using the adjusted Prado et al. cutpoints (6), we observed that nine females were not classified as having high adiposity. In addition to sex, this cutpoint is notably adjusted for age and BMI. Six females

were identified as having both lower %FM and FMI using the Zoico et al. (15) and Prado et al. (6) cutpoints respectively.

Considering all participants have obesity defined by BMI (and were seeking treatment for this condition), we then applied previously used definitions of sarcopenia to the entire cohort. Interestingly, the prevalence of sarcopenia ranged approximately from 0 – 84.5 % in females and from 0 – 100 % in males. The null prevalence using several cutpoints may be explained by the approach used to define sarcopenia. In our study, no participants were identified with sarcopenic obesity by definitions of LST (15, 16).

The majority of published studies on sarcopenia and sarcopenic obesity focus on older adults, defined with various ages starting at 60 years and older. This is a limitation to identifying sarcopenia in adults, as reference values developed from older cohorts may not represent a comparable reference population for younger adults. Although Cherin et al. (5) included younger individuals (4 – 83 years), their cohort's mean age was 63.1 ± 10.2 years and the prevalence of sarcopenic obesity was not reported.

Baumgartner et al. (18, 24) and others have used sex-specific cut points to identify sarcopenia based on ASMI below two standard deviations of the mean for a young reference group (8, 18, 20, 24, 28, 29). Applying each of the different cutpoints, no participants were identified with sarcopenic obesity. Although these young reference groups were North American and of similar age to the current study cohort, their BMI (described as "normal") would be much lower. Certainly, it would be of concern if participants within the current study had ASMI below these cutpoints. However, sarcopenic obesity may still be present but not identified as the cutpoints may not sensitive enough to identify relatively low lean mass in participants with larger total

body mass. Likewise, no participants were identified as sarcopenic using Newman et al. cutpoint that defined sarcopenia as the lowest 20th percentile of their cohort's ASMI distribution (19). Notably, applying the same method to our cohort, our ASMI cutpoints were 45 % and 31 % greater for females and males respectively, highlighting how differences in age and body size may impact comparison among different cohorts.

Although some may argue that the null prevalence using specific criteria simply implies sarcopenia is not present in the current cohort, an alternative explanation should be considered. It is obvious that adults with class II/III obesity have a greater body mass and therefore higher FM and LST compared with their normal BMI counterparts. Although the quantity of LST may meet or exceed reference values derived from normal, healthy reference populations (e.g., normal BMI or age 25 years), the higher LST amount is insufficient to maintain the larger body size (largely due to a larger FM amount). This phenomenon can be conceptualized as the metabolic load (due to FM) versus the capacity (of the LST/FFM) model previously described (23). Therefore, sarcopenia in those with obesity may be present at higher LST values and must be evaluated in relation to body mass or FM.

Our findings support the use of a combined definition of body mass or FM to a measure of sarcopenia for the identification of sarcopenic obesity in this cohort of younger adults with class II/III obesity. When considering measures of ASM with weight (21, 22), BMI (17), FMI (6) or FM (19, 23), the prevalence of sarcopenia in this cohort ranged from 12.6 – 84.5 % for females and 17.6 – 100 % for males. Likewise, in the Newman et al. (19) study group (70 – 79 year olds), higher prevalence rates were observed for both sexes (females 21 %, males 11.5 %) using the residual method that identified sarcopenia by regressing ASM to height and FM (residuals) compared to no one using non-adjusted ASMI cutpoints. The authors concluded this technique

captured the effect of both lean mass (as ASM) and high FM simultaneously, therefore identifying a greater proportion of people with obesity as being sarcopenic. Our findings are consistent with their results and highlight the potential importance of considering FM with LST indices together when evaluating sarcopenia in people with obesity.

We were able to identify three body composition phenotypes using the Prado et al. (6) previously established cut points. In this North American population-representative study, age, sex and BMI-specific reference curves were created to define body composition phenotypes based on FMI and ASMI above or below the 50th percentile. As the 50th percentile was used, the terms "obesity" and "sarcopenia" were avoided with individuals being classified using a combination of high/low adiposity and high/low muscularity. The concurrent high adiposity (HA) and low muscularity (LM), named HA-LM, is the "sarcopenic obesity-like" phenotype with an observed population prevalence of 10.3 % in females and 15.2 % in males. The advantages of this method are that it accounts for more variables associated with body composition than any other definition and it is based upon a large North American population-representative sample. Although participants >136 kg were excluded from that study thereby limiting the reference data, applying this method to the current study cohort produced similar results, identifying 12.6 % of females and 17.6 % of males with sarcopenic obesity.

The same dataset was used to propose the Siervo et al. (23) FM: FFM ratio reference curves and as in that analysis, we also found females had a higher FM/FFM ratio than men. Notably, the current study included participants with higher weights, with 17.5 % of females and 41.2 % of males with weights >136 kg. The load-capacity model is novel method that can identify low LST relative together with excess FM in participants with class II/III obesity.

Although our sample size of males was small, their prevalence of sarcopenia was higher than females for all definitions except for the Newman et al. residual method (19), where the prevalence was similar. The prevalence of sarcopenia by sex is controversial with some studies reporting higher prevalence among males, others among females and some finding no differences (26).

An important consideration for any definition is to understand the characteristics of the group from which the cutpoints were derived. Different cutpoints for the same variable are available as they may be derived from different reference groups (**Table 4.1**). This in turn can impact the prevalence of sarcopenia when applied to other cohorts. The study by Kim et al. (16) illustrates this point, where cutpoints for ASMI were derived from two different Korean reference groups. Their cohort-derived cutpoint was the highest ASMI value for amongst the reviewed studies and able to capture some participants with sarcopenia (n=6) with sarcopenic obesity, compared to none using the cutpoints derived from their young reference group. Notably, some definitions were developed from European or Asian cohorts that are ethnically different from a North American population. Widely recognized differences in body composition among different ethnicities preclude a direct comparison of sarcopenic obesity prevalence among different studies.

When a young reference group was not available, some cutpoints used to define sarcopenia were developed from the distribution of the study group, using the lowest one (20) or two (16, 19) quintiles for ASMI. Applying this approach to our dataset, our cohort-specific cutpoints were much higher than previously published ones, again highlighting that cutpoints derived from other cohorts or non-specific populations (i.e., older adults, individuals without obesity) may either fail to detect or underestimate the prevalence of sarcopenic obesity in adults with class II/III obesity.

Contrary to expectations, the prevalence of sarcopenia was not higher among older individuals (≥65 vs. <65 years) (6). Indeed, we reported ASMI was highly variable across the age spectrum; only one of the 23 individuals with an ASMI below the 20th percentile for this cohort was older than 65 years (**Figure 4.2**).

The large variability of LST (**Figure 4. 1 A, B**) in individuals with the same body size represents a clinical challenge for determining nutritional requirements. For example, protein and energy needs are often determined based on body weight, yet, considering lean mass drives protein requirements, people with the same body weight can receive varying amounts of protein per unit of lean mass (LST), a concept fully explored by Prado et al (30). In the selected example on Figure 1B, if protein requirements were assessed as 1 g/kg actual body weight (116 kg), the estimated amount of dietary protein would be equivalent to 1.6 – 2.2 g/kg LST.

Data on body composition of adults with class II/III obesity is limited, especially of those with BMI >40 kg/m^2. One barrier is related to equipment limitations (31). Individuals with class III obesity not only have increased weights, but increased body dimensions such as height or supine width. Although there are large body composition data sets available, participants above 136 kg were excluded due to equipment limitations (27). Recent DXA equipment improvements, such as the Lunar iDXA (GE Healthcare) and Discovery/Horizon models (Hologic, Inc.) have increased scan area widths and weight capacities, improving the capability to assess more people with obesity. However, as a newer technique, the availability of iDXA at this time is limited and may be dependant on the replacement of current working DXA machines.

Notably, this study was completed prior to initiation of obesity treatment at the clinic. Weight loss is associated with reductions in both FM and LST, with weight re-gain predominately as FM

(7). If people with low LST are not identified as such, initiating obesity treatments targeted to reduce weight can further reduce LST, thereby either creating or worsening a sarcopenic state.

To our knowledge, this is the first study to explore the prevalence of sarcopenic obesity using DXA within a younger adult cohort with class II/II obesity. However, some limitations should be considered. As the study selected participants seeking treatment for obesity at an ambulatory clinic, results may not be applicable to all adults with obesity or other care settings (i.e., acute care, long term care). Although the representation of males in the current study (14.2 %) appears low, it is comparable to other studies conducted in this clinic (32, 33). In general, males tend to be underrepresented in obesity treatment studies (34, 35). Additionally, compared to females, more males with class III obesity may be excluded from DXA due to height, width and weight limitations (as males tend to be larger than females, in general). Additionally, we were unable to explore definitions of sarcopenia using a measure of muscle function, as these were not collected as part of patient's initial assessment.

4.5 Conclusion

Sarcopenia was present in our cohort but masked by obesity. The basic measurement of body weight or BMI is inadequate to identify sarcopenia and hence sarcopenic obesity in these individuals. Therefore, sophisticated tools such as DXA are needed to identify and profile LST of adults with class II/II obesity and should be implemented as part of clinical assessment. The inclusion of measures of FM and body size in the definition of sarcopenic obesity identifies a greater proportion of individuals with this abnormal body composition phenotype compared to stand-alone definition of low lean mass. Different diagnostic criteria should be tested in prospective studies investigating the risk-prediction for metabolic, functional and clinical parameters of these adults with class II/III obesity.

Practice Implications

With much advancement in body composition technology, nutritional assessment of people with chronic diseases by anthropometric measurements, although cost effective, may no longer be seen as sufficient. BMI alone cannot provide body composition information to practitioners, researchers, or patients, especially in instances where a large body weight can mask low lean mass. With DXA, individualized treatment plans can then be developed to optimize body composition changes. As it is evidence-based practice to assess bone density to screen for osteoporosis, and DXA scans are widely available as such screening tool, it is now time to consider body composition analysis for the screening and treatment of sarcopenic obesity.

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4.7 Tables and Figures

Table 4.1. Variables and methods used to define sarcopenia amongst studies investigating sarcopenic obesity using dual-energy X-ray absorptiometry.

Variables[a]	Reference	Study Group	Method for sex-specific cutpoints	Females	Males
LSTI (kg/m^2)	Zoico et al., 2004(15)	Older females (67-78 y) Italy	Lowest 2 quintiles of the distribution of young reference group (female, 20-50 y)	<5.7	NA
LST/weight x 100 (%)	Zoico et al., 2004(15)	Older females (67-78 y) Italy	Class I: 1 SD below mean, Class II: 2 SD below mean of young reference group (female, 20-50 y)	23.1 - 26.7 <23.1	NA
	Kim et al., 2009(16)	Adults (20-88 y) Korea	2 SD below mean of young reference from study group	<30.7	<35.71
ASM (kg)	Batsis et al., 2015(17)	Older adults (>60 y) United States	Classification and regression tree analysis of adults >65 y	<15.02	<19.75
ASMI (kg/m^2)	Zoico et al., 2004(15)	Older females (67-78 y) Italy	Class I: 1 SD below mean, Class II: 2 SD below mean of young reference group (female, 20-50y)	4.7 -5.6 <4.7	NA
	Kim et al., 2009(16)	Adults (20-88 y) Korea	2 SD below mean of young reference group (20-40 y)	<5.14	<7.40
	Baumgartner et al., 1998(18)	Older adults (>64 y) United States	2 SD below mean of young reference group (18-40 y)	<5.45	<7.26
	Newman et al., 2003(19)	Older adults (70-79 y) United States	Lowest quintile (20^{th} percentile) of study group	<5.67	<7.23

Variables[a]	Reference	Study Group	Method for sex-specific cutpoints	Females	Males
	Bouchard et al., 2009(20)	Older adults (68-82 y) Canada	2 SD below mean of young reference group (20-35 y)	<6.29	<8.51
	Kim et al., 2009(16)	Adults (20-88 y) Korea	Lowest two quintiles (40th percentile) of study group	<7.36	<8.81
ASM/weight x 100 (%)	Levine & Crimmins, 2012(21)	Older adults (>60 y) United States	2 SD below mean of young reference group (20-40 y)	<19.43	<25.72
	Oh et al., 2015(22)	Older adults (>60 y) Korea	1 SD below mean of young reference group (20-39 y)	<23.4[b]	<29.6[b]
ASM/BMI (kg/m^2)	Batsis et al., 2015(17)	Older adults (>60 y) United States	Classification and regression tree analysis of adults >65 y	<0.512	<0.789
ASM by height, FM (residuals)	Newman et al., 2003(19)	Older adults (70-79 y) United States	Lowest quintile (20th percentile) of the distribution of residuals of study group	<-1.73	<-2.29
ASMI and FMI (phenotype)	Prado et al., 2014(6)	Adults (>18 y) United States	Age, sex and BMI-specific reference curves, by decile	HA-LM[c]	HA-LM[c]
FM/FFM ratio	Siervo et al., 2015(23)	Adults (>18 y) United States	Age-standardized reference curves, stratified by sex and BMI, by centile	≥85th percentile	≥85th percentile

[a]Terminology for variables selected for consistency and may differ from terms used by original authors; these depict the correct compartment being measured. [b]Cutpoints determined from reported sex-specific mean and standard deviation in Oh et al., 2015. [c]HA-LM: high adiposity (FMI 50-100) and low muscle mass (ASMI 0-49.99) with individual z- scores based upon age, sex and BMI. LST: lean soft tissue; LSTI: lean soft tissue index; NA: not applicable; SD: standard deviation; y: years; ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal mass index; BMI: body mass index; FM: fat mass; FFM: fat free mass; FMI: fat mass index.

Table 4.2. Prevalence of obesity in study cohort (n=120) using various sex-specific definitions determined by anthropometric and dual-energy X-ray absorptiometry measurements amongst studies investigating sarcopenic obesity.

Variables	Reference	Females (n=103)		Males (n=17)	
		Cutpoint	Prevalence, %	Cutpoint	Prevalence, %
BMI (kg/m^2)	Newman et al., 2003(19)	≥30	100	≥30	100
	Oh et al., 2015(22)				
Waist circumference (cm) [a]	Levine & Crimmins, 2012(21)	>88	100	>102	100
Fat mass (%)	Kim et al., 2009(16)	>31.71	100	>20.21	100
	Bouchard et al., 2009(20)	≥35	99	≥28	100
	Batsis et al., 2015(17)	≥35	99	≥25	100
	Baumgartner et al., 1998(18)	>38	99	>27	100
	Baumgartner et al., 2004(24)	>40	98	>28	100
	Zoico et al., 2004(15)	>42.9	90.3	NA	

[a] Waist circumference not available for the entire cohort: females (n=81, 78.6%) and males (n=13, 76.5%). BMI: body mass index; FMI: fat mass index; NA: not applicable.

Table 4.3. Participant characteristics, anthropometrics and body composition (n=120), by sex.

Variables[a]	Females (n=103)	Males (n=17)	P-value
	mean ± SD; median (range)		
Age (years)	46.5 ± 11.5; 48.0 (23-69)	49.4 ± 8.4; 51.0 (32-63)	0.352
Anthropometrics			
Height (cm)	164.1 ± 6.1; 163.6 (148.6-177.3)	177.2 ± 6.3; 176.2 (166.8-187.1)	<.0001
Weight (kg)	117.3 ± 18.3; 111.8 (88.9-176.8)[b]	138.2 ± 18.1; 133.7 (108.6-180.7)	<.0001
BMI (kg/m^2)	43.5 ± 5.8; 42.4 (34.9-58.5) [b]	44.0 ± 5.0; 43.0 (37.9-55.3)	0.960
Waist (cm)[c]	120.4 ± 11.2; 121.0 (93.5-143.0)	141.0 ± 11.0; 140.0 (122.5-163.0)	<.0001
Body Composition			
Fat mass (kg)	55.6 ± 11.0; 52.9 (37.3-93.4) [b]	56.5 ± 11.3; 52.5 (40.8-77.9)	0.759
Fat mass (%)	48.0 ± 4.2; 48.3 (32.3-57.4)	41.4 ± 5.6; 39.7 (31.9-53.2)	<.0001
FMI (kg/m^2)	20.6 ± 3.8; 20.0 (13.9-30.9) [b]	18.0 ± 3.7; 16.9 (13.4-24.9)	0.009
FM/FFM ratio	0.909 ± 0.151; 0.916 (0.47-1.28)	0.706 ± 0.182; 0.650 (0.45-1.20)	<.0001
LST (kg)	57.1 ± 7.8; 55.9 (41.1-78.3) [b]	76.2 ± 10.2; 75.4 (59.0-99.1)	<.0001
LSTI (kg/m^2)	21.2 ± 2.5; 20.9 (16.0-29.6) [b]	24.2 ± 2.6; 24.1 (20.8-30.1)	<.0001
LST/weight x 100 (%)	49.0 ± 4.6; 48.2 (38.8-64.5)	55.4 ± 5.4; 55.5 (46.2-64.2)	<.0001

Variables[a]	Females (n=103)	Males (n=17)	P-value
	mean ± SD; median (range)		
ASM (kg)	24.7 ± 3.7; 24.2 (17.4-35.4) [b]	34.2 ± 5.2; 35.3 (27.0-44.9)	<.0001
ASMI (kg/m^2)	9.2 ± 1.2; 9.1 (6.7-12.8)	10.9 ± 1.3; 10.9 (8.7-13.6)	<.0001
ASM/weight x 100 (%)	21.2 ± 2.1; 21.0 (16.2-28.3)	24.9 ± 2.8; 24.9 (20.2-29.2)	<.0001
ASM/BMI	0.572 ± 0.072; 0.571 (0.404-0.834)[b]	0.783 ± 0.112; 0.829 (0.596-0.958)	<.0001

[a]Terminology for variables selected for consistency and may differ from terms used by original authors. [b]Variable not normally distributed. [c]Waist circumference not available for the entire cohort: females (n=81, 78.6%) and males (n=13, 76.5%). SD: standard deviation; BMI: body mass index; FM: fat mass; FFM: fat free mass; FMI: fat mass index; LST: lean soft tissue; LSTI: lean soft tissue index; ASM: appendicular skeletal mass. p<.05.

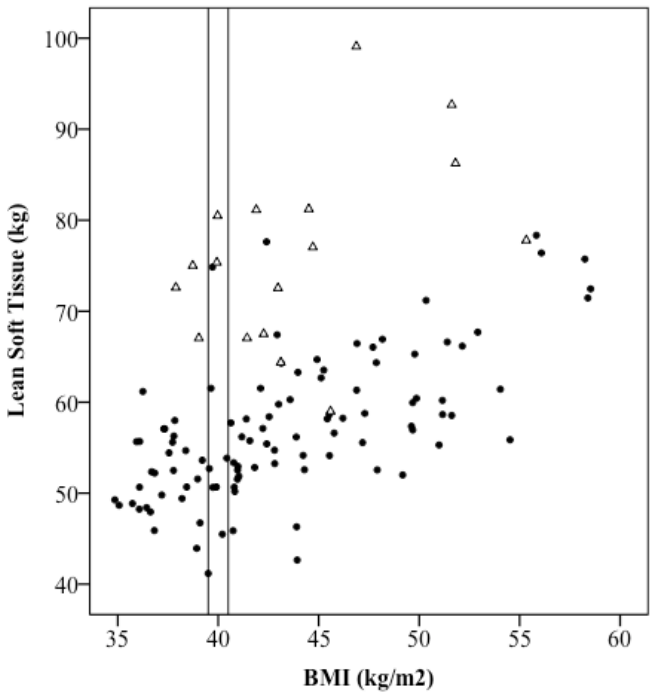
Table 4.4. Prevalence of sarcopenic obesity in the study cohort (n=120) using various sex-specific definitions determined by anthropometric and dual-energy X-ray absorptiometry measurements amongst studies investigating sarcopenic obesity.

Variables[a]	**Reference**	**Females (n=103)**		**Males (n=17)**	
		Cutpoint	**Prevalence, %**	**Cutpoint**	**Prevalence, %**
LSTI (kg/m^2)	Zoico et al., 2004(15)	<5.70	0	NA	NA
LST/weight x 100 (%)	Kim et al., 2009(16)	<30.70	0	<35.71	0
	Zoico et al., 2004(15)	I) 23.1 - 26.7	0	NA	NA
		II) <23.1	0	NA	NA
ASM (kg)	Batsis et al., 2015(17)	<15.02	0	<19.75	0
ASMI (kg/m^2) [b]	Zoico et al., 2004(15)	I) 4.7 -5.6	0	NA	NA
		II) <4.7	0	NA	NA
	Kim et al., 2009(16)	<5.14	0	<7.40	0
	Baumgartner et al., 1998(18), 2004(24)	<5.45	0	<7.26	0
	Newman et al., 2003(19)	<5.67	0	<7.23	0
	Bouchard et al., 2009(20)	<6.29	0	<8.51	0
	Kim et al., 2009(16)	<7.36	4.9	<8.81	5.9

Variables[a]	Reference	Females (n=103)		Males (n=17)	
		Cutpoint	Prevalence, %	Cutpoint	Prevalence, %
ASM / weight x 100 (%)	Levine & Crimmins, 2012(21)	<19.43	23.3	<25.72	58.8
	Oh et al., 2015[c] (22)	<23.4	84.5	<29.6	100
ASM / BMI (kg/m^2)	Batsis et al., 2015(17)	<0.512	18.4	<0.789	47.1
ASM adjusted for height and fat mass (residuals) [b]	Newman et al., 2003(19)	< -1.73	0	< -2.29	23.5
ASMI and FMI (phenotype)	Prado et al., 2014(6)	HA-LM[d]	12.6	HA-LM[d]	17.6
FM:FFM ratio	Siervo et al., 2015(23)	≥ 85th percentile	28.2	≥85th percentile	76.5

[a]Terminology for variables selected for consistency and may differ from terms used by original authors. [b]Where applicable, equivalent cutpoints derived from the study-specific cohort are listed in the text. [c]Cutpoints determined from reported sex-specific mean and standard deviation in Oh et al., 2015. [d]HA-LM: high adiposity (FMI 50-100) and low muscle mass (ASMI 0-49.99) with individual z-scores based upon age, sex, and BMI. LST: lean soft tissue; LSTI: lean soft tissue index; NA: not applicable; SD: standard deviation; y: years; ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal mass index; BMI: body mass index; FM: fat mass; FFM: fat free mass; FMI: fat mass index.

A.



B.

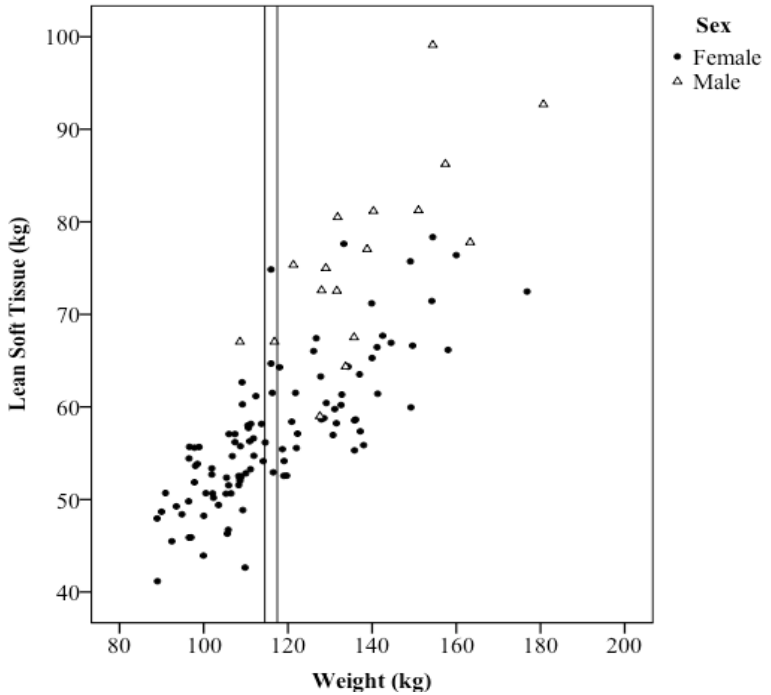


Figure 4.1. Variability of lean soft tissue by A) body mass index (BMI) and B) weight in adults with class II/III obesity (n=120, females=103).

The box illustrates selected examples of females with A) the same BMI (40 kg/m^2) but LST varying from 41.2 - 74.9 kg, and B) same weight (116 kg) but LST varying from 52.9 - 74.9 kg.

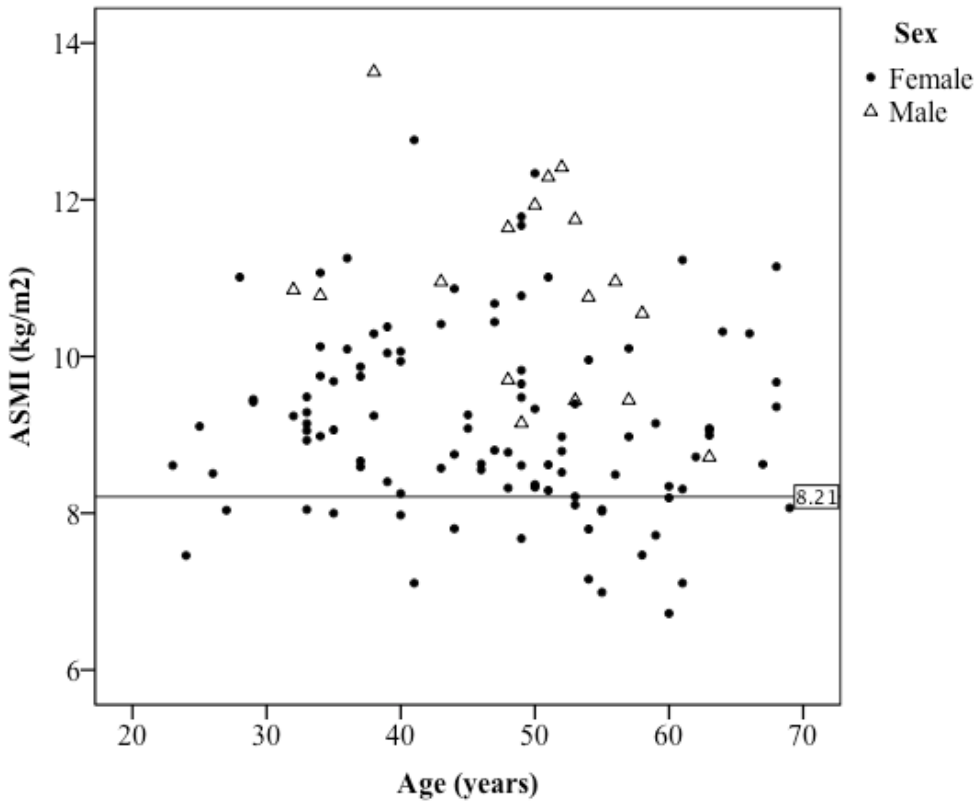


Figure 4.2. Variability of appendicular skeletal mass index (ASMI) by age (23 - 69 years) in adults with class II/III obesity (n=120, females=103).

The horizontal line on the figure indicates the 20th percentile of ASMI for females; participants below this level ranged in age from 24 to 69 years.

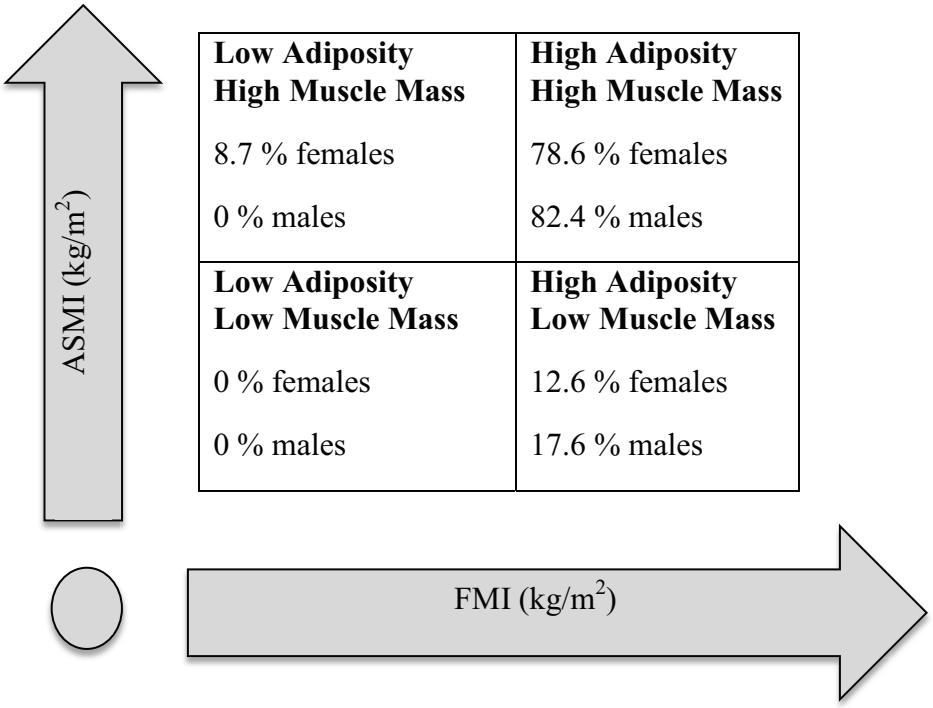


Figure 4.3. Body composition phenotype, by decile groups of appendicular skeletal mass index (ASMI) and fat mass index (FMI), for adults with class II/III obesity (n=120, females=103) (reference 6).

Chapter 5: Clinical characteristics of sarcopenic obesity in adults with class II/III obesity

Preface

In order to define and describe sarcopenic obesity in our cohort, this chapter builds upon the work from Chapter 4 and explored the five definitions that identified participants with sarcopenic obesity. The final selected definition needed to be clinically relevant to the sample; therefore it was determined to select the definition in relation to self-reported difficulty with activities of daily living. Sarcopenic obesity was then identified using cohort-derived and sex-specific cutpoints, which enabled comparisons to with the non-sarcopenic obese group. The clinical characteristics of both groups and the associated factors of sarcopenic obesity are presented.

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5.1 Introduction

Changes in human body composition are a natural part of the aging process. An increase in fat mass is typically seen from middle age up to age 60 – 70 years. Conversely, lean mass peaks around age 30, after which it begins to decline, with accelerated losses in older age (1). In addition to normal effects of aging, lower lean mass is associated with low physical activity, illness, low protein intake, inflammation, certain hormonal and neurological conditions, among others (2).

Obesity treatment can change body composition as weight loss may result in reductions in both fat mass and lean mass. Weight cycling (weight gain after weight loss) is common among individuals with obesity (3-5) and is associated with unfavourable body composition changes, as weight regain is mostly attributed to increased fat mass with lean mass remaining lower than baseline (i.e., prior to weight loss) (6). Numerous weight loss attempts, over time, combined with the normal aging trajectory, can put individuals at risk for abnormal body composition, particularly sarcopenic obesity (5).

Sarcopenic obesity is described as the co-existence of low lean mass with excess adiposity (7). Several definitions for sarcopenia exist mostly based on sex-specific cutpoints for low lean mass either derived from a young reference population or from the study cohort (i.e., one or two standard deviations below the mean of the distribution or the lower quintiles)(8). Definitions based on a health outcome of interest are highly relevant and have been increasingly used in non-clinical and clinical settings (9-11). Due to the variety of definitions (for obesity and sarcopenia) and methods to assess body composition, the estimates of the prevalence of this combined condition are highly variable (12). Studies have identified sarcopenic obesity in certain populations; older adults (13) and those with specific chronic diseases such as cancer (11, 14),

and end-stage renal disease (15), among others. In older adults, sarcopenia is associated with difficulties with activities of daily living (ADL) (13, 16) and functional impairment (17, 18). Excess adiposity and low lean mass can compound negative effects on cardiovascular and metabolic health (19-23). In fact, sarcopenic obesity has been shown to be associated with cardiovascular disease, vitamin D deficiency infection, disability, and mortality (24, 25). Although most studies to date have focused on older adults (defined as 60, 65, or 70 years and older), sarcopenic obesity has been identified in young-to-middle aged individuals (26, 27). However, to our knowledge, the clinical characteristics of this condition in a younger cohort with class II/III obesity has yet to be explored.

The purpose of this study was two-fold. First, to determine the definition of sarcopenia which best-discriminated adults with class II/III obesity based on a clinical outcome of interest. Second, to apply this definition and compare the clinical characteristics of participants with sarcopenic obesity versus their non-sarcopenic obese counterparts.

5.2 Methods

Participants

A cross-sectional, retrospective analysis was conducted on patients from an obesity specialty clinic. This publicly funded program is located within a large metropolitan area (population 1.2 million) (28), assessing patients from local and surrounding areas referred by their physician. Registered nurses completed the patient history and clinical assessment at the initial visit. Height (cm), weight (kg), waist circumference (cm) and blood pressure (mmHg) were measured using standardized procedures and recorded in the patient chart. Requisitions for body composition by dual-energy X-ray absorptiometry (DXA) and biochemical analysis (blood work values) were provided to each patient. Biochemical variables included in this analysis were based upon biomarkers previously explored in the sarcopenic obesity literature associated with metabolic health, and when the variables were available for the majority of participants (at least 75 %). Availability of DXA scans and further details on data collection have been previously described (8). Data collection form is available in **Appendix 1**. All participants were adults (18 – 69 years) with class II/III obesity (BMI ≥35 kg/m^2) who completed the initial assessment and had a DXA body composition scan in their medical record. Exclusion criteria included age (≥70 years), and those who had incomplete DXA data.

Body composition

BMI was calculated with measured values for height (cm) and weight (kg). Body composition analysis by DXA (Hologic Discovery A/W, Hologic Inc., Bedford MA.) was completed at a local imaging centre with collected values for fat mass (FM), lean soft tissue (LST), fat-free mass (FFM; composed of bone and LST) for whole body and segmental values (appendicular skeletal mass [ASM]; composed of the LST from arms and legs). Variables were adjusted by

height in square meters to calculate fat mass index (FMI) and ASM index (ASMI). DXA scans included in the analysis were ordered at the initial assessment (prior to obesity treatment) and available from January 2009 to June 2012.

Biochemical analysis and comorbidities

Completed biochemical analyses (blood work values) were reported as mean ± standard deviation (SD) and median [range], with the number of participants identified for variables with missing values. Abnormal results were identified based upon the reference values from the processing laboratory. Comorbid conditions were identified based upon review of medical history/prescription medications and values collected at the initial assessment.

Abnormal reference ranges for biochemical values included: estimated glomular filtration rate (eGFR) <60 ml/min /1.73 m^2, c-reactive protein (CRP) >10 mg/L, albumin <35 g/L, 25-OH vitamin D_3 <80 nmol/L, vitamin B12 <150 pmol/>, creatinine <50 μmol/L. Diagnostic criteria for certain comorbid conditions included: diabetes mellitus: fasting blood glucose (FBG) ≥7.0 mmol/L and/or glycated hemoglobin (HbA1C) ≥6.5 %; prediabetes: fasting blood glucose 6.1–6.9 mmol/L and/or HbA1C 6.0 – 6.4 %; dyslipidemia: total cholesterol (TChol) ≥6.2 mmol/L, low density lipoprotein (LDL) ≥3.2 mmol/L, high density lipoproteins (HDL) females <1.3 mmol/L and males <1.0 mmol/L, triglycerides (TG) >1.7 mmol/L, hypertension ≥140/90 mmHg. To account for all cases of abnormal glycemic control, participants with abnormal biochemical values meeting criteria for either diabetes or prediabetes were combined as a dichotomous categorical variable. Mental health was defined as a diagnosis and/or use of prescription medication for diagnosed mental health conditions. Metabolic syndrome was defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) reference values with three or more of the five criteria: hypertension (≥130/85 mmHg), elevated TG (≥1.7

mmol/L), low HDL (females <1.3 mmol/L, males <1.0 mmol/L), elevated FBG (≥5.6 mmol/L), and high waist circumference (females >88 cm, males >102 cm) (29).

To identify if individuals were affected by more than one chronic disease, a mulitmorbidity categorical score (0, 1, 2, 3 or more) was developed based upon available data from the clinic-specific patient initial assessment form. This score was based on similar mulitmorbidity scores in the literature (30-32) and included eight comorbid conditions (diabetes/prediabetes, hypertension, dyslipidemia, metabolic syndrome, mental health, chronic kidney disease, sleep apnea, and osteoarthritis). In order to explore the related impact of obesity and related comorbidities on health and function, a modified version of the Edmonton Obesity Staging System (EOSS) (33, 34) was developed from data available for this cohort (see supplementary material, **Table 5.1S)** using a method similar to Kuk et al. (35). Each participant was categorized with a stage, from 0 – 4, based upon the highest single ranking for any comorbidity if more than one was identified.

Activity level and difficulties with activities of daily living

At the initial clinic visit, patients were asked about their usual physical activities based upon type of activity, time spent performing each activity and the perceived intensity level. Physical activity levels for each participant were recorded on the participant data collection form then categorized as either "met" or "did not meet" Canadian Physical Activity Guidelines for Adults (CPAG), defined as accumulating 150 minutes or more of moderate-to-vigorous intensity activities in a week, in bouts of 10 minutes or more (36).

An occupational therapy (OT) referral screening questionnaire was developed by the clinic occupational therapist, in consultation with OT colleagues and based upon principles of the

Canadian Model of Occupational Performance (CMOP) (37), to identify patients to refer for an assessment by an occupational therapist (**Appendix 2**). The paper-and-pencil questionnaire was completed by each participant at their initial assessment visit with 11 items that asked about their experiences and ability to perform a variety of tasks, including: 1) Transfers: getting in/out of your car, bed, bathtub, or on/off the toilet; 2) Falls: recent falls or feeling unsteady with these activities; 3) Wash Body: ability to wash whole body; 4) Skin Problem: skin problems such as redness, infections or wounds; 5) Wipe Self: ability to wipe self after toileting; 6) Dress Self: ability to dress self; 7) Tired-Housework: cannot complete household tasks such as cooking, cleaning and laundry because of getting tired easily; 8) Tired-Leisure: cannot complete everyday tasks and enjoyable activities because of easily getting tired; 9) Excess Skin: excess skin on stomach making it hard to move around and complete daily activities; 10) Access Rooms: accessing areas of home such as bathroom, bedroom or laundry; 11) Footwear: use of custom footwear or orthotics, or considered getting them. Each participant identified their experienced difficulty with a dichotomous "yes" or "no" answer to each item, scored as 1 or 0, respectively. Participants also had the choice to report, "I have help" for some items, in which case a score of 1 was assigned. The maximum score for each item was 1. Therefore, the higher the score, the more items for difficulty with ADL were reported. A composite score for items on the questionnaire was also calculated as a continuous variable [range 0 – 11]. Additionally, a dichotomous categorical variable for the questionnaire was explored, defined as "0 – 2" or " ≥3 " items. This categorical variable was used to explore the selected definition for sarcopenic obesity, as described in the next section.

Defining sarcopenic obesity

As all participants had BMI ≥35 kg/m^2, therefore they all had obesity (class II and III).

Based upon our previous study, five DXA-derived definitions of sarcopenia were explored for identifying sarcopenic obesity in this study (8) but these were not tested in regards to its predictive ability. Following the approach of previous studies, sarcopenia was identified based on a clinically meaningful cutpoint, a value below which individuals would be at an increased risk for a health outcome (9-11, 38, 39). The choice of difficulty with ADL as the outcome of interest was due to the association with reduced physical function, increased disability, and poor quality of life (16, 24, 38, 40). Difficulties with ADL are notably a common health consequence of sarcopenia (41). Therefore, our sex-specific cutpoints and definition for sarcopenic obesity was developed based on its discriminative and predictive ability using a data-driven approach (39).

For each sex-specific sarcopenia definition (see supplementary material, **Table 5.2S)**, correlation of the continuous body composition variable was evaluated with the continuous variable for difficulty with ADL. The definition of choice being the one most significantly correlated with items of difficulty with ADL.

With the selected definition, the next step was to determine the cohort-specific cutpoint that would best-discriminate difficulty with ADL as a dichotomous variable. Receiver operating curves (ROC) were then used to determine sex-specific cutpoints of the continuous body composition variable selected to define sarcopenia based upon the two categories for difficulty with ADL (0 – 2 items vs. ≥3 items), with high sensitivity as the priority criteria to identify a greater number of true positives. The area under the curve (AUC) was then explored with sensitivity and specificity used to identify the optimal cohort- and- sex-specific cutpoints for the total difficulties with ADL score (continuous variable). These cutpoints were used to create a dichotomous categorical variable: sarcopenic obesity versus non-sarcopenic obesity. To

determine the level of agreement between the two definitions, the body composition variable calculated with the new cohort-derived cutpoints was then compared, using Chi-square test and kappa statistics, with the variable calculated using the original study cutpoints from the selected sarcopenic obesity definition.

Statistical analysis

Descriptive statistics were used for participant characteristics, anthropometrics, body composition analysis and biochemical analysis, reported as mean ± SD and median (range). Normality testing was completed with the Shapiro-Wilk test. Categorical variables were reported as frequencies and proportions. Mean values of two groups were compared using independent samples t-tests (Mann-Whitney U for non-parametric data). Chi-square test was used to examine the association between two categorical variables, except if frequency of variables was less than five, then Fisher's exact test was used. Pearson's correlation was used to test the correlation between two continuous variables (Spearman's rho for non-normally distributed continuous variables). As cutpoints to define sarcopenic obesity and non-sarcopenic obesity were sex-specific, comparisons among these variables were shown for the entire sample.

Cronbach's alpha was used to determine the internal consistency for the items on the questionnaire for difficulty with ADL. A p-value of $<.05$, based on two-tailed tests, was considered statistically significant. Binary logistic regression was used to determine the predictive factors for difficulty with ADL. Univariate logistic regression was used to select variables ($p<.10$) to be entered into multivariate models, with the final model was selected at $p<.05$, adjusted for age and sex. Data analysis was completed with IBM SPSS Statistics version 23 (IBM Corp., Armonk, N.Y., USA).

5.3 Results

Participant characteristics

Of 167 cases reviewed, a total of 120 participants had available DXA data (per inclusion criteria) and were included in the final analysis. Participant demographics and anthropometrics are presented in **Table 5.1.** The sample was predominately female, middle-aged, married/common law, well educated, and working outside the home.

Body composition

Results for body composition analysis are presented in **Table 5.1** for both females and males. Both weight and waist circumferences were highly variable, with differences of about 92 kg and 70 cm between the highest and lowest values, respectively. Body composition was different between sexes for all body composition variables. Compared to males, females had lower LST and higher fat mass with similar findings between derivatives of these variables.

Biochemical analysis and comorbidities

Results for biochemical analysis (serum, fasting) are presented in **Table 5.2**. Based on mean values, most results were within the normal reference ranges, with the exception of 25-OH vitamin D_3 that was below the normal limit (<80 nmol/L). Variables with the highest prevalence of abnormal values were: 25-OH vitamin D_3, HDL, LDL, CRP, and HbA1C. The lowest prevalence of abnormal values was identified for the following variables: total protein, albumin, eGFR, vitamin B12 and creatinine.

All participants presented with at least one comorbidity in addition to obesity, **Table 5.3**. Most prevalent comorbidities were dyslipidemia, followed by metabolic syndrome and hypertension. Multimorbidity was highly prevalent in the sample; 80.8 % had three or more comorbid

conditions in addition to class II/III obesity. The majority of participants were classified in EOSS Stage 2. No participants were classified in EOSS Stage 0 and because details regarding the severity of chronic diseases were not available, EOSS Stage 4 was not classified.

Activity level and difficulty with activities of daily living

Activity levels and items reported for difficulty with ADL are presented in **Table 5.3.** A higher proportion of younger participants met the activity guidelines: 36 % (18–39 years) vs. 14 % (40–59 years) and 11 % (≥ 60 years), p=.015. No differences were observed by sex (p=.695) or BMI category (p=.427) between those meeting or not meeting activity guidelines.

Of the 111 respondents (data unavailable for nine participants), 11 % reported no difficulties with ADL. Participants across all ages and BMI categories reported difficulties with ADL. More than half of the cohort reported difficulty with three or more items. Prevalence of comorbidities were not different comparing participants reporting difficulty with 0–2 items versus those reporting ≥3 items.

Sarcopenic obesity definition

From the five sarcopenia definitions explored (supplementary material, **Table 5.2S**), two were significantly correlated with items of difficulty with ADL for the entire cohort: ASM/weight x 100 (%) (21, 22) (r=-0.262, p=.005) and FM/FFM ratio (44) (r=0.230, p=.015). For both definitions, lower lean mass was associated with higher number of items of difficulty with ADL. Nonetheless, only the ASM/weight x 100 (%) definition was also significantly correlated for both sexes [females (r=-0.232, p=.024); males (r_s =-0.510, p=.037)]. Therefore, this variable was selected to define sarcopenia in our cohort. ASM/weight x 100 (%) for the entire cohort (n=120) was 21.7 ± 2.6 %; 21.5 [16.2-29.2]. Cohort-derived sex-specific cutpoints were then determined;

for females the value was 19.35 % (sensitivity 86 %, specificity 29 %) and for males the value was 24.33 % (90 % sensitivity, 86 % specificity). Applying these cutpoints, the prevalence of sarcopenic obesity in the entire sample was 25 % (22.3 % of females and 41.2 % of males). Mean values for ASM/weight x 100 (%) for participants with sarcopenic obesity was 19.3 ± 1.8 % and 22.5 ± 2.3 % for the group with non-sarcopenic obesity ($p < .0001$).

Correlations for the definition for sarcopenic obesity (as dichotomous categorical variable: sarcopenic obese vs. non-sarcopenic obese) with the categorical variable for difficulty with ADL (0-2 vs. ≥3 items) were significant ($p=.006$). The ability for these ADL categories to discriminate sarcopenia was moderate for females [AUC= 0.60, 95% CI (0.49 – 0.71)] and strong for males [AUC= 0.90, 95% CI (0.74 – 1.00)]. There was a high level of agreement ($k=0.915$) between our cohort-specific definition and the Levine & Crimmins (21) published cutpoints for ASM/weight x 100 (%) derived from a young reference group.

Clinical characteristics of sarcopenic obesity

No differences for most demographic variables were observed between participants in the sarcopenic obese versus non-sarcopenic obese groups, except for age and sex (prevalence for each sex reported above). Participants age ranged from 23 to 69 years in the sarcopenic obese group, compared to 24 to 68 years in the non-sarcopenic obese group. Mean age was higher for the sarcopenic obese group (50.7 ± 12.7 vs. 45.7 ± 10.3 years, $p=0.033$). Sarcopenic obesity was significantly higher among participants ≥ 65 years (66.7 vs. 22.8 %, $p=.016$). Smoking status (never vs. former) was not different between groups and no current smokers were identified with sarcopenic obesity. Although all participants waist circumference measurements exceeded recommendations, individuals with sarcopenic obesity presented with a higher mean waist circumference compared to their counterparts (130.2 ± 21.1 vs. 121.1 ± 11.7 cm, $p=.004$).

A comparison of clinical characteristics between sarcopenic obese and non-sarcopenic obese participants was presented in **Table 5.4.** No significant differences between groups were identified for most biochemical variables, with the exception of albumin and triglycerides. Only two participants had hypoalbuminemia and both were identified with sarcopenia. Compared to the non-sarcopenic obese group, participants with sarcopenic obesity presented with higher mean triglycerides levels (2.06 ± 1.00 vs. 1.62 ± 0.73 mmol/L, p=.040), which in turn overall exceeded the normal reference value (<1.7 mmol/L). Only a trend towards a difference was found between the groups using a comparison between abnormal vs. normal triglyceride levels, **Table 5.4.**

A greater percentage of participants with sarcopenic obesity had renal impairment (e-GFR <60 ml/min/1.73 m^2), yet overall the majority of the cohort had normal renal function. Low HDL was the most prevalent dyslipidemia value, but not different between the groups. There were no differences for mean CRP levels (sarcopenic obesity 8.07 ± 5.40 mg/L vs. 7.58 ± 6.51 mg/L for non-sarcopenic obesity, p=.731). Participants in both sarcopenic and non-sarcopenic obese groups had a high prevalence of low 25-OH vitamin D_3 levels, with no differences between groups.

The presence of comorbid conditions was not different between groups. For participants with sarcopenic obesity, use of medications for hypertension was higher compared to their counterparts, although no difference was identified for the prevalence of hypertension or blood pressure measures (systolic 130 ± 12 vs. 130 ± 14 mmHg, p=.955 and diastolic 77 ± 12 vs. 80 ± 9 mmHg, p=.146 for sarcopenic obese and non-sarcopenic groups, respectively). Individuals with sarcopenic obesity were less likely to meet physical activity guidelines, **Table 5.4**. In participants who met the guidelines, 95.8 % were in the non-sarcopenic obese group. All participants who met activity guidelines were categorized in EOSS stage 2.

Regarding ADL, the majority of participants responded "yes" to at least one item of the questionnaire. The ADL questionnaire had good internal consistency (11 items, α=.848). Participants with sarcopenic obesity responded "yes" to more items for difficulty with ADL, compared to their counterparts (p=.006). Nearly three-quarters of participants with sarcopenic obesity reported difficulty with ≥ 3 items compared to less than half (44 %) reporting 0 – 2 items. As shown in **Figure 5.1A,** values for ASM/weight x 100 (%) were significantly lower for participants who responded "yes" to five separate items on the questionnaire: transfers (p=.046), wiping self (p=.030), fatigue as a barrier to household (p=.017) and leisure activities (p=.009), and access to rooms in the home (p=.020), The prevalence of self-reported difficulty with ADL for each item between sarcopenic obesity and non-sarcopenic obese groups is presented in **Figure 5.1B,** with significant differences identified for six of the 11 items: transfers (p=.023), falls (p=.030), dress self (p=.021), fatigue as a barrier to household (p=.004) and leisure activities (p=.025).

Binary logistic regression analysis was used to identify significant predictors of ≥ 3 items of difficulty with ADL. The univariate analysis identified four variables, of which two were included in the final multivariate model (**Table 5.5**). Waist circumference was removed from the final model due to colinearity with sarcopenic obesity definition and missing data (22 % of the sample). Activity level was also excluded, as it did not contribute to the final model. Sarcopenic obesity emerged as an independent predictor for difficulty with ADL (≥3 items), in spite of sex, age and multimorbidity [OR=5.4 (95%CI= 1.81 - 16.42), p=.003].

5.4 Discussion

This is the first study to define sarcopenic obesity in a young-to-middle aged adult cohort class II/III obesity using a clinically relevant outcome of interest. Additionally, this is the first study that profiles the clinical characteristics associated with this condition. Although present across the age spectrum, sarcopenic obesity was significantly associated with older age, higher waist circumference, higher triglycerides, use of anti-hypertensive medications, inactivity and more items of difficulty with ADL. Importantly, sarcopenic obesity was an independent predictor for a greater number of items of difficulty with ADL, after controlling for age, sex, and multimorbidity.

The diagnosis of sarcopenic obesity is a challenge for both research and clinical settings (12). As explored in our previous publication (8), definitions accounting for measures of body mass or fat mass may better identify individuals with this body composition type. Here, lower ASM/weight x 100 (%) was correlated with a higher number of items for difficulty with ADL. Similar to our approach, Janssen et al. (18) defined sarcopenia by lean mass in proportion to total body mass using total skeletal mass, although body composition was measured by bioelectrical impedance analysis. This method was later adapted by Lim et al. (22) who used DXA-derived ASM/weight x 100 (%) to identify sarcopenia in a sample of elderly Koreans (≥ 65 years). Our approach has also been previously used by Levine & Crimmins (21) in a sample of elderly North Americans. The DXA-derived sarcopenic obesity, sex-specific cutpoints in the last two studies were based on young reference groups (21, 22). Lim et al. defined their cutpoint (females <25.1 %, males <29.9 %) as one standard deviation below the mean of Korean adults, reporting a prevalence of sarcopenic obesity in 48.1 % of females and 35.1 % of males (obesity defined as visceral fat area ≥ 100 cm^2) (22). Conversely, Levine & Crimmins defined their cutpoint (females <19.43 %,

males <25.72 %) as two standard deviations below the mean of a sample of American adults, reporting 10.4 % prevalence of sarcopenic obesity in their sample (obesity defined as waist circumference females >88 cm, males >102 cm) (21). As reported in our previous study (8), when the Levine & Crimmins (21) cutpoints were applied to the current cohort, sarcopenic obesity was observed among 23.2 % of females and 58.5 % of males. Due to the uniqueness of our cohort (younger individuals with class II/III obesity) and the interest to tie the definition to a clinical outcome, cohort-and sex-specific cutpoints were explored using the same body composition variable (ASM/weight x 100, %). The resulting cutpoints (females <19.35 %, males < 24.33 %) were very similar for females and slightly lower for males, compared to the Levine & Crimmins (21) values, leading to an overall higher prevalence of sarcopenic obesity (25 % vs. 10 % for the former study; sex-specific prevalence not reported).

In our study sample, sarcopenic obesity was identified in more males than females (41.2 vs. 22.3 %). The prevalence of sarcopenic obesity by sex in the literature is variable, with some studies reporting a higher prevalence for females (43, 45), others for males (16, 26, 46), and mixed results depending on the definition applied (42, 47). Interestingly, using data from the same hereby presented cohort, we previously shown a consistently higher prevalence of sarcopenic obesity in males among 18 definitions (8). In North America, class III obesity affects more females than males (48, 49). Differences in body composition between sexes may be associated with sex hormones including estrogen and testosterone, influencing both fat and lean tissues (50-53).

As explained in the methods section, the decision to base the cutpoints on a clinical outcome of interest (difficulty with ADL) was related to the clinical relevance of the sarcopenic obesity diagnosis. In our study, ASM in proportion of total body weight (ASM/weight x 100, %) was the

best variable identifying sarcopenic obesity in relation to difficulties with ADL. Several other studies reported an association between lower relative lean mass and greater difficulty with ADL and function (18, 21, 45). The cohort derived sex-specific cutpoints were based upon the sensitivity and specificity of ASM/weight x 100 (%) and the items of difficulty with ADL. Ideally, the selected cutpoint would have both high sensitivity, to correctly identify participants who have sarcopenic obesity (true positives), and high specificity, to correctly identify those participants who did not have sarcopenic obesity (true negatives). ROC curves were then used to explore the true positives plotted against the false positives. For males, the selected cutpoint achieved both high sensitivity and specificity. For females, when higher cutpoints were explored, the number of false positives was reduced (improving specificity), but the number of false negatives increased (reducing sensitivity). The decision was then to prioritize higher sensitivity in order to select a cutpoint for females that would best identify individuals with sarcopenic obesity. Specificity was still important, with the highest value at least in the moderate range in combination with high sensitivity guided the final decision for the cutpoints.

There were not as many differences as expected when comparing biochemical variables between sarcopenic vs. non-sarcopenic obese individuals. Although hypoalbuminemia (n=2) was correlated with sarcopenic obesity, a larger sample size is needed to explore its true association with sarcopenic obesity. Elevated CRP, a biomarker for systemic inflammation and associated with obesity, sarcopenia, metabolic syndrome and cardiovascular disease was identified in ~30 % of the study cohort, but the prevalence was not different between participants in either group. Our results are in agreement with those of Levine & Crimmins, who found no difference in CRP values between both participants in the obese groups (sarcopenic and non-sarcopenic) (21).

Although studies of older adults report an association between sarcopenic obesity with metabolic syndrome and insulin resistance (21, 22), we were unable to observe such differences in our study. In spite of the availability of fasting blood glucose, fasting insulin was not available. Therefore, calculation of a measure of insulin resistance using the homeostatic model assessment of insulin resistance (HOMA-IR) was not possible. Skeletal muscle is one of the largest users of glucose in the body, being essential to glucose metabolism (54). Sarcopenic obesity was been associated with impaired glucose tolerance and insulin resistance (45, 55).

The majority of the sample (80.8 %) had multimorbidity (three or more chronic conditions), in addition to class II/III obesity. Multimorbidity has been reported in 3.9% of the general adult Canadian population (31). In this Canadian study, although obesity was associated with multimorbidity, only 6.9 % of those with multimorbidity had obesity (31). Our results were nonetheless consistent with previous studies reporting a high prevalence of multimorbidity in adults seeking obesity treatment (30).

EOSS has been used as a way to profile the impact of obesity and related comorbidities. Higher EOSS stages have been previously associated with increased mortality (34). Information regarding the severity of comorbidities was limited at the time of initial assessment, restricting our ability to categorize participants into EOSS stage 4. This limitation was reported by Kuk et al., (35) who also developed a modified version of EOSS for their study. More information regarding the severity and impact of comorbidities is needed to further differentiate between EOSS stages 2, 3 and 4.

As mentioned earlier, the prevalence of metabolic syndrome was the same for both sarcopenic obese and non-sarcopenic obese groups. However, among those with sarcopenic obesity, two of

the five criteria for metabolic syndrome (high triglycerides and high waist circumference) were more prevalent. The hypertriglyceridemic waist phenotype has been used to identify those with increased visceral adiposity, which in turn is associated with increased cardiometabolic risk and mortality (56, 57). In addition to cardiometabolic risk, the difference in serum triglyceride levels between participants with sarcopenic obesity and those with non-sarcopenic obesity may serve as biomarker for other abnormalities. The combination of obesity, inflammation and metabolic abnormalities can impact fat accumulation in the liver (hepatosteatosis) and muscle (myosteatosis) (58). Evaluating triglycerides and waist circumference is also clinically relevant to the metabolic health of this cohort.

Regarding physical activity, 80 % of participants did not meet activity guidelines, which is similar to nationally reported activity levels (78 %)(59). In a Canadian survey, a greater proportion of younger adults (32 %, age 18 – 39 years) met guidelines than those aged 40 – 59 years (18 %)(59). This is consistent with our findings that a great proportion of younger adults (>40 years) met the guidelines compared to middle-aged participants. In the current study, there were no differences by sex or BMI categories between those who met or did not meet the guidelines. However, differences emerged when comparing the two body composition phenotypes. A greater proportion of individuals with sarcopenic obesity did not meet activity guidelines, when compared to their counterparts.

Individuals with sarcopenic obesity were 5.4 times more likely to report ≥ 3 items for difficulty with ADL, independent of age, sex and multimorbidity. Maintaining independence in ADL is essential for optimal quality of life (60, 61). Difficulties with ADL were collected using the occupational therapy referral screening questionnaire. Therefore, as a screening tool, this questionnaire was used by this obesity specialty clinic to identify patients reporting difficulties

with their ADL, and refer them to occupational therapy. There are some limitations with this tool: although each item addressed a category of ADL difficulty, such as transfers, the question as stated often included more than one option (i.e., car, bed, bathtub and toilet). It was not possible to evaluate, for example, if participants only had difficulty with transferring in/out of their car or if they experienced difficulty with transfers for all four examples provided. This screening tool did not request patients to identify the reasons for the difficulties or the level of difficulty they experienced. The number of items of difficulty reported may not necessarily reflect the level of difficulty experienced or impact on their quality of life. For example, a participant could have identified 3 items of difficulty, however the impact on their ability to participate in ADL is minimal because they have help or have made adaptations. In contrast, another participant may have identified just 1 item of difficulty, yet it presented a formidable barrier of greater negative impact on their daily life. Without information on the reasons for or level of difficulty with ADL, it was not possible to explore if the reported items of difficulty were related to sarcopenic obesity and/or any other causality. Nonetheless, sarcopenic obesity was associated with a higher incidence of reported difficulties, highlighting the potential to explore the use of this tool in future research and clinical settings. Unfortunately, no measures of muscle strength, quality or function were available for analysis. Further assessment of factors influencing difficulty in participation and performance of ADL, including physical function, cognition, and strength are needed (61).

Additional limitations of our study include a small sample size of a convenience sample, and the retrospective cross-sectional design. As such, no cause-effect relationships could be determined. However, we used state-of-the-art body composition data (DXA) contributing to the limited research on participants with BMI >40 kg/m^2 whom may be excluded from obesity studies due to

equipment weight capacity limits (62). Additionally, this study highlights the impact of sarcopenic obesity in young-to-middle aged adults, who, contrary to expectations, may also experience sarcopenic obesity and its clinical consequences. Further research is needed to validate cutpoints for sarcopenic obesity in relation to clinical outcomes, such as the items of self-reported difficulty with ADL, for adults with class II/III obesity.

The goal of obesity treatment is to improve the health and wellbeing of patients, not just to achieve weight loss. It is important to recognise that young-to-middle aged adults, who normally would not be considered "at risk", experienced difficulties with ADL that may in part be due to sarcopenic obesity. As body composition is related to metabolic and functional health, its accurate assessment could identify individuals at risk for sarcopenic obesity, while also being used to monitor effectiveness of treatment to improve clinical outcomes.

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5.6 Tables and Figures

Table 5.1. Demographic, anthropometric, and body composition characteristics of adults with class II/III obesity (n=120).

Variables	% or mean ± SD; median (range)
Demographics	
Sex	
Female	85.8 %
Age, years	46.9 ± 11.1; 49.0 (23-69)
Marital status	
Single	23.3 %
Married/common law	67.5 %
Divorced/separated/widowed	9.2 %
Education	
Some high school	2.5 %
Completed high school	97.5 %
Completed post-secondary	53.3 %
Employment	
Full-time	53.3 %
Part-time	14.2 %
Unemployed	6.7 %
On disability	7.5 %
Homemaker	5.8 %
Retired	12.5 %
Smoking	
Never	45.5 %
Former	47.3 %
Current	7.3 %
Age of obesity onset	
Pediatric, ≤ 19 years	46.7 %
Adult, ≥ 20 years	53.3 %
Anthropometrics	
Height, cm	166.0 ± 7.64; 165.0 (148.6-187.1)
Weight[a], kg	120.2 ± 19.6; 116.2 (88.9-180.7)
BMI[a], kg/m^2	43.5 ± 5.7; 42.3(34.9-58.5)
35.0-39.9	33.3 %
40.0-44.9	32.5 %
45.0-49.0	19.2 %
≥ 50.0	15.0 %
Waist circumference[b], cm	123.3 ± 13.2; 122.5 (93.5-163.0)

Variables	% or mean ± SD; median (range)
Body Composition [c]	
ASM, kg	F: 24.7 ± 3.7; 24.2 (17.4-35.4)[a] M: 34.2 ± 5.2; 35.3 (27.0-44.9)
ASMI, kg/m^2	F: 9.2 ± 1.2; 9.1 (6.7-12.8) M: 10.9 ± 1.3; 10.9 (8.7-13.6)
ASM/weight x 100, %	F: 21.2 ± 2.1; 21.0 (16.2-28.3) M: 24.9 ± 2.8; 24.9 (20.2-29.2)
FM, %	F: 48.0 ± 4.2; 48.3 (32.3-57.4) M: 41.4 ± 5.6; 39.7 (31.9-53.2)
FMI, kg/m^2	F: 20.6 ± 3.8; 20.0 (13.9-30.9) [a] M: 18.0 ± 3.7; 16.9 (13.4-24.9)

[a]Variable not normally distributed for females. [b]Waist circumference available for 78 % (n=94). [c]All body composition variables were statistically different between sexes. ASM: appendicular skeletal mass; ASMI: ASM index; BMI: body mass index; F: female; FM: fat mass; FMI: fat mass index; M: male; SD: standard deviation.

Table 5.2. Biochemical analysis (serum, fasting) of adults with class II/III obesity.

Variables	n	mean ± SD; median (range)	Reference[a]	%[b]
Fasting glucose, mmol/L	114	6.1 ± 1.9; 5.5 (3.3-15.4)	6.1- 6.9	14.0%
			≥7.0	17.5%
HbA1C, %	115	6.3 ± 1.1; 6.1 (4.7-11.2)	>6.5	26.1%
Creatinine, μmol/L	116	69.1 ± 16.1; 66.0 (40-151)	<50	7.8%
eGFR[c], ml/min/1.73m^2	116	(41-121)	<60	4.3%
TChol, mmol/L	115	4.8 ± 1.1; 4.8 (2.6-7.9)	>6.2	9.6%
LDL, mmol/L	115	2.9 ± 0.9; 3.0 (1.1-5.1)	>3.2	36.5%
HDL, mmol/L	115	1.2 ± 0.3; 1.2 (0.7-1.9)	F <1.3 M<1.0	61.7%
TG, mmol/L	115	1.7 ± 0.8; 1.5 (0.6-4.3)	>1.7	43.5%
CRP, mg/L	112	7.9 ± 6.3; 6.5 (0.2-29.4)	>10.0	28.6%
Albumin, g/L	114	42 ± 3; 43 (33-49)	<35	1.8%
Total protein, g/L	115	71 ± 4; 71 (63-82)	<35	1.7%
ALT, U/L	115	30 ± 19; 25 (7-152)	>50	10.4%
Ferritin, μg/L	113	87 ± 75; 65 (6-344)	<20	14.2%
			>160	15.0%
PTH, pmol/L	113	5.1 ± 1.7; 5.0 (2.2-11.6)	>6.8	12.4%
25-OH vitamin D_3, nmol/L	113	71 ± 27; 68 (16-184)	<50	23.1%
			<80	64.6%
Vitamin B12, pmol/L	113	345 ± 196; 297 (75-1400)	<150	4.4%

[a]Reference value used by local laboratory as criteria for abnormal results (high or low) values. [b]Percentage of results for the variable for the given reference. [c]Normal estimated glomular filtration rates (CKD-EPI equation) reported by lab as " >60 " for 81 % of participants; unable to calculate mean ± SD; median. ALT: Alanine aminotransferase; CRP: C-reactive protein; eGFR: estimated glomular filtration rate; F: female; HbA1C: glycated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; M: male; PTH: parathyroid hormone;

SD: standard deviation; TChol: total cholesterol; TG: triglyceride.

Table 5.3. Clinical characteristics of adults with class II/III obesity (n=120).

Variables	n	% or mean ± SD; median (range)
Comorbidities		
Abnormal glycemic control	114	44.7 %
Diabetes		41.2 %
Impaired Fasting Glucose		3.5 %
On medication		17.5 %
Blood pressure	115	
Systolic, mmHg		130 ± 13; 130 (100-167)
Diastolic, mmHg		79 ± 10; 79 (45-102)
Hypertension		69.6 %
On medication	120	34.2 %
Chronic kidney disease	116	4.3 %
Dyslipidemia	115	92.2 %
TChol		9.6 %
LDL		36.5 %
HDL		61.7 %
TG		43.5 %
On medication	120	18.3 %
Mental health	120	55.8 %
On medication	120	30.0 %
Metabolic syndrome	117	70.1 %
Osteoarthritis	120	27.5 %
Sleep apnea	120	36.7 %
Multimorbidity score	120	

1	5.0 %
2	14.2 %
≥ 3	80.8 %

Variables	n	% or mean ± SD; median (range)
Edmonton Obesity Staging System	120	
Stage 1		0.8 %
Stage 2		83.3 %
Stage 3		15.8 %
Activity Level	120	
Meets guidelines		20.0 %
Difficulty with ADL	111	
Any item		89.2 %
0 - 2 items		45.0 %
≥3 items		55.0 %

ADL: activities of daily living; HDL: high density lipoprotein; LDL; low density lipoprotein; S.D: standard deviation; TChol: total cholesterol; TG: triglycerides.

Table 5.4. Comparison of clinical variables between sarcopenic obese versus non-sarcopenic obese groups (n=120).

Variables[a]	All[b] (n)	Sarcopenic Obese[c] (n=30)	Non-sarcopenic obese[c] (n=90)	*p*
Biochemical				
Fasting glucose >6.0 mmol/L	114	30.8 %	31.8 %	.511
HbA1C >6.5 %	115	18.5 %	28.4 %	.306
eGRF <60 ml/min/1.73m^2	116	10.7 %	2.3 %	.055
TChol >6.2 mmol/L	115	11.1 %	9.1 %	.755
LDL >3.2 mmol/L	115	29.6 %	38.6 %	.495
HDL: F <1.3, M <1.0 mmol/L	115	55.6 %	63.6 %	.450
TG >1.7 mmol/L	115	59.3 %	38.6 %	.059
CRP >10.0 mg/L	112	28.0 %	28.7 %	.943
Albumin <35 g/L	114	100 %	0.0 %	.009
25-OH vitamin D_3 <80 nmol/L	113	61.5 %	65.5 %	.710
Comorbidities				
Abnormal glycemic control	114	34.6 %	43.2 %	.436
On medication	120	13.3 %	18.9 %	.588
Hypertension	115	71.4 %	69.0 %	.805
On medication	120	50.0 %	28.9 %	.035
Dyslipidemia	115	96.4 %	90.9 %	.342
On medication	120	26.7 %	15.6 %	.173
Mental health	120	56.7 %	55.6 %	.915
On medication	120	36.7 %	27.8 %	.358
Metabolic syndrome	117	72.4 %	69.3 %	.819
Osteoarthritis	120	40.0 %	23.3 %	.077
Sleep apnea	120	43.3 %	34.4 %	.382

Variables[a]	All [b] (n)	Sarcopenic Obese[c] (n=30)	Non-sarcopenic obese[c] (n=90)	*p*
Multimorbidity Score	120			
≥3		80.0 %	81.1 %	.885
Edmonton Obesity Staging System	120			.662
Stage 2		80.0 %	84.4 %	
Stage 3		20.0 %	14.4 %	
Activity Level	120			.007
Meets guidelines		3.3 %	25.6 %	
Difficulty with ADL	111			
Any item		85.2 %	78.6 %	.584
Less vs. more items				.008
0 - 2 items		25.9 %	56.0 %	
≥3 items		74.1 %	44.0 %	

[a]Variables were compared by category: biochemical (abnormal vs. normal); comorbidities (present vs. absent); multimorbidity score (<3 vs. ≥3); difficulty with ADL: any item (yes vs. no). [b]All: Total number of participants with data for each variable from the entire cohort. [c]Percentages reported as a total within each body composition group. ADL: activities of daily living; HbA1C: glycated hemoglobin; eGFR: estimated glomular filtration rate; F: female; M: male; CRP: C-reactive protein; TChol: total cholesterol; LDL; low density lipoprotein; HDL: high density lipoprotein; TG: triglyceride.

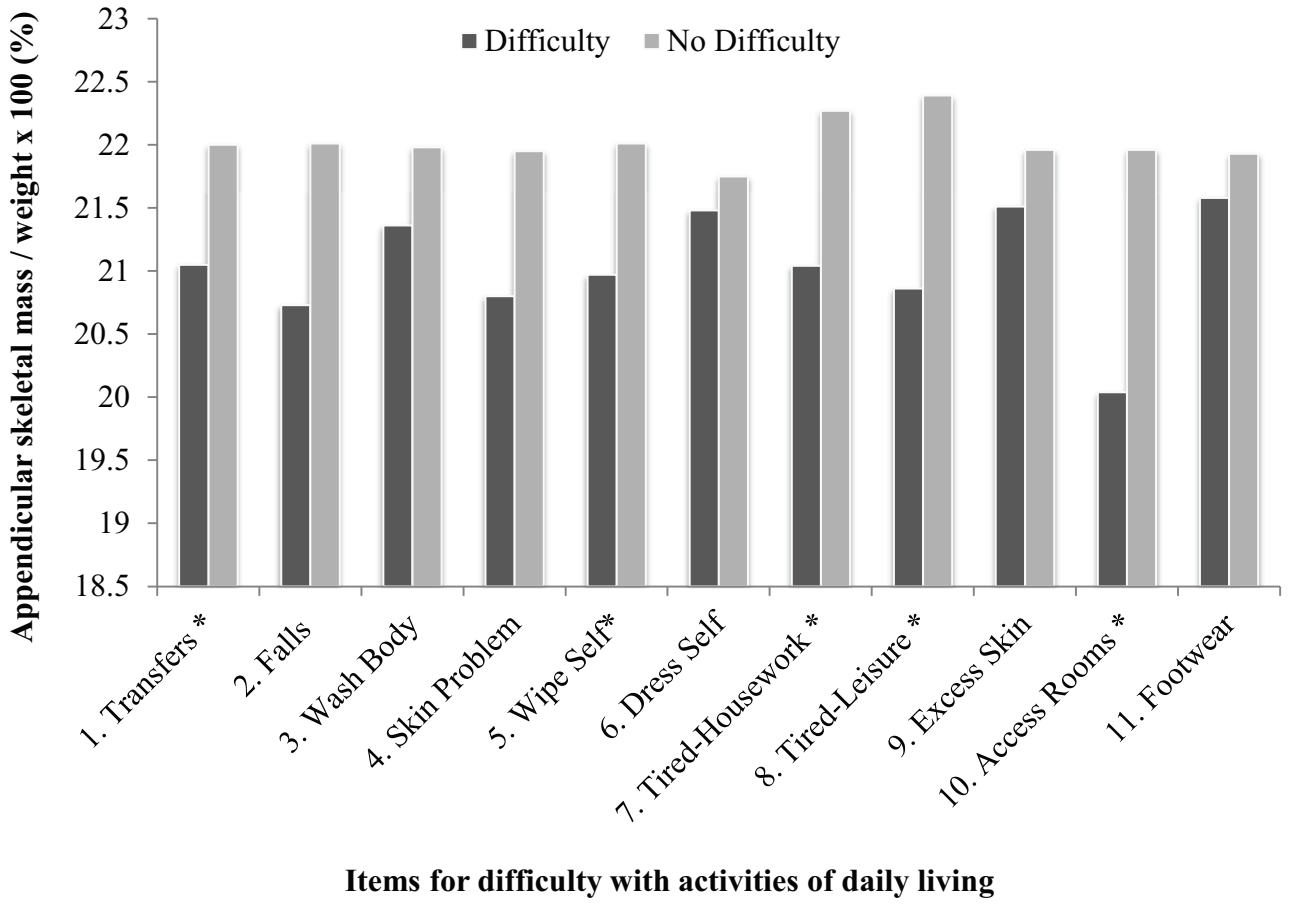
Table 5.5. Binary logistic regression for the clinical characteristics of adults with class II/III obesity with difficulty with activities of daily living (0-2 versus ≥3 items)[a].

Variables (reference category)	Univariate			Multivariate		
	Exp(B)	95% CI	*p*	Exp(B)	95% CI	*p*
Sarcopenic obesity (non-sarcopenic)	3.63	1.39-9.50	.009	5.44	1.81-16.42	.003
Multimorbidity ≥3 (<3 conditions)	2.98	1.05-8.44	.040	4.49	1.36-14.80	.014
Age	1.02	0.98-1.05	.393	1.00	0.96-1.04	.869
Female (male)	1.62	0.57-4.63	.365	2.97	0.91-9.76	.073
Inactivity (meets activity guidelines)	3.27	1.16-9.20	.025			
Waist circumference	1.04	1.00-1.08	.034			

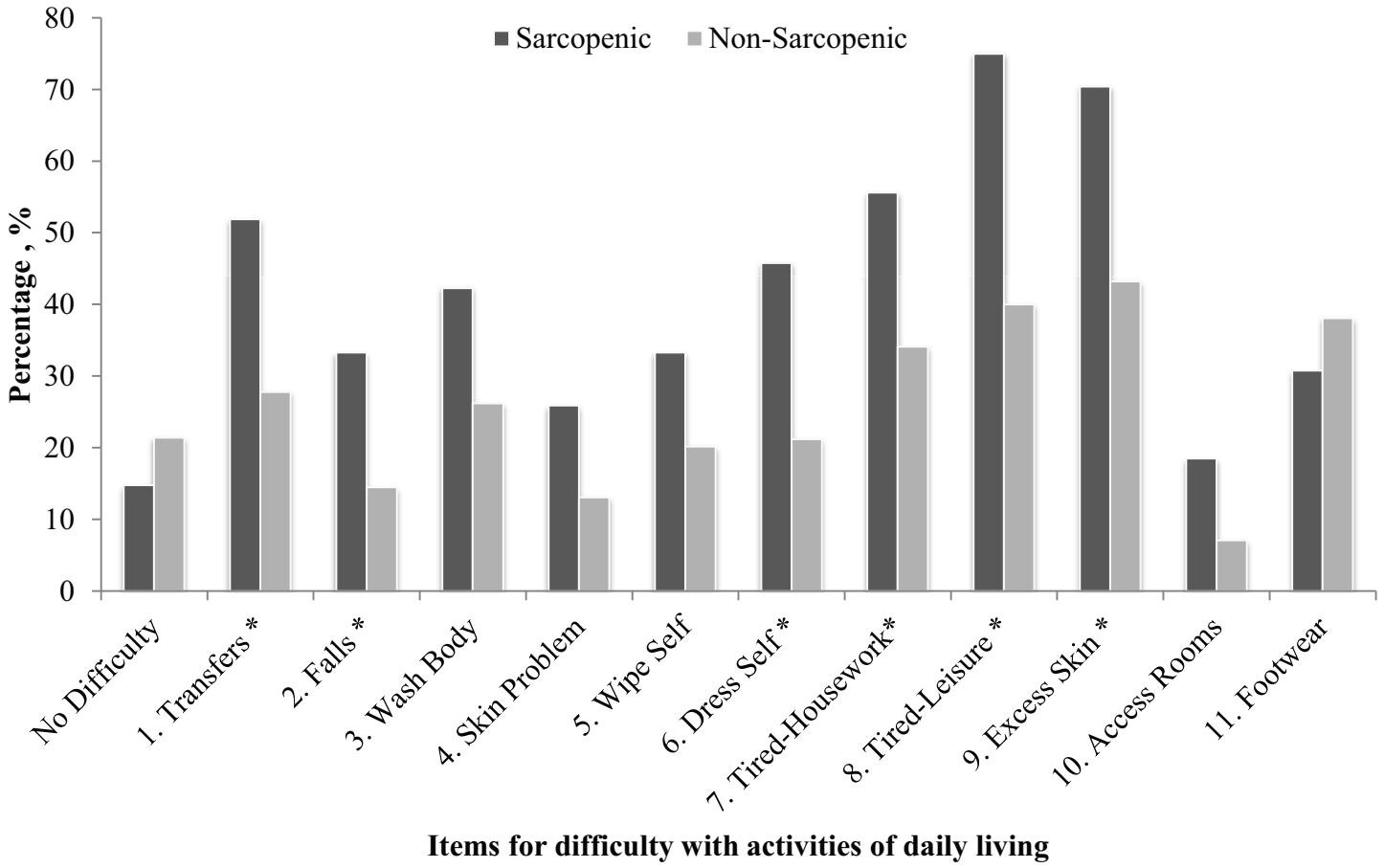
[a]Difficulty with activities of daily living (11 items) from the occupational therapy referral screening questionnaire completed for n=111. p-value <.05 CI: confidence interval

Figure 5.1. Comparison of items for self-reported difficulty with activities of daily living with A) appendicular skeletal mass/weight x 100 (%) and B) body composition phenotype groups: sarcopenic obese versus non-sarcopenic obese.

A.



B.



The occupational therapy screening questionnaire was completed by each participant at the initial clinic assessment with 11 items that asked about their experiences and ability to perform a variety of activities of daily living tasks, as illustrated in the figure **A)** n=111, **B)** sarcopenic obese (n=27) and non-sarcopenic obese (n=84) groups, *p<.05.

Supplementary Material

Table 5.1S. Modified criteria for the Edmonton Obesity Staging System (EOSS), based upon original criteria and adapted with available data for the current study.

Stage	Original EOSS criteria (ref 33)	Modified EOSS criteria[a]
0	No obesity-related risk factors • TChol <5.2 mmol/L • LDL <3.4 mmol/L • HDL ≥1.6 mmol/L • TG <1.7 mmol/L • Liver: normal labs, no diagnosis • Renal: eGFR ≥90 ml/min/1.73m^2 • No functional or ADL impairments	Absence of criteria for other stages, no diagnosis or medication, and normal values, including: • TChol <6.2 mmol/L • LDL <3.2 mmol/L • HDL: F ≥1.3 mmol/L, M ≥1.0 mmol/L • TG <1.7 mmol/L • ALT <50 U/L • eGFR >60 ml/min/1.73m^2 (normal) • No self-reported difficulty with ADL and no pain or other limitations for movement. • BP ≤120/80 mmHg and no medication • FBG ≤6.0 mmol/L, HbA1C <6.5 %
1	• Mild functional limitations, functional impairment but no ADL limitations • BP, mmHg Systolic: 130 – 139.9 (no DM, CKD) Diastolic: 85 – 89.9 • Glucose: 5.6 – 6.9 mmol/L • Liver: elevated enzymes • Renal: GFR 60 – 89.9 ml/min/1.73m^2 • TChol: 5.2 – 6.1 mmol/L • LDL: 3.4 – 4.0 mmol/L • HDL: 1.0 – 1.6 mmol/L • TG: 1.7 – 2.3 mmol/L	• Mild pain limiting movement or activity but no self-reported difficulty with ADL: "no" response to all 11 items on the occupational therapy referral screening questionnaire. • BP, mmHg Systolic: 120 – 139 and no medication Diastolic: 80 – 89 and no medication • ALT, eGFR and serum lipids values not classified for EOSS stage 1[b].

Stage	Original EOSS criteria (ref 33)	Modified EOSS criteria[a]
2	Established obesity-related chronic disease: • Hypertension ≥140/90 mmHg, diagnosis, medication • TChol ≥6.2 mmol/L • LDL ≥4.1 mmol/L • HDL <1.0 mmol/L • TG >2.3 mmol/L • FBG ≥7.0 mmol/L, diagnosed DM or medication • Liver enzymes elevated + diagnosis • Renal: GFR 30 – 59.9 ml/min/1.73 m^2 • Moderate limitations in activities of daily living and/or well-being	Established comorbidity: diagnosed (self-report or medical history), medication and/or meets diagnostic criteria, including: • Hypertension ≥140/90 mmHg • TChol ≥ 6.2 mmol/L • LDL ≥3.2 mmol/L • HDL: F <1.3, M <1.0 mmol/L • TG ≥1.7 mmol/L • Abnormal glycemic control: FBG ≥6.1 mmol/L, HbA1C ≥6.0 % • Liver: ALT >50 U/L • Renal: eGFR 30 – 60 ml/min/1.73 m^2 • Osteoarthritis • Sleep apnea: prescribed CPAP • Mental Health: self report, medication • CRP >10 mg/L • Self-reported difficulty with ADL: "yes" response to one or more of 11 items on the occupational therapy referral screening questionnaire.
3	• Established end-organ damage • Renal: GFR <30 ml/min/1.73 m^2 • Significant functional limitations	• Established end-organ damage • Renal: GFR <30 ml/min/1.73 m^2 • Significant functional limitations
4	• Severe disabilities • Disabling psychopathology, functional limitations, and/or impairment of wellbeing.	• Severity of comorbidity not indicated and/or data not available to classify this stage

[a]Criteria based upon availability of data for current study and reference values for biochemical analysis (serum, fasting) from processing lab. [b]EOSS Stage 1 not classified for certain biochemical markers as reference values from processing lab reported were classified as either normal (Stage 0) or abnormal (Stage 2 or higher). ADL: activities of daily living; ALT: alanine aminotransferase; BP: blood pressure; CPAP: continuous positive airway pressure; CRP: C-reactive protein; DM: diabetes mellitus; eGFR: estimated glomular filtration rate; F: female; FBG: fasting blood glucose; HbA1C: glycated hemoglobin; HDL: high density lipoprotein; LDL; low density lipoprotein M: male; TChol: total cholesterol; TG: triglyceride.

Table 5.2S. Bivariate correlations (Pearson's r, $p < .05$) for the number of items (0-11) for self-reported difficulty with activities of daily living with continuous body composition variables for the definitions of sarcopenia applied to the study sample.

Definitions	**Reference**	**Correlations with ADL difficulties, r (p-value)**		
		All[b] (n=111)	**Females (n=94)**	**Males[c] (n=17)**
ASM/weight x 100 (%)	Levine & Crimmins, 2012 (21)	-0.262 (.005)	-0.232 (.024)	-0.510 (.037)
ASM/BMI (kg/m^2)	Batsis et al., 2015 (42)	-0.187 (.049)	-0.158 (.127)	-0.526 (.021)
ASM adjusted for height and fat mass (residuals)	Newman et al., 2003 (43)	0.108 (.268)	0.195 (.060)	-0.177 (.496)
	Johnson Stoklossa et al., 2016 (8)	-0.084 (.380)	-0.150 (.148)	0.239 (.356)
FM/FFM ratio (centile)	Siervo et al., 2015 (44)	0.230 (.015)	0.231 (.025)	0.453 (.068)

[a]Based on definitions identified/discussed in Johnson Stoklossa et al.,(8) [b]Self-reported difficulty with ADL available for n=111. [c]Spearman's r reported for males due to small sample size (n <30). ADL: activities of daily living; ASM: appendicular skeletal mass; BMI: body mass index; FM: fat mass: FFM: fat-free mass.

Chapter 6: Discussion and Conclusions

6.1 Review of hypotheses

Hypothesis 1: In a sample of adults with class II/III obesity, sarcopenic obesity will be present, although highly variable (5 – 95 %) depending on the definition used (Chapters 4 and 5).

Hypothesis 1 was accepted, as the prevalence of sarcopenic obesity varied from 0 – 84.5% in females and 0 – 100% in males, depending upon the definition applied to the study sample (Chapter 4). Sarcopenic obesity was identified in 25 % (females 22.3 %, males 41.2 %) of the sample of adults with class II/III obesity with the selected definition, ASM/weight x 100 (%) using cohort derived sex-specific cutpoints (Chapter 5).

Hypothesis 2: In a sample of adults with class II/III obesity, participants with sarcopenic obesity will present with poorer clinical characteristics compared to their non-sarcopenic obesity counterparts, including:

a) higher prevalence of abnormal biochemical variables including:
    i) elevated markers of systemic inflammation, as assessed by c-reactive protein (CRP) levels (Chapter 5)
    ii) low 25-OH vitamin D_3 levels (Chapter 5)
    iii) elevated lipid values for total cholesterol, low-density lipoprotein, and triglycerides; lower levels of high-density lipoprotein (Chapter 5)
b) higher prevalence of comorbid conditions including:

i) the individual conditions of hypertension, dyslipidemia, metabolic syndrome, diabetes/impaired fasting glucose, chronic kidney disease, mental health, sleep apnea or osteoarthritis (Chapter 5)

ii) a composite score of multimorbidity, as assessed by 3 or more comorbid conditions (Chapter 5)

iii) higher prevalence of higher stage scores (2 – 4) for comorbidity and function, as assessed by the Edmonton Obesity Staging System (Chapter 5)

c) higher prevalence of self-reported difficulties with activities of daily living, as assessed by an occupational therapy referral screening questionnaire (Chapter 5).

Hypothesis 2a (i) was rejected, as no difference was identified for mean CRP values between sarcopenic obese and non-sarcopenic obese groups (8.07 ± 5.40 vs. 7.58 ± 6.51 mg/L, p=.731, respectively). **Hypothesis 2a (ii)** was rejected, as no differences were identified for the proportion of participants with low 25-OH vitamin D_3 levels between sarcopenic obese and non-sarcopenic obese groups (61.5 vs. 65.5 %, p=.710, respectively). **Hypothesis 2a (iii)** was partially accepted, as participants with sarcopenic obesity were found to have higher mean fasting serum triglycerides compared to participants without sarcopenia (2.06 ± 1.00 vs. 1.62 ± 0.73 mmol/L, p=.040, respectively). Nonetheless, no differences were found for the other lipid values, therefore the hypothesis was rejected for total cholesterol, low density lipoprotein, and high density lipoprotein.

Hypothesis 2b(i) was rejected, as the prevalence of comorbid conditions was not different for participants with sarcopenic obesity compared to non-sarcopenic obese, including abnormal

glycemic control: 34.6 vs. 43.2 %, p=.436; hypertension: 71.4 vs. 69 %, p=.805; dyslipidemia: 96.4 vs. 90.0 %, p=.342; metabolic syndrome: 72.4 vs. 69.3 %, p=.819; mental health: 56.7 vs. 55.6 %, p=.915; chronic kidney disease: 10.7 vs. 2.3 %, p=.055; sleep apnea: 43.3 vs. 34.4 %, p=.382; osteoarthritis: 40.0 vs. 23.3 %, p=.077, respectively). **Hypothesis 2b(ii)** was rejected as the percentage of participants with sarcopenic obesity presenting with multimorbidity (three or more) was not different from non-sarcopenic participants (85.2 vs. 78.6 %, p=.584, respectively). **Hypothesis 2b(iii)** was rejected, as the percentage of participants with sarcopenic obesity categorized into EOSS stages was not different from the non-sarcopenic obese group [EOSS Stage 2 (80.0 vs. 84.4 %) or Stage 3 (20.0 vs. 14.4 %), p=.662, respectively]. No participants were categorized into EOSS Stage 4.

Hypothesis 2c was accepted, as participants with sarcopenic obesity reported more items of self reported difficulty with activities of daily living (p=0.006), compared to the non-sarcopenic obese group. Furthermore, six specific items were reported more frequently by those with sarcopenic obesity, compared to their counterparts. Additionally, sarcopenic obesity was an independent predictor of increased risk of difficulty with activities of daily living (≥3 or items) [OR=5.4, 95%CI (1.81–16.42), p=.003)], after controlling for age, sex and multimorbidity score.

6.2 Discussion

As discussed in Chapter 2, body composition assessment of adults with class II/III obesity can be accurately done by DXA. As identified in the literature review, improvements to the technology, such as increasing equipment capacity and improving tissue penetration, and methodology (i.e., patient positioning) has enabled participants with larger body sizes and dimensions to be assessed.

This research project is one of the first studies to explore sarcopenic obesity in young-to- middle aged adults with class II/III obesity, contributing to the knowledge and understanding of the unique body composition and clinical characteristics of this cohort. One of the strengths of this research is the use of DXA, as a state-of-the-art technique to assess body composition. This provided precise total body and regional values of both fat and lean soft tissues (LST). From the regional values, appendicular LST, also termed appendicular skeletal muscle (ASM), can be determined and is commonly used in sarcopenia definitions. This is important as the LST composition from the trunk contains organs in addition to skeletal muscle, whereas as the arms and legs are mostly skeletal muscle mass, except from a negligible amount of skin (1). In this study, all DXA tests were completed using Hologic A/W scanners which accommodated up to 204 kg, permitting the assessment of participants >136 kg excluded from other studies due to equipment capacity limits.

This research could only have been made possible if DXA scans were available, as they are necessary to provide accurate assessments for different body composition compartments. With DXA scanners accessible across the province of Alberta and the foresight and advocacy for body composition to be included as part of the comprehensive assessment, the DXA scans were available for analysis. The results of this research may help health care providers to better

understand abnormal body composition phenotypes and consider the use of DXA as a tool for assessment of their patients who may have sarcopenic obesity, whom may be at risk for worse health implications.

With the DXA data and the clinical information available from medical records, we were able to explore the different diagnostic criteria using measures of body composition. A wide variability in LST was observed, even with similar body sizes, and presented across the age spectrum. In Chapter 4, several criteria for both sarcopenia and obesity were identified, leading to great diversity in definitions for and prevalence of this combined condition. This variability is a challenge in determining the prevalence and clinical significance of sarcopenic obesity for our cohort, especially due to its younger age and more pronounced obesity (i.e., class II/III). As both muscle and fat mass increase with weight gain, there is a need for a definition that is sensitive enough to detect relatively low LST in those with larger body size due to excess adiposity. Measures of body composition that account for fat mass or total mass such as ASM in relation to total body weight may identify those at risk for low muscle mass and poorer clinical outcomes.

The proportion of LST (as ASM) in relation to the body size is important for the participation and performance of activities of daily living (ADL), better than measures of ASM alone. In Chapter 5, we determined sex-specific cutpoints for our cohort based upon the sensitivity and specificity for this body composition variable, expressed as ASM/weight x 100 (%) and the self-reported items of difficulty with ADL. Similar statistical methods and approaches to balance sensitivity with specificity were reported by Janssen et al. (2). As part of their methodology, they used receiver operator curve (ROC) analysis to determine cutpoints for total skeletal muscle mass with two categories for physical disability (high and low likelihood ratios), selecting the cutpoint that maximized sensitivity (positive result) and minimized the chance of a negative

result (2). In our study, the selected cutpoint to define sarcopenic obesity were strong (males) and moderate (females) predictors for difficulty with ADL. As these cutpoints were derived from the list of 11 items for difficulty with ADL, the cutpoints apply to this variable only and may be different if the analysis used a different comparator (i.e., clinical outcome).

Other definitions for sarcopenic obesity are not only using body composition variables, but also linking these variables with disability including poor physical function and difficulties with performance of or participation in ADL (3-5). Our results are in agreement with these findings, as lower LST (ASM/weight x 100, %) was associated with more items of difficulty with ADL. Over time, sarcopenic obesity can increase disability risk. In a longitudinal study of older adults by Baumgartner et al., sarcopenic obesity was associated with an increased relative risk of 2.63 (95% CI=1.19 – 5.85) for disability related to ADL over eight years (6). Other studies of older adults confirm sarcopenic obesity is associated with disability (7, 8), including falls. Our study supports this association, as participants with sarcopenic obesity reported difficulty with several ADL items including falls/feeling unsteady when performing ADL more often than the non-sarcopenic obese group. Falls are important as they are associated with injury, fracture, hospitalization and disability and therefore highlighted in ADL assessments in previous studies (7-9).

In a recent study of older community-dwelling adults (≥65 years), seven definitions for sarcopenia were explored in relation a specific function or performance (predicted rates of falling by two definitions) (10). They found high variability in the prevalence of sarcopenia, 2.5 – 27.2 %, depending upon the definitions and the rate of falls also varied by definition, from 7.1 – 11 %. The study only stratified two groups, sarcopenic and non-sarcopenic, although the prevalence of sarcopenic obesity was not explored.

Overall, there are very few sarcopenic obesity studies including adults <65 years and investigating ADL. In a prospective observational study, middle-aged and older adults (51 – 79 years, n=674) participants were categorized into several body composition phenotypes measured by body composition including sarcopenic (obese and non-obese), or by muscle strength including dynapenic (obese and non-obese) (11). Subjects with sarcopenic obesity showed higher fall risk scores at baseline compared to non-sarcopenic obese (0.31 ± 0.89 vs. -0.10 ± 0.77, $p<.05$, respectively), and there were no significant changes in the score at year 5. An increase in fall risk score was reported for subjects with sarcopenic/dynapenic obesity although the p-value was only trending towards significance ($p=.052$). This study highlights that factors impairing ADL, including falls, are complex and adds to the discussion whether mass, strength or both are important variables relating abnormal body composition with poor function. We were unable to evaluate measures of muscle strength, as no assessments were conducted in the clinic therefore unavailable for evaluation.

This is the first study to define sarcopenic obesity in a young-to-middle aged adult cohort with class II/III obesity using a clinically relevant outcome of interest. Individuals with sarcopenic obesity were 5.4 times more likely to report ≥ 3 items for difficulty with ADL, independent of age, sex and multimorbidity. Maintaining independence in ADL is essential for optimal quality of life (12, 13). Difficulties with ADL reported by patients of this obesity specialty clinic were based on items from the occupational therapy referral screening questionnaire. As discussed in Chapter 5, there are some limitations with this tool based upon the items addressing more than one situation (i.e. transfers from car, bed, bathtub and toilet) and the lack of information regarding the reasons for the difficulties or the level of difficulty they experienced. We also discussed that the number of items of difficulty reported may not necessarily reflect the level of

difficulty experienced or impact on their quality of life. It was not possible to explore if the reported items of difficulty were related to sarcopenic obesity and/or any other causality. Nonetheless, sarcopenic obesity was predictive of a higher incidence of reported difficulties with ADL, highlighting the potential to explore the use of this tool in future research and clinical settings. Further assessment of factors influencing difficulty in participation and performance of ADL, including physical function, cognition, and strength are needed (12).

In Chapter 5, we explored if participants with sarcopenic obesity would present with different clinical characteristics compared to the non-sarcopenic obese group. In our study, participants with sarcopenic obesity did not have a higher prevalence of abnormal biochemical variables, such as CRP and vitamin D_3, compared to the non-sarcopenic obese group. As discussed in that chapter, elevated CRP is a biomarker for systemic inflammation and associated with obesity, sarcopenia, metabolic syndrome and cardiovascular disease. As such, high CRP levels were reported in ~30% of our cohort, but the prevalence was not different based upon sarcopenia status. Our results are in agreement with those of Levine & Crimmins, who found no difference in CRP values between participants in the obese groups (sarcopenic and non-sarcopenic) (3). It is possible that this is not the best marker or that the additional inflammation caused by sarcopenia is subclinical or masked by obesity, as chronic subclinical inflammation may be a marker for functional limitations (14).

The prevalence of low 25-OH vitamin D_3 levels was not different between sarcopenic obese and non-sarcopenic obese groups in our study, however most of the sample had low levels of this vitamin, with 64.6 % classified as insufficient (<80 nmol/L) and 23.1 % had deficient levels (<50 nmol/L). The prevalence in our cohort was greater than the prevalence of vitamin D deficiency reported in a national study, where 32% of Canadians had levels <50 nmol/L (15). The location

of the clinic in northern Alberta (above the 53rd parallel) may partially explain the lower levels of vitamin D in this cohort, as limited exposure to the sun's ultraviolet rays is insufficient to convert provitamin D3 in the skin. A study of Calgary residents (n=188) showed that 34 % of participants had insufficient levels of vitamin D (<40 nmol/L) in at least one season of the year (16). While the serum values to define insufficiency and deficiency vary, especially in view of obesity, the high prevalence of low values warrants consideration as part of their health profile. Within our study, it was not known if participants were taking vitamin D supplements. Assessment by a registered dietitian, which is required for all patients in this clinic after initial assessment, could evaluate nutritional status and intake (food and supplements) and help patients with recommendations to achieve normal vitamin D levels.

Participants with sarcopenic obesity had higher triglycerides and higher waist circumference compared to those with non-sarcopenic obesity. The exact reasons for these differences are unclear, but perhaps the combined finding is reflective of a difference in metabolic health. The hypertriglyceridemic waist phenotype has been used to identify those with increased visceral adiposity, which in turn is associated with increased cardiometabolic risk and mortality (17, 18). In addition to cardiometabolic risk, the difference in serum triglyceride levels between sarcopenic obese and non-sarcopenic obese groups may serve as biomarker for other abnormalities. The combination of obesity, inflammation and metabolic abnormalities can impact fat accumulation in the liver (hepatosteatosis) and muscle (myosteatosis) (19).

Although the majority (98.3 %) of the cohort had normal serum albumin levels, hypoalbuminemia was identified in two participants, both with sarcopenic obesity. Although a larger sample size is needed to explore its true association with sarcopenic obesity, low albumin levels have been associated with reduced ASM and /or LST in elderly (20, 21) and both older

and younger adults (22). Albumin is a controversial biomarker for nutritional status as it is non-specific and can be affected by renal function, liver disease, hydration status, infection, inflammation, and illness (23). Participants with low albumin certainly warrant further investigation, as this is an abnormal value, especially in medically stable ambulatory patients such as the ones hereby studied. However, interpreting the normal serum values as an indication of good nutritional status or adequate LST would be inaccurate.

All participants in spite of sarcopenia status were affected with multiple comorbidities, with the great majority of participants having three or more conditions in addition to class II/III obesity. To our knowledge, no studies of sarcopenic obesity included participants with such high levels of obesity. Higher rates of insulin resistance, metabolic syndrome and other cardiovascular risk factors are associated with sarcopenic obesity in studies of older adults with lower BMI (30 – 35 kg/m^2). It is unclear why a greater percentage of participants with sarcopenic obesity used hypertensive medications compare to the non-sarcopenic group. This difference cannot be explained by diagnosis, as the prevalence of hypertension was the similar between groups. As mentioned above, more participants with sarcopenic obesity reported they experienced falls or felt unsteady performing ADL. It is unknown if they experienced a hypotensive episode at the time of feeling unsteady or falling, which could provide an alternate explanation for this ADL difficulty.

Regarding physical activity, contrary to expectations that people with obesity are less active, 20% of our cohort meet the physical activity guidelines, which was similar to reported national activity levels (22 %) (24). A greater proportion of individuals with sarcopenic obesity did not meet Canadian activity guidelines, when compared to their counterparts. Notably, limitations to the use of self-reported levels of activity may lead to errors of both over and underestimation

(25). Therefore, the true activity levels reported by our cohort may be different, thereby influencing the proportion of people achieving activity guidelines. Use of a validated questionnaire to assess self-report activity or tools such as accelerometers may be useful to improve accuracy and inform activity recommendations. Low physical activity can create a vicious sarcopenic obese cycle in which low activity contributes to the loss of LST and increased FM, which in turn increases the workload for the LST to perform and participate in activity (26).

Several limitations from this work are noteworthy. This was a small, retrospective, cross-sectional analysis of a convenience sample of patients from a regional adult obesity clinic. As such, associations were reported but causality could not be determined for the variables analyzed. All data recorded in the medical record was completed by the clinic staff for the purpose of assessment, rather than collected prospectively by a trained researcher. As a result, several values (i.e., waist circumference, blood pressure) were missing for some participants, which may be due to factors related to a busy clinic, including prioritization of other needs during the visit or limited time to complete the measurements at the initial visit.

As part of the nature of retrospective analysis, data is limited to the variables collected during patient assessment, which is relevant for the type of clinic and it's purpose. As such, measurements of muscle strength and physical function are not routinely assessed at an obesity specialty clinic. From the available data, the occupational therapy referral screening questionnaire implemented by therapists at the clinic, provided 11 options of different difficulties with their ADL. Based on the results of this study, the majority of participants experiencing difficulty with ADL had sarcopenic obesity. This prevalence was higher for 6 of the 11 items but the specific ADL reported were not isolated to just upper or lower body functions. Our results highlight the need for assessment and support for patients with class II/III obesity, and especially

those with sarcopenic obesity in relation to their ADL. The use of basic, validated tests for physical function, such as timed walking tests or the timed-up-and-go should be considered. However it is important to note most tests are not validated in adults with severe obesity (12). Within the clinical environment, coordination of care with rehabilitation therapists for further assessment may be warranted. Unfortunately, we have not collected data on which of these patients received occupational therapy services. It would be interesting to compare the assessment of participants with sarcopenic obese to those without sarcopenic obesity in terms of function and health-related quality of life.

Patient-oriented research is one of the key objectives for both researchers and health care providers. Research within clinical settings takes collaboration; with the combined knowledge from clinicians and researchers, studies such as this one can identify clinically relevant issues and support evidence-informed care. The research was conducted in Alberta, potentially translatable to the local patients and health care environment. This research can help health care providers understand this cohort as we profiled selected clinical characteristics of adults with class II/III obesity. Most importantly, this research brings to light that not all people with obesity have the same body composition or health risks and that abnormal body composition can be observed across the age spectrum. We identified that young-to-middle aged patients seeking obesity treatment in Alberta can present with sarcopenic obesity, have poor clinical characteristics and are at increased risk for difficulty with ADL and therefore may require specialized treatment and support from the multidisciplinary heath care team.

6.3 Conclusions

Body composition is variable independent of body mass in a cohort of adults with class II/III obesity. Prevalence of sarcopenic obesity ranged from 0 – 84.5% in females and 0 – 100% in males depending on the definitions used, being higher when measures of body mass were used in conjunction with measures of muscle mass (e.g. ASM). Using a clinically relevant variable (ADL) we explored and defined a cohort-specific definition of sarcopenic obesity for ASM/weight x 100 (%): <19.35 % for females and <24.33 % for males. When these were applied to the sample, 25 % were identified with sarcopenic obesity (females 22.3%, males 41.2%). Compared to the non-sarcopenic obese group, sarcopenic obesity was significantly associated with older age (although present across all ages), higher waist circumference, higher triglycerides, hypoalbuminemia, use of anti-hypertensive medications, inactivity, and greater self-reported difficulty with ADL. Sarcopenic obesity was an independent predictor for a greater number of items of difficulty with ADL, after controlling for age, sex, and multimorbidity.

In summary, sarcopenic obesity in present in a sample of younger-to-middle aged adults with class II/III obesity and associated with poor clinical characteristics, when compared to non-sarcopenic obesity. Investigating the prevalence and clinical characteristics of sarcopenic obesity in this cohort is an important step towards recognition of this condition as a significant health problem, and for the establishment of adequate preventive and treatment strategies.

6.4 Future directions

This research supports the need for body composition assessment of adults with class II/III obesity. Future studies exploring sarcopenic obesity in larger cohorts of adults with class II/III are needed.

Sarcopenic obesity was identified in participants across the age span, however the majority of studies focus on older adults and examine body composition at a single time point (cross-sectional design). Longitudinal studies are needed to explore body composition changes with weight changes over time. At present, most definitions and their respective cutpoints are sex-specific but not age-specific. Future studies could explore if different cutpoints to define sarcopenic obesity improve the diagnostic ability in younger adults (i.e. 20 – 40 years) compared to the older (65 – 80 years) and very old groups (>80 years).

Individuals in this study were predominantly female and Caucasian. Body composition is known to vary by sex and ethnicity. Studies are needed that include a larger representative sample from the population, including more men and other ethnicities such as aboriginal adults, whose risk for obesity and related complications is elevated but the prevalence of sarcopenic obesity is unknown. The Canadian Longitudinal Study on Aging is releasing, for the first time, DXA body composition data in Fall 2016. This represents an unprecedented opportunity to explore the prevalence and health characteristics of sarcopenic obesity at a Canadian population-representative level, an effort being pursued by our laboratory.

Sarcopenic obesity is associated with several biomarkers, depending upon the study and the population. Future studies evaluating clinically relevant biomarkers and their predictive value could be helpful to identifying those at risk for sarcopenic obesity. Screening tools could then be

developed and tested for use in clinical settings to help health care providers identify patients at risk and make appropriate referrals for care.

Measures of strength and physical function were not available for analysis. Future studies could test direct measures of strength and function in patients attending obesity specialty clinics to determine the reliability within adults with class II/III obesity. Measures of strength and function combined with DXA analysis could help identify patients at risk for sarcopenic obesity and monitor body composition changes with treatment, including bariatric surgery. Therefore, further studies using a prospective design could examine sarcopenic obesity with DXA at different points in obesity specialty care treatment, providing a better understanding of the compositional changes with weight changes over time, especially the pronounced changes in weight associated with bariatric surgery and those experiencing weight regain after surgery. In addition, evaluation of nutritional status and metabolic rate could explore the relationship between energy requirements, protein intake and changes in body composition, leading to improved nutrition prescriptions to optimize lean mass.

Research to identify effective treatment strategies targeting the preservation of lean mass while reducing fat mass can support clinicians with evidence-informed practice to reduce the prevalence of sarcopenic obesity in those seeking treatment for class II/III obesity. This can positively impact the health and functional outcomes of their patients.

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Appendices

Appendix 1. Participant data collection form for sarcopenic obesity study

Patient ID # ☐☐☐☐ Patient Initials ☐☐☐ (F M L)

Signed consent on CRF? Yes ☐ No ☐

Date of Baseline Visit (initial consultation) ____/____/_____ (dd mm yyyy)

Date of DXA Scan ____/____/_____ (dd mm yyyy)

Demographics

Date of Birth ____/____/_____ (dd mm yyyy) Sex Male ☐ Female ☐

Current Marital Status

☐ Married/Common-law ☐ Separated/Divorced ☐ Single/Never Married

☐ Widowed ☐ Not answered

Current Highest Level of Education

☐ Primary (1-8gr) ☐ College/CEGEP ☐ Secondary (9-13 gr.)

☐ University Profession: _____

Current Employment Status (check all that apply) Other, specify _____

☐ Employed full-time ☐ Homemaker full-time ☐ Employed part-time

☐ Some post-secondary ☐ Unemployed ☐ On short-term disability

☐ On Long-term disability ☐ Retired ☐ Not answered

Living Arrangement

☐ By yourself ☐ In a nursing/retirement home ☐ With others

Household Members

☐ Spouse/partner ☐ Children ☐ Parents ☐ Grandchildren ☐ Grandparents

Body Composition Measurements

Anthropometric

Weight _____kg Height_____cm BMI _____kg/m^2

Waist circumference = _____cm

DXA

	BMC (g)	Fat (g)	Lean (g)	Lean + BMC (g)	Total mass (g)	% Fat mass
L arm						
R arm						
Trunk						
L leg						
R leg						
Subtotal						
Head						
Total						

BMD (cm^2): _____T –score: _____Z-score: _____

Weight History

Birth weight:_____

Age at which you were first considered overweight:

☐ 1-5 ☐ 5-10 ☐ 10-15 ☐ 15-20 ☐ 20-30 ☐ 30-40 ☐ 40-50 ☐ 50-60

☐ Over 60

Maximum weight since age 18? _____ year _____

Lowest weight since age 18? _____ year_____

What was your weight one year ago? _____

Was there an event triggering weight gain (e.g pregnancy, injury, arthritis, loss of close relative)?

☐ Yes ☐ No Event: _____

Desires bariatric surgery? Yes No Undecided

Family history

Siblings weight issues? ☐ Yes ☐ No ☐ Not applicable

Are you the biggest in the family? ☐ Yes ☐ No ☐ Unknown

Weight loss attempts ☐ Yes ☐ No

Stressors barriers to weight loss:

_____

Physical/Lifestyle assessment

Blood Pressure _____/_____mmHg
syst. diast.

Average steps/day (Pedometer) _____ Keeping food record Yes ☐ No ☐

Smoking history

☐ Current smoker *(i.e smoking now or in the past 12 months)* ☐ Former smoker

☐ Never smoked

Alcohol Intake

_____

Current activity level

_____

Mobility problems?

_____

Edmonton Obesity Staging System

Score ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Medical issues - Comorbidities				
Comorbidities	Self-report	Diagnosed	Medication	Lifestyle
Impaired glucose tolerance /diabetes mellitus				
Hypertension				
Dyslipidemia				
Cardiovascular disease				
Sleep apnea/hypoventilation				
Gastrointestinal/gastroesophageal reflux disease				
Liver/gallbladder disease				
Osteoarthritis				
Renal/incontinence				
Polycystic ovarian syndrome				
Hypothyroidism				
Cancer history				
Chronic pain/fibromyalgia				
Other				
Mental Health				
Depression/bipolar				
Anxiety				
Abuse				
Sexual				
Mental				
Physical				
Chronic grief/ post-traumatic stress disorder				
Binge eating				
Attention deficit disorder				
Obsessive compulsive disorder				
Addiction				
Drug				
Alcohol				
Nicotine				
Other				
Psychosis				
Borderline personality				

If diabetic: DM Type I ☐ DM Type II ☐

Current medications

_____

_____

_____

Operations and hospitalizations

Date	Procedure	Hospital or Clinic

Laboratory Results

Lab not available	Lab Test	Lab Value	Unit of Collection
☐	HbA1C		%
☐	Glucose (Fasting)		mmol/L
☐	Insulin		mU/L
☐	Creatinine		mmol/L
☐	GFR		mL/min/1.73/m2
☐	Fasting Lipid Panel		
☐	Total Cholesterol		mmol/L
☐	LDL		mmol/L
☐	HDL		mmol/L
☐	Triglycerides		mmol/L
☐	CRP		mg/L
☐	GGT		U/L
☐	Albumin		g/L
☐	TBIL		µmol/L
☐	ALP		U/L
☐	ALT		U/L
☐	Total Protein		g/L
☐	Ferritin		µg/L
☐	UALB/CR		mg/mmol
☐	Hemoglobin		g/L
☐	MCV		fL
☐	Uric Acid		mmol/L
☐	TSH		mU/L
☐	PTH		pmol/L
☐	Vitamin D3		nmol/L
☐	Vitamin B12		pmol/L

Completed by: _____Date: ____/____/_____dd mm yyy

Appendix 2. Occupational Therapy referral screening questionnaire

Occupational Therapists (OTs) can help you manage your daily activities. OTs look at how you complete your home, work and leisure activities, and may provide you with some helpful suggestions to make your daily activities easier. Please complete the following table to help us see whether you may benefit from seeing an OT while you are participating in the Edmonton Adult Bariatric Specialty Clinic.

Questions	Yes	No	I have help
Is it hard for you to get in and out of your car, bed or bathtub, or on and off your toilet comfortably?			
Have you had any recent falls or felt unsteady with any of the above activities?			
Is it hard for you to wash your whole body (reaching to wash your toes, buttocks, back)?			
Do you have skin problems (such as redness, infections and wounds) because it is hard for you to clean your skin?			
Is it hard for you to wipe yourself after using the toilet?			
Is it hard for you to dress yourself? (i.e., putting on pants, socks and/or shoes)			
Is it hard for you to complete household tasks such as cooking, cleaning and laundry because you get tired easily?			
Is it hard for you to complete everyday tasks and leisure activities that you enjoy because you get tired easily?			
Do you find that your stomach or having excess skin on your stomach makes it hard for you to complete your daily activities?			
Is it hard for you to access areas of your home such as the bathroom, bedroom or laundry area?			
If you have help with any of the above activities, please list what type of help you receive:			
Do you currently have custom footwear/shoe inserts or are you considering getting them?			
Have you previously received OT services?			