Clinical Screening and Identification of Sarcopenic Obesity in Adults with Knee Osteoarthritis

by

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ABSTRACT

Background: Obesity [defined using body mass index (BMI)] is associated with knee osteoarthritis (OA) and increased surgical infection risk in total knee arthroplasty (TKA). However sarcopenic obesity, a phenotype of low muscle mass with high fat mass, may have greater relevance and implications for adverse outcomes in this clinical population. This condition may be present in patients with knee OA but not identified using BMI measures alone. Sarcopenic obesity is associated with surgical infection, disability, and risk of mortality in other clinical populations, but not well-examined in clinical populations with OA. The purpose of this thesis was to examine sarcopenic obesity in adults with knee OA with respect to prevalence, diagnostic screening, and functional implications.

Objectives: 1) determine the current breadth and extent of evidence on sarcopenic obesity in adults with knee OA; 2) assess the prevalence of sarcopenic obesity in a clinical cohort of adults with end-stage knee OA using accepted diagnostic criteria. Further, determine if there are differences in pain, physical function and quality of life between those identified with and without sarcopenic obesity, and; 3) determine which strength or physical function measures and patient characteristics are associated with low muscle mass (relevant to sarcopenic obesity), and could be used to screen patients with knee OA and obesity in clinical practice.

Methods: This thesis includes three separate but inter-related studies: 1) a scoping review; 2) a cross-sectional clinical study, and; 3) an additional analysis of the cross-sectional cohort. The scoping review utilized a systematic search of Medline, CINAHL, Web of Science and EMBASE databases for keywords and subject headings related to obesity, sarcopenia and osteoarthritis. The cross-sectional study included adults with a BMI ≥30 kg/m^2 and unilateral or bilateral knee OA. Body composition was measured in 151 patients (59% female, mean age

65.1±7.9 years, mean BMI 37.1±5.5 kg/m^2) using dual-energy x-ray absorptiometry (DXA). Appendicular skeletal muscle mass (ASM) (adjusted to height^2, weight, and BMI) was used to identify muscle mass, and was compared to previously established sex-specific cut-points. Strength and physical performance were assessed with gait speed over four metres, the six-minute walk test, and maximal handgrip strength (absolute, and relative, adjusted by BMI). Patient-reported pain and function were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and health-related quality of life was assessed using the EuroQol Foundation 5-dimension 5-level instrument (EQ-5D-5L).

Results: The scoping review found only three clinical studies on sarcopenic obesity in adults with knee OA, identifying a knowledge gap and need to clarify prevalence in a North American clinical sample. The cross-sectional study found the prevalence of sarcopenic obesity varied depending on diagnostic approach (1.3% using ASM/height^2, 14.6% using ASM/weight, 27.2% using ASM/BMI, and 8.6% using a combined approach with low muscle and low strength or function). Regardless of the diagnostic approach used, patients with sarcopenic obesity had lower walking speed and endurance, and a higher proportion reported problems on the self-care dimension of the EQ-5D, compared to patients without this condition. In the analysis from the third study, relative grip strength and sex were associated with low muscle mass in this sample. Relative grip strength cut-points of <0.65 kg/m^2 in females and <1.1 kg/m^2 in males were identified as discriminators of low strength. When used in combination with low ASM/BMI, the prevalence of sarcopenic obesity was 19.9%. Patients identified with sarcopenic obesity had slower walking speed, lower walking endurance, and poorer health-related quality of life.

Conclusions: This research demonstrates that sarcopenic obesity was present in a sample of adults with obesity and knee OA. Prevalence varied depending on diagnostic approach, however

sarcopenic obesity negatively influenced mobility and quality of life in this patient population. Early identification of sarcopenic obesity in the clinical setting is important to prevent and minimize further muscle loss. Relative grip strength could be used to screen for low strength in patients with knee OA and obesity. Patients with low strength could then complete a body composition assessment to determine the presence of low muscle mass, and confirm or refute the identification of sarcopenic obesity.

PREFACE

This thesis is an original work by Kristine D. Godziuk. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Human Research Ethics Board, titled "Sarcopenia screening and risk assessment in adults with osteoarthritis and obesity," PRO 00070266, January 26, 2017.

Chapter 2 of this thesis was published as K. Godziuk, C.M. Prado, L.J. Woodhouse, and M. Forhan, "The Impact of Sarcopenic Obesity on Knee and Hip Osteoarthritis: A Scoping Review," *BMC Musculoskeletal Disorders*, 19:270, 2018. K. Godziuk was responsible for study design, data collection, analysis and manuscript composition. M. Forhan was the supervisory author and involved with all aspects of the study. C.M. Prado and L.J. Woodhouse contributed to study design, interpretation of results, and manuscript edits.

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LIST OF ABBREVIATIONS

ASM	Appendicular Skeletal Muscle Mass
BMI	Body Mass Index
DXA	Dual-Energy X-ray Absorptiometry
EQ-5D	EuroQol Foundation Five Dimension Quality of Life Measure
FM	Fat Mass
ICD-10	International Classification of Diseases, 10th Revision
OA	Osteoarthritis
OR	Odds Ratio
TKA	Total Knee Arthroplasty
VAS	Visual Analogue Score on the EQ-5D
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
6MWT	Six-Minute Walk Test

CHAPTER 1

1.1 Introduction

This doctoral thesis is an original body of work. It is a paper-based thesis that includes two peer-reviewed publications (Chapters 2 and 3), and one manuscript submitted to a peer-review journal (Chapter 4).

The purpose of this thesis was to contribute to a better understanding of sarcopenic obesity in adults with knee OA with respect to prevalence, diagnostic screening, and functional implications. This thesis includes five chapters. Chapter 1 provides background information on osteoarthritis, obesity and sarcopenia that informed the rationale for the thesis. This background assists in understanding the issues that led to the development of the research questions. This chapter also outlines the problem statement and specific research objectives of each study. Chapter 2 describes a scoping review study that aimed to determine the current breadth and extent of evidence on sarcopenic obesity in knee OA. Chapter 3 describes a cross-sectional clinical study that aimed to assess the prevalence of sarcopenic obesity in adults with end-stage knee OA. This study also explored the use of varied diagnostic approaches for sarcopenic obesity and the implications of this condition on pain, function and quality of life. Chapter 4 describes a further analysis of the clinical sample to determine which muscle function measures and patient characteristics were associated with low muscle mass (and relevant to sarcopenic obesity). These variables were then applied to identify subgroups of patients with and without sarcopenic obesity to compare outcomes of pain, function and quality of life. Chapter 5 provides a summary of the main results from this thesis research, with discussion on limitations, future directions, and relevance to clinical practice. This thesis contributes important findings and adds to clinical

knowledge on sarcopenic obesity in adults with knee OA, with potential to impact changes in OA care settings. Further, sarcopenic obesity is an important and relevant condition requiring attention and awareness from rehabilitation practitioners, as it can significantly influence functional mobility and quality of life.

1.2 Background

There is growing awareness and consideration of muscle as a relevant and vital organ for maintaining health and mobility in middle-aged and older adults. In particular, loss of muscle mass that can occur alongside aging and chronic diseases (originally defined as sarcopenia) has been identified as a key area of concern. Sarcopenia can occur across the age spectrum[1], and also in individuals with a body mass index (BMI) classified as obese (termed sarcopenic obesity). Yet muscle loss may not be recognized in the presence of higher adiposity[2]. Sarcopenic obesity may be present in adults with knee osteoarthritis (OA) and obesity, but missed by current assessment procedures that consider BMI alone[3]. Importantly, OA-related factors and weight loss recommendations for obesity could be contributing to the development and progression of this condition. As sarcopenia is now considered a reportable disease by the World Health Organization (WHO) with an International Classification of Diseases ICD-10 diagnostic code (M62.84)[4,5], it is important to increase knowledge and identification of this condition in adults with OA and obesity.

1.3 Osteoarthritis and Obesity

Osteoarthritis (OA) is a chronic and progressive joint disease that results in inflammation and damage to joint structures, primarily the synovium, articular cartilage and subchondral bone[6]. It occurs most frequently in the knee joint, but can also occur in the hip, feet, spine and hands. OA is characterized by joint pain and stiffness, which can limit physical function and

activity. OA-related pain can lead to a vicious cycle of inactivity, driving further declines in physical function, and resulting in impaired mobility, reduced quality of life, and increased use of healthcare resources[7,8]. OA is the leading cause of disability in Canada[9]. With a prevalence projected to double to one in four adults by the year 2040[9], it remains an important condition to address in healthcare.

Prevalence of OA increases with age, although it also affects young and middle-aged adults (nearly 60% of individuals with OA are younger than age 65)[10]. OA development is linked with obesity, however sex, genetics and injury or trauma are also strong risk factors. Obesity contributes to OA development and progression through several mechanisms. This includes adiposity-related systemic inflammation that impacts the integrity of the joint synovium, cartilage, bone and surrounding muscle[11], and through increased biomechanical joint stress related to higher body mass[12]. Obesity can alter centre of mass and gait kinematics, resulting in increased strain and wear on the medial and lateral aspects of the knee joint[12,13]. The relationship between obesity and OA progression differs between joints, but it has a stronger association with the knee[14]. As a result, current OA treatment guidelines recommend weight loss in patients with knee OA who are overweight or have obesity, to reduce compressive forces on the joint[15,16].

Unfortunately OA is a progressive disease, with no known cure. In some patients the disease will advance to an end-stage where there is significant pain and disability that is not ameliorated by conservative treatment. When this occurs, a surgical joint replacement (called a total knee arthroplasty, or TKA) is currently the best treatment available[17]. Although TKA is performed most frequently in adults over 65 years of age[18], individuals with obesity need TKA at an earlier age (typically between 45 and 64 years of age)[10]. This age group also has the highest rates of obesity in Canada[19,20]. TKA at an earlier age could mean a revision surgery will be

needed within the individuals' lifespan to replace worn prosthetic joint components[21]. With TKA demand currently outpacing capacity, and projected to continue[22], this could have important economic consequences for healthcare.

TKA in adults with obesity is associated with increased surgical infection risk when BMI is ≥30 kg/m^2, and greater risk when BMI is ≥40 kg/m^2 [23,24]. A patients' BMI is often used as a clinical indicator of surgical risk, whereby orthopedic surgeons may deny TKA based on patients' BMI[25], or require weight loss before deeming the patient eligible for surgery[24]. This can result in delays in surgery for patients with obesity[26,27], which could result in further deterioration of function in these individuals, potentially confounding TKA outcomes. Recovery times have been reported as longer after TKA in patients with obesity[28], however this could be due to poorer pre-operative function levels in adults with obesity as a result of surgical delays[29].

The use of BMI as a surrogate measure of surgical risk continues despite clear evidence that BMI is a poor measure of individual-level body compositions that impact health[30–33]. BMI is not correlated with muscle or bone mass compartments[34], and its relationship with adiposity is limited when considering individual health care and surgical decisions[35,36]. Body composition may be more relevant than BMI when considering surgical treatments for end-stage knee OA. Studies by Ledford et al.[37,38] found percent body fat (assessed using bioelectrical impendence analysis) had stronger associations with surgical risk and functional recovery after TKA compared to BMI. While the influence of muscle mass on surgical risk and recovery was not considered, this suggests the value of looking beyond BMI and examining body composition in this population.

1.4 Sarcopenic Obesity

A body composition phenotype termed sarcopenic obesity may be important in OA. Sarcopenia is a health condition defined by the presence of low muscle mass with low muscle strength or performance, originally investigated in older adults[39] but known to occur across the age spectrum[1]. When sarcopenia occurs alongside high fat mass, it is termed sarcopenic obesity[40,41]. However sarcopenic obesity may be more accurately considered a relative deficiency in the ratio between muscle mass and fat mass (not just an absolute value of low muscle mass)[42,43]. Whether there are additional distinctions between sarcopenia and sarcopenic obesity remains unclear[44,45].

The development of sarcopenic obesity is influenced by both age-related and disease-related factors that drive muscle loss and adiposity gains. With aging there is a shift in body composition, with increasing adiposity and reduced muscle mass resulting from changes that include altered endocrine function[46]. These changes become pronounced after age 50 years[47] and can be further accelerated by the presence of chronic diseases such as diabetes, insulin resistance, and hypertension[2,41,48,49]. Physical inactivity, nutritional status, and weight cycling can also contribute to body composition changes by increasing fat mass accretion and muscle loss[2,50–52].

Sarcopenic obesity has been identified in adults of middle-age (40-64.9 years of age)[42,53,54], and is associated with more severe physical function impairments compared to either sarcopenia or obesity alone[53,55]. Importantly, this condition is often missed by routine clinical assessments, with obesity masking the accelerated reduction in muscle mass[3]. Until disability is present, this condition may not be discerned without more rigorous screening. Additionally, by not recognizing sarcopenic obesity in this group, clinical recommendations that aim to improve

health (i.e. weight loss recommendations for obesity) could exacerbate this condition by further reducing already low muscle mass[56], creating a vicious cycle.

Sarcopenic obesity is a condition that requires attention in health care settings. It is associated with increased surgical infection risk in cardiology[57], and surgical complications and shorter survival in oncology[58–60]. In other clinical populations it is associated with systemic inflammation[61], poorer physical performance[61], increased risk of falls[62], disability[63], and risk of mortality[64,65]. This condition could be impacting function, disability and surgical outcomes in adults with OA.

1.5 Sarcopenic Obesity and Osteoarthritis

Individuals with OA may be at higher risk of sarcopenic obesity. Adipose-related metabolic and inflammation pathways associated with OA development and progression[12,66] are also associated with sarcopenia development and progression[2]. Whether sarcopenia influences OA development or the reverse is still unclear[67]. Regardless, both Karlsson et al.[68,69] and Erturk et al.[70] have identified a body composition phenotype of low muscle mass with high adiposity in adults with end-stage knee OA. Further, a cross-sectional study by Lee et al.[71] reported a stronger association between sarcopenic obesity and knee OA (OR 3.51) compared to obesity or sarcopenia alone (OR 2.38 and 0.94, respectively), when controlled for age and sex.

Although fat mass and BMI are associated with knee OA development[72,73], the influence of muscle mass is still unclear. A five year longitudinal study by Misra et al.[74] found both obesity alone and sarcopenic obesity increased the risk of development of knee OA. There was no increased risk with sarcopenia alone, suggesting that adiposity or a higher body mass were primary influencers in the development of knee OA (rather than low muscle mass). A thirteen year longitudinal study by Munugoda et al.[72] found that higher muscle mass was associated with

a lower relative risk for TKA (RR 0.96), compared to fat mass, waist circumference and BMI (RR 1.04, 1.03, and 1.08, respectively). This could indicate that a body composition with a higher component of muscle mass may be protective from needing TKA. Clarity is still needed on the role of muscle mass and sarcopenic obesity on OA development and progression.

Sarcopenic obesity may also be relevant in OA treatment, but this has not been well-examined in the literature. It is reasonable that physical function impairments related to sarcopenic obesity[75] would be important to consider when determining therapeutic treatment approaches in patients with OA. However, if impairments are primarily due to sarcopenic obesity rather than OA, or impairments are compounded by the presence of both conditions, this could change the accuracy of established functional assessment (i.e. gait speed or timed up and go tests) thresholds used to determine OA severity, appropriateness for TKA, or post-surgical outcomes[76,77]. In addition, sarcopenia may be a modifiable risk factor for prosthetic infection after arthroplasty[78]. Together, these potential implications require further investigation, supporting the importance of clinical identification and monitoring of treatment outcomes in adults with sarcopenic obesity and knee OA.

Identification of sarcopenic obesity in adults with OA requires additional measures beyond BMI. Results from Lee et al.[71] demonstrate that BMI and body weight in adults with knee OA were similar between groups with obesity versus sarcopenic obesity. This further supports that anthropometric indices alone may not be adequate to identify sarcopenic obesity in this population. Higher fat mass, body weight and BMI may actually disguise important reductions in muscle mass[59]. Utilization of additional identification strategies are required. Identification of sarcopenic obesity early in clinical settings would enable provision of targeted

treatment strategies to maintain muscle mass (and prevent further muscle loss), increase strength and improve physical function[79].

1.6 Sarcopenic Obesity Identification

Several different approaches have been used in the research literature to identify sarcopenic obesity[50,80–83], with the majority using a definition of low muscle mass in combination with a classification of obesity or adiposity. Many of the definitions of low muscle mass are based on criteria defined for sarcopenia. There have been more advances in this area, with several consensus papers published by experts on identification and diagnostic approaches. These include papers by the European Working Group on Sarcopenia in Older Persons (EWGSOP[39] and EWGSOP2)[44], the International Working Group on Sarcopenia (IWGS)[84], the Foundation for the National Institute of Health (FNIH)[85–88], the Society of Sarcopenia, Cachexia and Wasting Disorders[89], the European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG)[90], the Asian Working Group on Sarcopenia[91], 2018 clinical practice guidelines from the International Conference on Frailty and Sarcopenia Research (ICFSR)[79], and the 2019 Sarcopenia Definitions and Outcomes Consortium Conference (SDOC)[92]. There is agreement across these consensus groups that the presence or absence of sarcopenia in older adults (considered primary sarcopenia[44]) should be based on a combination of low muscle mass with either low strength or low physical function. No consensus papers on sarcopenic obesity have been published, however there is consideration that sarcopenic obesity identification should also include low muscle mass with low strength or function[82,93,94].

1.6.1 Low Muscle Mass

Low muscle mass can be assessed using a whole body dual energy x-ray absorptiometry (DXA) scan, currently considered the reference standard for identification of low muscle in

sarcopenia[95]. DXA enables differentiation of body composition compartments of bone, fat, and lean tissue. The lean tissue compartment includes muscle, connective tissue, skin and organs. Using total lean mass as a surrogate to define low muscle mass can affect the accuracy of the estimate of muscle as it also includes the trunk and organs. Therefore appendicular lean mass (lean mass of both of the arms plus both of the legs) is usually considered instead (herein termed appendicular skeletal muscle, or ASM). It has been suggested that ASM includes 75% of the lean mass in the body[96]. Several definitions and cut-points to distinguish low muscle mass using ASM have been employed in the literature, including absolute ASM[85,97], ASM adjusted by height squared (ASM/height^2)[98], ASM adjusted by weight x 100 (ASM/weight)[99], or ASM adjusted by BMI (ASM/BMI)[85,97]. Adjusting ASM by a measure of stature or mass is considered important as mobility and physical performance are influenced by body size[100]. Cut-points for low muscle mass using ASM/height^2 have been proposed based on two standard deviations below the mean of a young North American reference population (<7.26 kg/m^2 in males and <5.45 kg/m^2 in females)[98]. However using cut-points based on a young reference population may be flawed, as low muscle mass alone is not always associated with adverse outcomes[85]. Cut-points for low muscle mass using ASM/weight were also determined using reference data from young adults ages 20-40 years from the US National Health and Nutrition Examination Survey (NHANES) (<25.72% in males and <19.43% in females)[99]. These may be preferable to ASM/height^2 as ASM/weight adjusts for the ratio between muscle and non-muscle mass, which may be more relevant for functional mobility. The cut-points for ASM/BMI (<0.789 kg/m^2 in males and <0.512 kg/m^2 in females) were established using NHANES data and based on an association with clinically relevant outcomes of weakness[85,88], potentially making them the best criteria to

use in adults with obesity[101]. This is due to a stronger relationship between ASM/BMI and weakness[88], fear of falling[102], cardiovascular risk[103], and mortality[104].

Techniques for assessing body composition, other than DXA, have been utilized for identification of low muscle mass. These include magnetic resonance imaging (MRI), computed tomography (CT) scans, and bioelectrical impedance analysis (BIA). While MRIs and CT scans are considered more accurate assessments of muscle mass, their higher cost and limited availability (specifically MRIs) and higher radiation exposure (specifically CT scans) limit their use in clinical research and routine practice[105]. While BIA is more accessible and less expensive, its accuracy is more variable (particularly in patients with higher adiposity)[106]. Newer methods for assessing muscle mass using ultrasound or D3-creatine are currently being developed and tested[107,108], but not routinely used.

Although DXA remains as the current reference method for routine assessment of muscle mass[95], there is evidence of variability in the relationship between DXA derived muscle mass values with important clinical outcomes of mobility, falls and mortality[92,108]. As the relationship between age-related and disease-related loss of function is only partially explained by a loss of muscle mass, this supports the need to include an assessment of loss of strength or function[109] in the definition of sarcopenic obesity[93,94].

1.6.2 Low Strength or Low Function

Varied methods have been used to identify low strength or low function relative to sarcopenia in research and clinical settings. Gait speed (over various distances) is often used as an indicator of function as it has been shown to be predictive of mobility disability and mortality[89]. Gait speed cut-points of <0.8 m/s[39] and <1.0 m/s[89] have been used to indicate low function in individuals with sarcopenia. The six-minute walk test (6MWT) has been shown to be

predictive of hospitalization and mortality in individuals with sarcopenia[89], and it is commonly used as an assessment of function for OA[110]. Although a single cut-point of 400 m has been suggested to indicate low function in sarcopenia[89], 6MWT distance can vary depending on age, sex and height[110]. Further, 6MWT distances below 400 m are commonly reported in patients with knee OA waiting for TKA[111]. The challenge in identifying low function that is related to sarcopenic obesity in adults with knee OA is that reduced gait speed or 6MWT distance could instead be related to OA-associated pain or stiffness. Additionally, obesity is independently associated with impaired mobility in older adults[112]. These influences of OA and obesity on function could introduce confounding or limit the applicability of physical function assessments to identify sarcopenic obesity-related impairments.

Measures of low strength are also subject to this potential confounding due to OA, depending on the test. Handgrip (grip) strength is commonly used in sarcopenia screening, and has recently been recommended by the EWGSOP2 as a diagnostic tool[44]. Low grip strength is associated with higher odds of impaired mobility, poor or fair self-rated health, increased disability[113], and increased mortality[114]. Grip strength may be better than lower body strength tests (i.e. leg extensor strength) for adults with knee OA, as OA-related pain and stiffness may limit the ability to exert a maximal contraction at the knee. However, systemic inflammatory-related OA could also affect the hand joints in addition to the knee joints. Low grip strength has been associated with knee OA[115], suggesting there may be limitations to its use in assessing low strength related to sarcopenic obesity.

Few studies in sarcopenic obesity have included measures of low strength or function in their diagnostic definition[116], so there is limited data to support which measures are preferential.

Therefore, strength and function tests recommended and used for sarcopenia are currently the best available methods.

1.7 Treatment of Sarcopenic Obesity

A detailed examination of treatment approaches for sarcopenic obesity is beyond the scope and purpose of this thesis. However an understanding of current treatments for sarcopenia and sarcopenic obesity provides support and context for the importance of early clinical identification of this condition to preserve current muscle, and prevent inadvertent treatment recommendations that could hasten muscle loss progression.

Weight loss is routinely recommended for adults with obesity and knee OA, including patients with end-stage disease who are considering TKA. However recommending weight loss before TKA may inadvertently result in further muscle loss in patients who have sarcopenic obesity, exacerbating an already deleterious situation. Weight loss recommendations in adults with knee OA must examine the cost-benefit, as weight loss can contribute to muscle loss and functional decline, and perpetuate a vicious cycle. Muscle mass that is lost in conjunction with fat mass during caloric restriction is often not regained, even with a corresponding increase in weight as weight regain is primarily through increased adipose mass[117]. This further widens the disrupted body composition ratio between muscle and adipose mass, and could actually cause the onset of sarcopenic obesity if not already present[80]. Further, while exercise in conjunction with diet can attenuate some of the loss of muscle, patients with knee OA may be limited in their ability to exercise due to OA-related pain.

While a pharmacologic treatment for sarcopenia and sarcopenic obesity is the target of many studies and clinical trials, currently resistance training exercise and adequate protein intake are the primary effective approaches[93,118,119]. Therefore the focus of sarcopenia treatment is

preventing, limiting and treating further alternations in muscle mass[93]. Weight loss in older adults could worsen sarcopenia[94]. A study by Villareal et al.[120] showed that using diet alone, older adults lost a mean 3.2 kg of muscle mass over the period of six months. Clinical trials examining weight loss have shown that muscle mass declines concomitantly with diet only approaches, which is only partially mitigated when combined with exercise[120]. Additionally, weight loss can inadvertently result in loss of bone mass[121]. This could increase fracture risk, and potentially increase the risk of early prosthetic revision after TKA as bone is critical to hold the joint implant in place. Importantly, muscle and bone lost through voluntary or recommended weight loss may not be regained, even with future weight increases[121]. Further, there may be limitations in muscle gains with resistance training in older adults. A study in men and women ages 60-80 show the highest increase in muscle mass was only 1 kg after 6 months of training[122]. Considering that OA pain-related inactivity further influences muscle loss, preservation of existing muscle may need to be prioritized in adults with end-stage knee OA. Despite these indications, recommendations for weight loss in adults with obesity and end-stage knee OA prevail. Until clear evidence on sarcopenic obesity in knee OA can be provided, this is likely to continue.

1.8 Theoretical Framework

The research in this thesis is guided by the *International Classification of Functioning, Disability and Health (ICF)*[123], a conceptual framework published by the World Health Organization (WHO) in 2001. This framework contextualizes the complex development of disability through interactions between body structures/functions, activity and participation (within the milieu of personal and environmental factors). The ICF framework enables an exploration of the complex influences and interactions between OA, obesity and sarcopenia that

contribute to a loss of function and the onset of disability[124]. Each of these conditions uniquely impacts the structural integrity of the body (joint cartilage, synovium, bone, muscle and adipose tissues), and each can independently lead to impaired function, increased difficulty completing activities of daily living, and restricted participation in home, work or social tasks. Further, the co-presence of all three (OA, obesity and sarcopenia) can add complexity and possibly compounding influence on disability.

1.9 Statement of the Problem

Sarcopenic obesity is an important health condition requiring increased awareness, attention and identification in OA clinical care settings. It is likely occurring in patients with knee OA, potentially impacting TKA and rehabilitation outcomes, but missed by current assessment methods that only consider BMI measures alone.

The purpose of this thesis was to contribute to increased understanding of sarcopenic obesity in adults with knee OA with respect to prevalence, diagnostic screening, and functional implications.

1.10 Research Process

This thesis consists of three studies designed to 1) identify current evidence and knowledge gaps around sarcopenic obesity in clinical populations with knee OA, 2) explore and describe the occurrence, identification and implications of sarcopenic obesity on pain, function and quality of life in a clinical population with knee OA, and 3) examine methods to better identify this condition early in clinical knee OA settings (to support the provision of appropriate treatment approaches and recommendations). The results from these three studies will build upon each other respectively, and taken together will improve our understanding of sarcopenic obesity in adults with knee OA.

1.11 Research Questions

1.11.1 Study One

Study one (Chapter 2) aimed to determine the current breadth and extent of evidence on sarcopenic obesity in knee OA. This study used a scoping review methodology to systematically examine the extent of the published scientific literature on this topic. It was theorised that there would be few clinical studies and limited evidence on sarcopenic obesity in patients with knee OA.

1.11.2 Study Two

Study two (Chapter 3) aimed to assess the prevalence of sarcopenic obesity in a clinical sample of adults with end-stage knee OA. Specifically, we intended to determine the proportion of patients who had sarcopenic obesity using currently accepted diagnostic criteria. Further, we would determine if there were differences in pain, physical function and quality of life between those identified with and without sarcopenic obesity. It was hypothesized that sarcopenic obesity prevalence would be ≥10% in this population based on prevalence rates reported in other clinical and community populations. It was further hypothesized that adults with sarcopenic obesity would have poorer physical function and quality of life compared to those without sarcopenic obesity.

1.11.3 Study Three

Study three (Chapter 4) aimed to determine which strength or physical function measures and patient characteristics were associated with low muscle mass (relevant to sarcopenic obesity), and could be used to screen patients with knee OA and obesity in the clinical setting. It was hypothesized that gait speed and grip strength would not be the best muscle function

measures to screen for sarcopenic obesity due to the influence of OA and obesity on gait parameters and grip strength.

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CHAPTER 2

2.1 Synopsis

A version of this chapter was published as Godziuk K, Prado CM, Woodhouse LJ, Forhan M, The impact of sarcopenic obesity on knee and hip osteoarthritis: A scoping review, *BMC Musculoskeletal Disorders,* 2018.

2.2 Abstract

Background: The progressive, debilitating nature of knee and hip osteoarthritis can result in severe, persistent pain and disability, potentially leading to a need for total joint arthroplasty (TJA) in end-stage osteoarthritis. TJA in adults with obesity is associated with increased surgical risk and prolonged recovery, yet classifying obesity only using body mass index (BMI) precludes distinction of obesity phenotypes and their impact on surgical risk and recovery. The sarcopenic obesity phenotype, characterized by high adiposity and low skeletal muscle mass, is associated with higher infection rates, poorer function, and slower recovery after surgery in other clinical populations, but not thoroughly investigated in osteoarthritis. The rising prevalence and impact of this phenotype demands further attention in osteoarthritis treatment models of care, particularly as osteoarthritis-related pain, disability, and current treatment practices may inadvertently be influencing its development.

Methods: A scoping review was used to examine the extent of evidence of sarcopenic obesity in adults with hip or knee osteoarthritis. Medline, CINAHL, Web of Science and EMBASE were systematically searched from inception to December 2017 with keywords and subject headings related to obesity, sarcopenia and osteoarthritis.

Results: Eleven studies met inclusion criteria, with indications that muscle weakness, low skeletal muscle mass or sarcopenia are present alongside obesity in this population, potentially impacting therapeutic outcomes, and TJA surgical risk and recovery.

Conclusions: Consideration of sarcopenic obesity should be included in osteoarthritis patient assessments.

2.3 Background

Osteoarthritis is a chronic, progressive joint disease and leading cause of pain and mobility disability for over 27 million Americans[1] and 4 million Canadians[2]. Age, sex, genetics, joint trauma, and obesity all influence the development of this disease[3], and its progressive nature means advanced treatment options may be required in later stages to reduce pain, improve function and maintain quality of life. Surgical replacement of articular joint components, called a total joint arthroplasty (TJA), is currently the most effective treatment for severe pain and disability associated with end-stage knee or hip osteoarthritis that ceases to respond to other therapeutic interventions.

There has been a rapid and sustained increase in demand for TJA surgery around the world over the past two decades. TJA rates in the USA doubled from 336,000 patients in 1993 to 735,000 patients in 2005[4], and are projected to top 4 million patients by 2030[5]. In Canada, volumes are lower but the accrual rate tripled from 42,000 patients in 2000[6] to 117,000 patients in 2016[7], and similar persistent growth is apparent throughout Europe[8]. This increased demand is outpacing the supply of TJA, leading to longer wait times and pressure on health care systems to reduce delays in accessing care. To ensure timely and appropriate TJA access, optimization and prioritization of patient selection is critical. Clear, evidence-based guidelines for surgical appropriateness are lacking, resulting in a reliance on clinical judgement[9]. This has led to

subjectivity in risk stratification, conflicting approaches and barriers or delays in treatment access for patients with obesity due to evidence of increased surgical risk.

Two meta-analyses have found increased risk of superficial infections (OR 1.7-2.2)[10,11] and deep infections (OR 2.4)[10] after total knee arthroplasty (TKA) in patients with obesity (defined as a body mass index/BMI ≥ 30 kg/m^2) compared to patients without obesity (BMI < 30 kg/m^2). Those with severe obesity (BMI ≥ 40 kg/m^2) appear to be at even higher risk, with four times the rate of infection after TKA compared to those without obesity[11,12]. Increased infection after total hip arthroplasty (THA) is less clear[13]. Yet controversy exists around evidence of increased risk related to excess body weight. Methodological concerns regarding quality and comparability of studies have been raised, with underpowered sample sizes, BMI categorization/dichotomization, and absence of sub-classification by comorbidity status limitations in current evidence[14,15].

Suggestions for establishing a BMI threshold for withholding TJA surgery have been made[11,14,16], while others argue against using BMI as an outright contraindication for TJA[17,18]. Without clear guidelines, orthopaedic surgeons may decide to deny or delay surgery based on their interpretation of evidence of surgical risk. Of greater concern, many surgeons recommend that patients lose weight to reduce their BMI before returning for re-assessment of surgical eligibility[12,14,19]. This recommendation is in contrast to current evidence that suggests weight loss does not improve perioperative TJA risk. Lui et al[20] found weight loss of ≥ 5% of body weight in the year prior to TJA resulted in either no difference or an increased risk of deep infection (OR 3.8). Weight loss may inadvertently increase perioperative infection, as muscle lost concomitantly with fat may lower lean muscle reserves, which are critical to the wound healing process[21].

Reliance on BMI may result in misclassification bias and denial of surgery for patients with obesity. BMI is a poor indicator of individual health as it cannot discern individual body composition of muscle, bone or fat[22]. Significant deviations in body composition within BMI categories have been reported[22–24], including twofold differences in adiposity[25] and 30 kg differences in lean soft tissue[26] between patients who have the same BMI[27]. Relying on BMI as a screening tool for TJA ignores the influence body composition has on surgical risk, particularly in relation to the amount of skeletal muscle mass as shown in other clinical scenarios[28,29]. A high BMI could disguise important skeletal muscle mass depletion, as in the condition of sarcopenic obesity[26,30]

What is sarcopenic obesity?

Sarcopenic obesity is defined as the co-occurrence of high adiposity and sarcopenia. Sarcopenia is a health condition of low skeletal muscle mass, strength and physical function originally diagnosed in the elderly[31], but present across the age spectrum[32,33]. Sarcopenia is associated with physical disability, falls, extended hospital stays, infection and non-infection related complications, and increased overall mortality[34–36]. Importantly, sarcopenia is not restricted to people who appear thin or underweight. Aging is often paralleled by increased rates of muscle loss and concomitant gains in adiposity (both subcutaneous and intramuscular), which can culminate in sarcopenic obesity[37].

Compounding the effects of both sarcopenia and obesity, sarcopenic obesity is associated with poorer quality of life and greater disability, morbidity and mortality when compared with either obesity or sarcopenia alone[37–39]. Although the majority of studies to date have been conducted in elderly individuals, sarcopenia and sarcopenic obesity are not limited to this population. There are several clinical disorders where individuals are prone to muscle loss (with

or without concurrent obesity), including diabetes, cancer, chronic obstructive pulmonary disease, HIV, cirrhosis, and arthritis[40]. The presence of sarcopenic obesity may be particularly important to consider when surgery is indicated. In addition to increased length of hospital stay and increased mortality associated with this condition[40], there is convincing evidence of its relationship with increased infection rates[28,29,41].

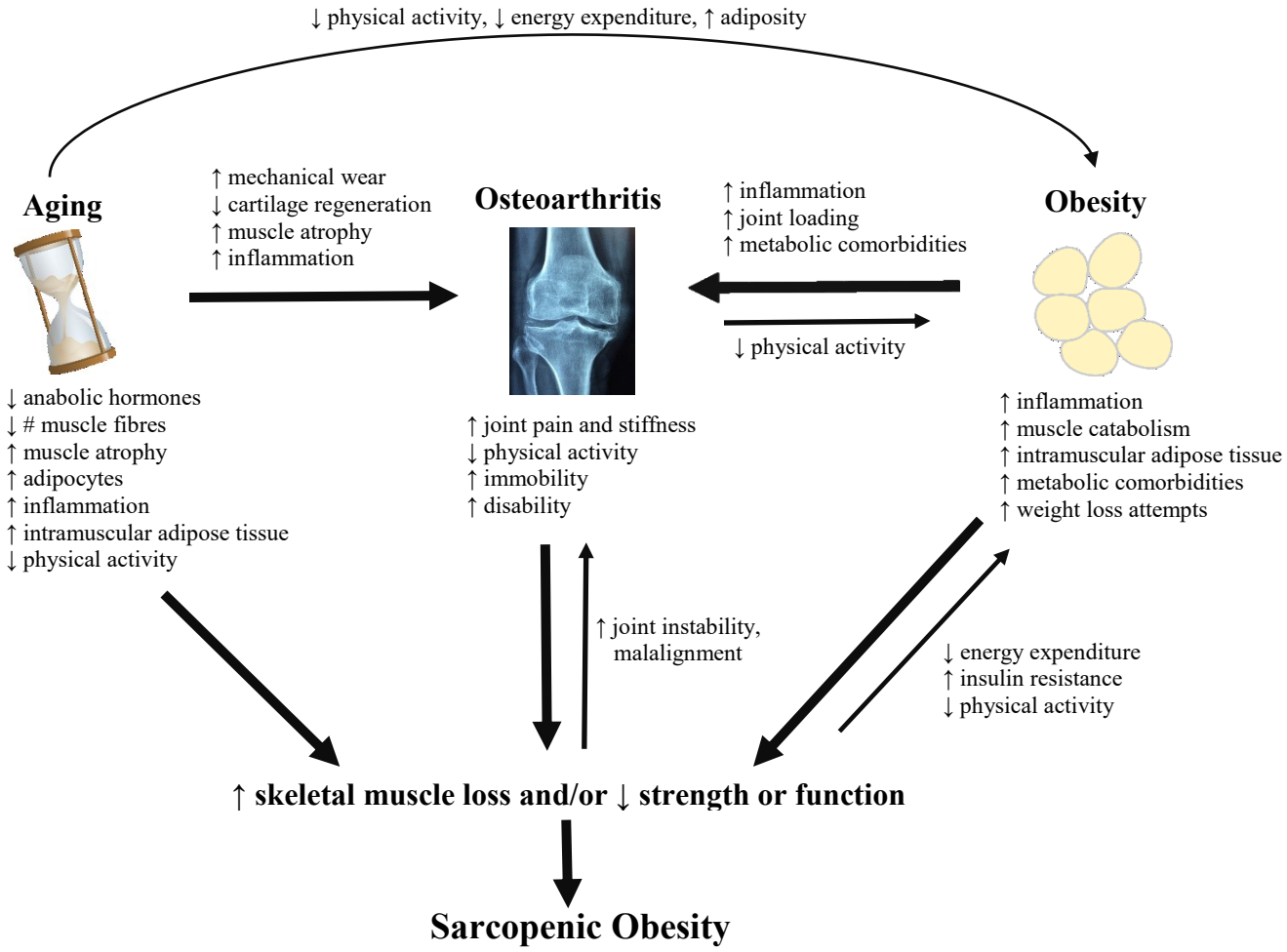
With obesity present in 26% to 38% of adults in Canada and the USA respectively[42], and an aging population with a longer life span, sarcopenic obesity may be a new epidemiological trend of current times[43]. Importantly, it cannot be identified by simply measuring body weight or calculating BMI[44].

Is sarcopenic obesity a concern in osteoarthritis?

Individuals with osteoarthritis may be at particular risk for sarcopenic obesity. The prevalence of osteoarthritis rises with age and obesity, and osteoarthritis-related pain can lead to inactivity and a decline in physical function. These factors in combination create a vicious cycle of inflammation, inactivity and aging-related muscle loss accompanied by aging-related gains in adiposity, giving rise and perpetuating the sarcopenic obesity phenotype[45–47] **(Figure 2.1)**. Chronic diseases associated with osteoarthritis[48], such as diabetes, metabolic syndrome, and hypertension, along with weight loss and subsequent re-gain (weight cycling), could exacerbate skeletal muscle loss, increase adiposity and contribute to the development of sarcopenic obesity[49]. Further, the development and progression of sarcopenia and osteoarthritis may occur through interrelated pathways[50,51].

Body composition phenotypes of low skeletal muscle and high adiposity have been reported in patients with knee and hip osteoarthritis by Karlsson[52–54], Purcell[55] and Visser[56], although sarcopenia or obesity were not specifically identified. Nevertheless, this is compelling

Figure 2.1. Relationship between aging, obesity and osteoarthritis and the development of sarcopenic obesity



evidence and may indicate that this condition is present in osteoarthritis but not recognized or identified as sarcopenic obesity.

To provide a more complete understanding of sarcopenic obesity in lower extremity osteoarthritis, a scoping review was conducted to determine the extent of reported prevalence and impact of low muscle mass, muscle weakness or sarcopenia in adults with obesity and knee or hip osteoarthritis. Scoping reviews enable a comprehensive and encompassing review of emerging literature on a topic[57], and can be preferable to systematic reviews when the research question is examining the breadth of evidence on a topic, as in this case. Scoping reviews utilize transparent processes and systematic search strategies much like systematic reviews, and while they don't typically include a grading system or formal quality assessment of included studies, a description of study limitations can be incorporated into the results.

2.4 Methods

This scoping review was conducted following the methodology of Arksey and O'Malley[58], including a systematic search of the published literature. Medline, CINAHL, Web of Science and Embase databases were searched from inception to December 2017 using MeSH terms and keywords related to osteoarthritis, obesity, and sarcopenia (including dynapenia, muscle weakness, muscle atrophy, low muscle mass, muscle loss, body composition, body compartment, lean soft tissue, lean body mass, lean mass, fat free mass, muscle size or muscle mass). Inclusion criteria was determined by the authors prior to search initiation. Studies were to be included if they were primary or secondary analyses, and subjects had knee or hip osteoarthritis. Additionally, studies must have conducted group/subgroup analysis by obesity (identified using body mass index/BMI, waist circumference, fat mass or percent body fat), and examined muscle mass, muscle strength/weakness or sarcopenia. Studies on animal models and

children were excluded, along with studies where participants did not have knee or hip osteoarthritis, or obesity, or if the study was an editorial, protocol or review article. Reference lists of relevant articles were hand searched to identify articles missed in the primary investigation. From each included study we extracted the author, publication year, study design, sample population, methodologies for assessing obesity and sarcopenia, study limitations and relevant findings. A summary of extracted information was tabulated and a descriptive analysis was conducted.

2.5 Results

A total of 796 articles were identified in the original search and 118 full text articles were screened for potential relevance (**Figure 2.2**). Eleven studies met inclusion criteria[59,60,69,61–68], and a summary of study characteristics and key findings are presented in **Table 2.1**.

Publication dates ranged from 2005 to 2017, with the majority (n=8, 73%) published in the last three years, potentially indicating a growing awareness and understanding of sarcopenic obesity. Ten of the eleven studies were cross-sectional[60–69], and one longitudinal[59]. Four studies (36.4%) were secondary analyses of the Korea National Health and Nutrition Examination Survey (KNHANES) population cohort[61,63,64,68], two (18.2%) were secondary analyses of the North American Osteoarthritis Initiative (OAI) population cohort[59,62], one (9%) was a secondary analysis of the French Knee and Hip OsteoArthritis Long-term Assessment (KHOALA) cohort[69], and the remaining four (36.4%) were independent studies with cohorts from Korea[60], Thailand[65], Japan[67] and the Netherlands[66]. Eight studies focused on osteoarthritis of the knee joint[59,61–65,67,68], with two additional studies examining both knee and hip[60,69], and one solely on hip osteoarthritis[66].

Figure 2.2. Systematic search strategy and results

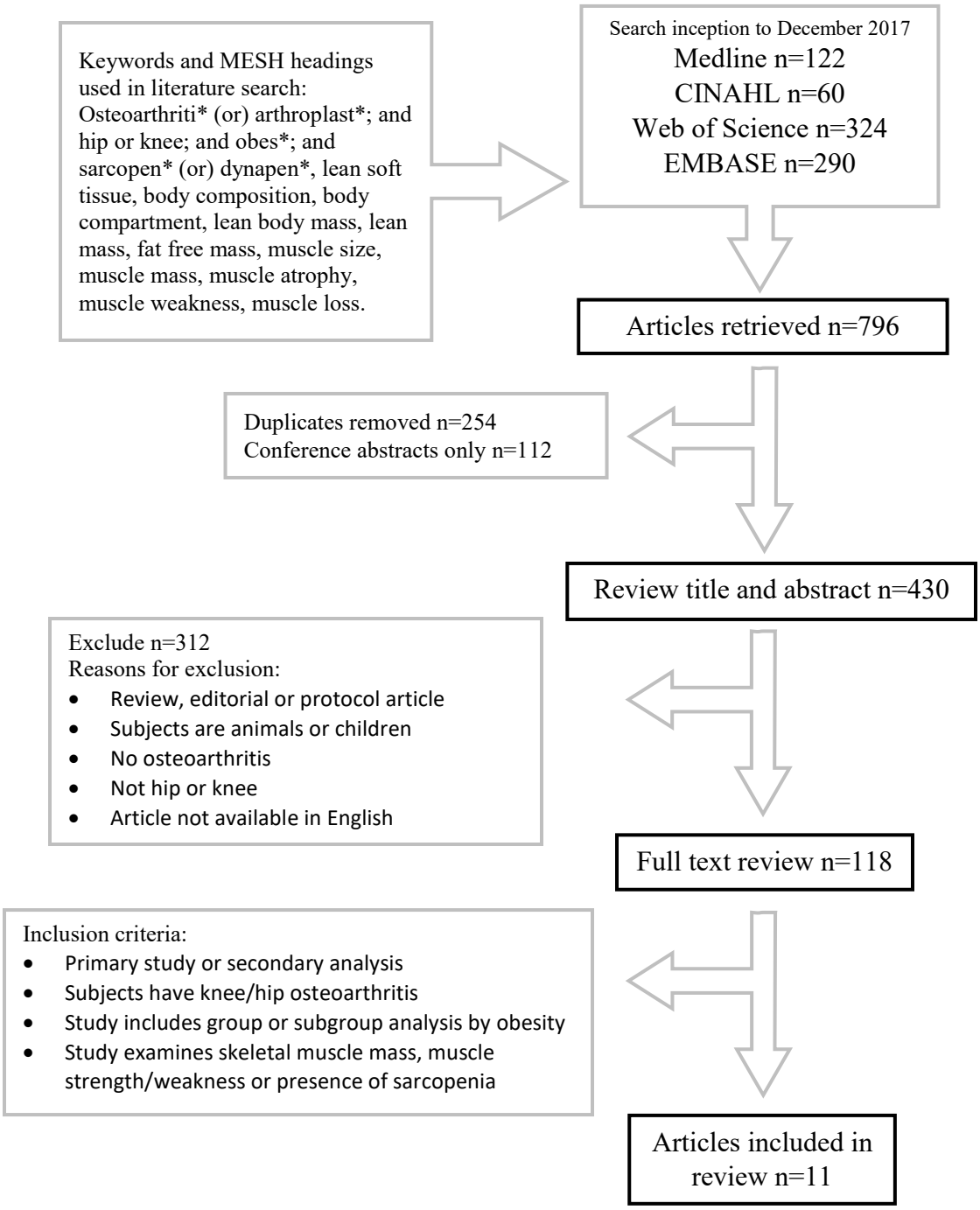


Table 2.1. Studies reporting low skeletal muscle mass and/or muscle weakness in adults with obesity and knee or hip osteoarthritis

Author, Year	Study purpose	Study design	Population	Definition of obesity	Body composition methodology	Definition of low muscle mass[a,b] or muscle weakness	Study limitations	Relevant findings
Batsis et al.[59], 2015	To describe the impact of dynapenic obesity on physical function in knee OA	Longi-tudinal,	North American population from OsteoArthritis Initiative (OAI), age ≥ 60 years, n=526 in subgroup with knee OA (rKOA),	BMI ≥30 kg/m^2	NI	Lowest sex-specific tertile of knee extensor strength (dynapenia)	Secondary analysis of prospective data from longitudinal cohort. Excluded severe knee OA. No assessment of muscle mass or body composition	Prevalence of dynapenic obesity was 16%.
Clemence et al[69], 2017	To analyze the association between low lean mass and clinical symptoms in knee and hip OA	Cross-sectional	French adults with hip and knee OA (KL grade ≥ 2) from KHOALA study, n=358, age 63.4 ±8.4 years	BMI ≥30 kg/m^2, or sex specific FM or WC cut-offs	DXA	ASM/BMI <0.789 for men and <0.512 for women (FNIH cutoffs)	Secondary analysis of prospective data from longitudinal cohort. No information on exclusion criteria. No assessment of muscle strength or function	SO prevalence was 16.2%. Low lean mass was associated with pain and impaired function in subjects with normal BMI, but not with obesity (no significant differences between NSO and SO groups).
Ji et al.[60], 2016	To identify the prevalence of SO in knee and hip orthopedic surgery (OS) patients	Cross-sectional	Korean orthopedic surgery patients (hip or knee TJA or femoral fracture repair) (OS, n=222) compared to control non-surgical outpatients (non-OS, n= 364)	BMI >25 kg/m^2	DXA	ASM/height^2, ASM/weight, and ASM/height and fat mass (residuals)	Retrospective analysis of data. No assessment of muscle strength or function	SO prevalence ranged from 1.3-35.4% in TKA and 0-18.4% in THA patients depending on definition used. SO rates were higher in OS patients compared to non-OS patients.
Jin et al.[61], 2017	To examine the associations between obesity, sarcopenia and OA in elderly	Cross-sectional	Korean population (KNHANES) age ≥ 65 years group with knee OA (K/L grade ≥ 2) (n=1865) compared to lumbar spondylosis group (n=1709)	BMI ≥25 kg/m^2	DXA	ASM/weight, 2SDs below average of sex-matched young reference group	Secondary analysis of population survey data. No assessment of muscle strength or function	Results indicate correlation between SO and NSO with knee OA, but no relationship with lumbar spondylosis. Females with SO had increased OR for knee OA when adjusted for age and waist circumference (OR 1.80, CI 1.03-3.12).
Knoop et al.[62], 2011	To identify distinct clinical phenotypes and their impact in knee OA	Cross-sectional	North American population with knee OA (K/L grade 0-4) from OsteoArthritis Initiative (n=842, age 63.2±9.1)	BMI ≥30 kg/m^2	NI	Low mean score of quadriceps and hamstring isometric strength	Secondary analysis of prospective data from longitudinal cohort. No assessment of muscle mass or body composition. No clear cut-off for defining weakness	Dynapenic obesity group ("obese and weak" phenotype) had higher pain and poorer physical function compared to "minimal joint disease", "strong muscle", and "non-obese and weak" phenotypes.

Author, Year	Study purpose	Study design	Population	Definition of obesity	Body composition methodology	Definition of low muscle mass[a,b] or muscle weakness	Study limitations	Relevant findings
Lee et al.[63], 2016	To investigate association between lower limb muscle mass and knee OA	Cross-sectional	Korean population (KNHANES) age ≥50 years, n=821 with knee OA (K/L grade ≥2), (n=821), and control group without knee OA (n=4103)	BMI ≥27.5 kg/m^2	DXA	ASM/weight, 2SD below the mean in sex-matched young reference group (<29.5% in men, <23.2% in women)	Secondary analysis of population survey data. No assessment of muscle strength or function	SO prevalence was 5.2% in knee OA group compared to 1.8% in control group.
Lee et al.[64], 2012	To analyze the association between knee OA, sarcopenia and obesity	Cross-sectional	Korean population (KNHANES) with bilateral knee OA (K/L grade ≥2) age ≥50 years, n=2893	BMI ≥27.5 kg/m^2	DXA	ASM/weight, 2SD below the mean in sex-matched young reference group (<26.8% in men, <21% in women)	Secondary analysis of population survey data. No assessment of muscle strength or function	SO prevalence was 3% overall. When adjusted for age and sex, SO had stronger association with knee OA (OR 3.51, CI 2.15-5.75) compared to NSO (OR 2.38, CI 1.80-3.15).
Manoy et al[65], 2017	To assess association between leptin, vitamin D, muscle strength and physical performance in knee OA	Cross-sectional	Thailand knee OA patients (K/L grade <3) (n=208), age 65±7 years	BMI >25 kg/m^2	BIA	ASM/weight <30.4% in men and <25.8% in women, and EWGSOP gait speed and grip strength cutoffs	Unclear if data collected retrospectively or prospectively. No description of sampling methods. Excluded severe knee OA	SO prevalence was 13.9%. Patients with SO had poorer performance on the timed up and go (TUG), sit to stand (STS) and 6 minute walk tests (6MWT) compared to those with NSO or NO.
Oosting et al.[66], 2016	To determine the association of obesity and recovery after THA when stratified by muscle strength	Cross-sectional	Netherlands THA patients (n=297), age 69±11 years	BMI >30 kg/m^2	NI	Maximal handgrip strength (<20 kg for woman and <30 kg for men)	Secondary analysis of prospective cohort. No assessment of muscle mass or body composition	Obesity and muscle weakness (dynapenic obesity) was associated with prolonged length of stay >4 days (OR 3.59, CI 1.09-11.89) and delayed inpatient recovery (>2 days to walk with gait aid) (OR 6.21, CI 1.64-23.65), but not in those with obesity alone.
Segal et al[67], 2005	To analyze the impact of low limb lean mass in knee OA distinct from body weight	Cross-sectional	Japanese female orthopedic knee OA (K/L grade ≥2) patients age ≥45 years (n=341), compared to control group with fracture, sprains or back pain (n=604)	BMI >24.9 kg/m^2	BIA	Lower limb LST	Unclear if data collected retrospectively or prospectively. No clear cut-off for defining low LST. No assessment of muscle strength or function	Females with knee OA had 5-15% less lower limb LST compared to control groups across BMI categories, with significant 1.8 kg and 1.5 kg differences in overweight and obesity groups, respectively.
Suh et al[68], 2016	To analyze the association between	Cross-sectional	Korean population (KNHANES) age ≥50 years with unilateral knee	BMI ≥27.5 kg/m^2	DXA	Lower extremity LST/weight, in lowest quartile	Secondary analysis of population survey data. No assessment of	In females, obesity and low muscle mass was strongly association with knee OA (OR

Author, Year	Study purpose	Study design	Population	Definition of obesity	Body composition methodology	Definition of low muscle mass[a,b] or muscle weakness	Study limitations	Relevant findings
	obesity, sex, and lower extremity lean mass in knee OA		OA (K/L grade ≥2) (n= 4246; 1829 men and 2417 women)				muscle strength or function	2.31, CI 1.35-3.93) compared to obesity and normal muscle mass (OR 1.03, CI 0.26-4.02).

[a]Varied indices for identifying low muscle mass: LSTI, LST/weight, ASM, ASMI, ASM/weight, ASM/BMI, ASM relative to height and FM (residuals), and FM:FFM ratio[26]. Indices that consider LST or ASM relative to weight, BMI or FM may be most appropriate in adults with obesity[26], and relevant to identify clinically relevant weakness[70].
[b]Terms from included studies were adjusted for consistency and accurate representation of body composition compartment, and may differ from original reports.
ASM = appendicular skeletal mass, ASMI = ASM/height^2, BIA = bioelectrical impedance analysis, BMI = body mass index, CI = confidence interval, DXA = Dual-energy x-ray absorptiometry, EWGSOP = European Working Group on Sarcopenia in Older People, FM = fat mass, FFM = fat free mass, FNIH = Foundation for the National Institute of Health, KNHANES = Korean National Health and Nutrition Examination Survey, K/L = Kellgren/Lawrence radiographic osteoarthritis score, LST = lean soft tissue, LSTI = LST/height^2, NI = not included in study design, NO = normal body composition, NSO = not sarcopenic obesity, OA = osteoarthritis, OR = odds ratio, rKOA = radiographic evidence of knee osteoarthritis, SD = standard deviation, SO = sarcopenic obesity, THA = total hip arthroplasty, TJA = total joint arthroplasty, TKA = total knee arthroplasty, VAS = visual analog scale, WC = waist circumference, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

2.6 Discussion

This scoping review identified eleven studies with clear indications that muscle weakness, low skeletal muscle mass, or sarcopenia occur in conjunction with obesity in lower extremity osteoarthritis. The majority of included studies examined prevalence and association of the sarcopenic obesity phenotype with the presence of knee or hip osteoarthritis[60,61,63,64,67,68], however others investigated the impact on pain, physical function, and quality of life[59,62,65,69] or arthroplasty outcomes[66].

The prevalence of the sarcopenic obesity phenotype in adults with knee osteoarthritis may be as high as 35.4%[60], although a wide range was reported across included studies (prevalence of 3%[64], 13.9%[65], 16.2%[69], and up to 35.4%[60]). Differences in prevalence are likely related to varied obesity and sarcopenia classification criteria utilized in each study, a problem previously addressed elsewhere[26]. Obesity was classified by BMI (in kg/m^2) in all studies, but different cut-offs were used in Asian populations (either BMI ≥ 25[60,61,65,67] or ≥ 27.5[63,68]), and North American and European populations (BMI ≥ 30[59,62,66,69]), making it difficult to compare across study groups and populations. Prevalence also varied depending on the sarcopenia assessment method used in the study. Ji et al[60] examined differences in sarcopenic obesity rates in hip and knee arthroplasty patients comparing low muscle mass (assessed with dual-energy x-ray absorptiometry/DXA) using three approaches: appendicular skeletal mass (ASM)/height^2, ASM/weight, and ASM relative to height and total fat mass, called the residual method[71]). They found prevalence of sarcopenic obesity differed between 1.3 - 35.4% in TKA patients and 0 - 18.4% in THA patients depending on the approach. Whether distinctions exist between low muscle mass present only in the lower extremities versus the whole body remains unclear[63,67,68]. Emerging evidence suggests that in patients with a larger body mass, the ratio between fat and

muscle compartments (a metabolic load-capacity model) may be most relevant for identifying clinically important sarcopenic obesity[26].

There is currently no definitive diagnostic criteria established to identify sarcopenic obesity[72–74]. Several consensus papers on defining sarcopenia in the elderly have been published, including the European Working Group on Sarcopenia in Older Persons (EWGSOP)[31], the European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG)[75], the International Working Group on Sarcopenia (IWGS)[36], and the Foundation for the National Institute of Health (FNIH)[70]. There is general agreement that the presence or absence of sarcopenia in the elderly should be based on a combined assessment of physical function (measurement of gait speed), muscular strength (measurement of handgrip or lower body strength), and body composition (to determine low skeletal muscle mass). However whether these measures are equally applicable to patients with concurrent chronic degenerative conditions remains to be explored.

Of the studies in this scoping review, seven used only body composition/low muscle mass for sarcopenia identification[60,61,63,64,67–69], three used only an assessment of muscle weakness (testing handgrip[66] or quadriceps strength[59,62]), and only one study utilized a combined approach following EWGSOP consensus criteria[65] including assessment of physical function with gait speed in addition to muscle strength and body composition. Using gait speed as an assessment of physical function may create challenges in the osteoarthritis population. Osteoarthritis-related joint pain and stiffness may impact testing methods or may require alterations or alternatives to currently used criteria thresholds[76] or modifications to gait speed parameters. Additionally, risk of falls is high in those with moderate to severe osteoarthritis[77], which may increase the challenge of assessing physical function in this population.

The relationship between the sarcopenic obesity phenotype and knee osteoarthritis may be unique compared to other orthopedic and musculoskeletal conditions. In the included studies, no association was found between sarcopenic obesity and lumbar spondylosis[61], or in patients with fractures, sprains and back pain[67], or non-orthopedic hospital outpatients[60]. The development and progression of sarcopenic obesity may be interrelated with osteoarthritis development and progression. Lee et al[63] found sarcopenic obesity was more prevalent in Korean adults with knee osteoarthritis compared to those without knee osteoarthritis (5.2% vs 1.8%, respectively). Batsis et al[59] found rates of muscle weakness with obesity were higher in adults with clinically diagnosed knee osteoarthritis compared to those at risk for knee osteoarthritis (16% vs 6%, respectively). Sex specific differences may exist in this relationship. Suh et al[68] found increased odds of knee osteoarthritis when low lower-extremity muscle mass was present in women with obesity (OR 2.31, CI 1.35-3.93), but not in men. Another study reported similar associations only in women over age 65[61].

The findings of this scoping review support the theoretical impact of sarcopenic obesity on therapeutic outcomes for osteoarthritis, and surgical risk and recovery after joint arthroplasty. To date, only one study has investigated outcomes after TJA, with results showing obesity with muscle weakness was related to delayed independent walking (more than 2 days) and prolonged hospital stays (more than 4 days) compared to obesity alone[66].

It is reasonable to infer that reduced muscle strength or skeletal muscle mass would influence short and long-term recovery after arthroplasty and rehabilitation requirements to return to daily life. Muscle depletion is indicative of a reduction in physiologic protein reserves, which can contribute to impaired wound healing, increased risk of infections and longer recuperation after surgery[78]. A study by Kumar et al[79] found that handgrip strength <15 kg was

associated with longer hospital stay after TJA, highlighting this potential relationship. Further, a study by Mau-Moller et al[80] reported that low thigh muscle mass was a better predictor than BMI for loss of bone mineral density after TKA. This is important as loss of bone mineral density can lead to early prosthetic loosening after TKA and a need for revision surgery, suggesting that muscle mass may be more relevant than BMI for long term TKA outcomes.

Identifying sarcopenic obesity early in the continuum of care for osteoarthritis is critical to avoid inappropriate treatment recommendations. The current practice of recommending weight loss prior to TJA based on assessment of body weight or BMI[64] may need further consideration as weight loss attempts may also result in loss of skeletal muscle mass[40,49], potentially exacerbating the sarcopenic obesity phenotype. Body composition measurement may be a critical assessment tool to distinguish between normal versus abnormal amounts of skeletal muscle mass and provide a more accurate assessment of adiposity[81], as anthropometric measures of obesity (using waist circumference, height, weight and BMI) may not differentiate between muscle and adipose tissue compartments. As previously discussed, body weight loss ≥5% in year preceding TJA was associated with increased surgical risk and higher readmission rates[20]. This may be a result of individuals with sarcopenic obesity losing weight, further reducing their already low muscle reserve, in turn impacting healing rates and perpetuating the vicious cycle of sarcopenia and obesity. Alternatively, it could suggest individuals with obesity and normal skeletal muscle mass (non-sarcopenic obesity) became sarcopenic post weight-loss (by losing more skeletal muscle mass without a substantial decrease in body weight to be considered non-obese)[40].

Study Limitations

Every effort was made to comprehensively search and include all relevant studies in the literature, however there is a possibility that some were inadvertently missed. Further, while a limitation of scoping reviews is the lack of a formal risk of bias or study quality assessment, we have included a descriptive analysis of study design and limitations in Table 1 of the results section to enable assessment of level of evidence.

2.7 Conclusion

Sarcopenic obesity may be impacting therapeutic and surgical outcomes in osteoarthritis treatment approaches, yet this cannot be discerned until assessments for sarcopenic obesity are explored and regularly applied. There is a need to move beyond BMI and simple obesity diagnosis in osteoarthritis models of care, possibly including more sophisticated assessments of body composition. As gait speed and handgrip strength assessments to identify patients at risk for sarcopenic obesity have not been well-tested in the osteoarthritis population, further research is required to clarify the effectiveness of these screening approaches in populations with physical function limitations. In the interim, incorporating clinical assessments for sarcopenic obesity through body composition may be essential to prevent misclassification bias and provide clarity on TJA surgical risk and recovery in adults with obesity.

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CHAPTER 3

3.1 Synopsis

A version of this chapter was published as Godziuk K, Prado CM, Woodhouse LJ, Forhan M, Prevalence of sarcopenic obesity in adults with end-stage knee osteoarthritis, *Osteoarthritis and Cartilage,* 2019.

3.2 Abstract

Objective To identify the prevalence of sarcopenic obesity, a phenotype of low muscle mass and high adiposity, in adults with end-stage knee osteoarthritis (OA). Various diagnostic criteria, including assessment of muscle/fat mass, muscle strength and physical function, were used to identify patients with and without sarcopenic obesity, and to compare outcomes of pain, function and quality of life.

Design Cross-sectional clinical study including adults with a body mass index (BMI) ≥30 kg/m^2 and knee OA. Body composition was measured by dual-energy x-ray absorptiometry (DXA). Assessments included gait speed, handgrip strength, six minute walk test, and self-reported pain, physical function, and health-related quality of life using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and EuroQol Foundation (EQ-5D).

Results 151 adults (59% female) aged 65.1±7.9 years, mean BMI 37.1±5.5 kg/m^2, were included. Prevalence of sarcopenic obesity using diagnostic cut-offs of appendicular skeletal muscle mass (ASM) relevant to height^2, weight and BMI varied from 1.3% (95% confidence interval: 0.2-4.7%) to 14.6% (9.4-21.2%) and 27.2% (20.2-35%), respectively. A combined diagnostic approach including low ASM with either low strength or low function yielded a

prevalence of 8.6% (4.7-14.3%). Sarcopenic obesity influenced walking speed, endurance, strength, and patient-reported difficulty with self-care activities, regardless of diagnostic approach.

Conclusion Prevalence of sarcopenic obesity varied depending on diagnostic criteria. Given the impact of this condition and OA on physical function, we suggest a combined diagnostic approach be used to clarify expected prevalence and enable early clinical identification and management of sarcopenic obesity in patients with knee OA.

3.3 Introduction

Obesity [defined using body mass index (BMI)] is associated with knee osteoarthritis (OA) progression and increased surgical infection risk in total knee arthroplasty (TKA)[1,2]. However sarcopenic obesity, a phenotype of low muscle mass and high adiposity[3], may have greater relevance and implications for adverse outcomes in this clinical population. This condition may be present in patients with knee OA but not identified using BMI alone. Sarcopenic obesity is associated with surgical infection[4,5], disability[6], and mortality[7] in other patient populations, but not well-examined in OA[8]. Importantly, OA, obesity and related chronic diseases, like diabetes[9], are pro-inflammatory conditions that can influence muscle catabolism and the development and progression of sarcopenic obesity. Combined with normal muscle senescence beginning in middle age and accelerated during menopause or andropause, individuals with OA are at additional risk of sarcopenic obesity due to the added influence of OA-related pain and disability, resulting in inactivity and further muscle loss. Taken together, these data suggest that comprehensive assessments for sarcopenic obesity should be completed in patients with end-stage OA for whom TKA is recommended.

Presently, sarcopenic obesity is not assessed in patients with OA, in part due to a lack of consensus on the definition and diagnosis of this condition, and partially due to insufficient recognition that sarcopenia occurs at any body weight. Few studies have examined sarcopenic obesity in knee OA. Our recently conducted scoping review[8] found only ten studies that examined sarcopenic obesity in knee OA. Prevalence rates between 1.3%-35.4% were reported[8], however studies were primarily based on Asian population studies using lower BMI cut-offs for obesity and varied identification methods for low muscle mass, limiting comparability. A primary concern with the lack of recognition and screening for sarcopenic obesity in end-stage knee OA is related to clinicians advising weight loss based on patients' BMI[2,10] without realization of the potential harm. Recommending weight loss prior to TKA eligibility could inadvertently exacerbate the sarcopenic obesity condition due to muscle loss that typically occurs during weight loss[11]. In patients with low muscle mass, any additional loss may contribute to reduced wound healing following TKA[12], poorer functional outcomes due to decreased strength to support joint structure and mobility[13], potential alterations to the pharmacokinetics of medications[14], and increased risk of mortality[7].

Greater awareness and screening for sarcopenic obesity in knee OA is essential. As sarcopenia is considered a reportable disease by the World Health Organization (WHO)[15], routine screening should be included in OA clinical care pathways. Several consensus diagnostic criteria have been proposed for sarcopenia in the elderly[16–20] with agreement that identification be based on a combination of low muscle mass with low strength or function. Although there is no current consensus on diagnostic criteria for sarcopenic obesity[21,22], there are several accepted diagnostic approaches using measures of body composition[23]. Regardless, in view of the

importance of sarcopenic obesity and the potential prevalence and impact in individuals with OA, screening for this condition should be a priority in clinical settings.

The purpose of this study was to examine the prevalence of sarcopenic obesity in a clinical cohort of adults with end-stage knee OA. Different diagnostic criteria, including assessments of muscle/fat mass, muscle strength and physical function, were used to identify patients with and without sarcopenic obesity, and to compare reported outcomes of pain, function and health-related quality of life.

3.4 Methods

Patients

Study patients were community dwelling adults undergoing TKA screening for unilateral or bilateral knee OA at a centralized intake orthopedic clinic in Alberta, Canada from May 2017-March 2018. Patients were referred to the clinic by their primary care provider. Inclusion criteria were a BMI $\geq$ 30 kg/m^2 measured in clinic, no history of hip or knee arthroplasty or bariatric surgery, and able to communicate and give written informed consent in English. All eligible patients were approached to enroll in the study in sequence after their clinical visit. Study data were collected prospectively and managed using REDCap[24] electronic data capture tools hosted and supported by the Women and Children's Health Research Institute at the University of Alberta. Ethics approval was provided by the Health Research Ethics Board at the University of Alberta, Edmonton, Alberta.

Patient characteristics

Socio-demographic and health information about each participant was collected, including age, sex, ethnicity, and comorbid conditions. Smoking status was categorized as

current, previous, or never smoked. Height and weight were measured in clinic with footwear and light clothing using wall-mounted measuring tape and electronic scales (Alimed Model CNS1101KG, and Seca Model 813), and measured again at body composition appointment, without footwear and wearing only a hospital gown, using an electronic scale (Seca Model 766). BMI was calculated and categorized according to WHO criteria[25]. Waist and hip circumference were measured to nearest 0.1cm over light clothing using a non-elastic tape measure. Waist circumference was measured at the top of the iliac crest, and hip circumference was measured at the largest diameter of the gluteal muscle. The average from three consecutive measures was recorded. In addition to collecting age as a continuous variable (in years), it was also dichotomized to enable comparisons between middle-aged (ages 40-64.9 years) and older adults (ages ≥65 years).

Body composition

Body composition was assessed using dual-energy x-ray absorptiometry (DXA) (GE Healthcare Lunar iDXA, analyzed with enCORE software version 16) on a separate date and location. Total body and regional lean soft tissue (LST), fat mass (FM) and bone mineral concentration (BMC) were collected. Percent fat mass (%FM) was calculated by total FM divided by the sum of total BMC, FM and LST, multiplied by 100. Fat mass index (FMI) was calculated as FM divided by height in meters^2. Appendicular skeletal muscle mass (ASM), considered an accepted proxy for skeletal muscle mass, was calculated as LST of arms plus legs. Obesity was identified by BMI ≥30 kg/m^2 at intake, and confirmed by the additional criteria for obesity of a waist circumference >88 cm in females and >102 cm in males[13], and %FM ≥35% in females and ≥25% in males[26].

Performance-based physical function

Normal ambulatory walking speed (in seconds) was timed over a four meter course, with untimed one meter allowances on either side as acceleration and deceleration zones. The faster of two attempts was recorded, and gait speed calculated. Patients used assisted walking devices (cane or walker) if normally used for ambulation. Maximal isometric handgrip strength was assessed in the dominant hand using a Jamar handgrip dynamometer. Grip position was adjusted to position 2 or 3 depending on patients' hand size. Patients were seated with elbow flexed to 90 degrees, and no contact with chair arm or backrest, if present. The highest of three attempts was recorded to nearest 0.5 kg. Functional physical performance was assessed in clinic using the six-minute walk test (6MWT), a valid and reliable measure in patients with knee OA[27].

Patient-reported quality of life, pain and function

Health-related quality of life was assessed using an electronic version of the EuroQol Foundation EQ-5D-5L[28]. The EQ-5D questionnaire has patients rate their perceived quality of life from 1 'no problems' to 5 'extreme problems' across five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Results were dichotomized into no problems (score of 1), and problems (scores of 2-5). Index scores that can be used for healthcare economic evaluations were calculated based on a Canadian value set[29]. Patients also rated their perceived overall health on the visual analogue scale (VAS) from 0 (worst health) to 100 (best health). The disease-specific Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[30] has patients rate, on a 5-point Likert scale, their pain(0-20; 5 items each scored 0-4), stiffness (0-8; 2 items each scored 0-4) and function (0-68; 17 items each scored 0-4), for a total of 0-96, normalized to 0-100 scale by multiplying total score by 100/96.

Sarcopenic obesity diagnosis and prevalence

Sarcopenic obesity was identified using four diagnostic approaches. Three used accepted criteria from international consensus groups[19,20] for identifying low muscle mass alone using ASM assessed by DXA, adjusted by body size, and compared to established sex-specific cut-offs[13,26,31]. The fourth diagnostic approach used a combination of low muscle mass with the presence of either low strength or low function[16]. Prevalence of sarcopenic obesity was reported as the frequency and proportion of the cohort meeting each identification criteria:

Low muscle mass, alone, assessed by adjusted ASM:

ASM/height^2 = ASM (in kg) divided by height (in meters^2), also called ASM index (ASMI). Cut-offs <5.45 kg/m^2 in females and <7.26 kg/m^2 in males identified low ASM/height^2 [31];

ASM by weight = ASM (in kg) divided by weight (in kg) x 100. Cut-offs <19.43% in females and <25.72% in males% identified low ASM by weight[13];

ASM by BMI = ASM (in kg) divided by BMI (in kg/m^2). Cut-offs <0.512 kg/m^2 in females and <0.789 kg/m^2 in males identified low ASM by BMI[26].

Combined diagnostic approach: a) low muscle mass with low strength, or b) low muscle mass with low function = low muscle mass (low ASM identified by any of the body-size adjusted criteria, as above) with either low muscular strength (maximal isometric handgrip strength <20 kg in females and <30 kg in males), or low physical function (gait speed <0.8 m/s), recommended by the consensus European Working Group on Sarcopenia in Older Persons (EWGSOP and EWGSOP2)[16,20].

Statistical Analysis

A priori sample size (n=143) was calculated[32,33] to provide a 95% confidence interval of the prevalence with a precision of 5%, based on a reported sarcopenic obesity prevalence of 10.4% (identified using ASM by weight and obesity identified by waist circumference) in a North American population study of adults age ≥60 years[13]. Analyses were conducted using IBM SPSS Statistics v24 (IBM Corp., Armonk, NY). There were no missing data on the patients included in the analyses. Normality of data distribution was tested with the Shapiro-Wilk test. Univariate analysis was completed and results reported as mean (standard deviation), median (interquartile range), or frequency (proportion). 95% confidence intervals for proportions were calculated using Clopper-Pearson exact. Between-group comparisons were conducted using Student's independent t-test, Mann-Whitney U test, Chi-square or Fisher's exact test, as appropriate, based on the distribution, variable type and number in each group. All testing analyses were two-tailed, and *p* values of <0.05 were considered statistically significant.

3.5 Results

Patient characteristics

A total of 208 adults consented to participate in the study, 16 withdrew or were excluded after consenting (8 due to personal time limitations, and 8 due to prior arthroplasty, bariatric surgery, or BMI<30 kg/m^2 at intake), and 41 declined to attend DXA body composition assessment appointment. Therefore, 151 patients were included in all analyses (see **Table 3.1**). Age differences were present between DXA completers (n=151) and non-DXA completers (n=41), with completers being older (65.1±7.9 *vs* 61.4±8.0 years, *p*=0.008) with a higher proportion retired (45%, *vs* 29%).

Table 3.1. Patient characteristics, by sex

	Female, n=89	Male, n=62
Demographics		
Age (years), mean (SD)	64.9 (8.5)	65.5 (7.1)
Age category		
40-64 years (middle-aged adults), n (%)	42 (47)	32 (52)
≥ 65 years (older adults), n (%)	47 (53)	30 (48)
BMI category, n (%)		
30.0-34.9 kg/m^2	30 (34)	33 (53)
35.0-39.9 kg/m^2	32 (36)	16 (26)
>40.0 kg/m^2	27 (30)	13 (21)
Ethnicity, Caucasian, n (%)	84 (94)	59 (95)
Current smoker, n (%)	7 (8)	9 (14)
Number of comorbid conditions, mean (SD)	1.7 (1.2)	1.6 (1.3)
Types of comorbid conditions		
Type II diabetes, n (%)	14 (16)	14 (22)
Dyslipidemia, n (%)	28 (31)	20 (32)
Cardiovascular disease, n (%)	5 (6)	5 (8)
Hypertension, n (%)	55 (62)	27 (43)
Sleep apnea, n (%)	25 (28)	21 (34)
Cancer, n (%)	11 (12)	11 (18)
Use mobility aid$^{\Delta}$	26 (29)	9 (14)
Anthropometrics and body composition		
Height* (cm), mean (SD)	161.6 (6.6)	176.0 (7.5)
Weight* (kg), median (IQR)	97.8 (21.6)	108.6 (24.3)
BMI* (kg/m^2), median (IQR)	37.0 (7.8)	34.3 (7.5)
Waist circumference (cm), median (IQR)	116.3 (13.1)	121.6 (17.5)
Hip circumference (cm), median (IQR)	128.3 (15.3)	119.9 (12.9)
Waist: hip ratio, mean (SD)	0.92 (0.06)	1.02 (0.05)
Fat mass (kg), median (IQR)	49.5 (13.8)	41.7 (14.3)
Fat mass (%), mean (SD)	50.3 (4.3)	39.5 (5.4)
FMI (kg/m^2), median (IQR)	19.0 (4.9)	13.0 (5.6)
LST (kg), median (IQR)	44.8 (6.2)	63.1 (9.6)
ASM (kg), median (IQR)	21.3 (4.4)	30.1 (5.8)
ASM by height^2 (ASMI)(kg/m^2), median (IQR)	8.19 (1.62)	9.85 (1.74)
ASM by weight x 100 (%), mean (SD)	22.1 (2.1)	27.1 (2.3)
ASM by BMI (kg/m^2), mean (SD)	0.574 (0.076)	0.83 (0.114)
Physical function		
Usual gait speed (m/s), mean (SD)	1.06 (0.31)	1.12 (0.24)
Gait speed < 0.8m/s, n (%)	18 (20)	7 (11)
Grip strength (kg), median (IQR)	27.0 (10)	42.0 (14)
Grip strength < sex specific cut-offs†, n (%)	9 (10)	10 (16)
6MWT (m), median (IQR)	340.2 (155.0)	390.5 (117.1)
Patient-reported outcomes		
WOMAC pain, 0-20, mean (SD)	10.0 (3.4)	8.8 (3.5)

		Female, n=89	Male, n=62
WOMAC stiffness, 0-8, mean (SD)		4.3 (1.6)	4.0 (1.6)
WOMAC function, 0-68, mean (SD)		34.7 (11.8)	31.0 (11.4)
WOMAC total, normalized 0-100, mean (SD)		51.1 (16.2)	45.7 (16.3)
EQ-5D Dimensions:			
Mobility, n (%)	No problems	4 (4)	3 (5)
	Problems	85 (96)	59 (95)
Self-care, n (%)	No problems	68 (76)	38 (61)
	Problems	21 (24)	24 (39)
Usual activities, n (%)	No problems	9 (10)	8 (13)
	Problems	80 (90)	54 (87)
Pain/discomfort, n (%)	No problems	3 (3)	2 (3)
	Problems	86 (97)	60 (97)
Anxiety/depression, n (%)	No problems	39 (44)	32 (52)
	Problems	50 (56)	30 (48)
EQ-5D VAS, 0-100, median (IQR)		71 (30)	70 (26)
EQ-5D Index, -0.148-0.949, median (IQR)		0.706 (0.315)	0.664 (0.251)

*at initial assessment

†<20 kg in females, <30 kg in males

Δmobility aids include cane (n=26), walker (n=8) or wheelchair (n=1)

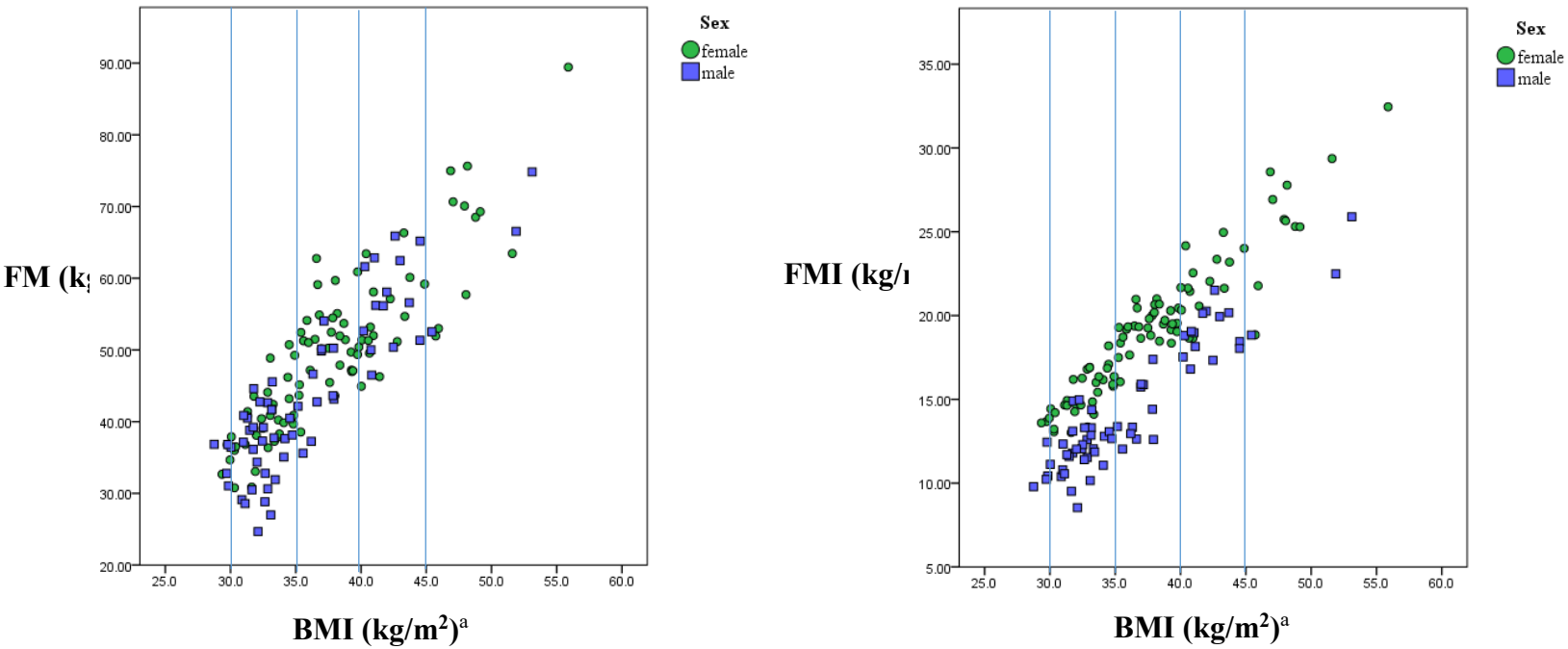
ASM = appendicular skeletal mass, FMI = fat mass index, LST = lean soft tissue, 6MWT = six minute walk test, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Cohort characteristics and outcomes are presented in Table 3.1, by sex. Patients were predominantly Caucasian (95%, n=143), with 5% either Indigenous (n=5), Black (n=1), Filipino (n=1), or South Asian (n=1). Mean age was 65.1±7.9 years (range 40.2-88.3 years). Expected differences in height, weight and body composition were present between sexes. Mean number of comorbidities was 1.6±1.2, with higher rates of hypertension in females. When comparing physical performance outcomes between age categories, middle-aged adults had faster mean gait speed (0.14 m/s, 95% CI 0.06-0.24) m/s higher mean grip strength (4.8 kg, 95% CI 1.6-8.0), and greater mean 6MWT distance (42.1 m/s, 95% CI 4.6-79.6) compared to older adults.

Body composition

All patients had a BMI ≥30 kg/m^2 at study intake, as per inclusion criteria. At the DXA appointment where weight and height were measured without clothing or footwear, six patients' BMI was <30.0 kg/m^2 (28.7-29.8 kg/m^2). These patients were included in the analysis as they met initial BMI criteria, along with waist circumference and %FM criteria for obesity. Waist circumference in the entire sample was above established cut-offs for obesity, ranging from 98.8-158.0 cm in females, and 107.7-162.6 cm in males. %FM was also above sex-specific criteria for obesity in entire cohort, ranging from 40.6-61.0% in females, and 26.7-50.5% in males. Analyses showed substantial variability in body composition between individuals within the same BMI category (**Figures 3.1.a and 3.1.b)**, and linearity in the relationship between FM (or FMI) and BMI.

Figure 3.1.a. Fat mass variability



In females:

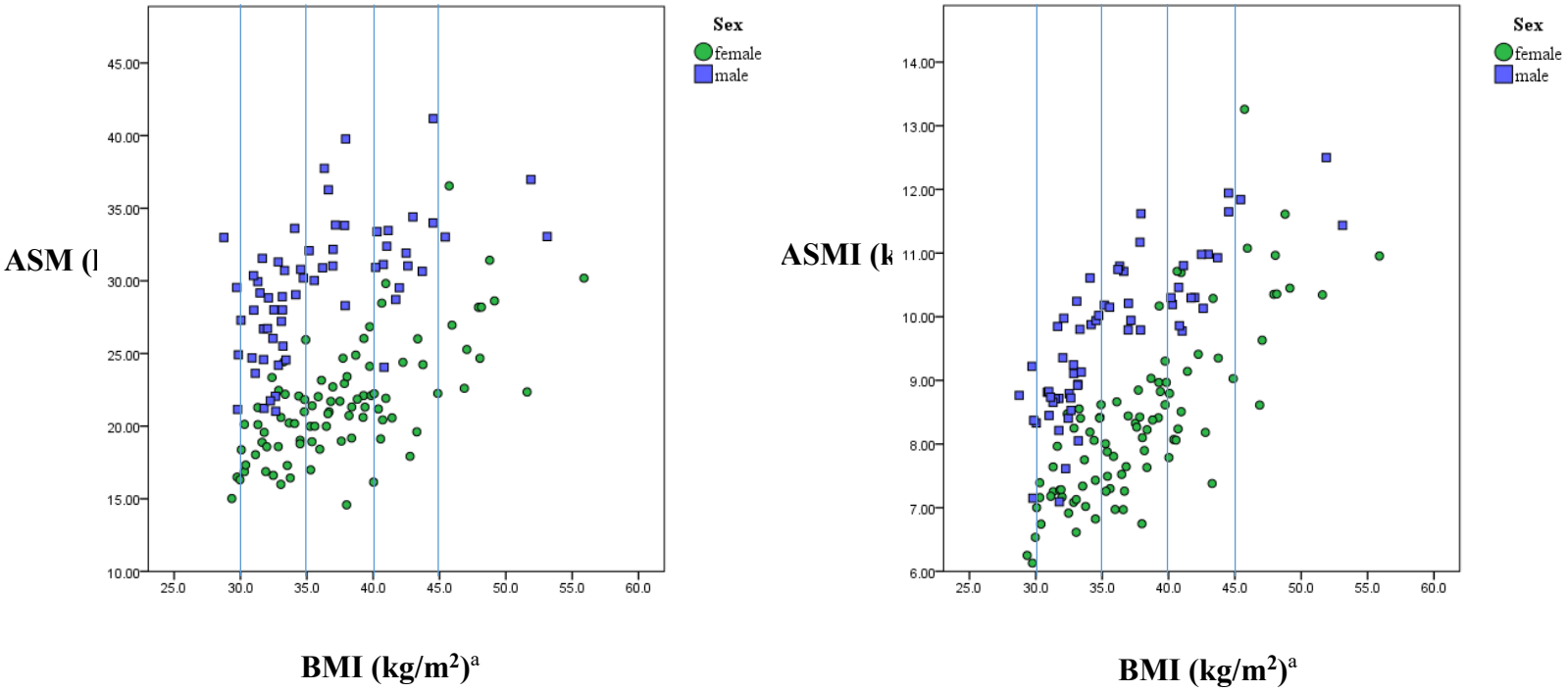
Within BMI category 30.0-34.9 kg/m^2, FM varied from 30.8 kg to 50.7 kg and FMI varied from 13.0 kg/m^2 to 18.2 kg/m^2
Within BMI category 35.0-39.9 kg/m^2, FM varied from 38.5 kg to 62.8 kg and FMI varied from 16.0 kg/m^2 to 21.0 kg/m^2
Within BMI category 40.0-44.9 kg/m^2, FM varied from 44.9 kg to 66.3 kg and FMI varied from 18.6 kg/m^2 to 25.0 kg/m^2

In males:

Within BMI category 30.0-34.9 kg/m^2, FM varied from 24.7 kg to 45.5 kg and FMI varied from 8.5 kg/m^2 to 10.6 kg/m^2
Within BMI category 35.0-39.9 kg/m^2, FM varied from 35.6 kg to 54.0 kg and FMI varied from 12.0 kg/m^2 to 17.4 kg/m^2
Within BMI category 40.0-44.9 kg/m^2, FM varied from 46.5 kg to 65.9 kg and FMI varied from 16.8 kg/m^2 to 21.5 kg/m^2

[a]BMI at DXA
BMI=body mass index (weight/height^2), FM=fat mass, FMI=fat mass index (FM/height^2)

Figure 3.1.b. Muscle mass variability



In females:

Within BMI category 30.0-34.9 kg/m^2, ASM varied from 16.0 kg to 26.0 kg and ASMI varied from 6.6 kg/m^2 to 8.6 kg/m^2
Within BMI category 35.0-39.9 kg/m^2, ASM varied from 14.6 kg to 26.8 kg and ASMI varied from 6.7 kg/m^2 to 10.7 kg/m^2
Within BMI category 40.0-44.9 kg/m^2, ASM varied from 16.1 kg to 29.8 kg and ASMI varied from 7.4 kg/m^2 to 10.7 kg/m^2

In males:

Within BMI category 30.0-34.9 kg/m^2, ASM varied from 21.0 kg to 33.6 kg and ASMI varied from 7.1 kg/m^2 to 10.6 kg/m^2
Within BMI category 35.0-39.9 kg/m^2, ASM varied from 28.3 kg to 39.8 kg and ASMI varied from 9.8 kg/m^2 to 11.6 kg/m^2
Within BMI category 40.0-44.9 kg/m^2, ASM varied from 24.0 kg to 41.2 kg and ASMI varied from 9.8 kg/m^2 to 11.9 kg/m^2

[a]BMI at DXA

ASM=appendicular skeletal muscle mass, ASMI=ASM index (ASM/height^2), BMI=body mass index (weight/height^2)

Prevalence of sarcopenic obesity

Prevalence of sarcopenic obesity in the overall cohort varied depending on diagnostic criteria (**Table 3.2**). A higher prevalence was observed in males when sarcopenic obesity was identified with low muscle alone, but not with the combined diagnostic approach. Alternatively, the combined diagnostic approach yielded a higher prevalence of sarcopenic obesity in older adults compared to their younger counterparts, which was not observed with low muscle alone.

Figure 3.2.a illustrates the overlap between the three diagnostic definitions for low muscle mass alone. There was some concordance between criteria, with ASM/BMI identifying 100% of those with low ASM/height^2, and 82% of those with low ASM/weight. There were n=27 patients uniquely identified as having low muscle mass by separate criteria (n=23 only with ASM/BMI, and n=4 only with ASM/weight). **Figure 3.2.b** illustrates the overlap between individuals identified with low muscle mass, low physical function, or low muscular strength when using the combined diagnostic approach.

Outcomes by sarcopenic obesity diagnosis

Table 3.3 presents differences in physical function and patient-reported outcomes by groups identified as having or not having sarcopenic obesity. The prevalence identified with ASM/height^2 alone was too low (1%) for meaningful comparisons, so only comparisons using ASM/weight and ASM/BMI are presented independently. The proportion of patients with type II diabetes was higher in all groups identified with sarcopenic obesity (difference of 10.2%, 14.7% and 30.2%) compared to the group without sarcopenic obesity when categorized using ASM/weight, ASM/BMI, and the combined approach, respectively. The proportion using mobility aids was higher in the sarcopenic obesity group only when categorized by the combined approach (difference of 33.5% compared to group without sarcopenic obesity). There were

Table 3.2. Prevalence of sarcopenic obesity by diagnostic criteria

	Sarcopenic obesity identified with low muscle alone						Sarcopenic obesity identified with low muscle[c] and low function[a] or strength[b]	
	ASM by height^{2†}		ASM by weight†		ASM by BMI†			
	SO	NSO	SO	NSO	SO	NSO	SO	NSO
Total, n (%) (CI)	2 (1.3) (0.2-4.7)	149 (98.7) (95.3-99.8)	22 (14.6) (9.4-21.2)	129 (85.4) (78.9-90.6)	41 (27.2) (20.2-35)	110 (72.8) (65-79.8)	13 (8.6) (4.7-14.3)	138 (91.4) (85.7-95.3)
Female, n (%) (CI)	0 (0) (0-4.1)	89 (100) (95.9-100)	6 (6.7) (2.5-14.1)	83 (93.3) (85.9-97.5)	18 (20.2) (12.4-30.1)	71 (79.8) (69.9-87.6)	6 (6.7) (2.5-14.1)	83 (93.3) (85.9-97.5)
Male, n (%) (CI)	2 (3.2) (0.4-11.2)	60 (96.8) (88.8-99.6)	16 (25.8) (15.5-38.5)	46 (74.2) (61.5-84.5)	23 (37.1) (25.2-50.3)	39 (62.9) (49.7-74.8)	7 (11.3) (4.7-21.9)	55 (88.7) (78.1-95.3)
Age 40-64.9 years, n (%) (CI)	0 (0) (0-4.9)	74 (100) (95.1-100)	12 (16.2) (8.7-26.6)	62 (83.8) (73.4-91.3)	17 (23) (14-34.2)	57 (77) (65.8-86)	2 (2.7) (0.3-9.4)	72 (97.3) (90.6-99.7)
Age ≥65 years, n (%) (CI)	2 (2.6) (0.3-9.1)	75 (97.4) (90.9-99.7)	10 (13) (6.4-22.6)	67 (87) (77.4-93.6)	24 (31.2) (21.1-42.7)	53 (68.8) (57.3-78.9)	11 (14.3) (7.4-24.1)	66 (85.7) (75.9-92.6)

†Cut-off criteria for females, males, respectively: ASM by height^2, kg/m^2 (<5.45, <7.26), ASM by weight, % (<19.43, <25.72), ASM by BMI, kg/m^2 (<0.512, <0.789)

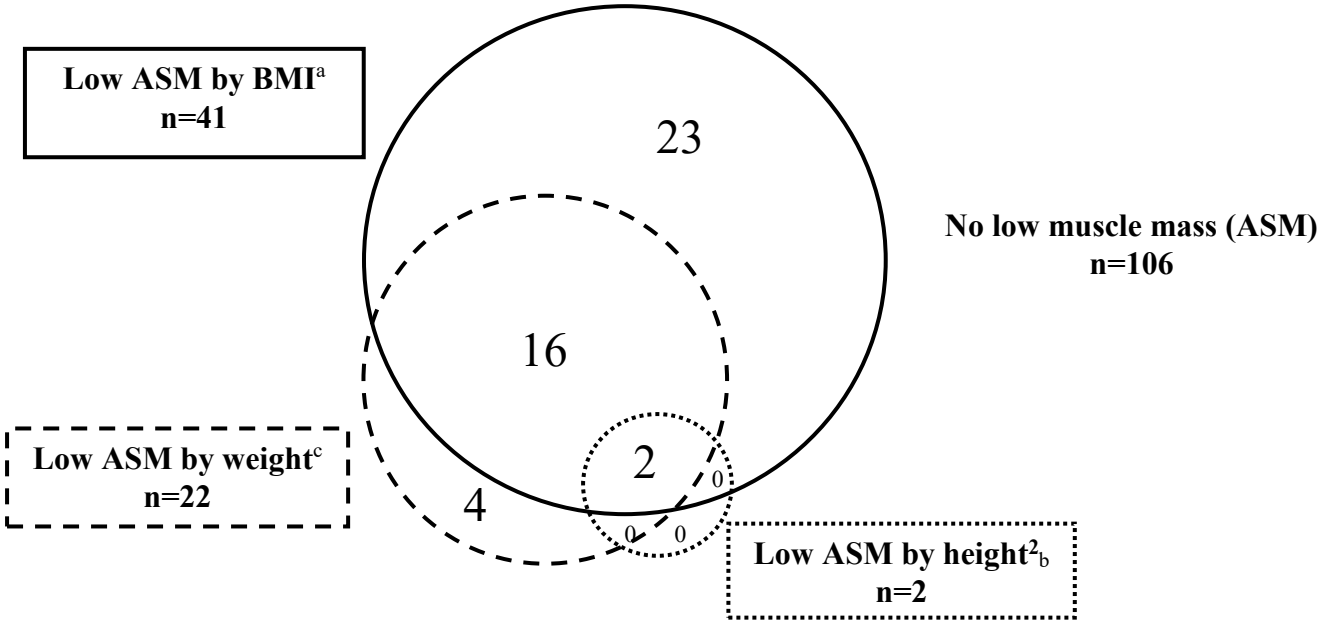
[a]gait speed <0.8 m/s

[b]handgrip strength <20 kg in females, <30 kg in males

[c]Any criteria for low muscle: ASM by height^2, kg/m^2 (<5.45, <7.26), or ASM by weight, % (<19.43, <25.72), or ASM by BMI, kg/m^2 (<0.512, <0.789) in females and males, respectively

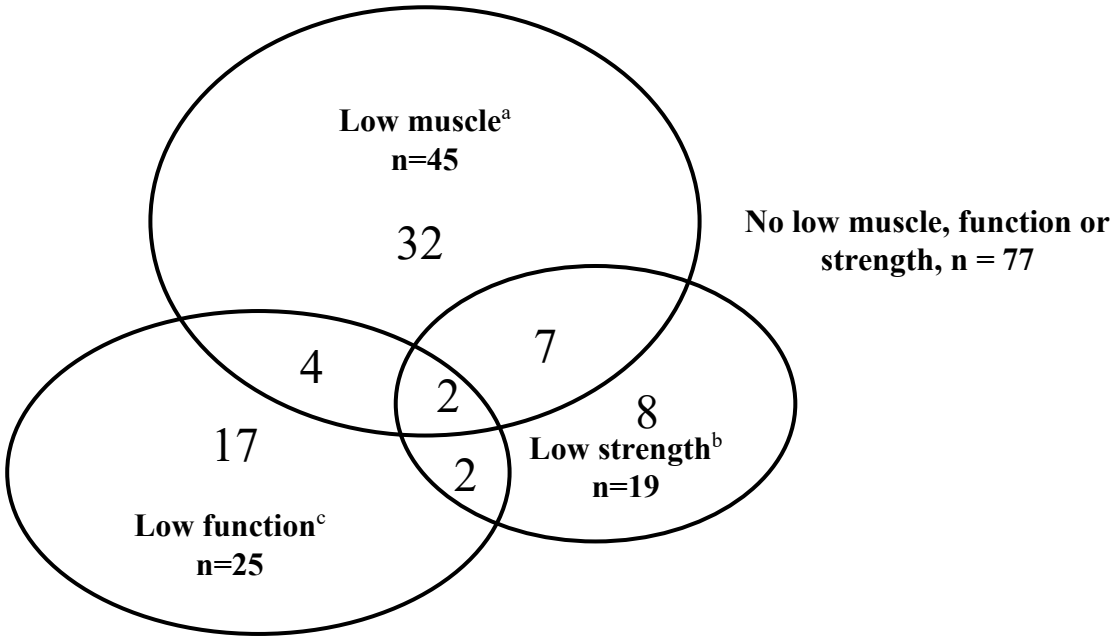
ASM = appendicular skeletal muscle mass, CI = 95% confidence interval, NSO = not sarcopenic obesity, SO = sarcopenic obesity

Figure 3.2.a. Overlap of different diagnostic criteria for sarcopenic obesity identified by low muscle mass alone



Low muscle mass identified by:
[a]ASM by BMI (kg/m^2) <0.512 in females, <0.789 in males
[b]ASM by height^2 (kg/m^2) <5.45 in females, <7.26 in males
[c]ASM by weight (%) <19.43 in females, <25.72 in males

Figure 3.2.b. Overlap of identification of low muscle mass, function or strength in study population



[a]Identified by any criteria: ASM by height^2, kg/m^2 (<5.45, <7.26), or ASM by weight, % (<19.43, <25.72), or ASM by BMI, kg/m^2 (<0.512, <0.789) in females and males, respectively

[b]handgrip strength <20 kg in females, <30 kg in males (based on EWGSOP criteria[19])

[c]gait speed <0.8 m/s (based on EWGSOP criteria[19])

Table 3.3. Difference in outcomes by sarcopenic obesity status and diagnostic criteria

	Sarcopenic obesity identified by low muscle alone		Sarcopenic obesity identified by low muscle[c] and either low function[↓] or low strength[†]
	ASM by weight[a]	ASM by BMI[b]	
	SO n=22[Δ] Compared to NSO n=129	SO n=41 Compared to NSO n=110	SO n=13[Δ] Compared to NSO n=138
Physical function outcomes:			
Gait speed (m/s)	-0.12 (-0.01 – 0.2)*	-0.12 (-0.22 – -0.01)*	-0.24 (-0.4 – -0.08)*[ϕ]
Grip strength (kg)	1.4 (-3.3 – 6.1)	-2.6 (-6.3- 1.1)	-9.9 (-15.6 - -4.2)*[ϕ]
Grip strength, female	1.4 (-3.7 – 6.6)	-4.1 (-7.3 - -1.0)*	-8.0 (-12.9 - -3.1)*[ϕ]
Grip strength, male	-6.3 (-11.8 - -0.9)*	-6.9 (-11.8 - -2.0)*	-15.4 (-22.2 - -8.5)*[ϕ]
6MWT (m)	-65.3 (-118.2 - -12.3)*	-50.9 (-92.9 - -8.9)*	-105.1 (-170.9 - -39.4)*[ϕ]
Patient reported outcomes:			
WOMAC pain 0-20	0.4 (-1.2 – 2.0)	1.2 (-0.05 – 2.4)	0.6 (-1.4 – 2.6)
WOMAC stiffness 0-8	0 (-0.7 – 0.7)	0.1 (-0.5 – 0.7)	0 (-0.9 – 0.9)
WOMAC function 0-68	0.7 (-4.7 – 6.1)	0 (-4.3 – 4.3)	0.8 (-6.0 – 7.6)
WOMAC total 0-100	1.1 (-6.4 – 8.6)	1.4 (-4.5 – 7.3)	1.5 (-7.9 – 10.9)
EQ-5D VAS, 0-100	-0.2 (-8.5 – 8.1)	-4.8 (-11.3 – 1.7)	-17.1 (-27.2 - -7.0)*
EQ-5D index score	0.006 (-0.086 – 0.097)	-0.029 (-0.101 – 0.044)	-0.052 (-0.167 – 0.063)
EQ-5D self-care dimension[$]	18.3	19.4*	34.7*

Values presented are mean differences (CI) in group classified as SO compared to group classified as NSO, unless otherwise indicated

[a]ASM by weight <19.43% in females and <25.72% in males

[b]ASM by BMI <0.512 kg/m^2 in females and <0.789 kg/m^2 in males

[c]Identified by any ASM criteria: ASM by height^2, kg/m^2 (<5.45, <7.26), or ASM by weight, % (<19.43, <25.72), or ASM by BMI, kg/m^2 (<0.512, <0.789) in females and males, respectively

↓low gait speed <0.8 m/s

†low grip strength <20 kg in women or <30 kg in men

[Δ]between group comparisons conducted using non-parametric Mann Whitney U test or Fishers exact

[$]difference in proportion (%) of SO group reporting problems compared to NSO group (no between group differences were present in other EQ-5D dimensions)

*p<0.05

[ϕ]caution should be taken when interpreting functional outcomes using the combined definition, as cut-points for low grip strength or low gait speed were used in the diagnostic definition

ASM = appendicular skeletal mass, CI = 95% confidence interval, NSO = not sarcopenic obesity, SO = sarcopenic obesity, VAS = visual analogue scale

differences in all physical function outcomes and in patient-reported EQ-5D self-care problems between those having and not having sarcopenic obesity, across all diagnostic methods. Age only differed between groups when using the combined diagnostic approach, with the sarcopenic obesity group being older (mean difference of 5.5 years, 95% CI 1.0-9.9). BMI was only different when using low muscle mass alone, with the sarcopenic obesity groups having a higher BMI (mean difference of 4.0 kg/m^2, 95% CI 1.3-6.8 with ASM/weight, and 2.5 kg/m^2, 95% CI 0.5-4.5 with ASM/BMI).

3.6 Discussion

In this cohort of patients with knee OA, we found compelling evidence that sarcopenic obesity is present and influenced physical function and aspects of quality of life. To the best of our knowledge, this is the first study to compare sarcopenic obesity diagnostic procedures that consider low muscle mass alone and in combination with low strength or function in a clinical OA cohort, and only the second study[34] to examine the influence of this condition on physical function in OA. Research on sarcopenic obesity in knee OA has been limited[8], with few population and clinical studies. Interestingly, sarcopenic obesity occurred across age categories in this cohort, illustrating its relevance across the age spectrum.

Prevalence of sarcopenic obesity

Sarcopenic obesity prevalence varied depending on diagnostic criteria used. Low muscle mass (low ASM) alone yielded a prevalence ranging from 1.3% to 27.2%. This variability is consistent with other studies on sarcopenic obesity in knee OA reporting prevalence from 1.3% using ASM/height^2, to between 3% and 35.4% using ASM/weight and ASM/BMI[34–38]. ASM adjusted by weight or BMI identified more individuals with sarcopenic obesity compared to ASM/height^2, suggesting that ASM/height^2 may not be sensitive to identify low ASM in adults

with higher body mass. This is consistent with findings from other studies[39,40]. Further, ASM relative to body weight and BMI have stronger associations with physical function[19,23], so they may be most relevant to identify sarcopenic obesity in adults with obesity and OA. More males were identified with sarcopenic obesity in this cohort, similar to the results of Ji et al.[37] who examined prevalence in patients undergoing orthopedic surgery (including TKA). Age-related reductions in testosterone hormones in men (andropause) have been associated with an increased decline in skeletal muscle mass[41]. Sex-related factors may be more important than age in the development of sarcopenic obesity in the OA population[42], but further examination is required.

When using the combined diagnostic approach to identify sarcopenic obesity, higher prevalence rates were observed in older adults. This could indicate that the tests and/or cut-offs used to assess low physical function or low muscle strength may preferentially identify limitations in older adults (≥65 years), the population age where the cut-offs were established[43]. In our cohort, middle-aged adults had higher scores on all physical performance tests compared to older adults. Different cut-off levels or types of tests may better discriminate low muscle mass impacting function in middle-aged adults with OA. A consensus definition for sarcopenic obesity is needed[21,22], and may need to include different diagnostic approaches for different populations, ages or disease specific groups[21]. Further, criteria are needed for early identification in clinical settings. There is a benefit of practitioners being able to easily identify the presence or absence of sarcopenic obesity before it impacts physical function and to prevent or mitigate disability (by treating with diet or physical activity, or avoiding recommendations for weight loss that could exacerbate skeletal muscle loss).

Sarcopenic obesity and performance-based physical function

Sarcopenic obesity significantly impacted physical function and strength in the study cohort, with slower walking speeds, lower grip strength, and lower walking endurance yielded using all diagnostic approaches. Sarcopenic obesity has been associated with negative impacts on functional mobility, including difficulty walking, slower walking speed, and difficulty climbing stairs in other populations[44], but in OA it may compound the impact of OA-related physical disability. Manoy et al.[34] also found sarcopenic obesity negatively influenced grip strength, gait speed and 6MWT distance in patients with knee OA independent from obesity. Low muscle mass likely contributes clinically significant functional limitations over and above those due to both obesity and OA, which should be considered in OA management approaches and recommendations.

Sarcopenic obesity and patient-reported pain, function and quality of life

Interestingly, there were only differences in one EQ-5D dimension, self-care activities, when classified by sarcopenic obesity status. This dimension has patients identify level of difficulty washing or dressing themselves. Sex differences were present prior to differentiating sarcopenic obesity, with more problems reported by males, which may reflect the higher prevalence of low muscle mass in males in our cohort. Visser et al.[45] also found that low fat free mass (assessed by bioelectrical impedance analysis) interacted with knee OA to further reduce health-related quality of life in men only. Sarcopenic obesity may impart additional or unique influence on self-care in males, independent from obesity and OA. Future studies should include formal assessments of self-reported difficulties with activities of daily living in addition to health-related quality of life, to see if this influence persists across instruments. We found no difference in WOMAC scores between those who had or did not have sarcopenic obesity, in

contrast to Manoy et al.[34] who reported higher WOMAC scores in patients with knee OA and sarcopenic obesity compared to those with obesity or normal weight. Differences in WOMAC scoring methods (they used a 0-10 scale-based system), in addition to methodological differences between studies likely accounts for the disparate findings.

Sarcopenic obesity and patient characteristics

Mean BMI was higher in the groups with sarcopenic obesity when identified using ASM by weight and ASM/BMI, reflecting greater disproportion in the load:capacity relationship between fat and muscle mass when body mass increases. Diabetes prevalence in the sarcopenic obesity groups were higher when compared to the groups without sarcopenic obesity, highlighting the relationship between diabetes and accelerated muscle loss related to sarcopenia[41]. This higher prevalence of diabetes alongside sarcopenic obesity is important for consideration of surgical risk with TKA, as both are independent risk factors for surgical infection and poorer outcomes, potentially magnified by interaction.

Other considerations

Muscle is a complex organ, and the quantity and quality of muscle tissue and muscle fibers are influenced by inflammatory, metabolic, and endocrine factors[46] including age and obesity[47,48]. Low muscle mass has been considered a primary proxy measurement for metabolic control and physical disability, yet the composition of the muscle may be an underlying factor that is not clearly investigated. Increased storage of fat within and between muscle cells (called myosteatosis) occurs with aging and obesity[49,50], reducing contractile strength per muscle unit and muscular endurance[21], in turn affecting mobility[51]. Unlike with cancer, where advanced body composition imaging with computerized axial tomography or magnetic resonance imaging is often completed, assessments of muscle mass in OA clinical populations may be limited to

imaging methods like DXA which cannot assess myosteatosis[47]. Increased myosteatosis with muscle loss and aging-related adiposity gains, further increased by OA pain-related immobility, could be a mitigating factor between differences in decreased function or strength and decreased muscle mass[49].

Body composition analyses in this study revealed large variations in adiposity and muscularity within BMI categories, adding further evidence of the limitations of BMI as a surrogate marker for individual-level body composition[52]. BMI alone does not adequately identify sarcopenic obesity in patients with OA. This is also a limitation in the research evidence on the impact of obesity (defined only as BMI $\geq$ 30 kg/m^2) on TKA surgical infection rates, as differentiation between body compartments of adipose and muscle tissue could elucidate which primarily influences infection risk in this population.

Strengths and limitations

Notable strengths of this study include the use of a DXA for body composition analysis with larger scanning surface and higher weight capacity, preventing exclusion of patients with larger body size. Further, performance-based physical function has not been well examined in patients with sarcopenic obesity and OA, and thus these results are uniquely informative. Limitations include the primarily Caucasian sample and cross-sectional design, with potential for reverse causation. Results on physical function and quality of life should be interpreted with caution. Gait speed and grip strength were used both in the combined diagnostic criteria (as cut-points to define low function or strength) and also as continuous outcome variables, limiting the interpretability of the functional outcomes in this subgroup. Additionally, we were not able to control for confounding due to smaller samples in subgroup analyses. Differences in self-reported pain and impairments of physical function may have been impacted by other treatment

interventions patients were receiving, including varied prescription pain medications, cortisone injections, and therapeutic rehabilitation, which were not controlled for. Further we did not collect information on physical activity or diet, which could be relevant for differences in muscle mass, and we did not control for weight change between initial clinic visit and DXA visit. Some patients may have been actively trying to lose weight during this period, but length of time between appointments was minimal (median 16 days). Furthermore, some patients may have had hand OA in addition to knee OA, which could have affected their maximal grip strength. Patients with severe pain or mobility limitations may have been less likely to complete the study, due to required attendance at the DXA appointment at an unfamiliar clinic on a separate day. However, efforts were made to reduce barriers to study completion (e.g. detailed maps, handicap parking stalls, access ramps and elevators, paid parking fees). Lastly, this study included patients referred to the orthopedic clinic by their primary physician, and not all patients may be interested, willing or eligible to undergo TKA. This sample may not be representative of all patients with end-stage knee OA.

3.7 Conclusions

Sarcopenic obesity (identified by low muscle mass alone, or low muscle mass with low strength or low function), was present in patients with end-stage knee OA, and impacted physical function and quality of life relative to self-care activities. While prevalence varied depending on diagnostic approach, it is apparent that BMI alone is inadequate to screen for this condition. Given the impact of sarcopenic obesity on outcomes in this population, increased clinical awareness and screening is important. A diagnostic method that considers a combination of low muscle mass with low strength or function is suggested to clarify expected prevalence and enable increased identification and management of this condition in patients with knee OA.

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CHAPTER 4

4.1 Synopsis

A version of this chapter was submitted for publication as Godziuk K, Woodhouse LJ, Prado CM, Forhan M, "Clinical screening and identification of sarcopenic obesity in end-stage knee osteoarthritis".

4.2 Abstract

Introduction: Sarcopenic obesity, defined as low muscle mass with low strength or function in the presence of high fat mass, is an important health condition requiring attention in knee osteoarthritis (OA). Identification of screening methods to discern low muscle function (low strength or physical performance) relative to sarcopenic obesity in this population is needed. The purpose of this study was to identify muscle function measures and patient characteristics associated with low muscle mass in patients with end-stage knee OA. These were then applied to identify subgroups of patients with and without sarcopenic obesity, to compare outcomes of pain, function and quality of life.

Methods: Adults with a body mass index (BMI) ≥30 kg/m^2 and unilateral or bilateral end-stage knee OA were included in this cross-sectional study. Body composition was measured in n=151 patients (59% female, mean age 65.1±7.9 years, mean BMI 37.1±5.5 kg/m^2) using dual-energy x-ray absorptiometry. Appendicular skeletal muscle mass (ASM) (adjusted by BMI) below pre-established sex-specific cut-points was used to differentiate low muscle mass. Strength and physical performance were assessed by four-metre gait speed, six minute walk test, and maximal grip strength (absolute and relative, adjusted by BMI). Logistic regression was used to assess the relationship between physical function measures (controlling for age, sex, BMI, and

comorbidities) and low muscle mass. Receiver operating characteristic curves and area under the curve (AUC) were used to test the performance of the final model, establish cut-points for low physical function, and discern groups with and without sarcopenic obesity.

Results: Relative grip strength, controlled for sex, was associated with low muscle mass in this cohort (AUC 0.774, $p<0.001$). Relative grip strength cut-points of <0.65 kg/m^2 in females and <1.1 kg/m^2 in males were identified as discriminators of low strength. When used in combination with low muscle mass to identify sarcopenic obesity, prevalence was 19.9% (14.6% in females, and 27.4% in males). Patients identified with sarcopenic obesity had slower walking speed, lower walking endurance, and poorer health-related quality of life.

Conclusions: Relative grip strength could be used in the clinical setting to screen for low strength in patients with knee OA and obesity. Patients with low strength could then complete a body composition assessment to determine the presence of low muscle mass, and confirm or refute the identification of sarcopenic obesity.

4.3 Introduction

Sarcopenic obesity is defined as low muscle mass with low strength or function in the presence of high fat mass[1,2]. It is an important health condition requiring attention in knee osteoarthritis (OA)[3] due to associations with impaired mobility[4] and increased surgical risk[5], as shown in other clinical populations. Adults with knee OA and obesity may be particularly at risk for sarcopenic obesity due to accelerated loss of muscle and strength associated with OA-related pain and mobility impairment, and obesity-related inflammation[3]. While low muscle mass has been associated with poor function and quality of life in patients with knee OA[6], the possible influence of sarcopenic obesity on surgical infections, recovery and mortality may be more concerning for patients with end-stage OA considering total knee arthroplasty (TKA). However,

as sarcopenic obesity is not usually identified in patients considering TKA, its influence on outcomes remains unknown.

Early identification of sarcopenic obesity in patients with OA is a clinical challenge. It may be most expeditious to first identify low strength or function and then confirm low muscle mass. In sarcopenia (defined as age-related loss of muscle mass and strength or function in older adults), the use of handgrip strength or gait speed to screen and identify low strength or function is well established[7–10]. The European Working Group on Sarcopenia in Older Persons (EWGSOP2) recommend grip strength as a diagnostic assessment for sarcopenia, and gait speed to determine severity[9]. International clinical practice guidelines recommend gait speed as a screening assessment[10]. However screening approaches using measures of strength and function are still being considered for sarcopenic obesity[11–13]. Grip strength and gait speed cut-points developed and tested in normal weight, older adults may not be relevant for sarcopenic obesity, as this condition also occurs in younger adults[12]. Further, OA and obesity have independent influences on strength and function, adding additional confounding. Obesity reduces gait parameters of stride length, balance and stance, resulting in slower gait speeds[14]. Similarly, OA-related pain and stiffness can alter gait kinematics and reduce gait speed. Importantly, these influences could be compounded in patients who have both obesity and OA[14]. With grip strength, systemic inflammatory-related OA can affect both the knee and hand joints, potentially reducing grip strength. Alternatively, adults with obesity may have higher grip strength compared to adults with normal body weight due to relatively higher muscle mass[15]. This additional confounding illustrates a challenge in using grip strength and gait speed to discriminate impairments that are due to low muscle mass rather than OA or obesity. Other measures or approaches may be better in this clinical population with OA.

Early identification of sarcopenic obesity in OA clinical pathways is important to mitigate disability, morbidity and mortality risk by preventing and minimizing any further muscle loss[12]. Few studies have examined strength or function measures and low muscle mass in patients with knee OA and obesity[16,17]. Manoy et al.[16] used low gait speed or grip strength with low muscle mass to discern sarcopenic obesity in patients with knee OA, but did not examine the relationship between these measures. Davis et al.[17] reported a relationship between lower muscle mass and lower physical performance in their cohort with knee OA, however they did not examine this from a screening or diagnostic approach. To our knowledge no studies have explored the use of muscle function measures to screen for sarcopenic obesity in knee OA.

Therefore, the purpose of this study was to determine which strength or physical performance measures and patient characteristics were associated with low muscle mass in adults with knee OA and obesity. Further, we used associated variables to distinguish patients with and without sarcopenic obesity, and compare outcomes of pain, function and quality of life.

4.4 Methods

This study is an additional analysis of data from a cross-sectional cohort of adults with end-stage knee OA and obesity, described in more detail elsewhere (Chapter 3). The study included community dwelling adults with unilateral or bilateral knee OA undergoing screening for total knee arthroplasty (TKA) at an orthopedic clinic in Alberta, Canada from May 2017-March 2018. Inclusion criteria were: BMI $\geq$ 30 kg/m^2; no history of hip or knee arthroplasty or bariatric surgery and; able to communicate and give written informed consent in English. A consecutive sampling approach was used to sequentially enrol eligible and consenting patients at their initial clinical visit. Study data were collected prospectively and managed using REDCap[18] electronic data capture tools hosted and supported by the Women and Children's Health Research

Institute at the University of Alberta. Ethics approval was provided by the Health Research Ethics Board at the University of Alberta, Edmonton, Alberta.

Patient characteristics

Socio-demographic and health information about each patient was collected, including age, sex, ethnicity, and smoking status. Comorbid conditions were identified by asking patients whether a doctor had told them they had type II diabetes, dyslipidemia, cardiovascular disease, hypertension, sleep apnea, cancer, or hand OA. Height and weight were measured at the patients' initial visit in clinic, and measured again at the patients' body composition appointment on a separate date and location. BMI was calculated. Waist and hip circumference were measured at initial visit over light clothing using a non-elastic tape measure, recording the average from three consecutive measures. Body composition was assessed using dual-energy x-ray absorptiometry (DXA) (GE Healthcare Lunar iDXA, analyzed with enCORE software version 16). DXA is considered a reference standard for measurement of muscle mass for identification of sarcopenia[19]. Total body and regional lean mass (LM), fat mass (FM) and bone mineral concentration (BMC) were measured. Appendicular skeletal muscle mass (ASM) was calculated as LM of arms plus legs. Obesity was identified as BMI ≥30 kg/m^2 at clinic intake, and confirmed by ensuring patients met additional criteria for obesity of a waist circumference >88 cm in females and >102 cm in males[20], and %FM ≥35% in females and ≥25% in males[21].

Identification of low muscle mass

While there is no current reference standard for identifying low muscle mass relative to sarcopenic obesity, ASM adjusted by body size is accepted by sarcopenia consensus groups[9,22]. We used previously established sex-specific cut-points to define low muscle mass as ASM/BMI <0.512 kg/m^2 in females and <0.789 kg/m^2 in males[21]. ASM/BMI is a preferred method to

identify low muscle mass in adults with obesity due to the adjustment for body size and stronger relationship with physical function[22,23]. Previous work completed by our research team found that ASM adjusted by height^2 was not as sensitive a measure in this cohort, and patients with low ASM/height^2 were also identified using low ASM/BMI (*reference OAC manuscript*). Results from our previous work reported a prevalence of low muscle mass in this cohort of 27.2%, with higher rates in males compared to females (37.1% *vs* 20.2%, respectively).

Measures of muscle function (strength and physical performance) and quality of life

Objective measures of muscle function (strength and physical performance) were assessed in the clinic, using grip strength, gait speed, and the six-minute walk test (6MWT). Gait speed was measured over four metres, and calculated in metres/second. Patients used assisted walking aids (cane or walker) during the assessment if normally used for ambulation. Maximal isometric grip strength of the dominant hand was assessed (using a Jamar handgrip dynamometer) in a seated position with elbow flexed to 90 degrees. Grip position was modified to fit hand size, and the highest score of three attempts was recorded. Grip strength adjusted to body size (termed relative grip strength) was calculated by dividing grip strength by BMI. Relative grip strength has been used elsewhere in sarcopenia screening[24,25], and was included to normalize grip as higher grip strength is linked to larger body size. The 6MWT has been used elsewhere in screening for sarcopenia[26] and is an appropriate test for patients with knee OA[27]. Therefore, it was included to distinguish between short and long distance walking function. The 6MWT was completed in the clinic, and assisted walking aids were used if patients normally used them for ambulation. Patient-reported health-related quality of life was assessed using an electronic version of the EuroQol Foundation EQ-5D-5L[28]. Patients rated their perceived level of problems across five health dimensions (mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression) and their overall health on a visual analogue scale (VAS) from 0 (worst health) to 100 (best heath). Patient-reported OA pain and function were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[29].

Statistical analysis

Descriptive statistics are reported as mean (standard deviation) or frequency (proportion). The association between muscle function (gait speed, grip strength, relative grip strength, 6MWT), patient characteristics (age, sex, FM, waist circumference, smoking status, and comorbidities of type II diabetes, cardiovascular disease, dyslipidemia, hypertension, sleep apnea, and hand OA), and the dichotomous outcome of low muscle mass present or absent was examined using logistic regression[30]. Univariate correlation was first examined between low muscle mass and each patient characteristic and muscle function measure to identify candidate variables for the regression analysis. Candidate variables were selected if correlated $p < 0.1$ with the outcome of low muscle mass. Partial correlation was also examined to determine the influence of age, sex, hand OA, and unilateral or bilateral knee OA on muscle function variables. A multivariable logistic regression model was built using a backwards stepwise approach, including examination of interaction between variables. Odds ratios (OR) and 95% confidence intervals are reported for the univariate and multivariable models. The discriminating ability of the final model was examined using receiver operating characteristic (ROC) analysis with the predicted probabilities, calculating area under the curve (AUC). Based on the final model, sex-specific cut-points were determined by examining separate ROC curves for males and females. Optimal cut-points were calculated using three parameters[31]: 1) Youden's index [maximum (sensitivity + specificity -1)], 2) the shortest distance to (0,1) [the upper left corner of the ROC curve[31]], and 3) similar values of sensitivity and specificity (an equivalent balance of both).

Between-group comparisons were conducted using two-tailed Student's independent t-test. A *p* value of <0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics v24 (IBM Corp., Armonk, NY).

4.5 Results

Sample Characteristics

The study included 151 patients (58.9% female), mean age 65.1±7.9 years (range: 40.2-88.3 years), mean BMI 37.1±5.5 kg/m^2 (range 30.0-56.7), predominantly Caucasian (95%). **Table 4.1** provides a summary description of this patient cohort. Low muscle mass (low ASM/BMI) was present in n=18 females (20.2%) and n=23 males (37.1%).

Association with low muscle mass

Age, FM, waist circumference, smoking status, dyslipidemia, cardiovascular disease, hypertension, sleep apnea, hand OA, and absolute grip strength were not correlated with low muscle mass. Sex, type II diabetes, gait speed, 6MWT, and relative grip strength were correlated (p<0.1) with low muscle mass (**Table 4.2**), and included in the multivariable model. Although not correlated, age was included in the multivariable model due to its clinical and biological relevance with low muscle mass. The results of univariate and multivariable models are reported in **Table 4.3**. Only sex and relative grip strength remained after backwards stepwise selection in the final model (OR 15.09 and 0.01, respectively). Using the predicted probabilities from the final model, a ROC curve was plotted (**Figure 4.1)** and AUC calculated (AUC 0.774, 95% confidence interval 0.692-0.856). Sex-specific ROC curves for relative grip strength were then explored (**Figure 4.2**). This enabled discrimination of optimal cut-points for low relative grip strength associated with low muscle mass in this cohort (<0.65 kg/m^2 in females, and <1.1 kg/m^2

Table 4.1. Description of patient cohort, n=151 adults with knee OA and obesity

Demographics	mean (SD) or n (%)
Age (years)	65.1 (7.9)
Sex, female	89 (58.9)
BMI (kg/m^2)	37.1 (5.5)
Smoker	16 (10.6)
Number of comorbidities	1.6 (1.2)
Type of comorbidities:	
Type II diabetes	28 (18.5)
Dyslipidemia	48 (31.8)
Cardiovascular disease	10 (6.6)
Hypertension	82 (54.3)
Sleep apnea	46 (30.5)
Hand osteoarthritis	55 (36.4)
Use mobility aid$^{\Delta}$	28 (18.5)
Anthropometrics and body composition	females, males
Height (cm)	161.6 (6.6), 176.0 (7.5)
Weight (kg)	98.6 (16.1), 112.3 (17.4)
BMI (kg/m^2)	37.8 (5.6), 36.0 (5.4)
Waist circumference (cm)	119.3 (12.1), 123.7 (11.3)
FM (kg)	49.5 (11.0), 43.8 (11.2)
FM (%)	50.3 (4.3), 39.4 (5.2)
LST (kg)	45.8 (7.0), 62.4 (8.1)
ASM (kg)	21.6 (3.9), 29.7 (4.4)
ASM/height^2 (kg/m^2)	8.3 (1.3), 9.7 (1.2)
ASM/BMI (kg/m^2)	0.574 (0.076), 0.83 (0.114)
Physical performance and strength	
Gait speed (m/s)	1.09 (0.28)
Gait, females	1.06 (0.31)
Gait, males	1.12 (0.24)
6MWT (m)	339.7 (118.1)
6MWT, females	321.5 (115.3)
6MWT, males	366.0 (117.9)
Grip strength (kg)	32.8 (10.2)
Grip, females	27.3 (6.1)
Grip, males	40.8 (9.8)
Relative grip strength (kg/m^2)	0.9 (0.32)
Relative grip, females	0.73 (0.17)
Relative grip, males	1.15 (0.31)

ASM = appendicular skeletal muscle mass, BMI = body mass index, FM = fat mass, LST = lean soft tissue, OA = osteoarthritis, OR = odds ratio, SD = standard deviation, 6MWT = six-minute walk test

Table 4.2. Bivariate correlations in sample (n=151)

	Sarcopenic obesity$^{\Delta}$	**Age (years)**	**Sex**	**Diabetes⸸**	**Gait speed (m/s)**	**Relative grip† (kg/m^2)**	**6MWT (m)**
Sarcopenic obesity$^{\Delta}$	---	0.054	0.187*	0.168*	-0.174*	-0.152*	-0.175*
Age (years)		---	0.023	0.03	-0.132*	-0.079	-0.11*
Sex (male, female)			---	0.087	0.092	0.531**	0.176*
Diabetes⸸ (yes, no)				---	-0.072	-0.052	-0.13
Gait speed (m/s)					---	0.235**	0.552**
Relative grip†(kg/m^2)						---	0.320**
6MWT (m)							---

Kendall's tau-b, two-tailed, was used for all correlations, except between gait speed and age where Pearson's correlation was used as both variables were normally distributed.

$^{\Delta}$identified as dichotomous outcome, present if ASM/BMI <0.512 kg/m^2 in females and <0.789 kg/m^2 in males

⸸type II diabetes

†grip strength divided by body mass index

*p<0.05

**p≤0.001

Table 4.3. Univariable associations and final model of patient characteristics and muscle function measures associated with low muscle mass[*]

	Univariable association with low muscle mass[*]		ϕFinal model for association with low muscle mass[*]	
Identifying variable	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Age	1.01 (0.97 – 1.06)	0.586		
Sex, male[Δ]	2.33 (1.12 – 4.83)	0.023	15.09 (4.66 – 48.84)	<0.001
Type II diabetes	2.43 (1.03 – 5.72)	0.042		
Gait speed	0.22 (0.06 – 0.84)	0.026		
Relative grip strength[†]	0.23 (0.06 – 0.88)	0.031	0.01 (0.001 – 0.08)	<0.001
6MWT	0.99 (0.99 – 1.0)	0.021		

[*]Identified as ASM/BMI, kg/m^2 (<0.512, <0.789) in females and males, respectively

ϕage, sex, type II diabetes, gait speed, relative grip strength and 6MWT were all included in the final model

[Δ]Female as reference category

†grip strength/BMI

BMI = body mass index, OR = odds ratio, 95% CI = 95% confidence interval, 6MWT = six-minute walk test

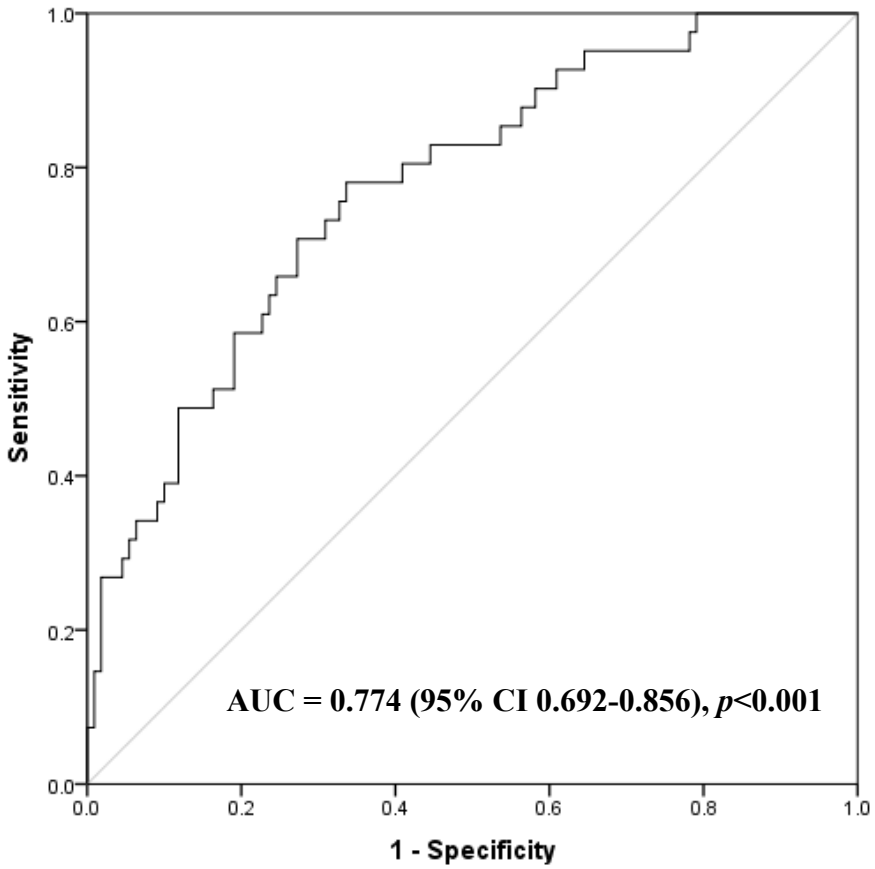

Figure 4.1. Receiver operating characteristic curve and area under the curve (AUC) of predicted probabilities from logistic regression model to identify low muscle mass* in n=151 adults with knee OA

Model includes sex and relative grip strength (grip/BMI); AUC = 0.774 (95% CI 0.692-0.856), $p<0.001$

* Identified as ASM/BMI, kg/m^2 (<0.512, <0.789) in females and males, respectively
ASM = appendicular skeletal muscle mass, AUC = area under the curve, BMI = body mass index, CI = confidence interval, OA = osteoarthritis

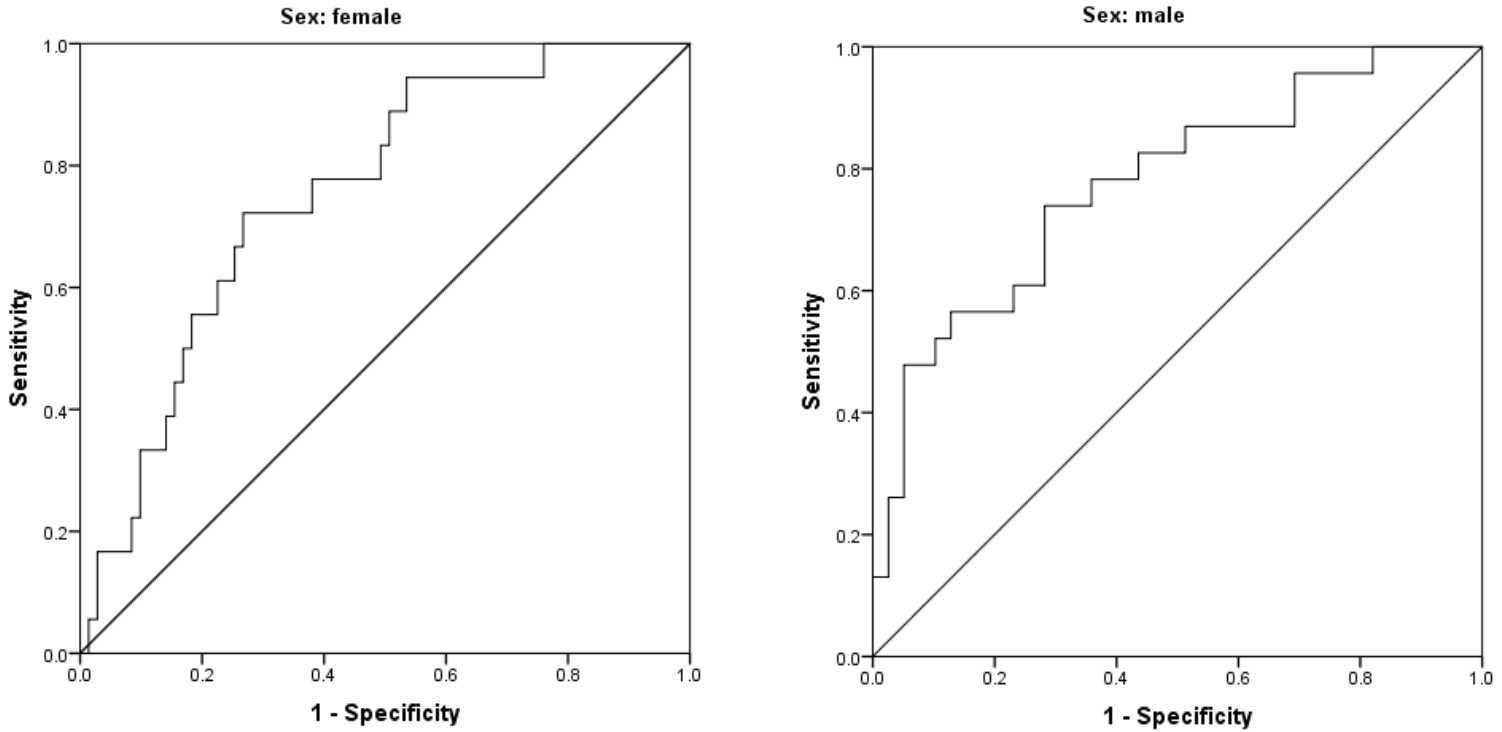

Figure 4.2. Receiver operating characteristic curve and area under the curve (AUC) for relative grip strength† to identify low muscle mass*, stratified by sex, in n=151 adults with knee OA

In females:

AUC = 0.754 (95% CI 0.640-0.869) p=0.001

A cut-off of <0.65 kg/m^2 for relative grip strength had maximal Youden index at 0.454, shortest distance to upper left corner at 0.38, and a balance of 72.2% sensitivity and 73.2% specificity.

In males:

AUC = 0.776 (95% CI 0.654-0.898) p<0.001

A cut-off of <1.1 kg/m^2 for relative grip strength had maximal Youden index at 0.457, shortest distance to upper left corner at 0.38, and a balance of 73.9% sensitivity and 71.8% specificity.

†grip strength divided by body mass index (BMI)

* Identified as ASM/BMI, kg/m^2 (<0.512, <0.789) in females and males, respectively

ASM = appendicular skeletal muscle mass, AUC = area under the curve, BMI = body mass index, CI = confidence interval, OA = osteoarthritis

in males). These cut-points were used to define low strength, which was present in n=32 females (35.9%) and n=28 males (45.2%). Sensitivity analyses for the cut-points to identify low muscle mass are reported in **Table 4.4**.

Sarcopenic obesity identification and comparison of outcome measures

The new low strength cut-points were used in combination with low muscle to screen and identify a subgroup of the cohort with sarcopenic obesity, illustrated using an algorithm in **Figure 4.3** (based on the algorithm from the EWGSOP2[9]). This was conducted to examine and validate the discrimination of these criteria to effectively screen and identify a subgroup of the cohort with sarcopenic obesity-related impairments. Based on this criteria, prevalence of sarcopenic obesity was 19.9% (95% CI 14.3-26.9%). In females, prevalence was 14.6% (95% CI 8.7-23.4%), compared to 27.4% in males (95% CI 17.9 -39.6%). When examined by age categories, prevalence was 16.2% in ages 40-64.9 years (95% CI 9.5-26.2%), and 23.4% in age ≥ 65 years (95% CI 15.3-34.0%). **Table 4.5** presents differences in physical function and patient-reported measures between those identified as having or not having sarcopenic obesity. The sarcopenic obesity group had slower gait speed (p=0.013), walked less distance in the 6MWT (p<0.001), and had lower absolute grip strength (p=0.012). Additionally, they had poorer health-related quality of life, with lower EQ-5D VAS scores (p=0.015), and more problems reported on the EQ-5D self-care dimension (washing and dressing themselves) (p=0.002).

4.6 Discussion

This study found that when controlling for sex, relative grip strength was associated with low muscle mass in patients with end-stage knee OA. Relative grip strength could be used to discern low strength relative to low muscle mass in patients with knee OA and obesity, and could

Table 4.4. Sensitivity analyses of proposed relative grip strength† cut-points to identify low muscle mass* in n=151 adults with knee OA

	True+ n	False+ n	True- n	False- n	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)	+LR (CI)	-LR (CI)
Females										
<0.65 kg/m^2	13	19	52	5	72.2 (51.5-92.9)	73.2 (62.9-83.5)	40.6 (23.6-57.6)	91.2 (83.9-98.6)	2.70 (1.67-4.36)	0.379 (0.178-0.809)
Males										
<1.1 kg/m^2	17	11	28	6	73.9 (56.0-91.8)	71.8 (57.7-85.9)	60.7 (42.6-78.8)	82.3 (69.5-95.2)	2.62 (1.5-4.57)	0.363 (0.178-0.743)

†grip strength/BMI

* low muscle mass identified by ASM/BMI, kg/m^2 (<0.512, <0.789) in females and males, respectively

ASM – appendicular skeletal muscle mass, BMI = body mass index, CI = 95% confidence interval, NPV = negative predictive value, OA = osteoarthritis, PPV = positive predictive value, + LR = positive likelihood ratio, - LR = negative likelihood ratio, + = positive, - = negative

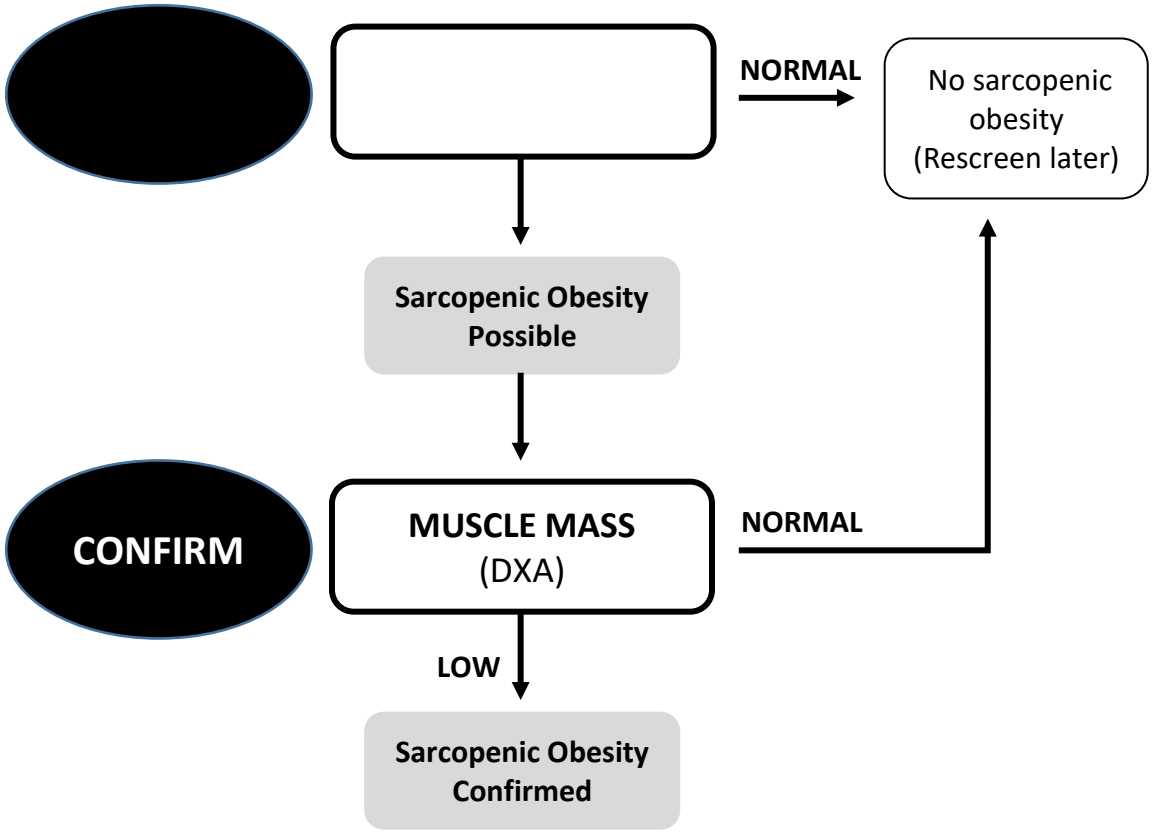

Figure 4.3. Algorithm to detect and identify sarcopenic obesity in adults with knee OA and obesity*

*Based on the algorithm from the EWGSOP2[9]

Table 4.5. Differences in physical performance and patient-reported measures by sarcopenic obesity[†] status in n=151 patients with knee OA

	Sarcopenic obesity identified by low strength[a] and low muscle mass[b] SO n=30 Compared to NSO n=121
Physical performance and strength measures:	
Gait speed (m/s)	-0.14 (-0.25 - -0.03)*
Gait speed, female	-0.13 (-0.3 - 0.0)
Gait speed, male	-0.18 (-0.3 - -0.05)*
Grip strength (kg)	-5.2 (-9.3 - -1.2)*
Grip strength, female	-6.0 (-9.5 - -2.6)*
Grip strength, male	-9.9 (-14.9 - -4.9)*
6MWT (m)	-81.5 (-127.4 - -35.6)*
6MWT, female	-54.1 (-122.3 - 14.1)
6MWT, male	-127.0 (-186.2 - -67.7)*
Patient-reported measures:	
WOMAC pain 0-20	1.0 (-0.4 - 2.4)
WOMAC stiffness 0-8	0.2 (-0.5 - 0.8)
WOMAC function 0-68	1.7 (-3.0 - 6.5)
WOMAC total 0-100	3.0 (-3.6 – 9.6)
EQ-5D VAS, 0-100	-9.0 (-16.2 - -1.8)*
EQ-5D self-care dimension[$]	29.3*

Values presented are mean differences (CI) in group classified as SO compared to group classified as NSO, unless otherwise indicated

†identified as having both low strength and low muscle mass

[a]low strength identified by relative grip strength <0.65 kg/m^2 in females and <1.1 kg/m^2 in males

[b]low muscle mass identified by ASM/BMI, kg/m^2 (<0.512, <0.789) in females and males, respectively

[$]difference in proportion (%) of SO group reporting problems compared to NSO group

*p<0.05

ASM = appendicular skeletal mass, EQ-5D = EuroQuol Foundation, CI = 95% confidence interval, NSO = not sarcopenic obesity, OA = osteoarthritis,

SO = sarcopenic obesity, VAS = visual analogue scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, 6MWT = six-minute walk test

be considered for use as a screening method for sarcopenic obesity risk in OA clinical practice. When used in combination with low muscle mass to identify sarcopenic obesity, it was able to discriminate a patient subgroup with mobility impairments (lower gait speed and walking endurance) and poorer quality of life. This illustrates its potential efficacy in identifying patients with knee OA who may require attention and treatment for sarcopenic obesity.

Relative grip strength is inexpensive and simple to administer. As the measures of height, weight and grip strength (using a handgrip dynamometer) are low burden, it could be easily integrated into clinical OA assessments. Patients could be screened (**Figure 4.3**) for low strength (below proposed sex-specific cut-points for relative grip strength). If low strength is present, sarcopenic obesity would be suspected. The patient would then be sent for body composition assessment (e.g. using DXA), to confirm the presence of low muscle mass (low ASM/BMI) and the diagnosis of sarcopenic obesity[9]. Patients with confirmed sarcopenic obesity (having both low relative grip strength and low muscle mass) could then be recommended for appropriate treatment[10].

Our results indicate that gait speed and 6MWT were poorer discriminators of low muscle mass compared to relative grip strength. This could be due to the influence of OA on lower limb function and ambulation. Our results differed from those of El Ghoch et al.[32] who examined clinical screening for low ASM/BMI in females with obesity. They reported gait speed was superior to grip strength or 6MWT when examined independently (using sensitivity analyses), however when examined in a multivariable model, only 6MWT was related to low ASM/BMI. This difference in findings between our studies could be due to their cohort not having knee OA, being all female, and no consideration of relative grip strength.

We did not find an association between absolute grip strength and low muscle mass in our cohort. While absolute grip strength has been used frequently as a screening tool for low strength in sarcopenia[9,10,22,33], it may be less discriminative in adults with obesity[34]. Adjusting grip strength by a measure of adiposity (such as BMI, weight, or FM) may be preferable as it accounts for differences in strength with increasing body size[34,35]. Relative grip strength may have a stronger association with mobility impairment compared to absolute grip strength[35], although varied sex-differences have been reported. In the Foundation for the National Institutes of Health (FNIH) Sarcopenia project[22,24,36,37], absolute and relative grip strength were equally associated with mobility impairment, however due to heterogeneity in females[37], absolute grip strength was selected as preferable as it was considered simpler to assess[36]. Sallinen et al[34] found relative grip strength better identified mobility limitations in males, with a weaker relationship in females. This differed from findings by Sampaio et al[38], who found a stronger relationship between relative grip strength and fear of falling in women. Clearly, sex-differences may be present, requiring further investigation. However it is noteworthy that the cohorts in these studies did not all have obesity, and as they were community samples they may be under-representative of adults with mobility limitations.

The prevalence of sarcopenic obesity in this cohort was 19.9% when identified using the combination of low relative grip strength with low muscle mass. This prevalence is higher than projected in our previous study when gait speed or grip strength cut-points were used with low muscle mass to identify sarcopenic obesity (prevalence of 8.6%) (Chapter 3). Further, using the new proposed criteria, sarcopenic obesity was similarly identified in both younger (ages 40-64.9 years) and older (age ≥ 65 years) age categories. This provides further indication that sarcopenic

obesity identification in knee OA may need to be different from identification approaches used in sarcopenia or other clinical conditions.

In our cohort, males had greater odds of low muscle mass compared to females when examined independently (OR 2.33 *vs* 0.43, respectively, p=0.023). This is likely due to the steeper decline in aging-related muscle mass and strength[39,40] common in males associated with declining endocrine function during andropause[41]. Males may be more sensitive to aging-related increases in adiposity and muscle loss driven by OA-related inflammation and inactivity, compared to females. These sex differences were magnified when adjusted for relative grip strength, with much higher OR for low muscle mass in males (OR 15.09 *vs* 0.07 in females, p<0.001). While this may be influenced by the higher prevalence of low muscle mass in males in our cohort (37.1% *vs* 20.2%, in females), it may also indicate underlying sex-differences as discussed previously. A correlation between low muscle mass and FM, gait speed, and 6MWT was only present in males in our cohort, providing further indication that the relationship between physical function, adiposity and muscle mass (relative to sarcopenic obesity) may differ by sex. Similarly, the FNIH project[22] found sex-differences in the relationship between BMI and gait speed in females, although the use of separate single-sex cohorts may have influenced their findings. Nevertheless, future studies may need to examine if the relationship between muscle function and low muscle mass differ between males and females, potentially leading to sex-specific screening approaches.

Interestingly, age was not correlated with low muscle mass in this study, supporting our understanding that sarcopenic obesity occurs across age categories and may be unique from aging-related sarcopenia. Although we found type II diabetes was independently associated with low muscle mass (OR 2.43), similar to reports elsewhere[42], it did not contribute in the final

model. Additionally, while the presence of hand OA can reduce grip strength[43], we did not find it associated with either absolute or relative grip strength in this cohort.

Assessing for low strength or function does not preclude the measurement of low muscle mass[2], which is still important for the diagnosis of sarcopenic obesity. However measuring body composition in every patient with knee OA is not yet feasible in most clinical settings. Therefore, using relative grip strength as a clinical screening measure would assist in identifying patients with low strength who are at higher risk of having sarcopenic obesity and require further investigation. Ultimately screening methods will need to determine whether specificity (ability to correctly rule in patients who have sarcopenic obesity) or sensitivity (ability to correctly rule out patients who do not have sarcopenic obesity) is more important[7]. There may be a benefit to increased specificity, as preserving muscle mass and preventing further loss will likely be easier than increasing muscle mass. Economic analyses of the costs of body composition assessments in comparison to the cost of misdiagnosis[44] will provide further clarity. Additionally, considering the implications of false positives and false negatives will be critical for determination of the most relevant criteria and cut-points. Realistically, no one clinical measure or assessment will be ideal for all populations with sarcopenic obesity[12], but increased awareness and screening in patients with OA is necessary.

As a result of our analyses, we were able to propose cut-offs for relative grip strength that balance sensitivity and specificity for identifying low muscle mass in this cohort of patients with knee OA and obesity. While further external validation is required, our results provide initial confirmation that assessing low relative grip strength has value in screening for the presence of sarcopenic obesity. Further testing of these cut-points in other cohorts with knee OA and obesity will clarify their effectiveness and validity as a screening measure.

Strengths and limitations

The relationship between muscle function and low muscle mass has not been well examined in patients with obesity and knee OA. Our findings provide an important contribution to this body of knowledge. Although the final model in this study provided moderate discriminatory power (AUC 0.774), we did not examine all physical performance tests that have been used in sarcopenia (i.e. timed up and go test, chair stand, short performance physical battery) so other tests may be found to be superior. Importantly, the relationship between strength, function and muscle mass could be confounded by OA severity[45] and comorbid chronic conditions, such as type II diabetes[46]. While we attempted to control for these influences, the discriminating power of strength and function measures may have some limitations in this heterogeneous OA population. Other study limitations include the cross-sectional approach and limited transferability to patients without knee OA and obesity. Additionally, we adjusted both muscle mass and grip strength by BMI, which could result in overfitting. Proposed cut-offs for relative grip strength were not validated internally using bootstrapping or externally with other samples, so further validation is important. Relative grip strength cut-offs were selected based on a balance between sensitivity and specificity, however clinical consideration may need to consider if maximizing sensitivity or specificity is preferential based on the cost and availability of body composition assessments. No blood tests were conducted, so examination of associations with biomarkers were not explored. Additionally, males and females were analyzed together in this cohort due to the limited sample, however nascent indications of sex-differences require further investigation in larger samples to provide clarity if screening approaches should differ between males and females.

4.7 Conclusion

Sex-specific relative handgrip strength provided the best discrimination of low strength related to low muscle mass in this cohort, and may be useful to identify patients with knee OA who have sarcopenic obesity. Relative grip strength is easy to administer, and integrate into clinical OA environments. Cut-points for relative grip strength of <0.65 kg/m^2 in females and <1.1 kg/m^2 in males are proposed, but further validation is required. Relative grip strength could be used to screen patients for low strength, who would then require a body composition assessment to confirm the presence of low muscle mass. Together these measures can be used to detect and identify sarcopenic obesity in patients with knee OA.

4.8 References

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CHAPTER 5

5.1 Discussion

The primary aim of this thesis was to improve understanding of sarcopenic obesity in adults with knee OA with respect to prevalence, diagnostic screening, and functional implications. Together, the three studies in this thesis have identified and answered some important questions about sarcopenic obesity in this population, while also revealing avenues requiring further inquiry. This chapter will provide a brief review of the objectives, hypotheses and results from each study, integrate the findings, and discuss overall limitations and future directions.

5.1.1 Study One

The aim of the first study[1] (Chapter 2) was to determine the current breadth and extent of evidence on sarcopenic obesity in knee and hip OA. This study used a scoping review methodology to systematically examine the extent of the published scientific literature on this topic and identify gaps in knowledge. It was hypothesized that there would be few clinical studies and limited evidence on sarcopenic obesity in adults with knee OA.

The results of this scoping review confirmed our hypothesis and support the use of this methodology. Ten studies were found that examined this condition in adults with knee OA[2–11]. Of these ten studies, only three were in clinical cohorts (from Korea[3], Thailand[8] and Japan[9]), with no clinical studies in North American cohorts. This is an important knowledge gap as classification of obesity[12] and body composition[13] differ between Asian and Caucasian ethnic groups, which limits the comparability of the current evidence. Further, there is a need for

investigation in clinical cohorts (compared to community or population samples) to better understand the relevance of sarcopenic obesity for healthcare and patient outcomes in OA.

The scoping review also revealed that sarcopenic obesity was present, but with a wide range of prevalence in both clinical[3,8] and population[6,7,11] samples (1.3%[3], 3%[7], 5.2%[6], 8.9%[3], 13.9%[8], 16.2%[11], and 35.4%[3]). This prevalence variability was likely due to different methods for identifying low muscle mass and obesity between studies. While appendicular skeletal muscle mass (ASM)/weight[6–8] was the primary method to classify low muscle mass in included studies, ASM/height[2 3], ASM/BMI[11], and a residual method[3] were also used. Ji et al.[3] compared ASM/height[2], ASM/weight and the residual method in adults undergoing TKA. They found sarcopenic obesity prevalence was lowest using ASM/height[2] (1.3%) and highest using ASM/weight (35.4%). Obesity classification also differed between studies, using varied BMI cut-points (25[3,8], 27.5[6,7] or 30[11] kg/m^2) or sex-specific fat mass and waist circumference[11]. Only one study included measures of low strength or low function in their definition of sarcopenic obesity[8].

This review also found indications that sarcopenic obesity was likely present in two other studies but not recognized as a distinct clinical condition. Batsis et al.[2] and Knoop et al.[5] identified a clinical OA phenotype as dynapenic obesity (low strength and high adiposity), however body composition and muscle mass were not considered in either study. Low strength could be related to low muscle mass in a proportion of the sample, and may indicate that sarcopenic obesity and dynapenic obesity were both present but only dynapenic obesity was identified.

Taken together, the results of this scoping review identified several gaps in knowledge and supported the need for a clinical study. Additionally, the findings support including several

definitions to categorize low muscle mass (low ASM) in the clinical study as prevalence varies depending on the approach. Further, there was an identified need to explore diagnostic approaches that include measures of low strength or low function with low muscle mass (as this was only examined in one previous study[8]).

5.1.2 Study Two

The second study (Chapter 3) aimed to fill the evidence gap, with an aim to assess the prevalence of sarcopenic obesity in a clinical cohort of adults with end-stage knee OA using different diagnostic criteria. Further, outcomes of pain, physical function and quality of life were compared between those identified with and without sarcopenic obesity. It was hypothesized that sarcopenic obesity prevalence would be ≥10% in this population (when using ASM/weight), and adults with sarcopenic obesity would have poorer physical function and quality of life compared to those without sarcopenic obesity.

The results of this study support acceptance of our hypothesis about prevalence, as the rate of sarcopenic obesity was 14.6% in our cohort when defined using ASM/weight alone. Our results provide further evidence that prevalence varies depending on identification method (1.3% using ASM/height^2 alone, 14.6% using ASM/weight, 27.2% using ASM/BMI, and 8.6% when combining low muscle mass with low grip strength or low gait speed). This aligns with findings elsewhere that show prevalence is higher when diagnostic approaches consider muscle mass alone versus in combination with a measure of low strength or function[14]. Additionally, prevalence calculated using ASM/height^2 was low at only 1.3%, similar to findings by Ji et al.[3], further supporting that allometric scaling of ASM by height doesn't capture relative low muscle mass in the presence of obesity[15,16].

This study also found that using current cut-points for low grip strength or low gait speed in the identification of sarcopenic obesity may preferentially identify more older adults (≥ age 65 years) compared to middle-aged adults (ages 40-64.9 years). This is likely due to the use of gait speed and grip strength tests and cut-points that were developed to identify functional impairments in older adults[17].

Importantly, we were also able to confirm our hypothesis about patient physical function and quality of life. Sarcopenic obesity was found to significantly impact these areas in the study cohort identified with sarcopenic obesity, with slower walking speeds, lower grip strength and lower walking endurance yielded across all diagnostic approaches. Further, sarcopenic obesity influenced patient-reported quality of life, with more problems reported in the self-care dimension of the EuroQol Foundation EQ-5D-5L (related to self-identified difficulty washing or dressing themselves).

5.1.3 Study Three

The third study (Chapter 4) aimed to determine which patient characteristics and muscle function measures were associated with low muscle mass (and likely related to sarcopenic obesity rather than OA) in the cross-sectional patient cohort. Associated variables were then applied to discern subgroups with and without sarcopenic obesity to compare outcomes of pain, function and quality of life. It was hypothesized that gait speed and grip strength would not be the best muscle function measures to screen for sarcopenic obesity due to the influence of OA and obesity on gait parameters and grip strength.

This study found that sex, type II diabetes, gait speed, relative grip strength and 6MWT were correlated with low muscle mass (low ASM/BMI) in the study cohort. Age was not correlated but still considered due to its biological relationship with declining muscle mass.

When all variables were examined in multivariable modeling, only sex and relative grip strength remained as significant. These findings confirm our hypothesis that gait speed and grip strength are not the best measures to screen for low strength or function related to sarcopenic obesity in this cohort with knee OA. Further, the results suggested that sex-specific relative grip strength may be a potential method to screen for low strength in patients who are also likely to have low muscle mass (and therefore sarcopenic obesity).

To test this potential method of screening, new sex-specific cut-points for low strength (relative grip strength <0.65 kg/m^2 in females, and <1.1 kg/m^2 in males) were established from receiver operating curve analyses. These cut-points were used in combination with pre-established low muscle mass cut-points (low ASM/BMI) to identify patients with and without sarcopenic obesity. The prevalence of sarcopenic obesity was 19.9% using this combined criteria. The patient group with sarcopenic obesity had mobility impairments (lower walking speed and endurance), and poorer quality of life (lower EQ-5D VAS scores and more problems reported in the EQ-5D self-care dimension), compared to the group without sarcopenic obesity. This suggests that this combination method to screen and identify sarcopenic obesity is able to discern a subgroup of patients with mobility and quality of life impairments. This highlights the potential applicability of relative grip strength as a screening measure in clinical OA settings, which could be used in conjunction with body composition to identify sarcopenic obesity in patients with knee OA.

5.2 Integrated Discussion

The studies in this thesis contribute several important findings to the literature on sarcopenic obesity. Primarily, this research confirms that this condition is present in adults with end-stage knee OA, with negative implications on mobility and quality of life. Mobility

limitations (lower gait speed and 6MWT distance) were revealed regardless of the approach used to identify sarcopenic obesity (low muscle mass alone or in combination with low strength or function). This supports that DXA-derived measures of low muscle mass were able to discern individuals with meaningful functional mobility impairments. This is in contrast to concerns reported about the poor discrimination ability of DXA body composition measures to identify older adults at risk of mobility disability[18]. Clinically relevant gait speed differences of >0.1 m/s and 6MWT differences of >50 m[19] were present between groups identified with and without low muscle mass in our clinical sample. While it is expected that larger between-group differences in function are present when low strength or function is included in the diagnostic definition for sarcopenic obesity, the ability of low muscle mass alone to distinguish these differences is of clinical interest. This is particularly important for patients whose function and strength is likely also impaired by knee OA and obesity, potentially confounding the diagnostic effectiveness of strength and function measures to discern sarcopenic obesity in this population.

Sarcopenic obesity's negative influence on function has been reported in other clinical populations[20], however it could create a critical problem in patients with end-stage knee OA. Poor functioning is often considered in the decision to proceed to a TKA[21]. However, if the poor function is primarily related to (or strongly influenced by) sarcopenic obesity, then a TKA may not resolve the functional impairment. The patient may be dissatisfied with their TKA outcome if mobility impairments persist. Further, TKA surgery-related immobility, inactivity and recovery could result in further loss of muscle mass, potentially exacerbating sarcopenic obesity if already present. Body composition changes can occur in short time duration with abrupt changes in health status and mobility. This further supports the importance of including an assessment of body composition to confirm the presence of sarcopenic obesity.

Results from the EQ-5D-assessed health-related quality of life in this thesis are also interesting. A higher proportion of problems on the EQ-5D self-care dimension (related to level of difficulty washing or dressing themselves) were reported by patients with sarcopenic obesity, compared to those without this condition. No between-group differences were present in other EQ-5D dimensions. This suggests that sarcopenic obesity has implications on activities of daily living (ADL) in this population, similar to reports elsewhere[20,22,23], despite the lack of specific measures to assess ADL in this research. Additionally, only when using combined diagnostic approaches in studies two and three (low muscle with low strength or low function), differences in EQ-5D overall quality of life (EQ-5D VAS scored from 0, worst health, to 100, best health) were present between those with and without sarcopenic obesity. VAS scores were -9.0 (in study three) and -17.1 (in study two) points lower in the groups with sarcopenic obesity, which is greater than suggested minimal clinically important differences for the VAS in adults with knee OA at 7.9[24]. Notably, there were no differences in VAS scores when only low muscle mass was used as a diagnostic criteria, suggesting that sarcopenic obesity-related influences on function and strength may be more relevant when considering overall quality of life. Including measures of low strength or low function when identifying sarcopenic obesity may assist in discerning patients who have more severe impacts on their well-being.

This research supports the rationale to include both a measure of low muscle mass with a measure of low strength or function in the diagnostic definition for sarcopenic obesity[25,26]. The findings also support that cut-points for low ASM/weight (<19.43 % in females, and <25.72 % in males)[27] or ASM/BMI (<0.512 kg/m^2 in females, and <0.789 kg/m^2 in males)[28] are preferred over ASM/height^2 (<5.45 kg/m^2 in females, and <7.26 kg/m^2 in males)[29] to classify low muscle mass in adults with obesity, as they account for the influence of body mass. ASM/height^2 cut-

points only identified two adults in this study, illustrating its limited ability to identify relevant low muscle mass in adults with obesity[16]. ASM/BMI appears to be superior to ASM/weight, as it identified the largest subgroup of patients with mobility impairments. This is likely due to its adjustment for both height and weight. Further, cut-points for low ASM/BMI were based on an association with weakness[30], rather than relative to a younger reference population, as with ASM/weight[27]. In this thesis research, adults across BMI categories were identified with low ASM/BMI [23.8% in BMI 30.0-34.9 kg/m^2 (n=15/63), 16.7% in BMI 35.0-39.9 kg/m^2 (n=8/48), and 45.0% in BMI >40 kg/m^2 (n=18/40)]. Rates were highest in the BMI category >40 kg/m^2. This reflects the increased possibility of a disproportionate ratio between fat mass (load) and muscle mass (capacity) with higher BMIs[31], however, this can still occur at any BMI.

This research confirms that BMI measures alone miss important individual differences in body composition[32]. Analyses in study two revealed large variations in adiposity and muscularity within BMI categories, supporting that examining BMI in isolation can be misleading as it doesn't distinguish between compartments of fat and muscle mass. Body composition is important. A recent study by Davis et al.[33] suggests that measuring body composition in addition to BMI provides a better understanding of differences in physical performance outcomes in adults with knee OA. Considering BMI alone misses some of this critical information. This supports our recommendations for moving beyond BMI and including body composition assessment in orthopedic settings, particularly when making individualized treatment recommendations (such as weight loss or decisions on proceeding to a TKA).

An additional important finding from this research is the proposed relative grip strength cut-points. While these cut-points require further validation in other cohorts with knee OA, they represent an important advancement to improve clinical screening and identification of low

strength relative to sarcopenic obesity. Although strength and function assessments (particularly grip strength and gait speed) are established as screening methods for sarcopenia[34–38], they have not been well-examined in younger adults with higher body size and relevant to sarcopenic obesity[39]. Regardless, relative grip strength appears to be an effective approach. It has previously been identified by Cawthon et al.[18] as able to discern older adults at risk for mobility disability, and by Sampaio et al.[40] to discern risk of falls. This thesis research provides further indication that relative grip strength may be appropriate to screen for sarcopenic obesity in OA clinical practice. Importantly, this type of simple measure is likely the best way to increase routine screening and identification of adults with knee OA who have a greater likelihood of having sarcopenic obesity.

This research also stimulates questions regarding the relationship between type II diabetes and sarcopenic obesity[41]. Although not a primary focus in this research, a higher prevalence of type II diabetes was observed in patients with sarcopenic obesity compared to patients without this condition (differences in proportion were: 10.3% using ASM/weight, p=0.254; 14.5% using ASM/BMI, p=0.038; 30.0% using the study two combined definition, p=0.016; and 27.7% using the study three combined definition, p=0.004). Type II diabetes was also independently associated with low ASM/BMI (OR 2.43, p=0.042) in study three, but did not contribute in the multivariable screening model. Diabetes is associated with increasing BMI[42], so the use of diagnostic approaches that adjust ASM by BMI could influence these findings. Kreideih et al.[43] reported 17.7% higher rates of type II diabetes in women with sarcopenic obesity compared to those without this condition, however they also used low ASM/BMI for diagnostic criteria. While type II diabetes is known to influence muscle mass[44] and strength[45], the true range of prevalence differences and the relationship with sarcopenic obesity and OA needs

further enquiry. This is especially relevant for consideration of surgical risk in TKA, as both type II diabetes and sarcopenic obesity are independent risk factors for surgical complications[46,47].

The study results from this thesis are not able to answer all questions about sarcopenic obesity in patients with knee OA, but support the understanding that muscle mass has important influences in this population. While not able to discern the influence of sarcopenic obesity on TKA outcomes, this thesis provides theoretical support that lower muscle mass in patients undergoing TKA could influence mobility and functional recovery after surgery. Further, this negative influence potentially extends to infection risk with TKA. A recent study by Babu et al.[48] shows that a marker for sarcopenia can predict risk of prosthetic joint infections in TKA and total hip arthroplasty. This further supports the theoretical link between sarcopenic obesity and TKA risk, suggesting that low muscle mass itself may confer a risk independent from adiposity. Preservation of current muscle mass may need to be a priority in OA management.

Switching from a focus on reducing weight or BMI, to a focus on maintaining or improving muscle mass or body composition before TKA is a paradigm shift in OA care, but it may result in benefits to both adipose and muscle mass compartments. As demonstrated in patients with colorectal cancer[49], pre-habilitation prior to TKA may attenuate further loss of muscle mass during the pre-and post-surgical periods, and potentially decrease adiposity secondarily.

Finally, this research provides a foundation from which further research and clinical recommendations can be developed. Importantly, increased awareness and identification of sarcopenic obesity is needed in clinical practice. Despite the development of the sarcopenia ICD-10 code in 2016[50,51], this condition is still under-recognized in orthopedic and OA clinical

communities[48]. Additional knowledge mobilization of these thesis results will be important to aid in increasing awareness and attention.

5.3 Strengths and Limitations

This thesis has several strengths. A primary strength is the clinical relevance of findings, as data was collected from a patient cohort. This is valuable for knowledge use and translation, with greater potential for the results to influence changes in clinical settings. A further strength is the novelty of this work. No studies were found that examined the use of muscle function assessments to screen for low strength or function relative to sarcopenic obesity in patients with knee OA. Further, few studies have examined sarcopenic obesity in clinical populations with knee OA. Only one study compared different diagnostic approaches (only using low muscle mass)[3], and only one study has examined the influence of this condition on physical function[8]. This research helps to fill these evidence gaps and extend current knowledge.

This research also has limitations. A primary limitation is the cross-sectional approach, which prevents any inference of causality when interpreting results on physical function and quality of life. Further, the cohort was primarily Caucasian, limiting the relevance of outcomes for other ethnic backgrounds. Other assessments for low strength or low function may be preferential to relative grip strength in screening for sarcopenic obesity, as we did not examine all measures used elsewhere to identify sarcopenia (i.e. chair stand[36], leg strength[52]). However, knee OA would likely confound outcomes using these measures due to its influence on quadriceps strength[53]. Further, indications of sex differences in the effectiveness of strength and function measures to screen for low muscle mass were emerging in study three. This was not unexpected, as in males there is a steeper decline in strength with age[54,55], and a stronger relationship between strength and function[55]. However, due to the limited sample and smaller

subgroups with sarcopenic obesity, these sex-differences were not thoroughly examined. Importantly, this research may have under-identified prevalence of sarcopenic obesity if patients with sarcopenic obesity-related impaired function did not complete the DXA due to perceived difficulties with travel to the additional appointment. While every effort was made to ease the burden of attending, a group of participants (n=41) did not complete DXA body composition assessment. Lower EQ-5D VAS scores (mean difference -10.0, p=0.04) were reported by DXA non-completers (n=41) compared to completers (n=151). This could indicate that patients with lower quality of life (and possible sarcopenic obesity) were not included in the analyses. However no differences in gait speed, grip strength, or 6MWT were present between DXA completers and non-completers. Nonetheless, it is possible that individuals with more severe mobility impairments were not included in our study, resulting in an under-estimation of the true prevalence of sarcopenic obesity in this population. Recruitment of patients with sarcopenia has been identified as a barrier to clearly understanding this condition in clinical practice[51].

5.4 Recommendations for Future Directions

5.4.1 Research

A number of research recommendations can be provided based on the findings of this thesis. Initially, further validation and examination of the proposed relative grip strength cut-points in other cohorts with knee OA is needed. Other strength and function measures should also be explored in this population to see if they are more effective, with additional examination of sex-differences in screening approaches. Longitudinal studies are also needed to clarify the influence of sarcopenic obesity on TKA and conservative treatment outcomes, and the influence of weight loss and resistance exercise on prevention, development, and progression of this condition.

Health-related quality of life was influenced by sarcopenic obesity in this research, assessed using the patient-reported generic EQ-5D. Future research should consider additional examination of disease-specific quality of life indices, with instruments designed to capture the specific influences of low muscle mass, high adiposity, or sarcopenia (i.e. SarQoL©, a quality of life questionnaire specific to sarcopenia[56]). Additionally, due to the suggested influence of sarcopenic obesity on self-care activities (washing and dressing), this should be further clarified and examined using specific measures (performance-based and patient-reported) to identify ADL difficulties.

The influence of muscle composition (also termed "muscle quality", related to the myosteatosis or fatty infiltration within and between muscle fibres) in this population with knee OA also requires further research. Myosteatosis may account for differences in the relationship between strength and muscle mass, as it is associated with poorer function[57]. Kumar et al.[58] found adults with knee OA had greater myosteatosis in the quadriceps muscle, with associated disability, compared to adults without OA. However it is unclear if myosteatosis precedes OA and is related to OA development and progression, or if OA-related immobility and inactivity results in increased fatty infiltration in the muscle[58]. Regardless, muscle composition cannot be distinguished with DXA, so additional testing measures would be required (i.e. MRI, CT scans, or potentially ultrasound echogenicity[59]).

5.4.2 Clinical Practice

There are a few recommendations that can be made for clinical practice based on the findings of this thesis. This is important as knowledge gained from clinical research should be translated, shared and utilized in clinical care settings. Primarily, this research supports the need for increased consideration and identification of sarcopenic obesity in clinical practice, as this

condition is present in patients and impacting functional outcomes. Study results indicate that sarcopenic obesity is missed by consideration of BMI measures alone, supporting the need for measurement of body composition to discern the presence of low muscle mass.

Currently in clinical practice there may be limited availability to measure body composition in every patient with knee OA using DXA. Therefore, the proposed relative grip strength cut-points could be used to screen and identify patients who are more likely to have low muscle mass. This will reduce the number of patients requiring body composition assessment, while still supporting an appropriate diagnostic approach. Only those patients identified with low relative grip strength would be required to have their body composition assessed, in order to confirm or refute the presence of low muscle mass and the diagnosis of sarcopenic obesity. Additionally, alongside this increased utilization of DXA body composition measurement to identify sarcopenic obesity, there should be consideration of appropriate procedures, equipment limitations, and measurement techniques to use when scanning adults with higher body size and mass using DXA[60].

While this research did not examine the implications of weight loss in patients who have sarcopenic obesity, there are theoretical recommendations that can be made. Weight loss should not be recommended in adults with end-stage knee OA unless there is no presence or risk of low muscle mass and sarcopenic obesity (which would need to be confirmed with appropriate screening and a body composition assessment). This is due to the risk of muscle and bone loss that occurs concomitantly with weight loss[61,62]. Further, as gains in muscle mass are more difficult as age increases[41], it may be even more critical to encourage and support preservation of existing muscle mass prior to and during TKA surgical recovery for all patients. Hospitalization for a procedure such as TKA, along with resultant surgical-related inflammation and inactivity,

could acutely precipitate muscle loss and the onset of sarcopenic obesity in patients with already low muscle reserves[63]. And finally, patients who are identified with sarcopenic obesity should receive current evidence-based treatment interventions to preserve muscle mass and strength[37,64–66], including appropriate protein intake advised by a dietitian, and resistance exercise training supported by a physiotherapist or exercise physiologist[37].

5.5 Conclusions

This thesis provides an important contribution to the literature, expanding our understanding about sarcopenic obesity in adults with knee OA. This work provides evidence that sarcopenic obesity is present in adults with obesity and knee OA, and recommends that it should be identified using diagnostic definitions that consider both low muscle mass and low strength or low function. Prevalence of sarcopenic obesity will vary depending on diagnostic approach, but ranges between 8.6% -19.9% are projected (using combination diagnostic approaches). Patients with sarcopenic obesity had poorer functional mobility and quality of life compared to patients without this condition. Early identification of sarcopenic obesity in the clinical setting is suggested to prevent and minimize further muscle loss. Relative grip strength is proposed as a pragmatic method to screen for low strength in patients with knee OA and obesity. Patients with low strength could then complete a body composition assessment to determine the presence of low muscle mass, and confirm or refute the identification of sarcopenic obesity.

5.6 References

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APPENDICES

APPENDIX A - Participant Information and Consent

Research Study

Sarcopenia screening and risk assessment in adults with osteoarthritis and obesity

Participant Information Sheet and Consent Form

Principal Investigator:

Dr. Mary Forhan
Department of Occupational Therapy
University of Alberta, Edmonton AB T6G 2G4
Email: forhan@ualberta.ca
Phone: 780-492-0300

Background and Purpose:

Some adults with higher body weight and knee osteoarthritis may have a condition called sarcopenia, where they have lower muscle mass and function than is normally expected. This condition can impact results from osteoarthritis treatments. We would like to find out how many adults with higher body weight and moderate to severe knee osteoarthritis may have sarcopenia. In order to do this, we will use a screening assessment for sarcopenia which involves walking tests, a handgrip strength test, and possibly a body scan to measure the amount of bone, muscle and fat in the body.

Procedures:

If you choose to join in this research study, you will be asked to sign a consent form to participate. For the study, you will be asked to answer some questions about your medical history, weight history, and current medications. You will also be asked to complete some additional tests today:

- A questionnaire about the pain and function you experience related to your knee osteoarthritis. This questionnaire is will take you approximately 5 minutes to complete using an electronic tablet.
- A questionnaire about your general quality of life. This questionnaire will take you approximately 5 minutes to complete using an electronic tablet.
- A walking speed test over a short distance of 4 metres. You will be asked to walk as fast as you are comfortable with. You can use your usual walking aids during this test (i.e. cane, walker). You will be asked to repeat this test two times to get your best measure.
- A handgrip strength test where you will be asked to squeeze a small device that measures the strength of your grip. You will be asked to repeat this test three times to get your best measure.
- A walking distance test that measures the farthest distance you can walk in 6 minutes on

a short roundabout course here at the clinic. You will be able to use your usual walking assistive devices during this test (i.e. cane, walker). You are also able to take as many rest breaks and sit as needed during this assessment. There is no minimum distance you need to walk, and you can stop walking at any time.

Based on the results of the walking and handgrip tests, you may be asked to complete a body scan using Dual Energy X-Ray Absorptiometry (DXA). DXA is a simple test that provides a very accurate measurement of the bone, muscle, and fat in your body. This test uses very low dose x-rays of two different levels to distinguish between bone and soft tissue. DXA is a painless, non-invasive test. The test requires that you put on a hospital gown and lie on an x-ray bed. The scan takes about 5 minutes and is very low dose radiation (equivalence to approximately 1 day of natural background radiation). This dosage is 1000 times less than the limit for trivial exposure, and is classified as a negligible dose according to the standards of the National Council of Radiation Protection and Measurement.

The DXA test will be completed on a separate day at the University of Alberta Human Nutrition Research Unit. Parking is available directly outside the building, and you will be reimbursed for your parking costs while having this test completed. You will be able to schedule a time for this test that is convenient to you. This test will be conducted by a Medical X-ray Technologist. The total time required to complete a body scan is 20 minutes, including the time required to change into the gown, get positioned on the table, and complete the scan.

Potential Benefits:

By participating in this study, you will be able to find out some information about your walking speed, grip strength, and possibly your body composition. You will be able to receive a copy of your body scan if you have it done.

Potential Risks:

There are a few risks to this study. You will be walking, and so changes in blood pressure, heart rate and fainting can happen, and very rarely heart attack or stroke. Someone will be with you at all times during the tests, and trained medical staff and emergency equipment are available in the event of an emergency. There is also a small risk that you will be tired or sore from the walking or grip strength tests. You will be able to decide how fast to walk or exert yourself depending on your ability, so you can rest or pace yourself during the testing to prevent overexertion. The x-ray dose in the DXA scan is very low and safe for repeated measurements. With the exception of pregnant women, there are no known risks associated with a DXA scan. The potential risks associated with radiation exposure to an unborn fetus are not known, and therefore we will ask females that have not completed menopause to undergo a urine sample pregnancy test to verify that they are not pregnant. Having a DXA scan does not make it unsafe for you to have other x-rays taken in the near future.

Stopping the Tests:

You may stop any of the tests at any time without any jeopardy to you.

Confidentiality

Confidentiality will be respected and no information that discloses your identity will be released or published. Your data will be saved in our database using an identification number known only to the research team for the study. The results of the tests will only be disclosed to the researchers and will not be communicated to the staff or clinicians at the Edmonton Musculoskeletal Clinic. The results of this study will not influence or change the care you receive at the clinic. By signing this consent form you are saying it is okay for the study team to collect, use and disclose information from your personal health record for the purpose of this study as described above.

Costs:

There is no cost to you for any of the procedures involved in the study.

Voluntary Participation:

Participation in this study is voluntary. If you choose not to participate, you will continue to access care at the Edmonton Musculoskeletal Clinic. If you choose to participate in this study, you can withdraw from the study at any time. You do not have to give a reason for withdrawing from the study.

Please contact the individual identified below if you have any questions or concerns:
Principle Investigator: Mary Forhan **Phone:** 780-492-0300

The plan for this study has been reviewed for its adherence to ethical guidelines and approved by the Health Research Ethics Board at the University of Alberta. For questions regarding participant rights and ethical conduct of research, contact the Research Ethics Office at (780)492-2615.

Research Study

Sarcopenia screening and risk assessment in adults with osteoarthritis and obesity

Consent Form

Principal Investigator:

Dr. Mary Forhan
Department of Occupational Therapy
University of Alberta, Edmonton AB T6G 2G4
Email: forhan@ualberta.ca
Phone: 780-492-0300

	Yes	No
Do you understand that you have been asked to be in a research study?		
Have you read and received a copy of the attached information sheet?		
Do you understand the benefits and risks involved in taking part in this research study?		
Have you had an opportunity to ask questions and discuss this study?		
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your future health care?		
Has the issue of confidentiality been explained to you?		
Do you understand who will have access to your records, including personally identifiable health information?		
Who explained this study to you? _____		
I agree to participate in this study: *Signature of Research Participant*_____ *Printed Name*_____ *Contact phone/email* _____ *Date(DD/MM/YYYY)*_____		

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE STUDY PARTICIPANT

APPENDIX B - DXA Scan Information and Consent

DXA Scan: Body Composition Testing

Information Sheet

Test Background:

Dual Energy X-Ray Absorptiometry (DXA) is a simple test that provides a very accurate measurement of bone density, lean tissue mass, and total and regional body fat (ie. abdominal body fat). This test uses very low dose x-rays of two different levels to distinguish between bone and soft tissue.

DXA is a painless, non-invasive test. The test requires that you put on a hospital gown and lie on an x-ray bed. The scan takes about 5 minutes and is very low dose radiation (equivalent to approximately 1 day of natural background radiation). This dosage is 1000 times less than the limit for trivial exposure, and is classified as a negligible individual dose according to the standards of the National Council of Radiation Protection and Measurements.

Preparation for the Test:

No special preparation is necessary. Pregnant women and individuals who have recently undergone barium tests/exams (within 2 weeks), or who have had a nuclear medicine scan or been injected with an X-ray dye (within 1 week) cannot have a DXA scan. We ask that you do not wear anything metal (metal may affect bone density values). We will ask you to remove all jewelry.

PREGNANT WOMEN CANNOT PARTICIPATE IN A DXA SCAN. Prior to taking part in the scan, women will be asked to provide a urine sample to verify that they are not pregnant. The pregnancy test that we are using meets WHO guidelines for pregnancy testing, and can detect pregnancy within 1 week after conception. No pregnancy test is, however, 100% accurate, and there is always the possibility of an incorrect result. All results should be confirmed by your physician. You may choose not to undergo this test if you are pre-pubertal (no regular menstrual cycle), taking oral/injection contraceptives, post-menopausal (no menstrual cycle for ≥ 6 months), or if you have had a hysterectomy. All other women must undergo a pregnancy test.

Purpose and Time Commitment:

The purpose of the DXA scan is to assess body composition by quantifying bone, muscle, and fat mass. This information helps researchers to monitor changes in body composition over time. An experienced certified Medical X-Ray Technologist will be conducting the scan. The total time required to complete a total body scan is 20 minutes, including the time required to change into the gown, get positioned on the table and complete the scan. Women will be asked to provide a urine sample for a pregnancy test prior to the DXA scan, and thus the test may take up to 30 minutes.

Potential Benefits

After participating in this DXA scan, you will find out information about your body composition; that is – details about your lean body mass, fat mass and/or bone mass.

Potential Risks

The x-ray dose associated with a total body scan is very low and safe for repeated measurements. With the exception of pregnant women, there are no known risks associated with a DXA scan. The potential risks associated with radiation exposure to an unborn fetus are not known, and therefore we ask that you undergo a pregnancy test to verify that you are not pregnant. Having a DXA scan does not make it unsafe for you to have other x-rays taken in the near future.

Stopping the Test

You may ask the technologist to stop the test at any time without jeopardy to you.

Confidentiality

Your scan will be saved in our database using an identification number known only to the researcher for your study. The results of your scan will only be disclosed to the researcher for your study and will be saved in our database for one year.

DXA Scan: Body Composition Testing

Consent Form

Consent*: (Please circle your answers)*

Sex	**M**	**F**
Females: Are you pregnant?	**Yes**	**No**
Females: Do you agree to undergo a pregnancy test?	**Yes**	**No**

If No, circle reason: Pre-pubertal (no regular menstrual cycle)

Taking oral/injection contraceptives

Post-menopausal (no menstrual cycle for ≥ 6 months)

Hysterectomy

Have you had a barium test/exam in the last 2 weeks?	**Yes**	**No**
Have you had a nuclear medicine scan or injection of an X-ray dye in the past week?	**Yes**	**No**
Have you read and received a copy of the Information Sheet?	**Yes**	**No**
Do you understand the benefits and risks involved in taking part in this test?	**Yes**	**No**
Have you had an opportunity to ask questions and discuss testing procedures?	**Yes**	**No**
Do you understand that you can stop the DXA testing at any time and that you do not have to say why?	**Yes**	**No**
Has confidentiality been explained to you?	**Yes**	**No**

_____	_____
Date	**Date of Last Menstrual Period (If applicable)**
_____	_____
Name of Participant	**Signature of Participant**
_____	_____
Name of Witness	**Signature of Witness**
_____	_____
Name of Investigator	**Signature of Investigator**

APPENDIX C - Participant Information and Map for DXA Scan Appointment

Research Study

Sarcopenia screening and risk assessment in adults with osteoarthritis and obesity

DXA body scan preparation

Dual Energy X-Ray Absorptiometry (DXA) is a simple test that provides a very accurate measurement of the bone, muscle, and fat in your body. This test uses very low dose x-rays of two different levels to distinguish between bone and soft tissue. DXA is a painless, non-invasive test. The test requires that you put on a hospital gown and lie on an x-ray bed. The scan takes about 5 minutes and is very low dose radiation (equivalence to approximately 1 day of natural background radiation). This dosage is 1000 times less than the limit for trivial exposure, and is classified as a negligible dose according to the standards of the National Council of Radiation Protection and Measurement. This test will be conducted by a Medical X-ray Technologist. The total time required to complete a body scan is 20 minutes, including the time required to change into the gown, get positioned on the table, and complete the scan.

The DXA test will be completed at the University of Alberta Human Nutrition Research Unit (HNRU) in the Li Ka Shing Centre for Health Research Innovation. Parking is available directly outside the south side of the building. Do not pay for parking, instead **bring your license plate number up to the clinic** and we will arrange payment for parking costs.

Your appointment will be scheduled to provide time to complete any documentation required and get changed into a gown before the scan.

Your appointment is scheduled for: _____

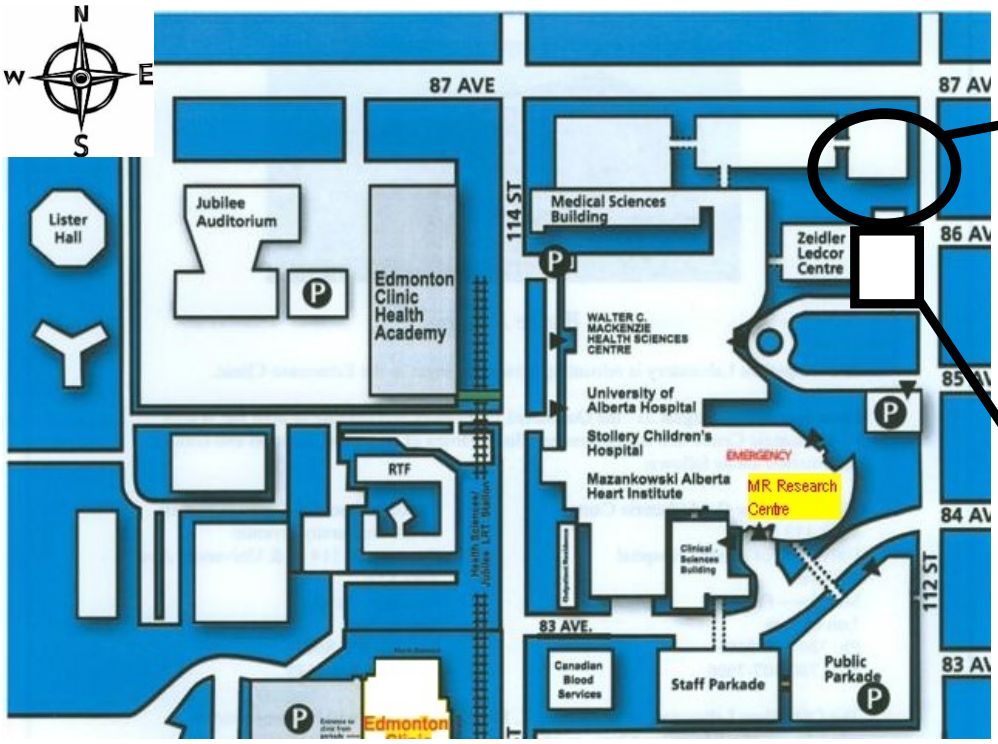
Address of HNRU: **2-004 Li Ka Shing Centre, 8602 - 112 Street, Edmonton, Alberta**

> The building can be accessed by taking 87 Avenue to 112 Street, and turning south onto 112 Street. Then turn right into the parking lot off of 112 St. The main entrance to the Li Ka Shing Centre is on 112 St, and there is a ramp to access the front door. Please take the elevator to the 2nd floor, where the HNRU is located. **A map and location of parking is provided on the back side of this page.**

Females should drink water ahead of time so you would be able to produce a urine sample for the pregnancy test if required. There will be washrooms available on site to use before your scan.

All metal will need to be removed for the scan (jewelry, watches, bobby pins, etc), so if possible, please leave excess jewelry at home on the day of the scan. If a certain jewelry item cannot be removed, then please let the technician know ahead of time.

Please contact our research team if you have any questions or concerns about your appointment.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Jubilee Auditorium
Edmonton Clinic Health Academy
114 ST
Medical Sciences Building
Zeidler Ledcor Centre
86 AV
WALTER C. MACKENZIE HEALTH SCIENCES CENTRE
University of Alberta Hospital
85 AV
Stollery Children's Hospital
EMERGENCY
Mazankowski Alberta Heart Institute
MR Research Centre
RTF
84 AV
Clinical Sciences Building
112 ST
83 AVE.
Canadian Blood Services
Staff Parkade
Public Parkade
83 AV
Edmonton

APPENDIX D - Participant Demographic Information Form

Sarcopenia screening in osteoarthritis

Study ID # ☐☐☐☐ Date ____/____/_____
dd mm yyyy

DEMOGRAPHICS

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

Marital Status (please check one)

☐ Never Legally Married ☐ Legally Married ☐ Separated

☐ Divorced ☐ Widowed ☐ Living with common law partner

Ethnicity (please check one)

☐ Aboriginal (First Nations/North American Indian, Metis, or Inuk/Inuit)

☐ White ☐ Black ☐ Filipino ☐ Latin American

☐ Chinese ☐ Korean ☐ Japanese ☐ Arab

☐ South Asian (e.g. East Asian, Pakistani, Sri Lankan, etc.)

☐ Southeast Asian (e.g. Vietnamese, Cambodian, Laotian, Thai, etc.)

☐ West Asian (e.g. Iranian, Afghan, etc.) ☐ Other, specify _____

Highest Level of Education (please check one)

☐ Less than high school ☐ High school diploma/equivalency certificate

☐ Registered apprentice certificate/diploma

☐ College or non-university certificate/diploma

☐ University certificate/diploma/degree

Current Employment Status (please check one)

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

☐ Unemployed ☐ On short-term disability ☐ On long-term disability

☐ Retired ☐ Other, specify _____

Average Household Yearly Income (please check one)

☐ Less than $10,000	☐ > $10,000	☐ > $15,000
☐ > $20,000	☐ > $25,000	☐ > $30,000
☐ > $35,000	☐ > $40,000	☐ > $45,000
☐ > $50,000	☐ > $60,000	☐ > $70,000
☐ > $80,000	☐ > $90,000	☐ > $100,000
☐ > $150,000	☐ > $200,000	☐ > $250,000

Living Arrangements (please check one)

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

If you are living with others, who are the other household members?

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

HEALTH BEHAVIOURS

Smoking status (please check one)

☐ Non-smoker

☐ Current smoker *(i.e. smoking within past 12 months)*

☐ Former smoker *(i.e. >100 cigarettes or 20 cigars in a lifetime)*

Alcohol Intake (please check one)

☐ 0 drinks/month ☐ 1-15 drinks/month ☐ > 15 drinks/month

WEIGHT HISTORY

What was your weight one year ago? _____ lbs or kg (circle)

☐ weight stable in past year ☐ weight gained in past year ☐ weight lost in past year

Were you trying to lose weight? Y N

If yes, what methods you were using (circle all that apply)?

- Ate less food (amount)
- Switched to foods with lower calories
- Ate less fat
- Ate fewer carbohydrates
- Exercised
- Skipped meals
- Ate "diet" foods or products
- Used a liquid diet formula such as Slimfast or Optifast
- Joined a weight loss program such as Weight Watchers, Jenny Craig, or TOPS
- Followed a special diet such as Atkins, South Beach, other high protein or low carbohydrate diets, cabbage soup diet, Body for Life
- Took diet pills prescribed by a doctor
- Took other pills, medicines, herbs or supplements not needing a prescription
- Started to smoke or began to smoke again
- Took laxatives or vomited
- Had weight loss surgery
- Drank a lot of water
- Ate more fruits, vegetables, salads
- Ate less sugar, candy, sweets
- Changed eating habits (didn't eat late at night, ate several small meals a day)
- Ate less junk food or fast food
- Other (specify) _____
- Don't know

How many times in your life have you lost 10 lbs or more because you were trying to lose weight?

- 1 to 2
- 3 to 5
- 6 to 10
- 11 times or more
- Never

How much did you weigh 10 years ago? (If don't know exact, what is best guess. If was pregnant, what was weight before pregnancy) _____lbs or kg (circle)

How much did you weigh at age 25? (If don't know exact, provide best guess)_____ lbs or kg (circle)

How tall were you at age 25? _____ ft/in or cm (circle)

What is the most you have ever weighed? (excluding pregnancy) _____lbs or kg (circle)

How old were you at that time? _____

Has your family doctor recommended weight loss to help your osteoarthritis? Yes No

MEDICAL CONDITIONS

Has a physician ever told you that you had:	Yes	No
Type I diabetes		
Type II diabetes		
Dyslipidemia		
Cardiovascular disease		
Heart failure		
Hypertension		
Chronic obstructive pulmonary disease (COPD)		
Liver disease (i.e. non-alcoholic fatty liver disease)		
Kidney disease		
Sleep apnea		
Cancer		
Polycystic ovarian syndrome (PCOS)		
Other *(specify)*		

Age at menopause (if occurred) _____
Have you taken hormone replacement therapy? (please check one)

☐ No ☐ Yes, currently ☐ Yes, previously

MEDICATIONS

Do you take prescription pain medication most days for osteoarthritis pain?

☐ No ☐ Yes, 1 medication ☐ Yes, more than 1 medication

Do you take over the counter pain medication most days for osteoarthritis pain (i.e. Tylenol)?

☐ No ☐ Yes, 1 medication ☐ Yes, more than 1 medication

List all currently prescribed medications (including statins):

_____

_____

APPENDIX E - Data Collection Form

Sarcopenia screening in osteoarthritis

Study ID # | | | | | Date of Testing ____/____/_____
dd mm yyyy

SURVEYS

Participant survey completed? Yes No

EQ-5D survey completed? Yes No

WOMAC survey completed? Yes No

ANTHROPOMETRICS

Weight _____kg Height_____cm BMI _____kg/m^2

Waist circumference _____cm _____cm _____cm Average : _____cm

Hip circumference _____cm _____cm _____cm Average : _____cm

PHYSICAL FUNCTION ASSESSMENT

Gait speed (over 4 metres)

1st attempt _____seconds 2nd attempt _____seconds

Walking assistive aids used? If so, list: _____

Grip strength

Dominant hand: Right ☐ Left ☐

1st attempt _____kg 2nd attempt _____kg 3rd attempt _____kg

Circle highest score

6 Minute Walk Test

# of full laps: _____

Partial distance: _____

Walking assistive aids used? If so, list: _____

DXA SCAN date and time booked _____

APPENDIX F - Western Ontario and McMaster Universities Osteoarthritis Index

The following questions concern the amount of pain you are currently experiencing in your knee(s). For each situation, please mark the amount of pain you have experienced in the past 48 hours.

How much pain do you have?	None	Mild	Moderate	Severe	Extreme
1. Walking on a flat surface	☐	☐	☐	☐	☐
2. Going up and down stairs	☐	☐	☐	☐	☐
3. At night while in bed	☐	☐	☐	☐	☐
4. Sitting or lying	☐	☐	☐	☐	☐
5. Standing upright	☐	☐	☐	☐	☐

For the next questions, think about the stiffness (not pain) you have had in your knee(s) in the past 48 hours. Stiffness is a sensation of decreased ease in moving your joint.

Stiffness	None	Mild	Moderate	Severe	Extreme
6. How severe is your stiffness after first awakening in the morning?	☐	☐	☐	☐	☐
7. How severe is your stiffness after sitting, lying or resting in the day?	☐	☐	☐	☐	☐

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the past 48 hours due to your knee(s).

How much difficulty do you have?	None	Mild	Moderate	Severe	Extreme
8. Descending stairs	☐	☐	☐	☐	☐
9. Ascending stairs	☐	☐	☐	☐	☐
10. Rising from sitting	☐	☐	☐	☐	☐
11. Standing	☐	☐	☐	☐	☐
12. Bending to the floor	☐	☐	☐	☐	☐
13. Walking on flat surfaces	☐	☐	☐	☐	☐
14. Getting in and out of a car/bus	☐	☐	☐	☐	☐
15. Going shopping	☐	☐	☐	☐	☐
16. Putting on socks/stockings	☐	☐	☐	☐	☐
17. Rising from the bed	☐	☐	☐	☐	☐
18. Taking off socks/stockings	☐	☐	☐	☐	☐
19. Lying in bed	☐	☐	☐	☐	☐
20. Getting in or out of the bath	☐	☐	☐	☐	☐
21. Sitting	☐	☐	☐	☐	☐
22. Getting on or off the toilet	☐	☐	☐	☐	☐
23. Performing heavy domestic duties (lawn mowing, lifting heavy items)	☐	☐	☐	☐	☐
24. Performing light domestic duties (tidying a room, dusting, cooking)	☐	☐	☐	☐	☐

APPENDIX G - EuroQol Foundation EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐