Evaluating the associations between physical performance and muscle and bone health outcomes in individuals with severe obesity with and without diabetes

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Abstract

Background: Individuals with severe obesity and type 2 diabetes (T2D) are at higher risk of falls and fractures despite having a normal or higher bone mineral density (BMD). Muscle strength and muscle-related force production can protect against falls and fractures by increasing functional mobility and bone strength. However, data comparing the associations between physical performance and indices of muscle and bone health in severe obesity with and without T2D are lacking.

Purpose: The objective of this thesis project is to describe and compare the associations between physical performance and muscle and bone parameters in pre-bariatric obese adults with and without T2D.

Methods: We recruited men and women with severe obesity (age ≥18 y, BMI >35 kg/m^2) for one-time measures. Total volumetric BMD (vBMD) at the total hip, femoral neck, and radius and cross-sectional analysis of soft tissues were determined using quantitative computed tomography (QCT). Areal BMD at the total hip, femoral neck, and lumbar spine was determined using dual-energy X-ray absorptiometry. Handgrip and knee extensor isometric muscle strength were measured using validated dynamometer protocols. Functional mobility, balance, and aerobic capacity were assessed through the Timed Up and Go, Fullerton Advanced Balance, and 6-minute walk tests, respectively. Physical activity levels were determined using accelerometers and the International Physical Activity Questionnaire. Pearson/Spearman correlations between physical performance and muscle and bone parameters were performed. Independent t-tests were used to compare these outcomes in participants with and without T2D.

Results: Thirty-three participants were included (79% female, 44±4 years, BMI 40.4±4kg/m^2, percent body fat 49.4±4%, 30% had ≥1 fall in the past year, and 50% had a diagnosis of T2D).

A modest inverse correlation was found between Timed Up and Go test time and femoral neck vBMD ($r=-0.415$, $p=0.02$), but not with total hip. Significant positive correlations were observed between knee extensor and handgrip strength and femoral neck vBMD ($r=0.447$, $p=0.015$ and $r=0.361$, $p=0.046$, respectively), but not at the total hip. Knee extensor and handgrip strength were positively associated with upper thigh muscle and intramuscular fat area ($r=0.442$-0.790, $p<0.05$), with no additional associations observed with other soft tissue composition parameters. No significant correlations were found between accelerometer-measured physical activity levels and any bone and muscle variables. No significant differences between groups were observed for muscle, bone, physical performance, or physical activity measures.

Conclusions: Our results suggest that functional mobility and muscle strength may be more strongly associated with muscle and bone parameters than aerobic capacity/balance tests and physical activity levels in individuals with severe obesity and T2D. Further analysis is required into the independent and combined influence of severe obesity and T2D on the functional muscle-bone relationship.

Résumé

Contexte: Les personnes souffrant d'obésité sévère et de diabète de type 2 (DT2) présentent un risque plus élevé de chutes et de fractures malgré une densité minérale osseuse (DMO) normale ou supérieure. La force musculaire et la production de force liée aux muscles peuvent protéger contre les chutes et les fractures en augmentant la mobilité fonctionnelle et la solidité des os. Cependant, les données comparant les associations entre la performance physique et les indices de santé musculaire et osseuse dans l'obésité sévère avec et sans DT2 manquent.

Objectif: L'objectif de ce projet de thèse est de décrire et de comparer les associations entre la performance physique et les paramètres musculaires et osseux chez des adultes obèses pré-bariatriques avec et sans T2D.

Méthodes: Nous avons recruté des hommes et des femmes présentant une obésité sévère (âge ≥18 ans, IMC >35 kg/m2) pour des mesures ponctuelles. La DMO volumétrique totale (DMOv) au niveau de la hanche totale, du col du fémur et du radius et l'analyse transversale des tissus mous ont été déterminées par tomographie quantitative par ordinateur (QCT). La DMO aréolaire au niveau de la hanche totale, du col du fémur et de la colonne lombaire a été déterminée par absorptiométrie à rayons X à double énergie. La force musculaire isométrique de la poignée de main et de l'extenseur du genou a été mesurée à l'aide de protocoles dynamométriques validés. La mobilité fonctionnelle, l'équilibre et la capacité aérobique ont été évalués respectivement par les tests Timed Up and Go, Fullerton Advanced Balance et le test de marche de 6 minutes. Les niveaux d'activité physique ont été déterminés à l'aide d'accéléromètres et du questionnaire international sur l'activité physique. Des corrélations Pearson/Spearman entre la performance physique et les paramètres musculaires et osseux ont été réalisées. Des tests t indépendants ont été utilisés pour comparer ces résultats chez les participants avec et sans DT2.

Résultats: Trente-trois participants ont été inclus (79 % de femmes, 44±4 ans, IMC 40,4±4kg/m2, pourcentage de graisse corporelle 49,4±4 %, 30 % avaient ≥1 chute au cours de la dernière année, et 50 % avaient un diagnostic de DT2). Une corrélation inverse modeste a été trouvée entre le temps du test Timed Up and Go et la vBMD du col du fémur (r=-0,415, p=0,02), mais pas avec la hanche totale. Des corrélations positives significatives ont été observées entre la force d'extension du genou et la force de préhension manuelle et le vBMD du col du fémur (r=0,447, p=0,015 et r=0,361, p=0,046, respectivement), mais pas au niveau de la hanche totale. La force d'extension du genou et la force de préhension étaient positivement associées aux muscles de la cuisse supérieure et à la surface de graisse intramusculaire (r=0,442-0,790, p<0,05), sans qu'aucune autre association ne soit observée avec d'autres paramètres de composition des tissus mous. Aucune corrélation significative n'a été trouvée entre les niveaux d'activité physique mesurés par accéléromètre et les variables osseuses et musculaires. Aucune différence significative entre les groupes n'a été observée pour les mesures des muscles, des os, de la performance physique ou de l'activité physique.

Conclusion: Nos résultats suggèrent que la mobilité fonctionnelle et la force musculaire peuvent être plus fortement associées aux paramètres musculaires et osseux que les tests de capacité aérobique/équilibre et les niveaux d'activité physique chez les personnes souffrant d'obésité sévère et de DT2. Des analyses supplémentaires sont nécessaires pour déterminer l'influence indépendante et combinée de l'obésité sévère et du DT2 sur la relation fonctionnelle muscle-os.

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Contribution of Authors

Alessandra Amato: Completed the data acquisition, analysis, and interpretation of data, and wrote the original draft and revised work for important intellect content.

Jenna C. Gibbs: Supervision, conception, design, analysis, and interpretation of data, and revised work for important intellect content

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Chapter 1: Executive Summary

Osteoporotic fractures are a major public health concern, and contribute to functional disability, excess morbidity and mortality, and substantial health care costs in Canada's increasingly obese and aging population. In Canada alone, 1.5 million individuals over the age of 40 have been diagnosed with osteoporosis, with women four times more likely to receive a diagnosis than men. (1) Obesity is a chronic disease in which excessive body fat accumulates causing negative health outcomes. Currently 25% of Canadian adults are obese and this number is growing at an unprecedented rate. (2) Obesity is the most important risk factor for type 2 diabetes (T2D), and T2D is up to 20 times more likely in those with a body mass index (BMI) >35 kg/m^2. (3) In adults with obesity, the risk of some fractures, such as humerus, femur, and ankle, is higher and increment central and visceral adiposity can have negative effects on bone health through pro-inflammatory cytokine pathways and intramuscular fat infiltration. (4-7) Further, individuals with severe obesity often present with muscle weakness, poor posture, and mobility and balance limitations, leading to a higher risk of falls and fractures. (8, 9) Although osteoporosis occurs in all populations, individuals with severe obesity and its comorbidities (T2D, metabolic syndrome) are at a higher risk of fracture despite having normal or higher bone mineral density (BMD). (10)

One in three Canadians have been diagnosed with diabetes or prediabetes and this number is expected to double in the next 15 years. (11) The mechanisms underlying bone fragility in diabetes mellitus are complex, and likely multifactorial. (3) They include low bone turnover, trabecular and cortical bone deterioration, and an accumulation of advanced glycation end products. (12-15) Collectively, these factors lead to deficits in bone strength and increased fracture risk. Increased frequency of falls secondary to diabetic complications, such as poor

muscle strength and neuropathy, also contribute to an increased fracture risk. (12, 16-18) According to the functional muscle-bone unit theory, muscle forces have a positive effect on bone strength by applying strains to stimulate bone formation, subsequently contributing to the regulation of BMD and bone structure. (19) Therefore, muscle strength and physical performance may represent modifiable targets for reducing bone fragility in individuals with T2D.

Currently, there are no data examining the muscle and bone quality determinants in severe obesity with and without T2D, and it is unclear whether T2D exacerbates obesity-related musculoskeletal declines. Further, we have a limited understanding of the modifiable targets for reducing fall and fracture risk in high-risk populations (severe obesity, T2D). This study is particularly novel as we are evaluating the muscle and bone as a unit using advanced imaging technology at fracture-prone sites. When people with severe obesity and T2D are measured by dual energy X-ray absorptiometry (DXA), they typically have a normal-to-high BMD, yet they are still at high risk of fracture. Recent advances in imaging technology enable the measurements of three-dimensional bone parameters as well as soft tissue composition (muscle, fat) using quantitative computed tomography (QCT), which may better explain fracture risk differences in individuals with severe obesity and T2D compared to those without these high-risk conditions. From this, we will identify relevant physical performance and physical activity-related factors to inform the design of a multimodal exercise intervention targeting muscle and bone outcomes important for fall and fracture prevention in severe obesity and T2D. Furthermore, our results will be used as pilot data for future larger investigations to develop and evaluate the potential efficacy of a prehabilitation exercise intervention to improve muscle and bone health after bariatric surgery. Therefore, the two main objectives of the proposed thesis are to examine the

associations between physical performance and muscle and bone quality outcomes, and to compare muscle and bone parameters in individuals with severe obesity with and without T2D.

Chapter 2: Literature Review

2.1 Burden of Osteoporotic Fractures

Osteoporosis is a systemic disease of the skeleton characterized by a low areal bone mineral density (aBMD) (2.5 standard deviations or more below the average value for a young healthy population) and a microarchitectural deterioration of bone tissue. (20) In Canada alone, 1.5 million people over the age of 40 have been diagnosed with osteoporosis, with women being four times more likely to receive an osteoporosis diagnosis than men. (1) Osteoporosis is a major public health concern primarily through its association with an increased risk of fragility fractures. A fragility fracture occurs with minimal or no identifiable trauma, such as a fall from standing height, and most commonly occurs at the wrist, spine, and hip. (21) The incidence of other fractures (non-hip, non-vertebral) are also highly prevalent and collectively, fragility fractures present with significant health and economic burden worldwide. (22, 23) Osteoporotic fractures become increasingly common in women after age 55 years and men after 65 years, resulting in substantial bone-related morbidity, functional decline, reduced quality of life, hospitalization, and even death. (1, 24-26) Seventy percent of all hospital admissions and hospitalized days are linked to fractures in women, with 81% of these fractures being attributed to osteoporosis. (27) Hip fractures alone account for half of these hospitalized days. (28) As of 2011, the costs associated with osteoporotic fractures, including emergency room visits, hospitalizations, same day surgeries, rehabilitation, and continuing care, exceeded $4.6 billion. (27, 28) With an increasingly aging population, the incidence of osteoporotic fractures and resulting complications will continue to rise, increasing the severity of the health and economic burden.

2.2 Risk Factors for Osteoporotic Fractures

Bone mass increases steadily during childhood and even more markedly during adolescence with >95% of the adult skeleton being formed. (29) Once peak bone mass is achieved around age 20, age-related declines in aBMD are approximately 1%-2% per year starting as early as age 30 and lead to the highest risk of fracture in older age. Primary aging, particularly in women, is associated with bone loss and deterioration of bone microarchitecture due to an increased rate of bone remodeling in both trabecular and cortical bone alongside a negative bone balance (higher bone resorption relative to bone formation). Additionally, there is an age-related thinning and loss of density in trabecular bone combined with reduced cortical thickness and increased cortical porosity. (30, 31) In women, during menopause, there is an accelerated loss of aBMD (1.6% and 1% loss per year at the spine and total hip during menopause; and 2% and 1.4% loss per year at the spine and total hip postmenopause) due to the cessation of ovarian steroid production, particularly estrogen. (32) Estrogen maintains bone mass by suppressing bone turnover and balancing the rates of bone formation and resorption. (33) In men, age-associated reductions in bone formation and low bone turnover are observed; usually presenting as a more gradual pattern of bone loss with aging compared to women.

Areal bone mineral density (aBMD), which is usually measured with dual-energy X-ray absorptiometry (DXA) in clinical practice, is a strong predictor of fracture risk. Fracture risk increases up to two times for every one standard deviation reduction in aBMD. (34) Thus, the majority of fracture risk assessment algorithms involve a DXA-based aBMD measurement. However, most fractures occur in individuals that do not meet the conventional diagnostic criteria for osteoporosis (aBMD T-score -2.5 or lower) and aBMD alone presents with low sensitivity during osteoporosis screening. (35) Many well-documented clinical risk factors for

osteoporotic fractures have been identified and are associated with fracture risk independent of aBMD, including age, sex, weight, height, previous fracture, parental fracture history, current smoking, oral glucocorticoid medication use, rheumatoid arthritis, secondary osteoporosis, and alcohol overconsumption. (36) The Fracture Risk Assessment Tool (FRAX) provides an accurate estimates of the 10-year probability of a major osteoporotic fracture and is used to classify patients into low, moderate, and high fracture risk categories. This stratified approach to risk assessment has been well-supported by evidence from several population-based, longitudinal studies. A large prospective study by Cummings et al. (20) followed 9516 white women over the age of 65 and revealed that multiple risk factors, regardless of baseline aBMD, resulted in an increased risk of fracture. However, those with low aBMD were at an especially high risk of hip fracture. (20) Espallargues et al. (37) further classified the risk factors into groups according to their strength of association with fracture: high risk, moderate risk, and no risk or protective. Similarly, a meta-analysis by Kanis et al. (38) demonstrated that the combination of clinical risk factors and aBMD provides more specific and sensitive predictions of hip and other osteoporotic fractures than the clinical risk factors alone. Following fracture risk assessment, individuals identified at moderate-to-high fracture risk are considered for treatment, while those with a low fracture risk are usually managed without medication. Screening of aBMD is recommended at age 65 years in all men and women, and treatment is advised based on osteoporosis aBMD T-score or in those with low aBMD (osteopenia) (T-score between -1 and -2.5), based on aBMD and a high fracture risk estimated from FRAX or another validated fracture risk assessment tool. (Scientific Advisory Council of Osteoporosis Canada, 2011)

2.3 Overview of Bone and Muscle Quality and Physical Performance Concepts

Bone quality is a term that encompasses both the material and structural properties of bone (including bone material composition, cellular activity, microarchitecture, geometry, and strength) and was operationalized herein to include advanced imaging-based measures of bone mass, structure, and strength. BMD or bone mass is commonly measured in clinical and research settings by DXA at the lumbar spine and hip and by QCT at the lumbar spine, femur, radius, and tibia. aBMD by DXA is defined as the BMC in the total area of bone and is considered less accurate and representative of true fracture risk than vBMD by QCT. vBMD is the total BMC in the volume of measured bone determined by QCT. QCT is an advanced imaging technique that provides a three-dimensional measurement of bone parameters at central and peripheral sites (spine, radius, tibia, femur) and discriminates between cortical and trabecular vBMD and bone microarchitecture. Factors related to microarchitecture include the cortical (thickness, area, vBMD) and trabecular compartments of bone (trabecular thickness, area, and vBMD). Bone strength is another important consideration for assessing bone health and fracture risk and can be estimated using QCT-based finite element analysis. Bone strength is the maximal amount of load tolerated before failure occurs and this can be calculated through mathematical models from QCT scans. (39) Although not a primary focus of this thesis, bone turnover is an important contributor to bone quality as it dictates the bone mass and BMD and can be evaluated by measuring circulating levels of the biochemical markers of bone formation (e.g., osteocalcin, procollagen type 1 N-terminal propeptide – P1NP) and resorption (C-telopeptide) or histomorphometry. Adaptive remodelling can even compensate for abnormalities in of bone quality, such as deficits in bone microarchitecture or geometry, which are commonly observed in obese and T2D populations. (40)

Muscle quality represents both the morphological and functional properties of skeletal muscle. In additional to its evaluation of bone quality parameters, QCT also provides an assessment of muscle cross-sectional area and density (expressed as attenuation values) at the previously mentioned sites. Muscle strength represents a clinically relevant measure of functional performance in obese and T2D populations. (41) Knee extensor strength is commonly measured using validated dynamometer protocols with well-established test-retest reliability and ability to predict the risk of falls and fractures. (42) Validated hand grip tests using the Jamar or similar hydraulic dynamometer have excellent test-retest reproducibility and reliability. (41) Hand grip strength, a correlate of general muscle strength, has also been shown to predict those at risk of sarcopenia, mobility limitations, falls, and fractures. (43-45)

Performance tests can be used to assess aerobic capacity, mobility, balance, and physical function and predict the incidence of future falls and fractures. TUG is a clinical measure of lower extremity function, mobility, and fall risk and has been recently shown to predict BMD and fracture risk. (46, 47) TUG performance correlates well with gait speed and is a sensitive and specific measure for identifying individuals who are at risk for falls. (48, 49) A TUG time over 13.5 seconds in community dwelling adults indicates an increased fall risk. (49) The Fullerton Advanced Balance Scale (FAB) is a reliable and valid assessment tool, which is suitable for use with functionally independent young and older adults. The FAB tests multiple dimensions of balance and can identify balance problems and falls risk, particularly in older adults. (50, 51) Finally, the 6-minute walk test is an inexpensive and validated tool to estimate submaximal aerobic exercise capacity in clinical populations. (52) For the 6MWT, participants walk up and down a 30-metre track and try to cover as much distance as possible within 6 minutes. BMI is

typically negatively associated with 6MWT distance. (53) The 6MWT is also sensitive to change after weight loss induced by medical treatment or bariatric surgery. (54, 55)

2.4 Obesity: An Overview

Obesity is a chronic disease in which excessive body fat is accumulated to the extent that there are negative health outcomes. Obesity is diagnosed in the presence of a body mass index (BMI) of 30 kg/m^2 or higher. Like osteoporosis, the proportion of adults classified as having obesity has increased at an unprecedented rate over the past 25 years, and currently 25% of Canadian adults are obese. (2) The dramatic increase in obesity can be attributed to changes in eating patterns, less physically demanding work, increased use of automated transport, and increasily sedentary lifestyles. (56) Obesity is a risk factor for numerous chronic diseases including hypertension, type 2 diabetes (T2D), sleep apnea and other breathing problems, and some cancers. (56) There is also an increased risk of falls and functional disability as a consequence of obesity. Rosenblatt et al. (57) found that in 88 community-dwelling women, aged 55 years and older, women with obesity were less likely to recovery due to an instability, such as tripping, resulting in an increased fall rate. Obesity is differentiated into three BMI classes based on fat accumlation to better categorize health risks. Class I obesity is a BMI between 30.0 and 34.9 kg/m^2, Class II obesity is a BMI between 35.0 and 39.9 kg/m^2 (severe obesity), and Class III is a BMI of 40 kg/m^2 and higher (extreme/morbid obesity). (58) Individual disease risk can be further classified with the addition of waist circumference (WC) measures, with a higher WC equating to higher risk of morbidity and mortality. (58)

2.4.1 Obesity and Bone Quality

The positive relationship between body mass and bone size has been well-documented, with substantial evidence in support of positive bone mass adaptations to applied mechanical loading

forces. (59) A possible mechanism for this increased aBMD in people with obesity is the increased passive loading and muscle-induced mechanical strain due to a higher body mass, particularly a higher fat mass. (60) Regardless of age, obese individuals tend to have a higher aBMD, higher cortical and trabecular volumetric BMD (vBMD), and greater trabecular number, particularly at weight bearing sites, compared to nonobese individuals, suggesting a chronic overload stimulus linked to higher absolute bone size and mass. (61-63) Evidence from HR-pQCT studies suggest finite element analysis-derived bone strength is higher in adults living with obesity versus normal-weight controls. (62) The protective effect of obesity on fracture risk, particularly hip fractures, was further justified by the greater soft-tissue thickness over the hip region in obese individuals, which can provide shock absorption of fall-related impact. (64)

Contrary to traditional understanding, obesity is not protective against fracture and higher fat mass can be detrimental to bone and muscle health, leading to a higher risk of falls and fractures. (4) Accumulating evidence suggests an inverse and nonlinear relationship exists between BMI and aBMD, with the lowest aBMD values observed at the BMI extremes (i.e., <15 kg/m^2 and >30 kg/m^2). (65, 66) Although the risk of osteoporotic fractures is highest in underweight individuals, most osteoporotic fractures occur in people with obesity, suggesting an even greater morbidity lies within this subset of the population. (66) In adults with obesity, prior evidence suggests that the relationship between fracture and BMI is site-specific. Although most findings show a lower risk of hip and vertebral fractures in obese adults, the risk of non-vertebral fractures is higher (odds ratios = 1.3-1.7), including proximal humerus, upper leg, and ankle fractures. (5, 8, 67) Alternatively, several studies have shown that obesity is more consistently associated with an increased prevalence of vertebral fracture when visceral adipose tissue (VAT) is accounted for, especially in women. (68, 69) BMI and WC are commonly used surrogate

measures of adiposity in clinical settings. (70) Yet, BMI is more strongly associated with nonabdominal and abdominal subcutaneous fat; whereas WC is a more reliable predictor of VAT. (70) Luo and Lee (71) found that WC, but not BMI, was associated with an increased risk of vertebral fracture in men but both WC and BMI did not influence fracture incidence in women. However, VAT and trunk fat mass were negatively associated with vertebral body BMD and geometry in both men and women but still not related to vertebral fracture risk. Therefore, there is a need to better understand the negative effects of obesity on fracture risk, particularly the mechanisms of action of whole-body and regional fat mass on bone.

Growing evidence supports that higher fat mass is detrimental to musculoskeletal health, due to its associations with impaired bone microarchitecture and strength. (8) Many DXA, pQCT, and HR-pQCT studies have been conducted to assess the relationship between fat mass and bone parameters. However, the relationship between fat mass and indices of bone quality is inconclusive with conflicting evidence demonstrating positive, negative, and no correlations. (72-76) In a cross-sectional study of 189 postmenopausal women, Sornay-Rendu et al. (63) found better bone quality parameters including higher total and trabecular vBMD, greater cortical thickness, greater trabecular number, and greater bone strength at the radius and tibia in the obese group versus the normal-weight group. However, after normalizing values for individual body mass, these HRpQCT parameters were relatively lower in the obese women compared to the normal-weight women. (63) In a cross-sectional study in 8833 men and women aged 18-65 years, Zhang et al. (77) demonstrated that VAT is inversely correlated with vertebral trabecular and cortical BMD, even after adjusting for BMI and age. Recent evidence by Edwards et al. (78) showed that fat mass and lean mass may in fact have differing associations with HR-pQCT-measured bone structure variables at the distal radius and tibia in men and women from

the Hertfordshire Cohort Study. Specifically, their findings suggest that fat mass index (fat mass/BMI) was independently associated with trabecular bone structure, whereas lean mass index (lean mass/BMI) was independently associated with cortical geometry. Furthermore, adults with higher fat mass, especially older individuals, have been shown to present with higher vertebral bone marrow fat, which has been linked to lower trabecular vBMD at the lumbar spine and prevalent vertebral fracture. (79) Therefore, the higher absolute BMD, trabecular and cortical microarchitecture, and strength indices associated with obesity may not necessarily reflect favourable bone quality and protection against fracture in adults with obesity.

The pathophysiological association between obesity and bone is complex, and likely explained by abnormal circulating levels of pro-inflammatory cytokines (interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a), and C-reactive protein (CRP)), leptin, and adiponectin released from VAT. (7) Obese individuals demonstrate higher levels of TNF-a in adipose tissue than lean individuals. (80) Circulating TNF-a and IL-6 activate osteoclast differentiation and increase bone resorption. (33) Adipokines (leptin, adiponectin) regulate inflammatory response, energy balance, and substrate metabolism, and demonstrate dysregulation with increasing abdominal obesity. Leptin is increased in obesity and has been shown to stimulate inflammatory responses in humans. (81) In contrast, adiponectin acts as an anti-inflammatory cytokine and plasma adiponectin concentrations are typically lower in obese individuals compared to non-obese individuals. (82, 83) Adiponectin receptors are expressed on osteoblasts and decrease osteoprotegerin expression and increase osteoclast activity. (84) Since an independent inverse association exists between adiponectin and aBMD, adiponectin is thought to be a negative regulator of bone metabolism. (85-88) Therefore, the negative effects of obesity on bone quality

are thought to be associated with low-grade chronic inflammation and adverse hormonal changes in the presence of higher fat mass and VAT, possibly leading to higher fracture risk. (89-91)

2.4.2 Obesity and Muscle Quality

Obesity has deleterious effects to skeletal muscle and its quality. People with obesity typically have greater absolute muscle strength, however, when adjusted for body mass, relative muscle strength is lower, suggesting that a higher fat mass may act as a chronic stimulus on antigravity muscles. (92) Tomlinson et al. (92) assessed the relationship between BMI, adiposity, and skeletal muscle isometric force production in 94 untrained women aged 18-49 years and found that obese individuals were significantly weaker than non-obese individuals when BMI was accounted for. Higher inter- and intramuscular adipose tissue infiltration, particularly at the thigh, is commonly observed in people with overweight and obesity and independently predicts lower physical function and increased falls risk (93, 94). In a study of 2627 men and women aged 70-79 years (mean BMI = 27 kg/m^2), Goodpaster et al. (95) reported positive associations between muscle attenuation (a surrogate measure of muscle density) and each of muscle cross-sectional area at the mid-thigh and voluntary isokinetic knee extensor strength. Additionally, higher knee extensor muscle attenuation values remained associated with higher muscle strength after adjustment for muscle cross-sectional area. (95) Scott et al. (96) found that greater calf muscle density measured by pQCT was a significant predictor of physical function, independent of insulin resistance, VAT, or inflammation, in 85 overweight and obese older adults. Knee extensor and hand grip strength tests have also been shown to predict clinically relevant musculoskeletal outcomes in people with obesity. Substantial evidence supports the inverse relationship between isometric and isokinetic knee extensor strength and muscle fat infiltration, reflecting the reduction in maximal voluntary contraction and force generating capacity of

skeletal muscle in the presence of obesity. (42, 97) However, the relationships between BMI and grip strength have been inconsistently reported. Meta-analysis results from several population-based cohorts found higher grip strength with increasing BMI in men, but no significant difference in grip strength across BMI categories in women. In contrast, Rolland et al. (98) reported that obese postmenopausal women did not differ from non-obese women in terms of hand grip or knee extension strength, except for a subset of physically active participants who performed better than both obese and non-obese women. Thus, indices of muscle quality (muscle attenuation values, relative muscle strength) are likely more indicative of muscle health and function in obese individuals and may represent important intervention targets to improve physical performance in this population.

2.4.3. Obesity and Physical Performance

Beyond its effects on skeletal muscle size and strength, obesity is associated with deficits in physical performance, static and dynamic balance, and mobility, which may lead to functional disability and a greater risk of falling. (9) In a study by Fjeldstad et al. (99), 25% of obese participants reported a history of falls versus only 15% of their normal-weight counterparts. Evidence from experimental and observational studies support that obese individuals are also at a significantly greater risk of experiencing an injurious fall including fractures, sprains, and dislocations. (100-102) Results from a cross-sectional, population-based study by Finkelstein et al. (100) revealed that individuals in Class III obesity category (BMI>40 kg/m^2) were 48% more likely to report an injurious fall compared to those without Class III obesity. Excess BMI and fat mass can affect functional mobility and balance during basic activities of daily living, such as gait alterations, postural instability, and greater risk of falling. (103-108) Similarly, Pataky et al. reported slower gait speeds, with shorter stride lengths, poorer sit-to-stand performance, and

endurance in obese versus non-obese women. (109) Obesity also negatively affects balance control. Hue et al. (110) studied the contribution of body weight to predict force plate measures of balance in 59 men aged 24-61 years. Their findings demonstrated that body weight accounts for 52% and 54% of the variance in balance with or without vision, respectively. (110) Greve et al. (107) demonstrated that higher BMI is associated with more displacements to maintain postural balance measured using a Biodex balance system in younger men. Many studies also confirm the detrimental influence of obesity on functional mobility assessed by performance-based measures, including the Timed Up and Go (TUG), repeated chair stand, and six-minute walk tests (6MWT). (48, 49, 111) In a study by Hergenroeder et al. (111), participants with severe obesity had the lowest levels of mobility on the TUG, timed balance, 6MWT, and timed chair stand tests followed by obese, overweight, and normal-weight participants. Hulens et al. (112) compared submaximal aerobic capacity via the 6MWT in lean, obese, and morbidly obese women and reported that the obese and morbidly obese groups walked on average only 81.9% (131 metres) and 74.9% (183 metres) of the distance of the lean women and had a higher perceived exertion. Recently, the combination of obesity and dynapenia (low muscle strength and power) has shown significant associations with longer TUG time and decreased 6MWT distance, sit-to-stand performance, reaction time, and postural balance in middle-aged and older adults, particularly those with abdominal obesity. (113-115) Therefore, the relationships between dynapenic obesity, functional mobility, and balance are likely stronger than those observed for obesity or dynapenia alone, further emphasizing the importance of targeting muscle quality to prevent functional declines in severe obesity.

2.5 Diabetes: An Overview

Today, 1 in 3 Canadians are diagnosed with diabetes or prediabetes, with the total number of cases expected to double by 2035. (11) Diabetes is a metabolic disorder characterized by the presence of hyperglycemia due to impaired insulin secretion, defective insulin action, or both. (116) Obesity is the most important risk factor for T2D, and T2D is up to 20 times more likely in those with a BMI greater than 35 kg/m^2. (56) Chronic hyperglycemia is associated with long-term microvascular complications of the eyes, kidneys, and nerves, and often leads to an increased risk of stroke, heart disease, nerve damage, amputations, and kidney failure. Bone fragility (osteoporosis, fractures), poor muscle quality, and functional disability are often overlooked as chronic complications of diabetes.

2.5.1 Diabetes and Bone Quality

The mechanisms underlying bone fragility in diabetes mellitus are complex, and likely multifactorial, including low bone turnover, accumulation of advanced glycation end-products (AGEs), insulin resistance, antidiabetic medication, and declines in muscle quality. (12-15, 117-121) Individuals with type 1 (T1D) and type 2 diabetes (T2D) are at a higher risk of fracture compared to the general population. Meta-analysis results show individuals with T1D and T2D are at a 6- and 2-fold higher risk of hip fractures (RR = 6.3 and 1.7, respectively), whereas aBMD is increased or normal in T2D and decreased in T1D. (122, 123) Population-based studies demonstrate a greater loss of aBMD at the femoral neck and total hip in patients with T2D and for increasing BMI category. (124, 125) Interestingly, aBMD only partially accounts for the excess risk of fracture in diabetes, especially when disease duration is greater than 10 years. (126, 127) Further, diabetic complications (e.g., hypoglycemia, neuropathy, retinopathy) may be responsible for increased fracture risk through an increased fall frequency. (119, 120, 128-130)

Despite consistent reports of higher or normal aBMD in T2D, advanced imaging studies reveal substantial deterioration in bone quality and strength that may contribute to bone fragility in diabetic populations. Evidence in postmenopausal women with T2D demonstrates deficits in cortical bone quality and greater holes in trabecular bone. (12, 117) Particularly, postmenopausal women with T2D and a history of fragility fracture had increased cortical porosity at the distal radius and tibia than nonfractured women with T2D as assessed by HRpQCT. (12) Meta-analyses have shown low bone turnover in people with T2D compared to those without T2D, which is often characterized by reduced markers of bone resorption and formation (3, 131, 132) Specifically, lower levels of osteocalcin, a common marker of bone formation, have been observed in diabetic individuals compared to nondiabetic controls, even when adjusted for lumbar spine and femoral neck aBMD. (131, 133) In individuals with T2D, there is a lower bone formation rate on cancellous, intracortical, and endocortical surfaces alongside reduced mineralized surface area, osteoid volume and thickness, number of osteoclasts, and mineral apposition rate, which contribute to greater cortical bone porosity and larger spacing in trabecular bone. (12, 117, 134) Due to the increasing life expectancy of individuals with T2D, age-related decline in osteoblast function and aBMD will further contribute to the pathogenesis of bone fragility and recurrent fractures in this population. (135)

Hyperglycemia represents a key pathophysiological factor contributing to poor bone health in T2D. Chronic hyperglycemia has been shown to down-regulate the expression of the osteocalcin gene and generate a higher concentration of AGEs in collagen, which may reduce bone material strength. (136, 137) AGEs are modifications of proteins or lipids that become glycated with exposure to sugars under certain pathological conditions, such as oxidative stress due to hyperglycemia. T2D results in greater production of AGEs in human tissues, including

skin, muscle, bone, blood vessels, and the brain. (60, 138, 139) While the exact mechanisms explaining poor bone quality in T2D are unclear, AGEs accumulation have been shown to enhance pro-inflammatory cytokine pathways, resulting in chronic inflammation, impaired bone turnover, reduced bone material properties, and lower muscle mass and strength. (14, 140, 141) Higher circulating AGEs have been associated with an increased risk of fracture in T2D, independently of aBMD. (127, 142) Leslie et al. (143) reported on the negative association between circulating AGEs and bone material strength and even abnormal biomechanical properties of cortical and cancellous bone. Thus, elevated AGEs are possibly an important contributing factor to the observed deficits in bone quality in individuals with T2D.

Antidiabetic medications are also known to interfere with bone quality and fracture risk. Prior evidence supports that metformin and sulfonylureas have no or slightly protective effects on fracture. (144) Metformin is believed to stimulate bone formation by increasing osteoblast activity and inhibiting bone resorption. (145) However, the direct effects of sulphonylureas and thiazolidinediones (TZDs) on bone are not well-understood. (118, 146) Current use of sulphonylureas, but not past use, is associated with an increased risk of hip fracture. (147) TZDs act to decrease insulin resistance and promotes differentiation of stem cells into adipocytes rather than osteoblasts and can result in negative effects on bone mass and increased fracture risk. (148) Loke et al. (149) showed a two-fold increase in fracture incidence in women with long-term TZD. There is conflicting evidence on the effects of sodium-glucose cotransporter-2 inhibitors however they appear to increase fracture risk, likely through increased bone resorption. (150-152) Importantly, Vestergaard et al. (118) showed that antidiabetic drugs were associated with decreased fracture risk, after adjusting for multiple covariates, however, this association was only present at common fracture sites in T2D (hip, spine, and forearm). Considering the wide

variety of antidiabetic medications and their diverse effects on bone quality, further research into the role of T2D medication in regulating bone health is warranted.

2.5.2 Diabetes and Muscle Quality

In addition to reduced bone quality, T2D has also been associated with a greater loss of muscle mass, strength, and density compared to those without T2D, especially those with poor glycemic control. (15, 153, 154) Impairment in muscle quality, mainly muscle strength, is a primary contributor to functional disability, lower gait speed, increased difficulty completing physical activity, and increased risk of falls in people with T2D. (15, 119, 154) Both knee extensor and hand grip strength are relevant measures of the deficits in muscle strength in T2D populations. (41) Both measures can also predict relevant clinical outcomes, including fall and fracture risk. (44, 45) In a 3-year longitudinal study in community-dwelling older adults with and without T2D, Park et al. (15) found that those with T2D had a 50% more rapid decline in knee extensor muscle strength and torque (ratio of knee extensor strength to leg mass from DXA) than those without T2D. Changes in handgrip strength did not differ greatly between adults with and without T2D, however, there was a greater loss of arm lean mass in those with T2D. (15) These findings remained significant after adjustment for age, sex, and race. Similarly, Leenders et al. (155) showed that older men with T2D displayed greater declines in leg lean mass, muscle strength, and functional capacity than aged-matched controls. Volpato et al. (156) also found that individuals with T2D demonstrated lower muscle density and strength and slower walking speed, even when adjusted for age and sex, compared to those without T2D, suggesting diabetes-specific walking limitations and impairments in physical performance. Despite this evidence, little is known about the interaction between the severe obesity phenotype and T2D on muscle

quality and whether muscle-related performance represents a modifiable target to improve muscle and bone quality in this population.

2.5.3 Diabetes and Physical Performance

Physical performance is a fundamental component of health-related quality of life and predicts functional decline, morbidity, and risk of falls and fractures. Diabetes can increase the risk of physical disability through its chronic complications, including macro- and microvascular disease, vision loss, and peripheral neuropathy. (157) It is well-understood that weight loss and improved cardiorespiratory fitness slows the decline in physical function and mobility in overweight and obese adults with T2D. (158) However, people with T2D consistently show poorer results on physical performance tests, such as the 6MWT, 5 Times Sit-to-Stand Test, Berg Balance Scale, and gait speed tests, likely due to impaired balance, slower walking speed, and lower relative muscle strength. (159, 160) Gregg et al. (161) reported that 32% and 15% of older women and men with diabetes, respectively, have a physical disability (defined as a self-reported inability to walk one-fourth of a mile, climb 10 stairs, and do housework). Additionally, the odds of having a physical disability are higher with longer duration diabetes, suggesting the importance of measuring physical performance in people with T2D as means to prevent further impairment in functional status. (161) Performance-based tests of walking speed, lower-limb functional strength, and aerobic capacity are effective tools to assess functional decline in people with T2D. Balance, another relevant aspect of mobility and fracture risk in T2D, is also often measured. Balance limitations and history of falling are well-observed in people with T2D due to diabetes-related complications. (119) Emerging evidence suggests that the complications of T2D can accelerate the age-related declines in sensorimotor and cognitive functions and muscle quality, contributing to an increased risk of falls, especially in older adults. (119) Knowledge of

diabetes-specific physical performance targets may enhance our understanding of intervention approaches to improve balance and reduce fall risk in individuals with T2D.

2.6 Functional Muscle-Bone Unit Relationship

Muscle size and strength play a critical role in developing bone quality, providing mechanical protection, and preserving musculoskeletal tissue. Ultimate bone strength is influenced by mechanical forces applied to bone, including internal muscle forces and external ground reaction forces (i.e., physical activity). The functional muscle-bone unit theory states that muscle forces positively impact bone strength by applying strains which stimulate bone formation. (162) Muscle and bone influence each other to the extent that they are proportionately matched in their function and geometric structure. (163) In addition to being a mechanical stimulus of bone, myokines localized to the muscle are known to influence bone mass and metabolism, furthering the importance of muscle's role in regulating bone strength. (164) Due to the growing evidence of adverse effects of severe obesity and T2D on muscle and bone outcomes, there is a need to advance our understanding of muscle and bone quality determinants in these high-risk populations by studying the muscle and bone as a unit.

Additionally, the positive effects of exercise and physical activity on bone parameters are well-documented. (165-167). Progressive resistance training (PRT) is recommended as an effective strategy to maintain bone mass, structure, and strength by loading bone via the direct pulling action of muscles and/or the increase in gravitational forces. However, PRT alone has small-to-no effects on hip and spine aBMD, despite improvements in muscle mass and strength. (165, 166, 168) Weight-bearing exercise, involving moderate-to-high magnitude loads (≥2-4 times body weight) and multidirectional movement patterns, is considered most effective at inducing changes in bone material and structural properties. (167) Multimodal exercise

interventions that include two or more activity modes, such as PRT, impact loading, and balance training, are recommended for fracture prevention due to their positive influence on osteoporosis and falls-related risk factors. However, individuals with goals of weight loss and fracture prevention may need tailored approaches for health behaviour change and lifestyle intervention (e.g., physical activity, diet), especially in the presence of severe obesity, poor metabolic health, and mobility difficulties.

2.7 Physical Activity to Improve Muscle and Bone Health in Severe Obesity and T2D

Lifestyle-based weight loss through exercise and dietary restriction is a first-line therapy for obesity as it can improve cardiometabolic outcomes, functional mobility, and quality of life while reducing the risk of morbidity and mortality. However, weight loss of more than 10% is associated with up to 25% loss of lean mass, 1-4% loss of aBMD dependent on the skeletal site, and an increased risk of hip, pelvis, and upper-arm fractures compared to controls. (169-171) While dietary intervention alone can improve quality of life and physical function in adults with obesity, significant weight loss using this approach is often accompanied by muscle and bone loss, and subsequently an increased risk of fractures and falls. (172) Resistance training at least 2 days/week is an optimal intervention approach for obesity as it enables bone tissue to adapt to whole-body energy requirements and maintain muscle and bone mass during weight loss. (172) In a study by Villareal et al. (173), adding RT attenuated the loss of bone and muscle mass during voluntary weight loss in 141 obese, older adults (174), while adding aerobic training (AT) improved cardiorespiratory fitness but did not affect lean mass loss. The combination of 26 weeks of RT and AT during caloric restriction showed the greatest improvements in overall fitness while still attenuating the loss of lean mass. (173) Therefore, combined AT and RT with caloric restriction may result in significant weight loss and have positive effects on body

composition, physical function, muscle strength, and quality of life in older adults with obesity. (175) Many randomized controlled trials (RCTs) have investigated the relationship between different exercise training modalities, voluntary weight loss, and changes in bone mass outcomes. In a study by Beavers et al. (174), 187 older men and women with obesity and cardiometabolic disease risk were followed over an 18-month community intervention. Beavers et al. (174) found that total hip aBMD was reduced by 2% in all groups at 18 months; yet, secondary analyses revealed that total hip and femoral neck aBMD were increased in the weight loss and weight loss + RT group compared to the weight loss + AT group at the 30-month follow-up. Similarly, Armamento-Villareal et al. (176) found that RT and combined RT + AT groups were associated with less weight loss-induced declines in total hip aBMD and bone turnover. Likewise, total-body lean mass typically decreases less following combined diet + exercise intervention and exercise intervention alone than diet intervention alone. (173, 177) Combined RT + AT interventions are similarly beneficial for maintaining or improving physical performance during voluntary weight loss. Villareal et al. (173) found that Physical Performance Test scores increased most in the combined RT + AT group compared to the AT or RT group alone (21% for the combination group, 14% for the AT and RT groups each) but all intervention groups increased more than the control group. In summary, combined RT + AT and RT alone are favourable exercise intervention strategies during voluntary weight loss programs in adults with obesity to protect against long-term bone and muscle loss and enhance physical performance.

Similar to obese populations, exercise is recommended as a preventative measure not only to improve health outcomes but also to reduce functional decline, bone and muscle loss, and the risk of falls and fractures in people with T2D. (146, 172) Previous studies have mostly focused on the effects of voluntary weight loss through diet and exercise in older adults with

T2D or metabolic syndrome. Following a 12-month intervention in 36 older men and women with T2D, RT + weight loss showed no change in total body aBMD and bone mineral content (BMC), but a decrease in the weight loss only group (0.9% in men and 1.5% in women). (178) In an intervention by Courteix et al. (179), 90 men and women aged 50 to 70 with metabolic syndrome were divided into intensive (15-20 hours a week) RT, AT, or a combination group, all with a restrictive diet, and were compared to 44 healthy controls. Despite changes in weight and body composition, no changes were observed in aBMD or BMC at the lumbar spine, non-dominant hip, and for the whole body between groups when compared to healthy controls. Additionally, decreases in the total-body lean mass independently contributed to decreases in lumber spine aBMD. (179) Similarly, Johnson et al. (171) did not observe any significant difference in incident total fracture or hip fracture in overweight and obese adults with T2D following an education and support group versus a lifestyle and physical activity group over 11 years. However, the lifestyle and physical activity group did show a significant 39% increase in risk of fragility fracture highlighting that the possible link between long-term weight loss and an increased risk of fragility fracture. (171) Presently, there is limited research that specifically focuses on the influence of long-term exercise interventions on muscle and bone quality in T2D. There is currently one RCT in progress examining a 2-year exercise program designed to improve bone quality and strength in 200 participants with T2D aged 65-75 years. (180) Possible exercise interventions in severe obesity and T2D are needed as there are currently no evidence-based approaches for safe and effective methods to prevent muscle and bone loss in this high-risk population.

2.8 Bariatric Surgery Intervention

With the obesity epidemic worsening globally, bariatric surgery has emerged as an effective intervention for managing weight loss, improving cardiometabolic outcomes and glycemic control, and even diabetes remission. However, individuals undergoing bariatric surgery are often vulnerable to muscle and bone loss and increased risk of falls and fractures. By identifying relevant modifiable targets for reducing fall and fracture risk in severe obesity, prehabilitation and rehabilitation programs can be implemented to improve long-term bariatric surgery outcomes in relation to muscle and bone health. (181-183) Bariatric surgeries are classified based on the mechanism implicated for weight loss. Restrictive surgery limits food intake by reducing the size of the stomach and includes gastric banding and sleeve gastrectomy. Combined restrictive and malabsorptive surgeries, such as Roux-en-Y gastric bypass, limit the size of the stomach and the absorption of food and nutrients by bypassing sections of the small intestine. (184) The number of bariatric surgeries has increased significantly in Canada over the last 10 years, and about a third of the surgeries now involve patients with T2D. These patients require a BMI $\geq$35 kg/m^2 to be eligible for the surgery but because of the numerous benefits of the procedure, there is an interest in lowering the eligibility BMI. (185) However, growing evidence suggests that bariatric surgery is detrimental to aBMD, cortical and trabecular bone structure, and bone strength, negatively affecting bone health and increasing the risk of fracture. Beavers et al. (186) found a 3-7% loss in bone mass at 6-24 months post-surgery and a 1.3-2.3-fold increase in fracture risk; with adverse outcomes appearing early after surgery and persisting even after weight loss stabilizes. (184, 187) Therefore, evidence-based interventions are needed to enhance bone and muscle health and prevent fractures after bariatric surgery.

Multifactorial lifestyle interventions following bariatric surgery, including RT and balance training, should be designed to manage bone loss and falls and fracture risk post-surgery. (186) A systematic review of 9 studies by Morales-Marroquib et al. (188) evaluated whether current RT guidelines could support the musculoskeletal health of a post-bariatric surgery population. Their findings infer that RT consistently prevented the loss of muscle strength and lean mass in younger obese populations. However, none of the combination, RT, or AT groups were able to alleviate a loss of fat free mass and aBMD associated with significant weight loss, yet combined RT + AT promoted fat mass loss. (188) Interestingly, Gilbertson et al. (189) explored whether adding aerobic exercise prior to bariatric surgery improved outcomes post-surgery. Their findings revealed that surgical outcomes improved, such as shorter operating time and shorter length of hospital stay, in the exercise + standard care group compared to standard care group. However, a reduction in fat free mass was observed in both groups. Overall, evidence on the effects of exercise interventions on bone health post-bariatric surgery are very low-quality due to small sample sizes, short intervention lengths (not able to observe full bone turnover rates), or inconclusive results. Limited but promising research highlights the potential benefits of implementing a prehabilitation exercise program to attenuate muscle and bone loss post-surgery but further evidence is needed to make any conclusive inferences. (190)

While exercise interventions pre- and post-surgery are important in the bariatric populations, many bariatric patients experience substantial barriers to exercise and physical activity. Sustaining an active lifestyle is a critical but often unmet goal of bariatric treatment, especially to limit bone and muscle loss. In a study by Dikareva et al. (191), 12 women 3-24 months post-surgery identified many barriers to exercise including body dissatisfaction, access to accommodating facilities, competing responsibilities, lack of exercise knowledge, exercise self-

efficacy, and social support. Facilitators included enjoyment, positive body image, supportive and active relationships, access to accommodating facilities, and exercise knowledge. (191) Joseph et al. (192) reported that less than 60% of participants with Class III obesity found exercise enjoyable or as a form of social interaction, while more than 60% identified barriers to exercise and physical exertion, including pain, musculoskeletal comorbidities, psychological factors, and higher body weight. They also found that participants with Class III obesity were sedentary for on average 10 hours a day, however, there was no significant association between their perceived barriers and their sedentary behaviours assessed by the Sedentary Behaviour Questionnaire. (192) In bariatric populations, it is apparent that physical activity interventions should account for individual barriers and be tailored to leverage individual facilitators to promote the adoption and maintenance of physical activity and exercise.

Traditionally, patients undergoing bariatric surgery will complete a presurgical lifestyle support program and a post-surgery diet and exercise plan. However, many bariatric patients return to their preoperative lifestyle one year post operation, and a significant proportion of these individuals lead physically inactive lifestyles. In a study of 398 men and women 1-16 years post-surgery, only 53% reported more than one moderate-to-vigorous- physical activity (MVPA) session a week and 53% reported less sitting time post- versus pre-surgery. (193) Age, sex, smoking status, pre-surgery BMI, time since surgery, and percent excessive weight loss were all significantly associated with physical activity and sitting time. Specifically, participants with 50% or more excessive weight loss were three times more likely to report more than one session of MVPA a week and four times more likely to report more physical activity post-surgery than pre-surgery compared to participants who did not reach ≥50% weight loss. (193) However, Possmark et al. (194) showed that patients significantly overestimate their time spent in MVPA

to a great extent post-surgery compared to pre-surgery. Comparing the results from a self-administered questionnaire and accelerometer from 3 months pre-surgery, and 9- and 48-months post-surgery, self-reported MVPA increased 46.9% and 36.5%, respectively, yet there was a 6.1% increase and a 3.5% decrease in accelerometer-based MVPA. In a study of adults who underwent bariatric surgery approximately 9 years earlier, participants demonstrated on average 9 hours of sedentary time and 6,500 steps per day, with a negative correlation between steps per day and sedentary time. (195) Interestingly, participants who were more active pre-surgery, did not have any significant differences in sedentary time compared to those who were less active pre-surgery. In general, objectively-measured physical activity levels after bariatric surgery is highly variable among patients, with the majority (89%) not meeting the recommendations. (195) Importantly, physical inactivity in this population is part of a vicious cycle with negative musculoskeletal and functional outcomes unless safe, effective, and engaging interventions are developed. Therefore, there is an urgent need to identify physical performance and physical activity-related factors to inform the design of a multimodal exercise intervention to improve muscle and bone outcomes important for fall and fracture prevention in severe obesity and T2D.

2.9 Knowledge Gaps and Rationale

Currently, there are no comparative data on muscle and bone quality determinants in severe obesity with and without T2D. Further, we have a limited understanding of the modifiable targets for reducing fall and fracture risk in severely obese and T2D populations. This study is particularly novel as we are evaluating the muscle and bone as a unit using advanced imaging technology at fracture-prone sites. When people with severe obesity and T2DM are measured by DXA, they typically have a normal to high aBMD yet they are still at high risk of fracture. Recent advances in imaging technology (i.e., QCT) enables the measurements of three-

dimensional bone parameters as well as muscle size and density, which may explain fracture risk differences in individuals with severe obesity and T2D compared to those without these high-risk conditions. From this, we will identify relevant physical performance and physical activity-related factors to inform the design of a multimodal exercise intervention targeting muscle and bone quality outcomes important for fall and fracture prevention in severe obesity and T2D. Furthermore, our results will be used as pilot data for future larger investigations to develop and evaluate the potential efficacy of a prehabilitation exercise intervention to improve muscle and bone health. Therefore, the main objectives of the proposed thesis are to examine the associations between physical performance and muscle and bone quality outcomes, and to explore the functional muscle-bone relationship in severe obesity with and without T2D. The secondary objective is to assess physical activity levels and barriers to and preferences for exercise in people with severe obesity with and without T2D.

Chapter 3: Thesis Manuscript

3.1 Introduction

3.1.1 Rationale

Osteoporotic fractures are associated with significant health and economic burden worldwide and can lead to impaired physical performance, reduced quality of life, pain, hospitalization, and even death. (27, 196-200) In Canada alone, 1.5 million people over the age of 40 have been diagnosed with osteoporosis, and one in three women and one in five men will have a fracture in their lifetime. (1) In 2011, 57% of all hospital admissions and hospitalized days were attributed to osteoporotic fracture and the associated costs exceeded $4.6 billion. (27) The proportion of obesity in the adult population has also increased at an unprecedented rate over the past few decades, and currently 26.1% of Canadian adults live with obesity. (2) Obesity was previously considered protective against fractures based on having normal or higher areal bone mineral density (aBMD) and soft tissue padding consistent with higher body mass index (BMI). (4, 19, 201, 202) However, recent evidence suggests an inverse and nonlinear relationship between body mass index (BMI) and aBMD, with the lowest aBMD values observed at the BMI extremes (<15 kg/m^2 and >30 kg/m^2). (65, 66) Population-based studies confirm an increased risk of fractures in individuals with obesity at several sites, particularly the humerus, femur, and ankle. (5, 67) Additionally, severe obesity (BMI>35 kg/m^2) contributes to lower muscle mass and strength, poor aerobic capacity, slower walking speed, balance impairment, and consequently a higher falls risk. (44, 45, 47, 110, 203, 204) Thus, contrary to traditional understanding, severe obesity is not necessarily protective against falls and fractures and higher fat mass may be detrimental to bone and muscle quality and physical performance. (4)

The mechanisms linking severe obesity and bone and muscle quality remain largely unclear. (4, 5) Higher visceral adipose tissue (VAT) is a negative predictor of bone mass, structure, and strength due to insulin resistance, adipocyte-derived hormonal factors, and systemic inflammation. (77, 205) Obesity often presents with hormonal changes that can negatively affect musculoskeletal and metabolic health, including dysregulation of the growth hormone/insulin-like growth factor-1 axis, suppressed gonadal steroid production (estrogen, testosterone), and lower adiponectin levels. (60) Obesity-related inflammatory cytokines (i.e., interleukin-6, C-reactive protein) can up-regulate bone resorption relative to bone formation leading to a net bone loss while also reducing muscle strength and mass. (89, 91, 206, 207) Obese individuals tend to have greater absolute muscle strength compared to nonobese individuals, but a lower relative muscle strength, which may reflect a lower muscle quality and a greater risk for functional disability. (9) Inter- and intramuscular fat infiltration is also higher in severe obesity and independently predicts lower physical performance and increased falls risk. (95, 156, 208-212) Studies of physical performance assessed through mobility, walking speed, balance, and aerobic capacity tests consistently demonstrate that people with obesity have a lower functional mobility, slower gait speed, and balance deficits associated with a higher risk of falls. (112, 204, 213) Additionally, individuals with severe obesity often participate in low physical activity levels and this inactivity perpetuates a vicious cycle of low activity, declines in physical performance, muscle and bone loss, and increased risk of falls and fractures. (9)

It is widely known that obesity is a critical and modifiable risk factor for type 2 diabetes (T2D) and T2D is 20 times more likely in individuals with a BMI greater than 35 kg/m^2. Chronic T2D is associated with many serious, long-term health complications (e.g., heart disease, nerve damage), yet reductions in bone and muscle quality remain underrecognized diabetes-related

consequences. Substantial evidence demonstrates that individuals with T2D are at a higher risk of fracture, even after adjustment for aBMD. (10, 150) Yet the mechanistic pathways to bone fragility in patients with T2D are complex and likely multifactorial, including reduced bone turnover, hyperglycemia, antidiabetic medications, and poor muscle quality. (3) Assessment of bone turnover markers in people with T2D consistently demonstrate low bone formation but variable bone resorption. (131) Additionally, osteoblast activity and mineral apposition rate is reduced in T2D, which may explain the deterioration in bone quality in diabetic populations including greater cortical porosity and larger holes in trabecular bone. (12, 117) Hyperglycemia results in advanced glycation end products (AGEs) accumulation, which may interfere with bone turnover, leading to a reduction in bone material strength. (14, 141) Anti-diabetic treatments can have direct and indirect effects on fracture risk, although results are inconsistent about each treatment. (3, 150) Similar to severe obesity, people with T2D demonstrate reduced muscle quality, characterized by skeletal muscle fat infiltration and lower muscle cross-sectional area, density, and strength; possibly leading to functional disability and slower gait speed. (15, 119, 153, 154, 156, 207) Diabetic complications (e.g., neuropathy, reduced vision) may also be responsible for increased fracture risk through an increased frequency of falls. (119, 120, 128-130, 159, 214, 215)

Despite the extensive evidence in support of the higher risk of functional disability, falls, and fractures in people with severe obesity and its comorbidities, it is unknown whether physical performance is an effective intervention target to improve bone and muscle quality in this population. Muscle forces influence bone strength by applying strains to stimulate bone formation, and contribute to the regulation of bone mass, structure, and strength (also known as functional muscle-bone unit theory). (19) Performance-based tests of gait speed, functional

strength, and balance have been shown to predict falls and fracture risk; yet less is known about the influence of physical performance on bone and muscle health in severe obesity and T2D. (44, 45, 47, 203) Currently, there are no comparative data to determine the associations between physical performance and indices of bone and muscle quality in severe obesity with and without T2D. Additionally, the influence of muscle-related factors on bone fragility in severe obesity is not well-understood and it is unclear whether T2D further exacerbates any obesity-related decrements to bone and muscle health. Bariatric surgery has emerged as a popular obesity management strategy in North America with evidence of improvements in cardiometabolic outcomes, glycemic control, and even diabetes remission. (181-183) However, bariatric surgery results in a significant loss of muscle and bone mass, leading to adverse musculoskeletal outcomes and an increased fall and fracture risk. (184) Therefore, our study will examine the physical performance factors (i.e., functional mobility, balance, aerobic capacity) related to bone and muscle parameters to inform future intervention studies to enhance musculoskeletal health and prevent falls and fractures after bariatric surgery. Additionally, given that people with severe obesity and T2D tend to be physically inactive, identifying barriers to and preferences for exercise will provide targets to improve muscle and bone outcomes post bariatric surgery.

3.1.2 Objectives and Hypotheses

The present study explored the associations between physical performance and muscle and bone quality in severe obesity and T2D (**Table 5.1**). The primary objective was to determine the association between performance-based tests of mobility, dynamic balance, and aerobic capacity and muscle and bone outcomes in pre-bariatric obese adults with and without T2D. The secondary objective was to compare these determinants of muscle and bone quality in those with and without T2D. The third objective was to determine the relationship between physical activity

and muscle and bone outcomes and to describe the exercise barriers and preferences in this sample to inform future interventions.

We hypothesized that better performance on mobility, dynamic balance, and aerobic capacity tests would be positively associated with better muscle and bone quality. We also hypothesized that higher moderate-to-vigorous physical activity (MVPA) levels would be associated with better muscle and bone quality in our sample of participants. Refer to **Table 5.1** for a more detailed overview on the objectives, variables, and methods of analyses.

3.2 Methods and Procedures

3.2.1 Study Design

The present study (referred to as BODI2) was part of a larger, multi-centre, cross sectional, cohort study designed to describe and compare the associations between muscle and bone quality, strength, and function in severely obese men and women with and without T2D. For BODI2, we recruited a group of obese participants without T2D, who had not undergone bariatric surgery, for one-time measures to compare with baseline measurements (pre-bariatric surgery) in obese participants with T2D from a 1-year prospective multicentre observational cohort study known as "Bone health after bariatric surgery in patients with type 2 diabetes" (BODI) led by Dr. Claudia Gagnon (Université Laval, Québec). The purpose of the BODI study was to investigate the impact of bariatric surgery on bone quality in individuals with T2D. Participants in the BODI study had T2D, were undergoing bariatric surgery, and were followed pre- and post-operation. The BODI2 study received ethics approval from the Research Institute of the McGill University Health Centre and Research Centre of CHU de Québec – Université Laval. Participants arrived at the Centre for Innovative Medicine and Institute Universitaire de

Cardiologie et Pneumologie de Québec, having fasted for 12 hours and completed a series of study assessments.

3.2.2 Participants

For the severe obesity group, an equal number of men and women with severe obesity (≥18 years with BMI ≥35kg/m^2) without T2D from diabetes and bariatric surgery clinics affiliated with McGill University Health Centre (n=7) and Institute Universitaire de Cardiologie et Pneumologie de Québec (n=10) were recruited. Participants must not have been previously diagnosed with diabetes or prediabetes (fasting glycated hemoglobin <5.7% AND fasting plasma glucose <5.6mmol/L) and must be free of any disease (uncontrolled thyroid disease, malabsorptive or overt inflammatory disorder, metabolomic bone disease, creatine clearance >60 ml/min) or medication (glucocorticoids, anti-epileptic drugs, osteoporosis therapy, thiazolidinediones) that affects bone metabolism. Additional exclusion criteria included BMI ≥61 kg/m^2, indication that a quantitative computed tomography (QCT) and dual-energy X-ray absorptiometry (DXA) scan was impossible to complete, a history of esophageal, gastric, digestive, or bariatric surgery, and pregnant/breast-feeding. The data from these recruited participants (n=17) was analysed with previously collected data from a comparison group (n=16) with T2D from the BODI study. Eligibility for the severe obesity + T2D group from the BODI study shared the same inclusion criteria with the exception of participants (n=16) requiring a T2D diagnosis (fasting glycated hemoglobin >6.5%, fasting plasma glucose >7.0 mmol/L). Fasting blood was sampled for the measurement of hemoglobin A1c (HbA1c) as an indicator of T2D status at both sites. Participants were matched for age (±5 years), sex, and BMI (±3 kg/m^2) to ensure approximate equal distribution of confounding factors between the two groups. For women, efforts were made to match for menopausal status. No participants had undergone

bariatric surgery prior to study participation, however some participants from both groups were recruited from bariatric clinics as they were eligible for the surgery. All participants provided written informed consent prior to study participation.

3.2.3 Outcomes

3.2.3.1 Medical History, Quality of Life and Physical Activity Questionnaires

A comprehensive medical history questionnaire focusing on personal history, family history, lifestyle habits, fall and fracture history, and medication and natural health product use was administered by trained research personnel. (38) The International Physical Activity Questionnaire (IPAQ) short form version was used to assess physical activity in the previous 7 days comparing time spent sitting, and participating in light, moderate, and vigorous physical activity (expressed as minutes per week). (216) The remaining questionnaires were self-administered prior to the participant's study visit and were only done in the severe obesity group (n=17). The Life Space Mobility is a 5-question survey inquiring about community participation by determining time spent at home, in their neighbourhood, and their town. A score is determined by calculating the number of days in five different Life Spaces (bedroom, house, property, neighbourhood, and town) in the past 4 weeks. (217) The short form health survey has 7 Likert scale questions, with scales ranging through none of the time to all of the time, assessing the impact of health on everyday quality of life. (218) Finally, the exercise barriers and preferences survey assessed barriers to physical activity and exercise related to health, motivations, and comfort level on a 5-point Likert scale (scoring the statement from strongly disagree to strongly agree) and preferences for exercise programming in a bariatric clinic setting.

3.2.3.2 Anthropometry

Height was measured using a wall-mounted stadiometer. The participant's heels, buttocks, shoulders, and head were lined up against the wall, with eyes looking straight ahead. After an inhalation, the head plate was brought down to the top of the participants head to determine the height, which was recorded in cm to the nearest 0.1 and repeated for accuracy. Weight was determined using an electronic scale (Scale-Tronix, Welch Allyn, Skaneateles, NY). The scale was zeroed, and the participant stepped on the scale and remained until the reading was completed. Weight was recorded in kg to the nearest 0.1 and repeated for accuracy. The NHANES protocol for waist circumference was followed. The top of the iliac crest was palpated and marked with a washable marker. A measuring tape was extended around the waist at the level of the marks, snug against the skin, without compressing the skin. Following a normal exhalation, the measurement was recorded in cm to the nearest 0.5 and repeated for accuracy.

3.2.3.3 Physical Performance Tests

The timed up and go (TUG) test is a clinical measure of lower-extremity function, mobility, and fall risk and is predictive of aBMD and fracture risk. (46, 47) The participant stood from a standard chair without aid, walked three meters (marked on the floor), turned around and returned to a seated position in the chair as quickly as possible. (48) The time taken to complete the task was recorded; a TUG time over 13.5 seconds in community-dwelling adults indicates an increased fall risk. (49) This test was done twice, and the best result was used. The Fullerton Advanced Balance (FAB) Scale is a 10-item battery used to assess multiple dimensions of balance to predict the risk of falling in older adults. (51) Only the first 9 items were used because the research personnel were not physically capable of safely executing the final test in certain participants (n= 26) due to safety concerns that participants might fall during the test despite supervision by research personnel. Therefore, the FAB scores were evaluated out of 36.

A score was given to each of the tests based on the success or failure of the test and the ease to which it had been completed. A FAB score of ≤25 indicates a higher risk of falls in older adults. (51) The 6-minute walk test (6MWT) is a validated tool to estimate submaximal aerobic exercise capacity in obesity. (52) A 30-metre track was measured out on a flat, hard surface. Participants walked around the track for 6 minutes, slowing down, and taking breaks as needed. They received standard encouragement at every minute. The distance walked at 2, 4, and 6 minutes was recorded in metres, and a modified Borg scale was used to determine rate of perceived exertion (RPE) at the end of the test to confirm it was a submaximal aerobic test. (219) Normative 6MWT distance values for men and women over the age of 60 are 572 metres and 538 metres, respectively. (220)

3.2.3.4 Muscle Strength

To assess muscle strength, validated isometric knee extensor and hand grip strength tests were performed. Both tests have been shown to predict relevant clinical outcomes including falls and fracture risk. (44, 45) Knee extensor strength was determined using a Biodex Pro 3 leg dynamometer (Biodex Medical System, New York, NY, USA); the test-retest reliability of this test has been well-established. (42) The participant was strapped into the seat of the dynamometer at the waist, the opposite shoulder and thigh of the testing leg was secured. After adjusting the chair to the appropriate position and setting the range of motion limits, the dynamometer was calibrated. Testing began with the participant completing 4 isometric contractions for 5 seconds, with a 60 second rest in between each contraction. Both the right and left leg were tested, twice each and the maximal strength and torque for each isometric contraction was recorded in kg and N/m, respectively, to the nearest 0.1.

To measure hand grip strength, the Southampton protocol was followed using a Jamar hand dynamometer (Model 5030J1 Sammons Jamar Hydraulic Hand Dynamometer). (41) Participants were seated in a chair with both feet resting flat on the ground and their forearms resting on the armrests and wrists in a neutral position over the end of the armrest. The dynamometer was adjusted to their hand size and was supported by a member of the research team during the assessment. First with the right hand, the participant squeezed the dynamometer as tightly as possible until the needle stopped rising, then they were instructed to stop squeezing. The maximal strength was recorded in kg, to the nearest 0.1. Each participant repeated this three times with each hand, alternating between the right and left side. (41)

3.2.3.5 QCT Imaging

A QCT was performed at the proximal femur (top of the femoral head to ~50% of the femur) and radius (distal one third) by a trained radiology technologist. QCT acquisition parameters are set as follows: 1 mm slice thickness and 120 kVp (radius and hip), target noise level of 20 HU. Images will be analysed using QCT Pro™ CT-BIT extension software (Mindways Software Inc, Austin, TX). Total, trabecular, and cortical vBMD and cortical thickness were derived from the scans at the proximal femur and radius. (221, 222)

Cross-sectional area and attenuation values of muscle and fat content of the muscle groups in the QCT scan at the hip/upper thigh (quadriceps muscle slice taken at 50% femur). (223) Images of the upper thigh (same slices as the QCT images) were used to determine cross-sectional areas of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).

3.2.3.6 DXA

aBMD was determined at the lumbar spine (L1-L4), femoral neck, and hip, and body composition was derived from DXA (GE Lunar, GE PRODIGY or Hologic). This noninvasive

technique measures body composition and provides quantification of the major body compartments including bone mineral and soft tissue, with the latter divided into fat and fat-free tissue. Each DXA scan involved lying on an open scanner for approximately 10 minutes while two X-ray beams with different energy levels were aimed at the subjects' bones, fat mass, and lean mass. DXA scanning presents a low within-subject coefficient of variation (approximately 1.5%) and strongly correlates with a four-compartment body composition model and a multi-slice computed tomography. Lean and fat soft tissue mass, and bone mass were quantified. All densitometers were cross-calibrated at the start of the study, to ensure site-to-site comparability. All data was converted into standardized aBMD values. Daily machine calibration, daily and weekly quality assurance tests and longitudinal stability were monitored. If a participant was out of the DXA scan range, a half-scan was taken from the right side of the body and the contralateral side was set equal to it. (224) This procedure has been validated and closely approximates those results obtained with a whole-body scan.

3.2.3.7 Accelerometer

Participants wore a commercially available accelerometer (Actigraph GT3X+, ActiGraph, FL, USA) over the hip for 7 consecutive days. At the end of the 7 days, the participants returned the accelerometer by mail. Tri-axial accelerometer data was used to compute the number of minutes spent in three intensity levels of activity (sedentary, light, and moderate-vigorous) based on counts/minute (cpm)-based cut-points reported by Santos-Lonzano et al. (225) Time spent in sedentary activity was defined as ≤100 cpm, light PA as 101–3027 cpm, and MVPA as ≥3028 cpm. Data was analyzed in 15 second epochs. Vector magnitude activity counts, calculated as the square root of the sum of the vertical, medio-lateral, and antero-posterior axes, were used according to previous studies performed with this population. (226,

227) Non-wear time was excluded if there were ≥60 minutes of continuous zeros. (228) Only participants who wore the accelerometer for at least 4 days and 10 hours/day were analyzed. (229)

3.2.3.8 Statistical Analyses

Descriptive analyses were stratified by sex and the means, medians, standard deviations, and percentages were calculated as appropriate. Standard tests (Chi-Square, T-test) were used to compare continuous and categorical outcomes between pre-bariatric obese participants with (N=17) (severe obesity group) and without T2D (N=16) (severe obesity + T2D group).

The unadjusted and adjusted associations between physical performance (TUG, FAB, 6MWT, accelerometer and questionnaire-based physical activity), muscle strength (hand grip and knee extension), and soft tissue (muscle, fat) cross-sectional area and bone mass, structure, and strength were studied. Pearson and/or Spearman correlation coefficients were calculated to assess the correlations between outcomes of interest adjusted for age. For the primary objective of the larger study, a sample size of 20 participants per group, with an alpha=0.05 and power=80%, was detecting a mean difference in vBMD=15 mg/cm^3 and a standard deviation=20 between groups. For the present study, the primary and secondary objectives were of a hypothesis-generating, exploratory nature and intended to inform sample size calculations for future interventional studies.

3.3 Results

3.3.1 Descriptive Statistics

Our study included 33 participants, 79% (n=26) were female, with a mean age of 44 years (±11.1), and 19% (n=5) of the female participants were postmenopausal. The participants' mean BMI was 40 kg/m^2 (± 3.8) and their mean percent body fat was 49.4% (± 5.1). Most

participants were within Class II (BMI of 35.0-39.9 kg/m^2) (45%, n=15) and Class III (BMI ≥ 40kg/m^2) obesity (48%, n=16), with a smaller proportion within Class I obesity (BMI of 30.0-34.9 kg/m^2) (6%, n=2). The participants' mean blood pressure was within a normal range (SBP: 129.4 ± 14.1 mmHg, DBP: 81.2 ± 12.6 mmHg). However, all participants were above the waist circumference threshold (≥94 cm for men, ≥80 cm for women) indicative of an increased risk of metabolic syndrome (124.1 cm ± 10.8). Twenty-four percent (n=8) of participants reported hypertension with other comorbidities, including dyslipidemia (18%, n=6), cardiovascular disease (15%, n=5), and gastrointestinal disorders (12%, n=4), being reported to a lesser extent.

Only 3% (n=1) of participants reported a history of a nontraumatic fracture in the past year and 37% (n=12) had a low impact fall in the past year (n=4 tripped while walking, n=6 slipped on ice, n=2 fell from other circumstances). **Table 5.3** presents the descriptive characteristics of the severe obesity and severe obesity + T2D groups. As expected per the matching protocol, there were no between-group differences in sex and BMI. The severe obesity + T2D group had higher HbA1C levels (mean±SD=0.06 ± 0.01, t=-4.866, $p<0.05$) but otherwise there were no group differences in any descriptive outcomes.

3.3.2 Physical Performance & Physical Activity Comparisons

Physical performance data in both groups are found in **Table 5.4**. The mean TUG test time was 7.26 seconds (±1.54), the mean FAB score was 32.6 points (±4.0); no statistically significant differences were found between groups for both tests. The mean 6MWT distance was 487.31 metres (±72.4) with a mean RPE of 5 (±2.7). No statistically significant between-group difference was observed for the distance walked during the 6MWT however, the severe obesity + T2D reported a greater RPE (p=0.015). The mean handgrip strength was 33.7 kg (±9.1), and the

mean knee extensor strength was 214.7 kg (±74.2). There were also no statistically significant differences for hand grip or knee extensor strength between the groups ($p>0.05$).

Based on the accelerometer measures of PA, 75% (21/28) participants had more than 150 minutes of MVPA over 7 days (293 minutes/week ± 198). The mean time spent completing light PA was 1803 minutes/week (± 617) and the mean time spent sedentary was 13 hours (±4) per day. There was no difference in the mean PA levels between groups for either the accelerometer or the IPAQ (**Table 5.4**). Only the severe obesity group (n=17) completed the Life Space Mobility questionnaire, participants had a mean score of 73 out of the maximum score of 120.

The severe obesity group (n=17) also completed an exercise barriers and preferences questionnaire (**Figure 1**); 35% (n=6) reported a preference to exercise alone, 29% (n=5) preferred a small group format (less than 5 people), and 29% (n=5) had no preference. Most participants preferred moderate intensity exercise (69%) compared to low (13%) or high (19%) intensity exercise. Forty-four percent of participants preferred self-paced exercise while 19% said they preferred supervised exercise. Seventy-one percent (n=12) of participants were willing to participate in strength training and 59% (n=10) indicated they would be willing to participate in balance training. Participants expressed many barriers to exercise including difficulty returning to exercise after a break in routine (35%, n=6), hopelessness about using exercise to manage weight (35%, n=6), and discomfort with exercising in public (35%, n=6) (**Figure 1**).

3.3.3 Muscle and Bone Parameter Comparisons

All 33 participants completed acceptable QCT and DXA scans (**Table 5.5**). The severe obesity + T2D group had a higher femoral neck cortical vBMD compared to the severe obesity group ($p=0.035$). There were no other differences in bone outcomes found between groups. No

statistically significant differences were observed for the upper thigh muscle, intramuscular fat, or subcutaneous fat cross sectional area (CSA) between groups (**Table 5.5**).

3.3.4 Associations between Physical Performance and Physical Activity and Bone

Modest inverse correlations were found between TUG test time and femoral neck total vBMD (r=-0.415, p=0.02), total hip trabecular vBMD (r=-0.488, p=0.005), and femoral neck cortical thickness (r=-0.381, p=0.035). The FAB score was moderately correlated with total hip trabecular vBMD (r=0.453, p=0.01). The 6MWT distance was not significantly associated with any bone variables (p>0.05). Significant correlations were observed between knee extensor and handgrip strength and total hip trabecular vBMD (r=0.514, p=0.004 and r=0.367, p=0.042, respectively), all femoral neck bone outcomes (r=0.447-0.546, p<0.05 and r=0.361-0.538, p<0.05), and radius integral vBMD, cortical vBMD, and cortical thickness (r=0.532-0.642, p<0.001-0.003 and r=0.625-0.697, p<0.001).

When adjusted for age, a negative correlation remained statistically significant between TUG and femoral neck total vBMD (r=-0.444, p=0.034). Correlations between knee extensor strength and radial integral vBMD (r=0.598, p=0.003), cortical vBMD (r=0.636, p=0.005), and cortical thickness (r=0.673, p=0.002) remained significant even after adjustment for age. Handgrip strength remained associated with femoral neck trabecular vBMD (r=0.564, p=0.018), radius integral vBMD (r=0.617, p=0.002), radius cortical vBMD (r=0.699, p=0.001), radius cortical thickness (r=0.648, p=0.004), and radius total CSA (r=0.786, p<0.001) when adjusted for age (**Table 5.6**).

Accelerometer-measured MVPA was associated with total hip trabecular vBMD (r=0.460, p=0.016) and femoral neck trabecular vBMD (r=0.470, p=0.013). No associations were found between accelerometer-measured light PA and sedentary time and bone outcomes. When

adjusted for age, accelerometer MVPA was still associated with total hip cortical vBMD (r=-0.634, p=0.006) but no other bone outcomes.

3.3.5 Associations between Physical Performance and Physical Activity and Muscle

The 6MWT distance was negatively associated with upper thigh subcutaneous fat CSA (r=-0.434, p=0.034). Knee extensor and handgrip strength were positively associated with upper thigh muscle and intramuscular fat CSA (r=0.442-0.790, $p<0.05$). No additional associations were observed between physical performance tests and muscle parameters (**Table 5.7**).

Moderate-to-strong positive correlations remained statistically significant between knee extensor strength and upper thigh muscle CSA (r=0.524, p=0.015), and upper thigh intramuscular fat CSA (r=0.772, $p<0.001$) when adjusted for age. After adjusting for age, moderate-to-strong positive correlations were still observed between handgrip strength and upper thigh intramuscular fat CSA (r=0.771, $p<0.001$). No associations were observed between physical activity and upper thigh muscle outcomes.

3.4 Discussion

3.4.1 Summary of Findings

The results of this cross-sectional, exploratory study found no significant differences between the severe obesity and severe obesity + T2D groups for muscle, bone, physical performance, or physical activity measures. These findings are contrary to our hypothesis wherein we expected T2D to exacerbate the negative influence of severe obesity on bone and muscle parameters and as a result, we were unable to distinguish the independent and combined influence of severe obesity and T2D on muscle and bone health and its determinants. The lack of diabetes-specific differences was likely due to the wide age range of our participants (range: 20-64 years) and the shorter length of T2D diagnosis compared to other studies examining muscle

and bone outcomes in obese and diabetic populations. Functional muscle strength tests were moderately correlated with most bone outcomes at the hip and radius, more so than any of the physical performance or physical activity variables; yet some associations with physical performance tests emerged after adjusting for age, mainly TUG test time, which is a well-known indicator of fracture risk independent of clinical risk factors and BMD. (230, 231) It is notable that our sample was more physically active and functionally capable than traditionally reported for a pre-bariatric population, likely affecting our potential to observe associations between physical performance, physical activity, and musculoskeletal outcomes. Similarly, knee extensor and handgrip muscle strength were positively associated with muscle and fat CSA at the upper thigh, indicative of a site-specific relationship between muscle-related force production and leg tissue composition in severe obesity and T2D. Our results provide valuable comparative evidence on muscle and bone parameters in severe obesity and T2D and infer the potential importance of targeting functional muscle strength and mobility (TUG) to improve muscle and bone outcomes in pre-bariatric populations.

3.4.2 Comparisons of Bone and Muscle Parameters Between Groups

To our knowledge, this is one of the first studies to compare the influence of severe obesity and T2D on bone and muscle outcomes measured by QCT. Contrary to our hypothesis, there were no significant differences between the severe obesity and severe obesity + T2D groups for muscle, bone, physical performance, or physical activity measures. The mechanisms underlying bone and muscle declines in severe obesity and diabetes are complex, and we do not know whether worse musculoskeletal outcomes manifest in the presence of both conditions versus severe obesity alone. Pritchard et al. (117) compared bone microarchitecture in 30 postmenopausal women with and without T2D and found greater deterioration of trabecular bone

in women with T2D, suggesting an elevated fracture risk in the diabetic population. In a large, prospective registry-based study, Leslie et al. (124) demonstrated greater BMD loss at the femoral neck in women with T2D compared to women without T2D. Notably, BMI did not significantly affect hip or lumbar spine BMD loss in the overweight and obese women without T2D, and therefore, factors other than BMI may explain higher fracture risk in diabetes and obesity. (124) In the present study, only cortical vBMD at the femoral neck showed a trend towards a significant difference between groups. The lack of diabetes-specific differences may be explained by the shorter length of T2D diagnosis in the severe obesity + T2D group (mean diagnosis length of 3 years) as well as the favourable physical performance and activity characteristics in both groups. Typically, negative changes in bone outcomes occur in older individuals with severe obesity with a longer T2D diagnosis. Results from the Manitoba BMD Cohort of women aged 40 years and older suggests that a diabetes diagnosis greater than 10 years must be present to observe clinically relevant increases in fracture risk. (232) Our sample of participants were also notably younger (average 44 years of age) and included a smaller proportion of postmenopausal women (19%) compared to most studies evaluating musculoskeletal outcomes in severe obesity and T2D, which largely focus on postmenopausal women and older adults.

Severe obesity and diabetes have deleterious effects on skeletal muscle and its quality. At a cellular level, obesity can disrupt the signalling pathways involved in skeletal muscle excitation contraction coupling. Adipokines released from accumulated adipose tissue are associated with systemic inflammation and affect the overall strength and composition of muscle. These cellular and hormonal factors, in addition to the increased passive loading from an excess body mass, leads to higher absolute muscle strength but a decrease in force produced per muscle mass (also

known as muscle quality). (233) Insulin resistance also inhibits proper glucose metabolism in peripheral tissues, including skeletal muscles, reducing the energy available to the muscles, limiting their contractility and functionality. (234) Nonetheless, our study did not demonstrate any significant differences in QCT-measured muscle and fat CSA at the upper thigh. Therefore, it is difficult to distinguish whether T2D confers additional negative influence on bone and muscle health in individuals with severe obesity. Since most of the research in this area focuses on older adults, particularly postmenopausal women, future studies should consider targeting higher-risk men and women across a range of age and BMD status to further evaluate the effects of severe obesity and T2D on muscle and bone outcomes.

3.4.3 Associations between Physical Performance and QCT Bone Outcomes

Despite our multifaceted evaluation of physical performance, only TUG test time demonstrated significant correlations with total hip trabecular vBMD and femoral neck total vBMD. There is a large body of literature in older adults and clinical populations that supports the importance of the TUG test as a predictor of falls and fracture incidence, independent of clinical risk factors and BMD. (46, 47, 49) Prior research studies demonstrate that better TUG performance is associated with a higher BMD at the hip and spine and a lower 10-year fracture risk due to an improved physical function and reduced fall risk. (47, 235-237) In our study, the associations between balance and submaximal aerobic exercise capacity and QCT-measured bone outcomes were not statistically significant, except for a modest association between FAB score and total hip trabecular vBMD. Alternatively, the literature consistently shows a moderate-to-strong inverse association between BMI and mobility. (111, 238, 239) People with severe obesity, especially those with a high fall rate, often present with postural instability and decreased balance performance. (108, 240) Future studies should explore the relationship

between physical performance and bone quality in older, less functionally capable individuals with severe obesity, which would likely yield more clinically significant correlations than those presented herein.

Interestingly, our participants were quite physically active (75% participated in >150 minutes/week of MVPA), performed well on most of the physical performance tests, and were likely not representative of the broader severe obesity population. As such, it is difficult to infer whether similar or more significant associations would be seen in a higher risk group. Our results suggest that participants performed at the upper end of the functional spectrum for the physical performance tests (i.e., a ceiling effect), particularly on the FAB and TUG tests. Specifically, 100% of participants completed the TUG in <13.5 seconds and most participants (94%) scored above 25 on the FAB, indicative of a lower falls risk on both measures. Therefore, the use of more intensive batteries of dynamic balance, aerobic capacity, and functional mobility may have been better suited to capture physical performance and its association with bone outcomes in our sample. Despite these considerations, our findings provide exploratory evidence in support of the possible influence of functional mobility and balance (TUG, FAB) on vBMD in individuals with severe obesity and diabetes.

3.4.4 Associations between Muscle Strength and QCT Bone Outcomes

As expected, moderately strong relationships were observed between functional muscle measures (handgrip and knee extensor strength) and QCT-measured bone outcomes, particularly at the radius and femoral neck. These results are consistent with other studies of the functional muscle-bone relationship that demonstrate a positive association between muscle strength and bone parameters in healthy young and older populations. (241, 242) Interestingly, certain associations were no longer statistically significant after adjusting for age, suggesting that the

muscle-bone relationship in severe obesity may vary by age. With aging, there is a well-known decline in physical activity and functional mobility, contributing to muscle and bone loss and an increased risk of falls and fracture in older adults. There are also non-mechanical muscle factors that can influence bone, referred to as muscle-bone crosstalk. Both muscle and bone are endocrine organs that secrete hormones including leptin, interleukin-6, and insulin-like growth factor-1, which can reciprocally affect muscle and bone metabolism. (243) Additionally, an increase in pro-inflammatory cytokines in severe obesity can further contribute to declines in muscle and bone quality. (7) Our cross-sectional findings provide exploratory insight into the functional muscle-bone relationship in severe obesity, yet further longitudinal investigation in a larger sample is required to determine the strength and direction of this association.

3.4.5 Associations between Physical Performance and QCT Muscle Outcomes

Upper- and lower-body muscle strength tests, and not physical performance, were significantly associated with muscle and intramuscular fat CSA at the upper thigh. These results contrast with existing evidence of significant associations between physical performance, physical activity, and muscle and fat properties in people who are overweight or obese. Notably, most of the previous research on this topic has been conducted in postmenopausal women and older adults with overweight/obesity and T2D. (15, 42, 95-98) Goodpaster et al. (95) found that lower midthigh muscle attenuation values were associated with more intermuscular and subcutaneous thigh adipose tissue; whereas higher muscle attenuation values were associated with greater force production in 2627 healthy men and women aged 70-79 years. This finding was supported by longitudinal studies from Park et al. (15) who found that older adults with long-standing diabetes experienced a greater loss of leg muscle strength and mass compared to older adults without diabetes. Additionally, Park et al. found no differences in arm muscle

strength and quality between groups, suggesting even greater age- and diabetes-related losses are observed in lower-body than upper-body muscle groups, which could translate to decrements in functional performance and mobility. The lack of association between submaximal aerobic capacity (6MWT) and muscle quality is inconsistent with the literature. (244, 245) There are a plethora of studies highlighting the detrimental impact of overweight and obesity on physical performance and muscle size and strength. (9, 48, 49, 111, 113-115) Similarly, people with T2D consistently show poorer results on physical performance and muscle strength tests compared to those without T2D. (119, 159, 160) The inconsistency of our results is likely due to the wide age range and shorter length of T2D diagnosis in our participants in addition to our small sample size. Taken together, our findings suggest the importance of exploring muscle-specific performance as a modifiable target to improve lower-body tissue composition in individuals with severe obesity regardless of T2D status.

3.4.6 Associations between Physical Activity and Bone and Muscle Outcomes

Unlike the muscle strength and physical performance tests, we observed minor or no statistically significant associations between objectively-measured physical activity levels and bone and muscle outcomes in participants with severe obesity with or without T2D. Specifically, accelerometer-measured MVPA was associated with total hip and femoral neck trabecular vBMD but no muscle outcomes. Due to possible measurement bias inherent to the IPAQ, no significant correlations were found with bone and muscle variables suggesting that self-reported physical activity is not as accurate as objective methods consistent with other studies of physical activity patterns in bariatric population. (194) Our participants were mostly physically active despite presenting with severe obesity; 75% of participants met/exceeded recommended physical activity levels known to elicit health benefits. Studies in bariatric populations traditionally report

inactive lifestyles and considerable barriers to physical activity and exercise including time limitations, embarrassment, and avoidance of physical exertion. (192) Based on previous accelerometer studies, bariatric patients perform less MVPA compared to normal-weight controls. (246) In fact, less than 5% of bariatric patients have been found to meet the national physical activity guidelines (>150 minutes per week of MVPA). (246) Due to the favourable activity levels in our cohort, it was not surprising that participants performed well on physical performance measures (TUG, FAB, 6MWT). Thus, our findings may not be generalizable to the broader population with severe obesity. Additionally, accelerometer measures of physical activity intensity/accelerations may have missed valuable information on the type of activity being completed. As such, it is unclear whether participants were adhering to strength and balance exercise recommendations which have greater benefits for musculoskeletal health. Further attention to reporting strength and balance exercise participation would be of interest to fully understand the effects of physical activity on musculoskeletal targets in severe obesity.

Our findings suggest that muscle strength and functional mobility may represent modifiable targets for exercise interventions to improve bone and muscle outcomes in participants with severe obesity and T2D. Accordingly, evidence from longitudinal trials in individuals with obesity and diabetes demonstrate that combined RT and AT interventions may prevent reductions in muscle and bone mass induced by voluntary weight loss. (173-176) Since weight loss is a first-line therapy in bariatric populations, it is important that prescribed interventions support weight loss/management goals in additional to improving musculoskeletal health. A key objective of this study was to inform the design and testing of a future trial investigating the effects of a multimodal exercise program to improve bone and muscle health and prevent falls and fracture in pre-bariatric populations. Based on the exercise preferences

results, a feasible intervention may involve moderate-intensity strength and balance training in either a small group or individual format. Incorporating wearable technology would allow for more intensive monitoring of physical activity adherence and identify safe and effective training parameters (frequency, intensity, type) associated with favourable muscle and bone outcomes. Based on the key barriers identified, targeting motivation and establishing a regular physical activity routine would help to promote exercise behaviour change.

3.4.7 Strengths and Limitations

There were many strengths to this investigation. Primarily, this is a comparative study to explore whether T2D exacerbates muscle and bone outcomes in severe obesity. Several studies have been conducted to assess the role of T2D in declines in musculoskeletal health (15, 117, 153), however, to our knowledge, few studies have directly compared bone and muscle indices using advanced imaging technology in severe obesity with and without T2D. Further, this investigation was a matched cross-sectional study in both sexes across a range of age and functional capacity levels and involved comprehensive, validated measures of physical performance and both objective and self-report physical activity assessments to explore their associations with QCT-derived muscle and bone measures.

Despite the study strengths, there are several limitations worth mentioning. First, the sample size for this investigation is small and as a result, there is a low power to discern statistically significant differences/associations. This investigation is a pilot study to provide new knowledge about the independent and combined influence of severe obesity and T2D on muscle, bone, and physical performance outcomes which can be used to inform larger prospective and multimodal intervention studies. Next, our inclusion criteria focused on wide age range of participants (≥18 years), which reflects the average age of patients undergoing bariatric surgery.

We acknowledge that targeted recruitment of older individuals presenting with long term T2D (≥10 years since diagnosis) may present with a greater incidence of musculoskeletal decline consistent with fragility fractures than the current sample. Thus, future investigations should include more specific eligibility criteria related to age, time since diabetic diagnosis, and comorbidities. We also acknowledge the reporting bias inherent to the IPAQ. Certain participants overestimated the time they spent completing MVPA and underestimated sedentary time. As a result, the range of time spent in MVPA and sedentary behaviour may be inaccurate, making it difficult to draw conclusions from the self-report physical activity data.

3.4.8 Conclusions

Our findings revealed that no significant differences in muscle and bone outcomes were observed between the severe obesity and severe obesity + T2D groups. Knee extensor and handgrip strength tests were moderately associated with QCT-measured bone and muscle outcomes, including total hip trabecular vBMD, femoral neck total, cortical, and trabecular vBMD, radius integral and cortical vBMD, and upper thigh muscle and intramuscular fat CSA. Overall, the observed muscle-bone associations were site-based, highlighting the importance of tailored exercise interventions to target muscle and bone as a unit in severe obesity. Interestingly, physical performance (TUG, FAB) and physical activity measures demonstrated modest or no significant correlations with bone and muscle parameters. This sample was largely an active and functionally capable group, and it is possible that ceiling effects may have influenced the results on the physical performance tests and their associations with QCT measures.

Future studies should consider assessing physical performance and activity-based determinants of muscle and bone outcomes in individuals with severe obesity and T2D at a higher risk of falls and fractures (i.e., older individuals with a longer T2D diagnosis, individuals

with osteoporosis/history of fracture). More intensive physical performance measures may also be explored, such as repeated chair stands, to better capture associations with bone and muscle health. Regardless of the methods and population characteristics, future longitudinal research should include a larger, closely matched sample comparing muscle-bone quality determinants in severe obesity with and without T2D, with equal representation of sex.

Chapter 4: References

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Chapter 5: Tables and Figures

Table 5.1. Study Objectives and Analysis Plan

Primary Research Question	Independent Variable	Dependent Variable	Method of Analysis
Is there an association between physical performance and muscle quality in severely obese adults?	6-minute walk test, Timed up and go, Fullerton Advanced Balance scale	Absolute and relative grip strength and knee extensor muscle strength Muscle cross-sectional area and density of the lumbar region, quadriceps, calf (QCT)	Pearson/Spearman correlations
Secondary Research Questions			
Is there an association between physical performance and bone quality in severely obese adults?	6-minute walk test, Timed up and go, Fullerton Advanced Balance scale	Bone mass and strength at proximal femur, radius (QCT) and lumbar spine aBMD (DXA)	Pearson/Spearman correlations
Is there an association between physical activity and muscle quality in severely obese adults?	Moderate-to-vigorous PA (Accel, IPAQ) Exercise barriers scale Life-space mobility	Absolute and relative grip strength and knee extensor muscle strength Muscle cross-sectional area and density of the lumbar region, quadriceps, calf (QCT)	Pearson/Spearman correlations
Is there an association between physical activity and bone quality in severely obese adults?	Moderate-to-vigorous PA (Accel, IPAQ) Exercise barriers scale Life-space mobility	Bone mass and strength at proximal femur, radius (QCT) and lumbar spine aBMD (DXA)	Pearson/Spearman correlations
Is there an association between muscle strength and bone quality in severely obese adults?	Absolute and relative grip strength and knee extensor muscle strength	Bone mass and strength at proximal femur, radius (QCT) and lumbar spine aBMD (DXA)	Pearson/Spearman correlations
Is there an association between diabetes status and muscle quality?	Diabetes status (with versus without T2D)	Absolute and relative grip strength and knee extensor muscle strength Muscle cross-sectional area and density of the lumbar region, quadriceps, and calf (QCT)	Independent t-tests
Is there an association between diabetes status and bone quality?	Diabetes status (with versus without T2D)	Bone mass and strength proximal femur, radius (QCT)	Independent t-tests

Table 5.2. Study Outcomes and Assessments

Bone Quality Outcomes	
Bone mass and strength	Proximal femur, and distal radius vBMD, cortical thickness, and unidirectional stiffness and strength by QCT Lumbar spine (L1-L4), femoral neck, total hip, and radius aBMD by DXA
Fractures	Clinical fractures (Questionnaire)
Muscle Quality Outcomes	
Soft tissue composition (muscle, fat)	Quadriceps muscle and fat cross-sectional area by QCT
Muscle strength	Absolute and relative muscle strength at lower limb (knee extensor strength) and at upper limb (handgrip strength)
Physical Performance Outcomes	
Mobility	Timed up and go test
Aerobic capacity	6-minute walk test
Balance	Fullerton advanced balance scale
Physical activity	Accelerometry, questionnaires (life-space mobility assessment, international physical activity questionnaire short version, exercise barriers and preferences)

Note: BMI: vBMD: volumetric bone mineral density; QCT: quantitative computed tomography; aBMD: areal bone mineral density; DXA: dual-energy X-ray absorptiometry

Table 5.3 Descriptive characteristics in study participants

	All (n=33)	Severe Obesity (n=17)	Severe Obesity + T2D (n=16)	p-value
Age (years)	44.4 ± 11.1	41.3 ± 13.4	47.8 ± 7	0.089
Female	26 (79%)	13 (77%)	13 (81%)	0.737
Height (cm)	1.65 ± 0.8	1.66 ± 0.08	1.64 ± 0.08	0.552
Weight (kg)	111.03 ± 16.3	113.1 ± 17.8	108.8 ± 14.7	0.753
BMI (kg/m^2)	40.4 ± 3.8	40.6 ± 3.8	40.1 ± 4	0.394
Percent Body Fat (%)	49.4 ± 5.1	49.6 ± 5.9	49.2 ± 4.2	0.208
Fat Mass (kg)	52.6 ± 9.3	53.7 ± 8.7	51.2 ± 10.2	0.726
Lean Body Mass (kg)	54.0 ± 10.8	55.20 ± 12.8	52.5 ± 7.7	0.670
Waist Circumference (cm)	124.1 ± 12.0	122.4 ± 13.6	125.9 ± 9	0.415
Systolic Blood Pressure (mmHg)	129.4 ± 14.1	129.8 ± 14.7	128.9 ± 13.7	0.185
Diastolic Blood Pressure (mmHg)	81.2 ± 12.6	84.1 ± 14.6	78.1 ± 9.6	1.369
Time Since T2D Diagnosis (Years)	N/A	N/A	3.2 ± 3.6	-
HbA1C Levels (mmol/mol)	0.06 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	<0.001
Ethnicity				0.396
White	30 (91%)	14 (82%)	15 (94%)	
Black	1 (3%)	1 (6%)	0 (0%)	
Asian	1 (3%)	1 (6%)	0 (0%)	
First Nation	1 (3%)	0 (0%)	1 (6%)	
Education Level				0.883
Academic	11 (33%)	6 (35%)	5 (31%)	
Collegial	9 (27%)	5 (30%)	4 (25%)	
Secondary	13 (40%)	6 (35%)	7 (44%)	
Employment Status				0.504
Student	1 (3%)	1 (6%)	0 (0%)	
Employed	25 (93%)	15 (88%)	15 (93%)	
Unemployed	1 (3%)	0 (0%)	1 (6%)	
Weight Change in Last 3 Months				0.015
Gained	4 (12%)	4 (24%)	0 (0%)	
Loss	13 (40%)	3 (17%)	10 (63%)	
Stable	14 (42%)	10 (59%)	4 (25%)	
Post-Menopausal Status	5 (19%)	3 (23%)	2 (15%)	
Osteoporosis Diagnosis	1 (3%)	1 (6%)	0 (0%)	0.212

Non-traumatic Fracture	1 (3%)	1 (6%)	0 (0%)	0.034
Falls	12 (37%)	5 (29%)	7 (44%)	0.163
Alcohol Use (Servings Per Week)	3.8 ± 6.1	5.1 ± 7.8	2.5 ± 3.4	0.310
History of Smoking	12 (37%)	2 (12%)	10 (63%)	
Cortisone Use	1 (3%)	0 (0%)	1 (6%)	0.295
Comorbidities				
Hypertension	8 (24%)	7 (41%)	1 (6%)	
Kidney Disease	3 (9%)	1 (6%)	2 (12%)	
Asthma	3 (9%)	2 (12%)	1 (6%)	
CVD	5 (15%)	2 (12%)	3 (19%)	
GI disorder	4 (12%)	1 (6%)	3 (19%)	
Depression	3 (9%)	2 (12%)	1 (6%)	
Liver Disease	3 (9%)	3 (18%)	0 (0%)	
Bursitis	1 (3%)	1 (6%)	0 (0%)	
Dyslipidemia	6 (18%)	2 (12%)	4 (25%)	
Endometriosis	4 (12%)	1 (6%)	3 (19%)	
Sleep Apnea	2 (6%)	1 (6%)	1 (6%)	
Arthritis	1 (3%)	1 (6%)	0 (0%)	
PCOS	1 (3%)	1 (6%)	0 (0%)	

Note: BMI: Body Mass Index; HbA1C: Hemoglobin A1c; CVD: Cardiovascular disease; GI: Gastrointestinal; PCOS: Polycystic ovarian syndrome

Table 5.4 Physical performance and physical activity outcomes in severe obesity and severe obesity and T2D groups.

	All (n=33)	**Severe Obesity (n=17)**	**Severe Obesity + T2D (n=16)**	**p-value**
Muscle Strength				
Handgrip: Absolute (kg)	33.7 ± 9.1	34.6 ± 2.2	32.7 ± 9.5	0.580
Knee Extensor: Absolute (Nm)	214.7 ± 74.2	215.6 ± 18.3	213.5 ± 75.3	0.938
Handgrip: Adjusted for weight	0.302 ± 0.069	0.308 ± 0.067	0.297 ± 0.072	0.659
Knee Extensor: Adjusted for weight (Nm/kg)	1.908 ± 0.509	1.89 ± 0.509	1.93 ± 0.529	0.852
Physical Performance				
TUG (Time, s)	7.26 ± 1.54	7.50 ± 0.40	7.00 ± 1.60	0.328
FAB Score	32.6 ± 4.0	33 ± 0.7	32.1 ± 5.0	0.517
6MWT: Distance (m)	487.31 ± 72.4	479.79 ± 10.5	500.2 ± 107.2	0.578
6MWT: Borg RPE	5.00 ± 2.70	4.00 ± 2.60	6.80 ± 1.90	0.015
IPAQ				
MVPA (minutes/week)	307.0 ± 624.5	499.3 ± 855.6	138.8 ± 234.4	0.148
Walking (minutes/week)	724.5 ± 1833.8	996.8 ± 2424.0	435.3 ± 856.3	0.388
Sedentary time (hours/day)	4.91 ± 3.8	5.53 ± 3.3	4.55 ± 4.4	0.470
Accelerometer				
MVPA (minutes/week)	293.4 ± 197.6	265.8 ± 160.0	241.2 ± 84.1	0.174
Light (minutes/week)	1802.9 ± 617.0	1702.5 ± 603.6	1896.6 ± 635.3	0.407
Sedentary time (minutes/week)	5257.4 ± 1344	4961.6 ± 1453.1	5533.4 ± 1219.3	0.260
Life Space Mobility	N/A	73.1 ± 34.9	N/A	N/A

Note: T2D: Type 2 Diabetes; kg: kilogram; Nm: Newton metre; s: seconds; m: metres; RPE: rate of perceived exertion

Table 5.5 Bone and muscle outcomes in severe obesity and severe obesity + T2D groups.

	Severe Obesity (n=17)	**Severe Obesity + Diabetes (n=16)**	**p-value**
Total Hip QCT			
Total vBMD (mg/cm^2)	461.9 ± 19.5	453.5 ± 68.9	0.756
Trabecular vBMD (mg/cm^2)	148.4 ± 21.9	139.8 ± 16.2	0.226
Cortical vBMD (mg/cm^2)	1028.1 ± 55.2	1061.6 ± 57.8	0.105
Femoral Neck QCT			
Total vBMD (mg/cm^2)	359.7 ± 13.2	355.6 ± 41.6	0.811
Trabecular vBMD (mg/cm^2)	153.6 ± 27.1	140.0 ± 19.0	0.113
Cortical vBMD (mg/cm^2)	986.7 ± 103.6	1059.4 ± 79.3	0.035
Cortical thickness (cm)	2.50 ± 0.6	2.45 ± 0.44	0.776
Radius QCT			
Integral vBMD (mg/cm^2)	0.58 ±0.05	0.56 ± 0.05	0.329
Trabecular vBMD (mg/cm^2)	0.12 ±0.01	0.12 ± 0.01	0.185
Cortical vBMD (mg/cm^2)	0.86 ±0.04	0.84 ± 0.04	0.198
Cortical thickness (cm)	3.4 ±0.4	3.32 ± 0.40	0.471
Lumbar Spine (L1-L4) DXA			
L1-L4 aBMD (mg/cm^2)	1.30 ± 0.2	1.24 ± 0.13	0.351
Total Hip DXA			
Total Hip aBMD (mg/cm^2)	1.16 ± 0.2	1.13 ± 0.15	0.557
Femoral Neck DXA			
Femoral Neck aBMD (mg/cm^2)	1.10 ± 0.2	1.03 ± 0.16	0.235
Upper Leg Muscle			
Thigh muscle CSA (mm^2)	146.9 ± 37.0	142.8 ± 17.9	0.708
Subcutaneous fat CSA (mm^2)	179.8 ± 60.3	164.0 ± 38.1	0.457
Thigh intramuscular fat CSA (mm^2)	18.8 ± 13.3	15.0 ± 5.6	0.377

Note: QCT: quantitative computed tomography; vBMD: volumetric bone mineral density; mg: milligram; cm: centimetre; CSA: cross-sectional area; DXA: dual-energy x-ray absorptiometry; aBMD: areal bone mineral density; mm: millimetres

Table 5.6 Correlations between physical performance and physical activity and bone outcomes in severe obesity and severe obesity + T2D groups.

	Total Hip Total vBMD (mg/cm^2)		Total Hip Cortical vBMD (mg/cm^2)		Total Hip Trabecular vBMD (mg/cm^2)		Femoral Neck Total vBMD (mg/cm^2)		Femoral Neck Cortical vBMD (mg/cm^2)		Femoral Neck Trabecular vBMD (mg/cm^2)		Radius Integral vBMD (mg/cm^2)		Radius Cortical vBMD (mg/cm^2)		Radius Trabecular vBMD (mg/cm^2)		Radius Cortical Thickness (cm)	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Knee Extensor Strength (Nm)	0.320	0.091	-0.231	0.228	**0.514**	0.004	**0.447**	0.015	**-0.486**	0.008	**0.546**	0.002	**0.532**a	0.003	**0.620**a	0.000	-0.160	0.399	**0.642** a	0.000
Handgrip Strength (kg)	0.301	0.100	-0.144	0.438	**0.367**	0.042	**0.361**	0.046	**-0.538**	0.002	**0.490** a	0.005	**0.62**a	0.000	**0.697**a	0.000	-0.118	0.520	**0.647**a	0.000
Timed Up & Go (Time, s)	-0.212	0.253	0.136	0.466	**-0.488**	0.005	**-0.415**a	0.020	0.114	0.541	-0.308	0.009	0.014	0.951	-0.120	0.513	-0.170 a	0.351	-0.233	0.200
6 Minute Walk Test (Distance, m)	0.291	0.149	0.143	0.487	0.316	0.115	0.266	0.190	-0.049	0.812	0.268	0.185	0.058	0.791	0.166	0.407	0.246	0.215	0.345	0.078
Fullerton Advanced Balance Scale r	0.266	0.148	-0.222	0.248	**0.501**	0.005	0.282	0.124	0.052	0.780	0.299	0.102	0.023	0.918	0.000	0.998	0.021	0.909	0.058	0.755
IPAQ MVPA r	0.078	0.686	0.020	0.918	0.151	0.435	0.106	0.585	0.020	0.918	0.151	0.435	-0.271	0.147	-0.226	0.230	0.112	0.554	-0.225	0.231
IPAQ Sedentary Time	0.002	0.992	0.079	0.667	-0.180	0.325	-0.220 a	0.226	0.155 a	0.296	-0.085	0.645	-0.265	0.151	-0.126	0.486	-0.152 a	0.397	-0.185	0.304
Accelerometer MVPA	-0.174	0.385	-0.292 a	0.139	**0.460**	0.016	0.092	0.649	-0.016	0.936	**0.470**	0.013	0.034	0.864	0.000	1.000	0.062	0.754	0.117	0.554
Accelerometer Light Time	0.069	0.727	0.197	0.315	0.093	0.639	0.009	0.965	-0.007	0.972	0.176	0.371	0.191	0.322	0.121	0.531	0.063 a	0.744	0.233	0.224
Accelerometer Sedentary Time	-0.023	0.908	-0.119a	0.545	0.058	0.770	-0.009	0.965	-0.131	0.507	0.044	0.824	-0.123	0.524	-0.011	0.955	-0.298	0.117	0.016	0.933

r = Spearman Correlation

a = significant when adjusted for age

Note: vBMD: volumetric bone mineral density; mg/cm^2: milligram per centimetre squared; cm: centimetre; Nm: Newton metre; kg: kilogram; s: seconds; m: metres; IPAQ: International Physical Activity Questionnaire; MVPA: moderate-to-vigorous physical activity

Table 5.7 Correlations between physical performance and physical activity and muscle outcomes in severe obesity and severe obesity + T2D groups.

	Upper Thigh Muscle CSA (mm^2)		Upper Thigh Intramuscular Fat (mm^2)		Upper Thigh Subcutaneous Fat (mm^2)	
	r	P	r	p	r	p
Knee Extensor Strength (Nm)	**0.546** a	0.006	**0.790** a	0.000	-0.270	0.225
Handgrip Strength (kg)	**0.442**	0.024	**0.707** a	0.000	-0.128	0.552
Timed Up & Go (Time, s)	0.103	0.616	-0.018	0.932	0.272	0.198
6 Minute Walk Test (Distance, m)	0.162	0.429	-0.021	0.919	**-0.434**	0.034
Fullerton Advanced Balance Scale ṛ	-0.240	0.237	-0.109	0.597	-0.132	0.538
IPAQ MVPA ṛ	-0.199	0.352	0.041	0.849	0.07 a	0.758
IPAQ Sedentary Time	-0.048	0.811	-0.078	0.700	0.137	0.513
Accelerometer MVPA	0.201	0.359	0.333	0.120	0.081	0.727
Accelerometer Light Time	0.031	0.887	0.128	0.551	-0.257	0.248
Accelerometer Sedentary Time	0.034	0.875	0.079	0.713	0.114	0.612

Note: mm^2: milometers squared; Nm: Newton metres: kg: kilograms; s: seconds; m: metres; IPAQ: International Physical Activity Questionnaire; MVPA: moderate-to-vigorous physical activity

ṛ = Spearman Correlation
a = significant when adjusted for age

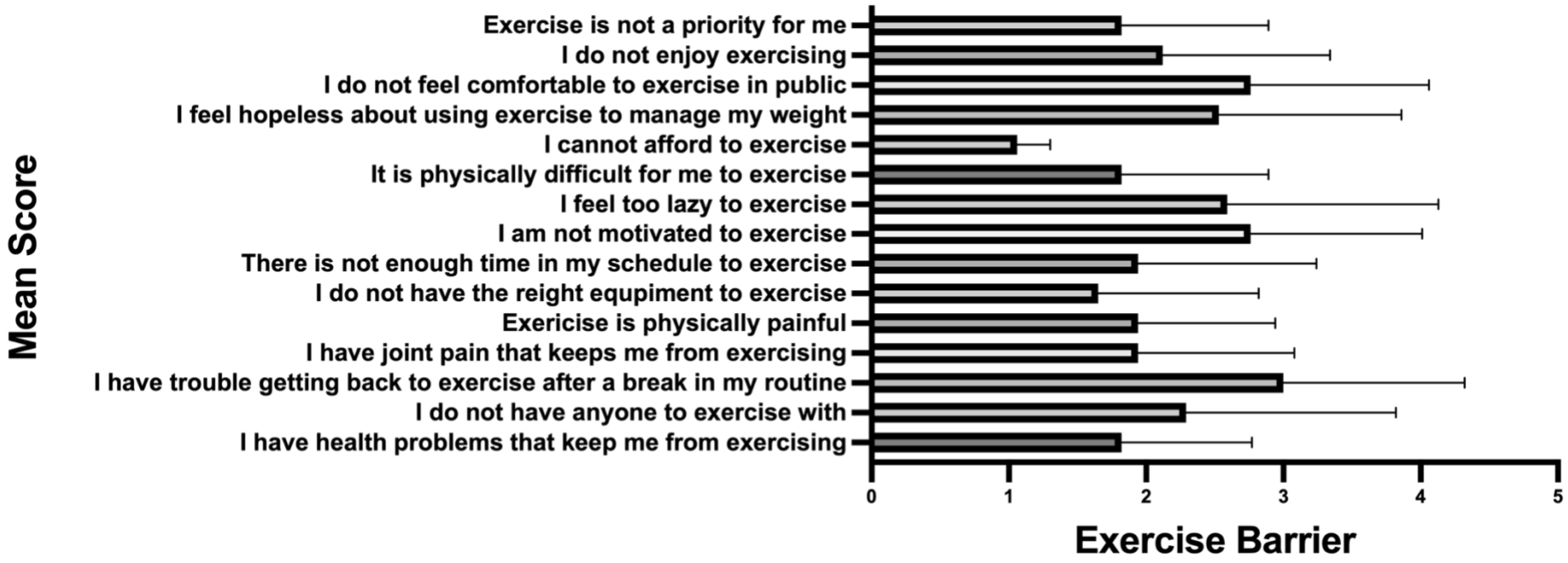

Figure 1. Bar graph of the mean score (1 = never true, 5= always true) of exercise barriers based on the responses from the exercise barrier and preferences survey

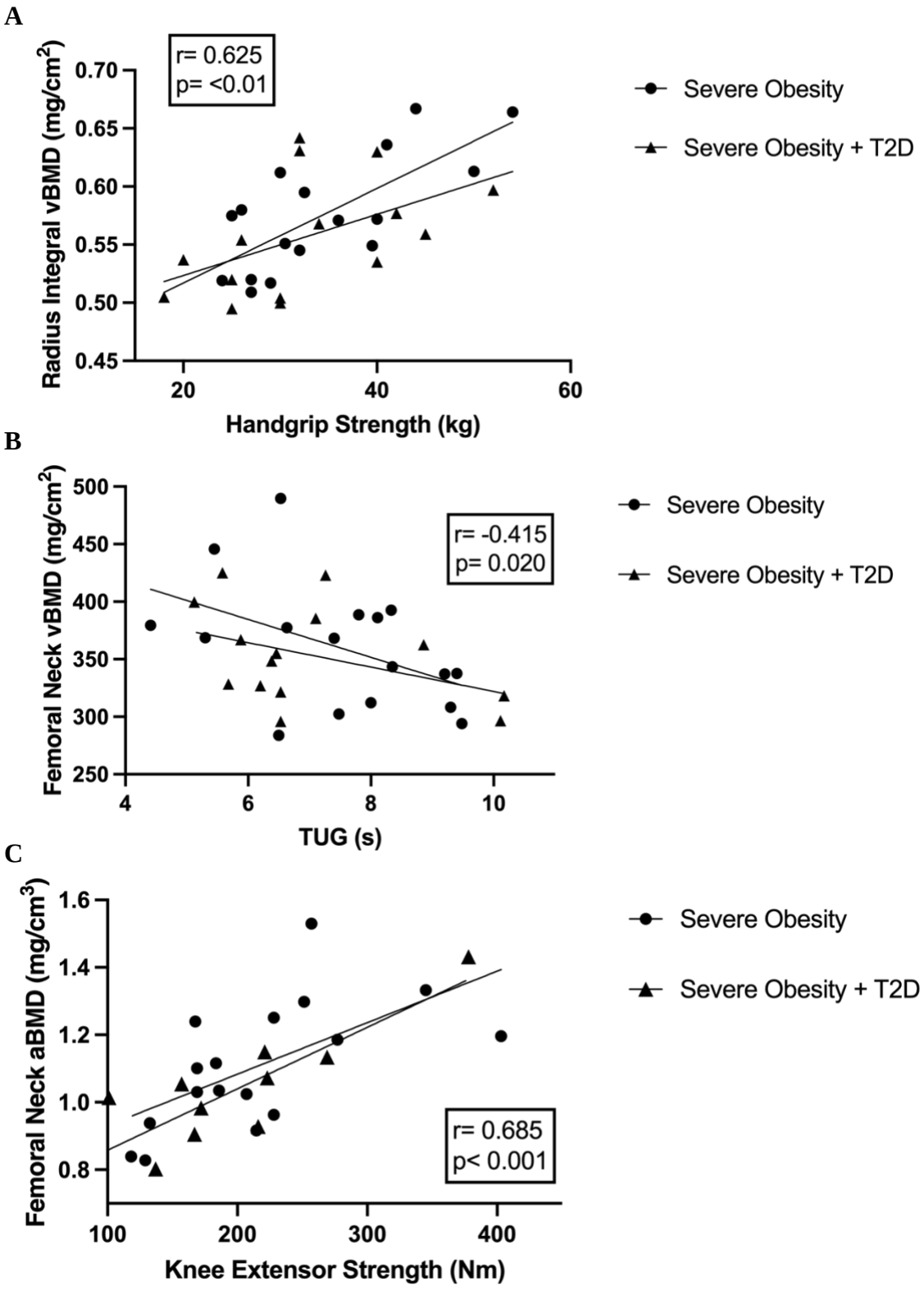

Figure 2. Scatterplots depicting the relationship between A) Handgrip strength (kg) and radius integral vBMD (mg/cm^2) B) TUG time (s) and femoral neck vBMD (mg/cm^2) and C) knee extensor strength (Nm) and femoral neck aBMD (mg/cm^3) in the severe obesity and severe obesity + T2D groups