OBESITY, BARIATRIC SURGERY, AND BONE STRENGTH: A REVIEW AND
STUDIES IN ADULT COHORTS

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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May 2011

Acknowledgements

I must first thank my advisor, Moira Petit, for providing me the opportunity to embark on a course of study that I have so thoroughly enjoyed. In addition, my fellow lab mates have been a fantastic source of inspiration, support and laughter over the past few years.

The support of my friends, family, and my amazing husband helped me to maintain perspective when it seemed as though I would never leave my office. I will always be grateful for their support.

Dedication

This dissertation is dedicated to my husband, Roman Scibora, who continues to be my greatest source of support.

Abstract

Bone mass and strength changes proceeding weight loss in obese individuals are important for determining risk for skeletal fragility. Understanding the relationship between obesity and bone strength is significant for describing bone's response to changes in body composition. The three manuscripts presented in this dissertation focus on obese adult populations (aged 18 – 64 years). Peripheral quantitative computed tomography (pQCT) was used to assess volumetric bone mineral density, bone geometry, indices of bone strength, and muscle cross-sectional area. Manuscript I reviews the association between bariatric surgery, changes in bone mineral density, and osteoporosis. The review demonstrated significant loss of bone density at hip and spine sites in the first year following bariatric procedures. However, existing research fails to support the concern over risk of osteoporosis in these individuals. Manuscript II of this dissertation, a cross-sectional study, demonstrated that despite greater absolute bone strength observed in obese women compared to their healthy-weight counterparts, bone strength was low relative to their high body weight. Manuscript III was a prospective observational pilot study to examine changes in bone strength and body composition in morbidly obese adults submitted for bariatric surgery. The results showed that bariatric surgery produced significant weight loss that was predominately due to reduction in fat mass, rather that fat-free mass. Despite significant weight loss bone strength indices were not compromised, suggesting that maintenance of lean mass may preserve bone strength. This dissertation contributes to the knowledge base in several ways. First, it provides a comprehensive summary of bariatric surgery and bone density research, while providing an alternative perspective for interpreting dual x-ray absorptiometry-based bone outcomes. Second, bone strength was assessed using pQCT, which provides an understanding of bone from a mechanical perspective that has not been used when interpreting bone outcomes in severely obese populations. Finally, this dissertation includes the first known study to examine changes in bone strength following bariatric surgery in morbidly obese individuals.

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Rationale, Specific Aims, and Hypotheses

1.1 Rationale

Understanding the relationships between obesity, weight loss, and bone health has important theoretical and clinical implications for preventing skeletal fragility and reducing fracture risk. Research in both animals and humans suggest that bone is primarily responsive to its mechanical loading environment and that forces provided by muscle are an independent determinant of bone strength[1, 2]. The current knowledge between body weight and bone, and the effects of weight loss on bone health have been predominately based on studies using dual energy x-ray absorptiometry (DXA) providing outcomes of bone mass and areal bone mineral density. While much has been learned from these studies, future studies are needed to explore bone responses to mechanical loading using new technology that assesses bone volumetric density, bone geometry and bone strength.

Overall, there are several gaps in the adult body weight, weight loss and bone literature that this dissertation will address:

1) Many studies in overweight and obese individuals have lacked a theoretical approach in understanding the effects of body weight and weight loss on bone. They rely on a plethora of factors, with little emphasis on the role of lean mass-generated mechanical loading, to explain outcomes of bone mass or mineral density. The mechanostat and theories of functional adaptation provide an alternative approach to understanding and interpretation of seemingly contradictory findings.

2) While significant bone loss is reported to occur following rapid and substantial weight loss induced by bariatric surgery, there is not a comprehensive summary of the association between bariatric surgery and changes in bone mineral density or its effect on the development of osteoporosis. It is important to understand and interpret the implications of weight loss surgery on skeletal health.

3) Published studies examining the effect of bariatric surgery on bone health have relied on DXA-based bone mass and areal bone mineral density outcomes. However, this

technology is not able to consider the geometric or strength changes known to occur subsequent to changes in mechanical loading. Further, DXA's technological limitations in obese populations may preclude accurate assessments of prospective bone changes following substantial weight loss. Thus, there is a need to employ newer technologies, such as pQCT, to examine changes in bone volumetric density, geometry and strength after bariatric surgery.

The overall purpose of the dissertation is to explore the effect of mechanical loading via body weight and its components on bone in obese cohorts. This dissertation consists of three manuscripts that address components related to the overall purpose. The first manuscript reviews the bariatric surgery literature, focusing on bone density studies and outcomes of osteoporosis incidence (Specific Aim 1). The reviewed studies were gathered through a PubMed search using the key words 'bariatric surgery',' weight loss surgery', 'obesity surgery', 'bone', 'bone mass', 'bone mineral density', and 'bone strength'. The second manuscript explores differences in bone strength, relative to body weight and muscle, in obese adult women compared to healthy weight women (Specific Aim 2). The data in healthy weight women was drawn from the Women in Steady Exercise Research study at the University of Minnesota. The obese women data was collected by recruiting through the University of Minnesota Weight Loss Surgery Center and from community-based nutritional weight management classes, prior to weight loss. The third manuscript examines changes in body weight, body composition and bone strength in a morbidly obese cohort undergoing bariatric surgery for weight loss (Specific Aim 3). The data collected for this study comes from morbidly obese adults recruited from pre-operative bariatric patient education classes at the University of Minnesota Weight Loss Surgery Center. The specific aims and hypotheses for each manuscript are addressed below.

1.2 Specific Aims and Hypotheses

Specific Aim 1: To comprehensively review the association between bariatric surgery, bone mineral density and osteoporosis incidence. This aim is accomplished by summarizing and interpreting studies reporting bone mineral density and osteoporosis outcomes in the bariatric surgery literature.

Specific Aim 2: To examine the effect of body weight and lean mass (muscle cross-sectional area) on differences in bone volumetric density, bone geometry, and estimates of bone strength in obese and healthy weight women.

The *primary hypothesis* for this aim is that obese women will have greater absolute estimates of bone strength, due to greater bone area, compared to healthy weight women. The *secondary hypothesis* is that estimates of bone strength in obese women will be low relative to their body weight.

Specific Aim 3: To prospectively examine the effect of bariatric surgery on body weight, body composition (fat mass, fat-free mass, and muscle cross-sectional area), bone volumetric density, bone geometry and estimates of bone strength in a morbidly obese adult cohort.

The *primary hypothesis* for this aim is that body weight will be significantly reduced, primarily due to a reduction in fat mass, following bariatric surgery for weight loss. The *secondary hypothesis* is that bone strength will decrease, secondary to substantial weight loss, following bariatric surgery.

2

Literature Review

2.1 Introduction

Osteoporosis is a disorder of compromised bone strength leading to skeletal fragility and increased risk of fracture, and is a significant public health concern. After the age of 50 years, nearly 60% of women and 30% of men will experience an osteoporotic fracture[1, 2]. Among individuals who lose weight without surgery, epidemiological evidence supports increased rates of hip bone loss in older individuals, irrespective of body mass index or intention to lose weight[3, 4], and an increased risk for hip fracture in middle-aged and older women[5]. Importantly, death occurs in approximately 20% of individuals in the first year following a hip fracture[6]. Skeletal fragility results from loss of bone mass[7], poor bone structure and geometry[8, 9], and an age-associated inability to sufficiently repair microdamage[10]. Therefore, studies that examine bone parameters related to skeletal fragility secondary to weight loss are important for development of future clinical and public health strategies to prevent osteoporosis and fracture in at-risk populations.

The following literature review is separated into two parts. In Part I, I provide a background of bone biology, bone growth, measurement, and the theoretical framework pertinent to all three specific aims. In Part II, I review literature pertinent to the three manuscripts of this dissertation: (1) a review of bariatric surgery and bone density studies; (2) the effect of obesity on bone in adult women; and (3) the effect of bariatric surgery on body composition and bone in a morbidly obese adult cohort.

Part I: Overview and Theoretical Framework

2.2 Bone Biology and Function

As a living, dynamic and adaptive tissue that is constantly replenished over the course of a lifetime, bone serves numerous functions. The primary function of the skeleton is body locomotion, which is achieved when bone functions to maintain stiffness and strength for the purpose of resisting deformation from internal (primarily muscle forces) and external loads[11, 12]. The bony skeleton protects internal organs, provides multiple attachment sites for muscles, ligaments and tendons, and functions as levers for locomotion. It also serves as the body's main calcium reservoir and as a site for hematopoiesis (formation of blood cells)[13, 14]. Bone's functional capacity that

allows efficient locomotion must be maintained throughout the lifespan. The optimal functioning of bone tissue, and of whole bones, is significantly influenced by bone's mechanical properties.

2.2.1 Bone Tissue: Composition and Organization

Bone tissue is a composite material, comprised of both calcium hydroxyapatite (inorganic phase), and type I collagen (organic phase). Collagen, an organic fibrous protein organized into fibrils, is the major structural component of bone matrix and give bone its flexibility and tensile strength. Inorganic mineral crystals, which give bone rigidity and compressive strength, surround and fill the collagen fibrils[15].

Bone is structured into cortical (or compact) and trabecular (spongy or cancellous) bone[16]. Both cortical and trabecular bone are found throughout both the axial and appendicular skeleton. Despite an analogous composition, their distinctive structures portend their mechanical structural and functional properties[17]. On one hand, trabecular bone exists as a three-dimensional lattice structure composed of individual trabeculae (struts and plates) and is found at the medullary cavities of long bones (i.e. tibia) and in the vertebral bodies. The highly porous trabecular bone (75-95%), with its vast surface area and marrow cavity, provides an environment for metabolic activities such as bone turnover and hematopoiesis.

In contrast, cortical bone is arranged cylindrically and is significantly less porous (5-10%) than trabecular bone[18]. Haversian bone (secondary osteons) is the most complex form of cortical bone. The osteons are densely arranged in cylindrical channels of vasculature surrounded circumferentially by lamellae of bone. The high density of this cortical bone (80-90% for cortical bone vs. 15-25% for trabecular bone) primarily protects internal organs and provides mechanical structure[15].

2.2.2 Whole Bone Structure

Within the human skeleton, bones can be roughly grouped as either long (e.g. tibia), short (e.g. metacarpal), flat (e.g. skull or scapula), irregular (e.g. vertebrae) or sesamoid (e.g. patella)[19]. This review will focus on long bones. As illustrated in Figure 1, a growing long bone is constructed of a cylindrical diaphysis that widens at both ends (the epiphyses). Separating the epiphyses from the diaphysis is layer of cartilage called growth plates, which are the sites of endochondral ossification. The periphery of the long bone diaphysis is composed of cortical bone, with an

internal medullary (marrow) cavity containing bone marrow. The funnel-shaped metaphyses are transitional zones comprised of both cortical and trabecular bone. Finally, epiphyseal ends of the long bones are filled with trabecular bone[20]. The broad epiphyses are optimally shaped to distribute forces at the joints and reduce stress (force per unit area) transmitted from trabecular bone in the metaphysis to cortical bone in the diaphysis[21].
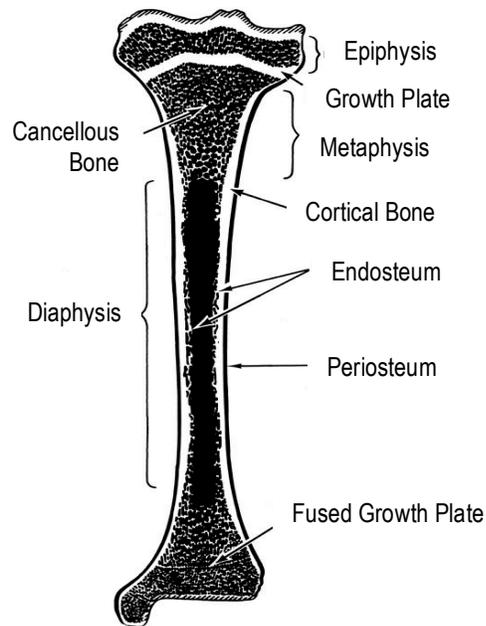
FIGURE 2-1. Illustration of a growing long bone. Adapted from Jee et al.[22]

As a result of the organization of cortical and trabecular compartments, two bone surfaces maintain soft tissue contact [17]. The internal (endosteal surface or endosteum) and the external surface (periosteal surface or periosteum) of cortical bone are lined with osteogenic cells, and are are sites for bone tissue turnover. Each of three cell types (osteoblasts, osteoclasts, and osteocytes) found in bone have a specific role in regulating bone turnover [23]. Osteoblasts, or bone-forming cells, secrete unmineralized protein (osteoid) that forms the basic framework of bone tissue. Once the osteoid is mineralized, it becomes an osteocyte, the predominant cell in fully formed bone. Osteoclasts, or bone resorbing cells, are found mainly in cavities on bone surfaces called resorption pits. They secrete lysosomal enzymes and hydrogen ions that function to dissolve bone matrix. During growth, osteoblasts and osteoclasts function to either independently to modify the size and shape of bones or in concert to repair and maintain bone.

2.3 Bone Response to Mechanical Loading

To serve its most primary function, bone has evolved to achieve a structural design for optimizing strength, which will bear the mechanical loads of daily life and prevent fracture later in life. To withstand the complex functional requirements imposed on the skeleton requires that bone, as an organ, meet those demands[24]. Tissue-level characteristics of bone define its *material properties* that contribute to overall bone strength. These material properties of bone are best understood by understanding the basic biomechanics. Bone is subjected to forces (mechanical loading) generated mainly from muscle contractions and ground reactive forces comprised of any number of complex patterns. Those patterns of force can be distilled into three fundamental types: tension, compression, and shear forces [25]. It is unlikely that bone will experience any of these exclusively, but will be subject to myriad combinations of these basic forces. Under conditions of loading, bone will experience deformation from its original dimensions. This phenomenon is known as **strain**, and is defined as the change in length of the bone divided by the bone's original length [25]. In addition, an internal resistance of equivalent magnitude opposite the applied load is generated, referred to as **stress**, and is measured by force (Newton) divided by the area (m^2) of bone over which it acts[26].

2.3.1 Stress and Strain

The four *material properties* of strength, stiffness, toughness and deformation can be derived from the stress-strain curve (Figure 2). The stress-strain plot illustrates the relationship between loading (stress) and deformation (strain). The slope of the linear portion of the curve represents the material **stiffness**, or the Young's modulus (**elastic region**). Stresses on bone prior to the **yield point**, will produce a temporary deformation. That is, the bone will assume its original shape upon removal of the load. The **yield point** signifies the limit of the elastic region. Beyond this point, loading will induce permanent deformation (**plastic region**) up to the point of maximum stress, which will inevitably result in **failure** (fracture) of the bone [25]. The ability of bone to absorb energy, its material **toughness**, is measured by the area under the curve. As bone becomes tougher, it is able to effectively absorb greater loading stresses and becomes more

resistant to fracture [27]. Long bones are uniquely prepared to bear the loads imposed upon them due to their unique balance of stiffness and toughness [21].
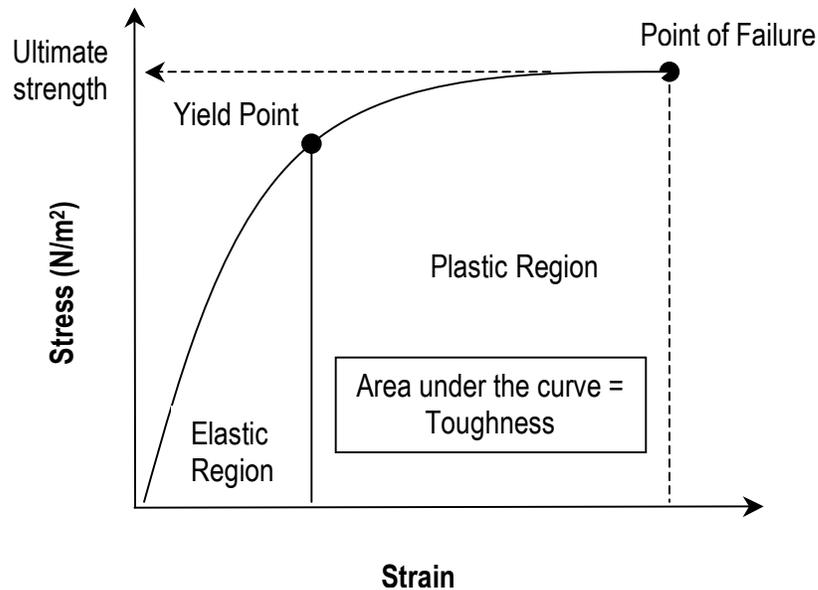
Figure 2-2. A standard stress/strain curve of a bone specimen produced during mechanical testing. This curve can also be used to represent whole bone properties (load/deformation curve). Adapted from Einhorn [25].

Bone's material *quality* is also an important component of the stress-strain relationship. As bone becomes more mineralized (less stiff), tissue toughness increases so that loading stresses will generally produce minimal strains (deformation). However, poorly mineralized bone generally experiences larger deformation (strains) in response to an equivalent loading stress[25]. Furthermore, the material properties in both cortical and trabecular bone compartments influence their mechanical properties. Within cortical bone secondary osteons influence mechanical integrity through the orientation of collagen fibers, degree of mineralization, and overall porosity. In addition, repair of aging bone or fatigue-induced microdamage also influences the mechanical integrity of cortical bone[28].

Trabecular bone's unique heterogeneity of tissue, which persists across skeletal sites, ages, and species[29], results in differing mechanical properties. Variations in porosity (or apparent density), the material properties of individual trabeculae (thickness), and orientation (anisotropy) of trabecular architecture[29, 30] all function to influence trabecular tissue integrity. The architecture of

trabecular bone provides the requirements for optimal load transfer by combining appropriate strength and stiffness with minimal weight[31, 32].

2.4 Bone Functional Adaptation and Mechanostat Theory

Given that the skeleton functions as a system of rigid levers acted on by muscles to hold the body upright and locomote, it follows that bone is primarily sensitive to its mechanical loading environment. Under continual exposure to a changing loading environment throughout life, the skeleton is sculpted and shaped to meet its mechanical demands. This relationship between physical loads and bone structure was theorized over a century ago by Roux [33] and is commonly referred to as *bone functional adaptation*[34-37]. In recent decades, theories of bone functional adaptation were further developed by Harold Frost - who coined the term 'mechanostat'. Frost claimed that load-bearing bone strength appropriately adapts to its typical peak voluntary mechanical loading environment for the prevention of nontraumatic fractures. Specifically, the mechanostat theory postulates that skeletal physiology is regulated by interconnected negative feedback loops, influenced by both mechanical and non-mechanical factors[38, 39], with the goal of maintaining a "customary" strain level in the presence of bone strain[40]. Similar to the thermostat in a room designed to maintain temperature within a narrow range, Frost suggested that bone adapts it mass or strength to keep strain (deformation) within a certain range or "thresholds". For example, an increase in bone strain, through an increase in physical activity, results in bone formation, which in turn reduces bone strain to its original customary level. The corollary is that a decrease in bone strain, through a decrease in physical activity, results in bone resorption, which in turn returns strain to its customary level. Despite the fact that skeletal physiology functionally adapts to customary strain levels, there is not a singular level of customary strain, but rather site-specific ranges of strain necessary for specific bone adaptation.

Frost outlined typical peak strain threshold ranges necessary for bone adaptation, including a minimum effective strain (MES) that is necessary for bone formation (Minimum Effective Strain for modeling; MESm) and bone resorption (Minimum Effective Strain for (re)modeling; MESr). Bone *modeling*, for example, predominates during skeletal growth, as a result of mechanical loading subsequent to increases in body weight and muscle. Thus, bone *formation modeling* results as peak bone strains rise above MESm (e.g. increases in physical activity or increased muscle/body weight) to adapt to the new mechanical loading environment. Reduction of

peak bone strains (e.g. physical inactivity or weight loss) below the MESr initiate (re)modeling to preserve/conserve bone, most often upon reaching skeletal maturity.   Peak bone strains below the MESr result in *resorption (re) modeling*, which causes gradual bone loss of the endocortical surfaces, residing alongside the marrow cavity[41]. Based upon continual mechanosensory feedback of minimally effective bone strains (MES), bone is *(re)modeled* to maintain its mechanical competence to cope with ever-changing mechanical demands. The purpose of the mechanostat is to ensure that bones adaptively increase or decrease strength to sustain typical loading environments.

Bone *modeling* involves the *independent* actions of osteoclasts or osteoblasts on a bone surface. Formation modeling alters bone morphology by adding new bone to a surface (e.g., the outer periosteum or inner endosteum). Resorption modeling removes bone from a surface over time (e.g., endocortical surface). Bone *remodeling* involves the combined action of osteoclasts and osteoblasts. Remodeling replaces older, fatigue-damage bone with new bone, resulting in maintenance of overall bone strength[15]. Osteoclasts first resorb a pit of bone, and then followed by osteoblasts which fill the cavity with newly-formed bone, which is subsequently mineralized. However, there is a lag between the osteoclastic and osteoblastic activity. In human bone this entire process can take from 2-4 months.

Mechanostat theory has been tested through animal experimentation [42-45]. Perhaps the best example is that by Uhthoff and Jaworski[46].   In growing dogs, disuse osteopenia in the casted forelimb was the result of both reduced formation modeling on the periosteal surface (decrease in periosteal expansion) and increased disuse modeling on the endosteal surface (increased endosteal expansion) [44]. Remobilization of the dogs reversed both of these trends such that periosteal apposition increased and endosteal apposition was also restored.

2.5 Bone Measurement

2.5.1 Structure and Geometry

Geometric characteristics of whole bone define bone's structural properties. The cross-sectional geometric parameters that contribute to bone's overall strength include cortical thickness and cross-sectional area. Generally hollow tubes with walls of varying thickness, the cross-sectional geometry of long bones in the appendicular skeleton is complex and non-uniform across the length of the bone. The unique and complex cross-sectional geometry of long bones allows

them to carry loads, such as body weight, efficiently without buckling. Mechanically, the distribution of cortical bone along the diaphysis (cross-sectional property) primarily functions to resist such forces.

Despite the fact that bones with greater mineral or mass are stronger than those with less mineral or mass, the cross-sectional geometric properties of long bones may be more significant than the properties of mass or density[25, 47]. For example, without a change in mass or the amount of material present in a bone's cross-section, doubling its diameter increases the bone's bending strength by a factor of eight [48]. That is, given equivalent bone mass, long bones with greater cross-sections[15] will have greater strength in bending and torque than those with lesser cross-sections [49].
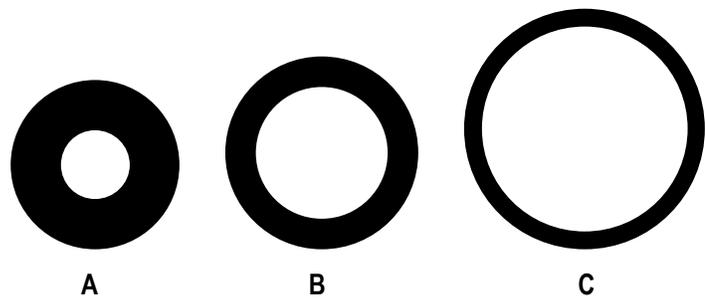
	A	B	C
Areal BMD (DXA)	1.00	0.53	0.36
Volumetric BMD (QCT)	1.00	0.46	0.27
Section Modulus (Z)	1.00	1.00	1.00
Bone Cross-Sectional Area (or BMC)	1.00	0.66	0.53

Figure 2-3. Schematic representation of three bone cross-sections with expanding periosteal diameter (A-C) and constant section modulus (strength). The areal BMD (by DXA) or volumetric BMD (by QCT) is reduced despite constant bone bending strength (section modulus; Z). This is because the contribution of the bone surface to the section modulus varies exponentially with distance from the center of mass of the cross-section; as the diameter increases, less material is needed for the same bending stiffness.

Geometrically, this optimizes the strength/lightness ratio. That is, the bone remains light to allow for the greatest efficiency of locomotion and yet is strong enough to resist the loads placed on it. Cross-sectional area of a bone is directly proportional to its ability to resist axial compressive forces, where the load is distributed uniformly in long bones. However, long bone has been demonstrated to appropriately adapt to more dominant bending forces[15]. The ability to resist bending forces is best described by the cross-sectional moment of inertia (I or CSMI). As a measure of bone's material distribution about a given axis[28], CSMI is measured about a neutral axis that experiences no compressive or tensile forces during bending. For a long bone such as the

tibia, the most efficient cross-sectional shape is one in which the mineralized tissue is placed as far from the neutral axis of the load as possible. The polar moment of inertia (J) is calculated as the sum of any two perpendicular measures of I (e.g., $I_x + I_y$) [50]. Section modulus (Z), an additional strength parameter, may be calculated using the cross-sectional moment of inertia. Dividing CSMI by the maximum distance from the central axis to the outer surface; I / (D/2) where D is the cross-section's diameter in the bending plane[50, 51]. Age-related changes in bone formation/resorption on the periosteal and endosteal surfaces contribute to the gain in bone strength during growth and strength maintenance during aging[52].

2.5.2 Technology

Dual energy x-ray absorptiometry (DXA) is a widely utilized imaging modality to assess bone mineral status of the skeleton in both clinical practice and research studies[53], and is a well-accepted and reliable measure of clinically relevant sites (lumbar spine and proximal femur). Imaging by DXA produces bone mass results of bone mineral content (BMC, g) and areal bone mineral density (aBMD, g/cm^2). For example, osteopenia and osteoporosis are clinically defined as DXA-measured *T*-scores (aBMD relative to young adult norms) of less than -1.0 S.D. and -2.5 S.D., respectively. Assumed a surrogate for bone strength, aBMD is used as a primary factor to determine fracture risk - more bone material is generally thought to confer a stronger bone. However, bone becomes heavier as aBMD increases, so this assumption contradicts a necessary mechanical function of bone – to be as strong and light as possible to facilitate efficient locomotion.

Despite its usefulness in measuring bone mass, traditional DXA outcomes provided limited information regarding bone strength adaptations, for example, in obese populations or following weight loss. This is primarily because aBMD and BMC outcomes are unable to distinguish between cortical and trabecular bone, or the geometric changes that underpin bone strength. While DXA-based aBMD outcomes have been shown to correlate strongly with fracture risk, studies show that bone strength indices, obtainable by newer technology are better predictors of fracture risk than aBMD [54]. These limitations are particularly important when exploring models, such as bariatric surgery, where changes occur in the mechanical loading environment. Animal studies show that when the mechanical stimulus is increased, bone is laid down where mechanical strains are the highest, typically on the periosteal surface. Small increases in bone mass, that may not be apparent in aBMD outcomes, can increase bone bending strength substantially[55]. In animal

studies where the mechanical loading is absent or diminished, bone is lost primarily from the endocortical and trabecular surfaces of bone[46], allowing at least some of the bending strength to be maintained despite the loss of bone material. While much has been learned from DXA-based research, studies are needed that explore bone parameters using newer technologies to assess bone geometry, bone volumetric density, and estimates of bone strength.

Theories of bone adaptation and the use of newer technologies have helped to guide bone research – measuring bone strength outcomes in addition to bone mass. From a mechanical perspective, the strength of any structure depends on material properties, mass, and the spatial layout of the material. In recent years, peripheral quantitative computed tomography (pQCT) has been used to measure volumetric bone density (vBMD, g/cm^3) and mechanically meaningful measures of bone geometry, such as bone cross-sectional area and cortical thickness, that confer strength differences evident between populations such as athletes and non-athletes or between overweight and healthy weight individuals[56, 57 53]. Given the planar nature of DXA, pQCT provides a more accurate characterization of bone's three-dimensional structure. For example, pQCT-derived bone parameters showed that 16-month increases in tibia bending strength in overweight compared to healthy-weight children resulted from increases bone geometry (e.g., total cross-sectional area and cortical area) that would not have been otherwise observed from DXA-based aBMD outcomes[57]. Thus, assessing bone by pQCT derivatives is important to understand bone health.

Part II: Review of Key Literature Specific to Manuscripts

2.6 The Effect of Bariatric Surgery on Bone Health

Given the widespread obesity epidemic, bariatric surgery has emerged as an increasingly viable long-term treatment option. In fact, the prevalence of bariatric surgery increased over 700% worldwide as a therapeutic approach to morbid obesity[58]. Unlike short-term weight loss outcomes (~10%) following lifestyle-modification interventions[59], bariatric surgery produces substantial and durable weight loss of 25 – 42% of initial weight. Further, bariatric procedures attenuate or resolve obesity-related comorbid conditions, including type 2 diabetes, hypertension, and dyslipidemia in greater than 60% of patients[60] while reducing mortality by nearly 24%[61]. Despite dramatic improvements in body weight, obesity-related risk factors and quality of life, there is growing

concern that bariatric surgery may increase skeletal fragility and risk of fracture by accelerating bone loss. Thus, it is important to understand the impact of dramatic weight loss after bariatric surgery on skeletal fragility as surgical weight management continues to rise in popularity.

In the following section I provide a brief description of bariatric surgical procedures, followed by a discussion of the current understanding of bone health outcomes subsequent to surgical weight loss. Manuscript I will provide an in-depth examination of the bariatric surgery and bone density literature.

2.6.1 Bariatric Surgical Procedures

Bariatric procedures may be roughly divided into three basic categories: restrictive, malabsorptive, and mixed procedures. Restrictive procedures including vertical banded gastroplasty (VBG), sleeve gastrectomy, and adjustable gastric banding (AGB), reduce gastric volume to approximately to 10-20 ml, limiting food consumption at meals and inducing early satiety[62]. Laparoscopic adjustable gastric banding (LAGB), for example, utilizes a saline-filled band fitted around the proximal stomach to create a small pouch that empties in the distal stomach through a narrow outlet. Banding procedures have grown in their use worldwide and some have suggested that LAGB is a safer, potentially reversible, and effective alternative to traditional gastric bypass procedures[63]. Malabsorptive procedures such as the biliopancreatic diversion (BPD) induce weight loss by shunting ingested foot directly into the distal small intestine. Malabsorption is influenced by: (1) resecting the stomach, (2) reducing absorption of ingested nutrients by altering the length of intestine that involves the digestive effect of bile, and (3) by altering the length of the intestine in contact with diverted nutrients[64]. Finally, the Roux-en-Y gastric bypass is a mixed procedure, combining stomach restriction with intestinal malabsorption. This procedure creates a small gastric pouch (20 - 30ml), which is anastomosed to a Roux limb (50 - 100 cm in length) of the jejunum[62]. In circumventing a majority of the stomach, entire duodenum, and proximal jejunum, the length of the Roux limb may be varied to alter the degree of malabsorption (i.e. longer length of bypassed small intestine alters the degree of malabsorption and subsequent weight loss). Weight loss is known to differ between procedures, with 32 – 42% one-year reductions observed following malabsorptive and mixed procedures and approximately 25% weight reductions following restrictive procedures. Laparoscopic adjustable gastric banding and Roux-en-

Y procedures (laparoscopic and open) have increased most in prevalence and comprise 90% of the bariatric procedures performed worldwide[65].

2.6.2 Bone loss is an accepted consequence of bariatric surgery

The correlation between weight loss and bone loss has been studied extensively in adult populations over the past three decades. Epidemiological studies provide demonstrable evidence that weight loss, irrespective of BMI, increases rates of bone loss. In a 2006 review, Shapses and Riedt concluded that even losses of 10% body weight are associated with 1 – 2% greater losses of bone compared to weight maintenance[66]. It is important to note that DXA-based studies of weight loss through lifestyle intervention show that changes in aBMD appear to differ relative to the magnitude and/or rapidity of the weight loss. For example, less than 10% weight loss over six months resulted in marginal, but significant, losses of total body aBMD (0.8 – 1.7%)[67-70] in overweight and obese women. Similar significant regional aBMD losses at the spine, trochanter, and distal radius (1.7%, 0.9%, and 1.2%, respectively) occurred more quickly (3 months) in diet-restricted premenopausal obese women who lost 14% body weight[71]. Finally, a study of 21 obese women (mean age 38 years) who reduced their body weight 18 - 21% after a 24-week dietary restriction lost 3 – 4% femoral neck aBMD[72], suggesting that magnitude of weight loss may influence bone outcomes. These DXA-based studies rely solely on aBMD outcomes, but considering bone structural adaptation to weight loss and the potential impact on strength indices should be a focus of future research.

Assessing bone strength using pQCT-derivatives provides a way to study bone adaptation to weight loss, rather than rely on aBMD as a bone strength surrogate for assessing risk of skeletal fragility. Only two known studies have used pQCT to track changes in bone density, bone geometry and bone strength following traditional weight loss interventions. In a sample of 37 obese premenopausal women (42 years, BMI 35.2 kg/m^2) following a 12-week weight loss program, Uusi-Rasi et al[73] found no signs of bone loss, structural degradation, or loss of strength in the radius or tibia. However, weight loss was minimal (4.4%) and may not have been sufficient to induce significant bone changes. In a later study of 75 obese premenopausal women who lost up to 19% body weight after a 3-month lifestyle intervention, the same group found only a non-significant decrease in strength at the distal radius (- 3 to - 4%), but no strength reductions at any other site nine months after the intervention[74]. However, it is possible that continued weight loss over a

longer duration might have elucidated measurable changes in bone structure and strength. Results of these studies contrast with DXA-based aBMD outcomes in other weight loss studies, and highlight a need to further evaluate bone from a mechanical strength perspective.

To the extent that weight loss through lifestyle modification results in bone loss, it is important to examine whether similar changes occur in bariatric populations. Several retrospective and cross-sectional studies have investigated the relationship between bariatric surgery and aBMD across skeletal sites. These studies have focused mainly on RYGB procedures and examined aBMD outcomes at post-operative time points ranging from just under one year to 10 years, and reported similar or greater bone mineral density up to four years following bariatric surgery at the femoral neck, lumbar spine, and radius compared to control groups matched by post-surgery BMI. The majority of studies reported no significant differences in femoral neck aBMD in women (BMI 26 – 33 kg/m^2) up to a mean four years post surgery compared to men[75], and overweight[76-78] and obese women[79]. Of two studies comparing postmenopausal women matched by post-surgery BMI (29 – 33 kg/m^2), only Valderas et al[76] reported 3% lower femoral neck aBMD (P = 0.3) in the surgical group. Matching control groups to pre-surgery weight or BMI would elucidate any bariatric surgery-induced differences, but cross-sectional comparisons to healthy weight or overweight control groups in these studies are not likely to fully represent bone changes, particularly at weight-bearing sites such as the femoral neck.

Similarly, lumbar spine and radius aBMD outcomes favored post-bariatric patients compared to both obese and non-obese controls. As an example, post-bariatric women had up to 18% greater lumbar spine aBMD compared to non-obese controls up to 10 years following surgery[77, 78]. At the radius, men and women who had undergone RYGB nearly one year earlier had 5 – 7% greater radius aBMD compared to morbidly obese controls. Similar to studies examining hip sites, post-bariatric cohorts were shown in comparison to groups matched to post-surgery BMI, rather than pre-surgery BMI, likely explaining the observed differences. With the exception of Coates et al[80], studies compared bariatric groups to controls whose mean BMI ranged from 27 to 33 kg/m^2. Interestingly, bariatric cohorts remained obese and so it is not surprising that bone density was greater than non-obese cohorts. It is also possible these outcomes could be explained by a greater absolute lean mass in bariatric patients. Compared to healthy weight counterparts, greater absolute lean mass is observed in overweight and obese individuals (+23 – 35%)[57, 81]. Mechanostat theory postulates that bone mass and strength follow closely with lean

mass rather than body weight[56, 81-83], which is observed in cross-sectional data showing a positive linear association between lean mass and radial bone mass[84]. A number of studies suggest that post-bariatric lean mass remains unchanged compared to BMI-matched controls[85, 86] and greater compared to normal weight counterparts[87] - which could also explain the higher aBMD observed in cross-sectional studies[49]. Contrary to traditional weight loss and bone outcomes, cross-sectional bariatric studies do not support the notion of accelerated bone loss and increased risk of fragility fracture, particularly in women.

Prospective cohort studies that assess bone change for several months after bariatric procedures should provide a higher level of evidence for change in bone density with surgery-induced weight loss. Studies exploring bone change after bariatric restrictive, malabsorptive, and mixed procedures suggest that bone loss appears to preferentially affect the hip region[88, 89], including the trochanter[80, 90, 91] and femoral neck[77, 92-94]. Evidence in premenopausal women indicates that bone loss may appear as early as six months after adjustable gastric banding (AGB) [94, 95], but most studies clearly demonstrate bone loss at the first post-operative year when the majority of weight loss has occurred (body weight reductions of 25% for restrictive procedures and 32 - 42% for malabsorptive and mixed procedures). Overall, greater magnitudes of one-year bone loss are observed following malabsorptive/mixed procedures with reductions of 9.2 – 10.9% at the femoral neck and 8 – 10.5% at the total hip. As an example, Giusti et al[94] found that femoral neck aBMD significantly declined 2.3% one year following LAGB in premenopausal women, while Vilarrasa et al[92] reported femoral neck aBMD declines of 11% in women one year after RYGB. Vertebral bone changes following bariatric procedures are less clear than hip sites, with vertebral aBMD reductions observed subsequent to malabsorptive procedures but not restrictive procedures. Most studies found one-year declines of 4 – 8% in vertebral aBMD following RYGB and BPD procedures, but there was no change or slight gains in lumbar spine aBMD following restrictive procedures[90, 94-96]. For example, one study of premenopausal LAGB women reported lumbar spine aBMD gains of 2.4% beginning six months post surgery that progressed to a total of 3.5% at the first year, which then stabilized at the second year[94]. Further, effects on the total body and weight-bearing sites such as the radius are less clear. Based on research by Fleischer et al[93] and Johnson et al[89], it appears that radius aBMD remains stable or increases slightly (+1.5%) in the months following surgery.

Bone mineral density declines in bariatric patients are similar to those observed in studies of bone loss following bed rest and space flight. After 60 days of bed rest participants lost 4% of aBMD at the hip[97], and following six months of space flight, astronauts experienced nearly 7% reduction in hip aBMD[98]. While these examples describe bone changes following complete disuse (unloading), aBMD by DXA is ostensibly lost at a similar rate of approximately 1% per month following weight loss surgery[99]. Given that these patients remain ambulatory this reduction is dramatic and deserves further investigation. Initially, it may lead clinicians to conclude that adults undergoing bariatric surgery will be at an increased risk for osteoporosis and related fracture. However, the existing literature remains equivocal regarding this notion. For example, two studies in pre- and post-menopausal women undergoing RYGB reported baseline mean total body, spine, and pelvis T-scores (1.23, 0.68 - 1.49, and 1.1 - 1.28, respectively), well above that which would indicate osteopenia or osteoporosis[88, 92]. Further, at one year post surgery, T-scores remained at healthy levels (1.19, 0.25 - 1.38, and 0.13 - 1.14, respectively). Understanding these changes in aBMD provides valuable information regarding the possible effects of bariatric surgical procedures on the skeleton.

2.6.3 Mechanisms for bone loss

Several mechanisms have been offered to explain significant bone loss following bariatric surgery, including severe energy restriction, malabsorption of calcium and vitamin D, bone-active hormones produced by adipocytes and pancreatic β-cells, and diminished mechanical loading on the skeleton. Calcium supplementation during behavioral weight loss interventions has been shown to assuage bone loss[70, 100]. Impaired calcium intake and malabsorption, particularly following malabsorptive and mixed bariatric procedures[101], predisposes patients to hypocalcemia[102] and increased risk of bone loss. Further, malabsorption of vitamin D and the presence of secondary hyperparathyroidism leading to increased bone remodeling and reduced cortical density is a plausible explanation for negative bone changes following bariatric procedures. However, prospective studies in which participants were daily supplemented with up to 1800 mg calcium and 800 IU vitamin D for the observation period that routinely reported 12-month hip aBMD declines up to 11%[77, 89, 92, 93] were similar to those patients who were not allowed calcium supplementation (-13%)[90]. Moreover, a recent 12-month prospective in two groups of premenopausal women who underwent BPD found no beneficial effect of additional 2g/day calcium on lumbar spine aBMD loss

(-8% non-supplemented group vs. -7% supplemented group). There are inconsistencies in the literature regarding the post-operative incidence of secondary hyperparathyroidism as a consequence of low vitamin D. Vitamin D insufficiency is well documented in morbidly obese individuals prior to bariatric surgery, so it should not be assumed that low vitamin D is necessarily a deleterious consequence of bariatric procedures. In fact, studies have shown significant aBMD loss at the hip and spine in the absence of secondary hyperparathyroidism following both restrictive and malabsorptive procedures[94, 103]. Given that patients in the reviewed studies were not vitamin D replete prior to surgery and lacked control groups to measure the effect of additional vitamin D, the effect of vitamin D malabsorption on bone health remains unknown.

Hormonal changes may have a role in bone changes following bariatric procedures, but their influence is not well understood. Bone-positive insulin, and its co-factors amylin and preptin, secreted by pancreatic β-cells are positively correlated with obesity[104]. These hormones stimulate osteoblast growth and inhibit resorption by osteoclasts[105]. Weight loss causes reductions in circulating levels of insulin and increased insulin sensitivity, which may have a negative secondary effect on bone, however no known studies have prospectively evaluated this effect.   Several authors have speculated on the role of sex steroids (e.g. estrogens and androgens) on bone loss[66, 91]. Serum levels of estrogens, produced by adipocytes, are high obese women and estradiol, for example, is an important predictor of femoral bone strength in young women[56]. Decreases in estradiol have been reported during surgical[90] and dietary weight loss[106], and may influence bone loss. Finally, there is likely a complex interaction between leptin and bone following bariatric procedures. Leptin, an adipocyte-produced hormone that is positively correlated with obesity, potentially acts both centrally to induce bone resorption and peripherally to increase bone formation[107]. Complicating the effect of leptin is the development of leptin-resistance in obese individuals. One known study of 20 adults reported that the reduction in leptin was correlated with increased bone turnover markers, but the effect on bone density is unknown[108].

It is widely believed that diminished mechanical loading secondary to weight loss likely influences bone loss observed across both restrictive and malabsorptive procedures, and in both men and women. Similar to outcomes observed following traditional behavioral weight loss interventions, bone density loss may be related to the magnitude and/or rapidity of weight loss. And some have suggested that bone loss may be a physiological adaptation to the present-day mechanical load. In one study of 23 men and women following Roux-en-Y gastric bypass,

Fleischer et al[93] reported that the significant decrease in femoral neck aBMD (-9%) was strongly associated with the magnitude of weight loss (r = 0.90, $P < 0.05$). Additionally, Cundy et al[91] reported that VBG-operated patients who lost the most weight at six months (25% weight loss) had a significantly greater loss of bone mass at the trochanter than those patients who lost less than 21% of their pre-surgery weight at one and two years post surgery. However, the mechanical loading effect of overall body weight may only partly explain the observed effects on bone. Given that bone strength is primarily adapted to lean mass rather than body weight or fat mass, it follows that an inability to preserve lean mass following bariatric surgery may mediate loss of bone mass and strength. However, few studies have explored the relationship between lean mass and bone loss. Among 62 women who lost nearly 11% femoral neck aBMD one year after gastric bypass, lean mass was negatively correlated with the percentage aBMD loss (r = -0.38, $P < 0.05$). Further, Vilarrasa et al[92] reported that both pre-and post-operative total body lean mass was significantly lower in women with T-scores less than -1.0 (SD) compared to those with normal aBMD, despite similar total body fat mass.

There is concern in the literature regarding excessive lean mass loss following bariatric procedures, and some have suggested that less than 10% of patients maintain pre-surgical lean mass[109]. In a recent meta-analysis, Chaston[110] and colleagues found that fat-free mass, on average, constituted 26%, 31%, and 18% of total weight loss following BPD, RYGB, and LAGB procedures, respectively. This was slightly more than the 14% - 23% of total weight loss observed secondary to diet-restricted weight loss interventions. Body composition outcomes from more recent studies reported that lean mass, as a percentage of weight loss, was 23%[88], 30%[85], and 33%[111] six months after gastric bypass procedures. There is currently no consensus regarding what constitutes 'excessive' loss of lean mass. Based on data from 104 Caucasian women, Webster et al[112] suggested that fat-free mass should not exceed 22% of weight loss for the preservation of normal physiological processes, but this threshold would likely vary by gender, age, ethnicity, and other unknown physiological factors. If muscle loss exceeds ranges necessary to maintain the prevalent loading environment, then the widely reported bone loss following bariatric procedures may hold and is worthy of future study.

An important limitation of the current bariatric literature may be the technology. Bone outcomes by DXA (e.g. aBMD) have been the primary outcome in assessing bone changes in post-bariatric patients. Based on this technology, significant bone loss is the accepted

consequence of bariatric surgery. However, bone changes must be interpreted with caution in light of inaccuracy associated with DXA measurement of aBMD in obese populations. Variability of aBMD significantly increases with increasing tissue depths[113], and excess fat around bone overestimates aBMD nearly 6% [114]. A significant portion of weight lost following bariatric surgery is attributed to changes fat mass (35 – 45%)[87, 88, 92, 115], and work by Bolotin and colleagues cautioned that changes in fat to lean mass ratios at the site of measurement further contribute to DXA aBMD inaccuracy[116]. As the fat/lean mass ratio decreases so follows the DXA aBMD values[114], without an actual change in the true aBMD – mistakenly leading previous investigators to conclude that significant bone loss followed bariatric surgery. Thus, preoperative aBMD may have been falsely high and actual losses, if any, may have been less than observed. Further, the planar nature of DXA is not able to characterize bone volumetric density or geometric parameters that underpin bone strength. While much has been learned from DXA-based research, studies are needed that explore bone parameters using new technology, such as pQCT, that is able to assess site-specific bone structure, bone geometry, and estimates of bone strength.

The lack of a widespread understanding of bone mineral density and osteoporosis outcomes in the bariatric literature highlights the need to comprehensively review and interpret this literature in light the of the limitations of DXA technology. Further, there is a clear need to study the effects of bariatric surgery on bone strength outcomes using newer pQCT technology.

2.7 Obesity and Bone

Affecting nearly 34% of US adults over the age of 20 years[117], obesity continues to be a significant public health concern associated with co-morbid conditions including type 2 diabetes, hypertension, dyslipidemia, and chronic obstructive sleep apnea. In contrast to these deleterious conditions, obesity is thought to be protective of bone by safeguarding against age-related bone loss and increased risk of skeletal fragility. Epidemiological studies provide evidence that body weight is a strong predictor of aBMD, and that aBMD increases with body weight. Numerous studies have shown this association with aBMD in children, adolescents, men, and women across

skeletal sites[118-120]. That the skeletal bone mass or density is an important determinant of fracture risk has led researchers to conclude that high BMC and aBMD associated with obesity decreases the risk of fracture[118, 121, 122]. This association holds for central body fractures – individuals with BMI > 25 kg/m^2 have lower rates of hip fractures[81, 122] - but overweight and obese individuals experience higher rates of extremity (i.e., distal tibia, ankle/foot) than healthy weight individuals[81, 123]. Increasing evidence in overweight children[56, 57] and older women[81] suggests that bone mass may be low relative to their body weight. Understanding this relative bone strength deficit may help to shed light on this paradoxical finding. Therefore, the relationship between body weight and bone mass and strength is an important area of research, particularly for individuals at the extremes of obesity.

2.7.1 Obesity confers greater absolute bone strength

In an absolute sense, overweight and obese individuals have greater bone mass and strength than their healthy weight counterparts. DXA-based cross-sectional studies in children, adolescents, and women have demonstrated that overweight individuals have greater absolute bone strength at weight-bearing sites, including the hip and tibia. Findings from a cross-sectional study in children reported significantly greater femoral neck aBMD (+ 8%) in overweight compared to healthy-weight children[56]. Regardless of menopausal status, overweight and obese women also exhibited 16 – 29% greater total hip aBMD than women whose BMI was less than 25 kg/m^2 [124]. In a 4,642 sample subset of postmenopausal women of the Womens' Health Initiative Observational Cohort (WHI-OC), Beck et al[81] showed 6 – 7% greater total hip and femoral neck aBMD among overweight post-menopausal women (BMI 25.0 – 29.9 kg/m^2) and 13 – 25% greater aBMD in obese women (BMI $\geq$ 30 kg/m^2) compared to their healthy-weight counterparts. Using hip structural analysis (HSA), the authors further showed that femur bone strength indices (CSA and Z) were nearly 8% and 13 – 37% higher in overweight and obese women, respectively, compared to women of healthy weight.

Longitudinal studies in children and young adults also provide evidence that increasing body mass confers greater absolute bone density and strength compared to those who maintain a healthy weight. For example, young adult women who gained significant weight over six years compared to those whose weight remained stable demonstrated significantly greater increases in hip aBMD (+2.2%)[82]. Using pQCT, Wetzseon et al[57] found significantly greater tibia volumetric

density (+4%), bone compressive strength (+14%), and bending strength (+12 – 14%) in a sample of overweight children (aged 9 – 11 years) relative to their healthy weight counterparts.

Despite greater bone density, variations in bone strength indices observed in these studies have been primarily underpinned by geometric parameters – not captured by using DXA-based aBMD as a primary outcome. Wider bones (+6 – 10%) and/or thicker cortices (+6 – 9%) – derived from pQCT - in overweight children[56, 57] contributed to greater strength outcomes. Similarly, post-menopausal women exhibit more robust femur geometry, including 7% greater femoral neck cross-sectional area[81]. These studies, in absolute terms, support the notion that overweight/obesity strengthens the skeleton, and is consistent with lowered reported incidence of hip and osteoporotic fractures. Apart from higher aBMD, few studies examined structurally-based strength adaptations to high body weight, which is critical in fully understanding the effects of overweight and obesity on the skeleton. Aside from small portion of the WHI-OC study sample, few studies have examined differences in bone density and strength in obese populations, particularly using pQCT-derived outcomes. And, it remains unclear whether these observations hold among individuals at the extremes of obesity.

2.7.2 Lean mass and fat mass influence bone mass and strength

Obesity generally infers that an individual possesses excess fat tissue relative to their body size (i.e. BMI). An implicit assumption is that the association between high body weight and aBMD may not be mediated by overall mechanical loading on the skeleton, in general, but through the effects of fat or lean mass, specifically. Existing research remains inconclusive regarding the osteogenic effect of either component of body composition. The positive association between BMI and body fat, along with BMI-associated increases in aBMD, is supported by studies suggesting that fat is an important factor in determining bone mass and density[119, 125-127]. Possible explanations include the overall weight-bearing effect of excess fat mass on the skeleton, or metabolic effect through adipose-produced hormones (e.g., estrogen) and adipokines (e.g., leptin), or pancreatic-derived hormones (e.g., insulin). Predominately observed in postmenopausal women, but not in young women or men, studies have demonstrated positive associations between fat mass and aBMD[119, 127, 128]. However, the nature of these relationships may lead to spurious conclusions. Whereas Pluijm et al [127] showed positive associations between fat mass and hip aBMD, others found that fat distribution, but not total fat mass, was positively associated with

lumbar spine aBMD[128]. Moreover, positive associations with whole-body aBMD[119] provide little information regarding clinically-relevant skeletal regions. That the osteogenic effects of fat mass on the skeleton are ostensibly observed only in select populations (i.e., postmenopausal women) and are marginal, at best, does not conclusively support fat's role as a determinant of bone mass or strength.

Other data suggest that fat is not beneficial to bone in children, adolescents and women[129-131]. Fat may be deleterious to bone[132], and its relationship with osteoporosis has been comprehensively examined in a recent review[133]. To further understand its role, it is important to separate the effect of fat mass on bone by evaluating it independent of lean mass or the overall loading effect of body weight, which has not been routinely done in previous research. To independently assess the effect of fat mass on bone density, Zhao et al[134] adjusted bone mass outcomes for body weight in a cross-sectional examination of 6477 Chinese and white men and women. After eliminating the confounding effect of body weight on bone mass, fat mass (or percentage fat mass) was negatively correlated with lumbar spine and femoral neck aBMD (r = -0.23, P < 0.01) in both Caucasian and Chinese adults. A study involving a large cohort of Chinese adults (n = 13970) demonstrated that fat mass was inversely related to bone mass and interestingly, a higher percentage of body fat, independent of body weight, significantly increased the risk of osteoporosis and osteoporotic fracture[135]. Although further research is needed to elucidate any beneficial physiological or environmental effects of fat mass on the skeleton, results of these studies challenge the notion that obesity is protective of the skeleton, and that another component of body composition may play an important role one bone mass and strength.

Several lines of research advocate the mechanical action of lean mass as the predominant factor mediating the relationship between elevated body weight/BMI and bone density and strength.   Numerous studies have demonstrated that lean mass is a dominant factor for bone strength in children[56, 57], women[81, 136], men[83, 84, 125], or both[134, 135]. Overweight individuals require more lean mass to move their higher body weight, and so have greater absolute lean mass than their healthy weight counterparts[49]. Given that muscles produce the greatest physiological load on bone[7], it follows that bone strength should be adapted to the greater lean mass observed in overweight and obese individuals. This is also consistent with Frost's mechanostat theory that bone strength adapts primarily to the prevailing dynamic loading environment. For example, findings from the WHI-OC study showed that in older women, 8% greater femoral neck strength

index in overweight women was scaled proportionately to their greater total body lean mass (+6%), rather than total body fat mass (+43%)[81]. Further, in the Zhao study cohort lean mass remained positively correlated with aBMD at the lumbar spine and femoral neck (r = 0.33 and r = 0.28, respectively; both $P < 0.01$), unlike fat mass, regardless of adjustment for body weight[134]. Cross-sectional and longitudinal studies that have controlled for the dynamic loading effect of muscle cross-sectional area or lean mass in children[56, 57], women[81, 137] and athlete populations[138], demonstrated that bone strength parameters were normalized to lean mass. As one example, in a study of 200 Chinese adults, Wu et al[137] showed that overweight individuals had 14% greater absolute femoral neck bone strength (Zp, section modulus), but that differences no longer remained after adjusting for total body lean mass, suggesting that bone strength was appropriately adapted to lean mass.

Overweight individuals have greater absolute bone strength, but increasing research suggests that aBMD and bone strength may not scale proportionately with increasing BMI or body weight, as illustrated by the negative associations with fat mass when controlling for body weight or lean mass. That bone strength scales predominately with lean mass may be problematic when body fat is excessive, and may help to explain increased peripheral fracture incidence in overweight children[123] and adults[81, 139] despite normal aBMD[140]. Intuitively, this would suggest that bone mass and strength in overweight and obese individuals is low relative to body weight. Previous longitudinal studies in children and cross-sectional studies in children, adolescents and adults have shown that bone strength was low for body weight. Studies in overweight children revealed that femur strength indices were reduced relative to body weight[56, 141]. Results of the large BACH/Bone study (n = 1171) showed that proximal femoral geometric properties (i.e., cross-sectional area), in men, were also mediated by lean mass[83]. Moreover, femoral neck cross-sectional area increased by nearly 3% for every 10-kg increase in fat mass prior to adjusting for lean mass, but *decreased* nearly 3% per 10-kg increase in fat mass when accounting for total body lean mass. Among older women, increased absolute femur strength indices (+ 8 – 15%) in the overweight and obese did not scale with their high body weight[81]. When adjusted for total body lean mass, femur strength was as much as 8% lower in obese relative to healthy weight women. Thus, bone strength in overweight and obese individuals is higher in an absolute sense, but may not be high enough to withstand the high impact forces during a fall.

DXA-based studies in adults show that absolute bone mineral density and strength is greater in overweight individuals, but low relative to body weight.   This illustrates a clear need to employ newer technology such as pQCT to understand the structural underpinnings of these results and whether they are consistent in individuals at the extremes of obesity.

3

The Association Between Bariatric Surgery, Bone Loss, and Osteoporosis: A Review of Bone Density Studies

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Abstract

As the popularity of bariatric surgery to treat morbid obesity has risen, so has a concern of increased skeletal fragility secondary to accelerated bone loss following bariatric procedures. We reviewed cross-sectional and prospective literature reporting bone density outcomes following bariatric surgical treatment for morbid obesity. Prospective research provides evidence of hip and lumbar spine areal bone mineral density (aBMD) reductions primarily in women despite calcium and vitamin D supplementation. Femoral neck aBMD declines of 9 – 11% and lumbar spine aBMD reductions up to 8% were observed at the first post-operative year following malabsorptive procedures. Mean *T*- and *Z*-scores up to 25 years following surgery remained within normal and healthy ranges. Of those studies reporting development of osteoporosis following gastric bypass, one woman became osteoporotic after one year. Despite observed bone loss in the hip region post surgery, data do not conclusively support increased incidence of osteoporosis or increased fracture risk in post-bariatric patients. However, given the limitations of dual energy x-ray absorptiometry (DXA) technology in this population and the relative lack of long-term prospective studies that include control populations, further research is needed to provide conclusive evidence regarding fracture outcomes in this population.

Introduction

In the last decade the number of bariatric surgical procedures performed worldwide increased 761% from 40,000 (1998) to 344,221 (2008), including a rise in laparoscopically-performed procedures, such as the Roux-en-Y gastric bypass (RYGB) and adjustable gastric banding (AGB)[58]. Bariatric surgery produces substantial durable weight loss and patients who undergo RYGB and AGB procedures lose 62% and 47% of excess weight, respectively[60]. Bariatric treatment of obesity also attenuates or resolves comorbidities including diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea in greater than 60% of patients[60, 142].

Despite significant improvement in weight and comorbid conditions, there is growing concern that bariatric surgery may exert a negative effect on the skeleton by accelerating bone loss, thereby increasing bone fragility[143]. Osteoporosis and osteomalacia, resulting from defective mineralization, have been recognized as long-term complications of gastrectomy, an early model for bone change with gastric bypass[144]. Osteomalacia following gastric bypass has been estimated to occur in ~2.5% of patients in the United States[145]. Among individuals who lose weight without surgery, epidemiological evidence supports increased rates of hip bone loss in older individuals, irrespective of body mass index (BMI)[3, 4], and an increased risk for hip fracture in middle-aged and older women[5]. Thus, the concern of possible accelerated bone loss leading to skeletal fragility secondary to bariatric surgery is important to understand as surgical weight management continues to rise in popularity.

In clinical settings measurement of areal bone mineral density (aBMD, g/cm^2) by dual energy x-ray absorptiometry (DXA) is accepted as a surrogate marker of bone strength and fracture risk[146, 147]. Although there are some limitations associated with DXA technology[114, 116, 148] and new technological advances in ways to assess bone strength[149], a majority of studies have used DXA aBMD as the primary outcome for bone health in post-bariatric patients. A 2006 review of aBMD changes with weight loss through lifestyle changes showed that losing even 10% body weight is associated with 1-2% greater rates of bone loss compared to weight maintenance[66]. However, studies that explore the change in aBMD after bariatric surgery have not been comprehensively reviewed to our knowledge.

The purpose of the present review is to summarize the literature exploring the association between bariatric surgery and changes in aBMD. First, we summarize cross-sectional and

retrospective studies linking bariatric procedures and bone mineral density, followed by a review of prospective studies evaluating the effect of restrictive, malabsorptive, and mixed restrictive/malabsorptive bariatric surgical procedures on changes in bone density. Finally we discuss the link between changes in aBMD and osteoporosis in patients with bariatric surgery and suggest avenues of future research.

Bariatric Surgery: procedure types

Bariatric surgery induces weight loss through mechanical and metabolic mechanisms, and by newer theories of neurohormonal pathways[150, 151]. Bariatric surgical procedures are mechanistically defined as restrictive, restrictive/malabsorptive, and primarily malabsorptive. Predominately restrictive procedures including vertical banded gastroplasty, sleeve gastrectomy, and adjustable gastric banding reduce gastric volume to approximately 10-20 ml, limiting food consumption at meals and inducing early satiety[62]. Laparoscopic adjustable gastric banding (LAGB), for example, is considered a purely restrictive procedure that reduces stomach size by fitting a saline-filled band fitted around the proximal stomach. The band creates a narrow stoma that may be adjusted in size to control food emptying into the lower stomach pouch. Despite a smaller degree of weight loss, banding procedures have grown in their use worldwide and some have suggested that LAGB is a safer, potentially reversible, and effective alternative to traditional gastric bypass procedures[63]. Predominately malabsorptive procedures such as the now-defunct jejunoilieal bypass and currently utilized biliopancreatic diversion (BPD - with or without duodenal switch) induce weight loss by shunting ingested foot directly into the distal gut. Malabsorption is influenced by resecting the stomach, reducing absorption of ingested nutrients by altering the length of intestine that involve the digestive effect of bile, and by altering the length of the gut in contact with diverted nutrients[64]. As the current standard of care the Roux-en-Y gastric bypass (RYGB) has been considered a mixed restrictive/malabsorptive procedure; creating a small gastric pouch (20 - 30ml) anastomosed to a Roux limb (50 - 100 cm in length) of the jejunum[62]. In circumventing a majority of the stomach, entire duodenum, and proximal jejunum, the length of the Roux limb may be varied to augment the degree of malabsorption (i.e., longer length of bypassed small intestine alters the degree of malabsorption and subsequent weight loss). Newer research has elucidated the role of neurohormonal changes following procedures such as RYGB. For example, hormones such as ghrelin and glucagon-like peptide-1 secreted from the surgically-

modified digestive tract likely alter vagal afferent signals to the brain resulting in appetite regulation, food intake, and effects on glycemic control, leading to weight loss and resolution of diabetes[152, 153]. For the purpose of this review bariatric procedures will be divided roughly into two categories: predominately restrictive procedures and predominately malabsorptive procedures, including mixed restrictive/malabsorptive procedures (i.e., RYGB).

I. Cross-Sectional and Retrospective Studies

The data regarding the relationship between bariatric surgical techniques and aBMD at skeletal sites has been assessed in several retrospective and cross-sectional investigations, which have focused mainly on RYGB procedures and examined aBMD outcomes at post-operative time points ranging from just under one year to 10 years. Cross-sectional studies compared surgical patients to controls matched by sex, pre-operative[80] and post-operative BMI[79, 154], age, and menopausal status. Studies are summarized in Table 3-1. As results appear to be site specific, we discuss results below by bone region.

Cross-sectional studies: Femoral neck

In all five cross-sectional studies that report femoral neck aBMD in patients post surgery, there were no significant differences in femoral neck aBMD in women (BMI 26 – 33 kg/m^2) up to a mean four years post surgery compared to men[75], and overweight[76-78] and obese women[79]. Of two studies comparing postmenopausal women matched by post-surgery BMI (29 – 33 kg/m^2), Valderas et al[155] reported 3% lower aBMD (P = 0.3) in the surgical group, but group mean femoral neck aBMD values reported by Goode et al[79] were equal. Another study found non-significantly lower femoral neck aBMD among premenopausal surgically-treated women compared to non-obese controls (0.821 vs. 0.886 g/cm^2)[77]. At the weight-bearing femur, pre-surgery body weight may be the primary confounding factor. In one study, extremely obese women had up to 16.6% higher aBMD at the femoral neck compared to overweight women and 25% higher femoral aBMD compared to healthy weight controls[81]. While matching control groups to pre-surgery weight or BMI would elucidate any bariatric surgery induced differences, cross-sectional comparisons to healthy weight or overweight control groups may not fully represent bone changes, particularly at weight-bearing sites.

Cross-sectional studies: Lumbar spine

Consistent with the femur and radius, lumbar spine bone density outcomes were similar or significantly greater among post-bariatric women compared to non-obese women. Among men, one small study reported 13.5% lower lumbar spine aBMD approximately 14.8 years post gastric bypass compared to postmenopausal women who had undergone surgical reversal seven years earlier[75]. Ott et al[78] reported 18.2% greater lumbar spine aBMD nearly 10 years after surgery in RYGB-operated women (body weight 98.5 kg) compared to age-matched women (body weight 80.8 kg) who lost weight by dietary restriction (41.2 vs. 9.8 kg weight loss; P = 0.0016). Periera et al[77] also demonstrated 15.6% greater lumbar spine aBMD in bariatric-operated premenopausal women compared to non-obese matched controls within the first year. While differences were not evident among premenopausal women, Goode et al[79] found 10.3% greater lumbar spine aBMD after four years in postmenopausal bariatric-treated women compared to postoperative BMI-matched (BMI 33 kg/m^2) postmenopausal controls. However, Valderas et al[76] reported no differences between postmenopausal groups nearly 3.5 years after RYGB. In three of the five lumbar spine cross-sectional studies reporting control group BMI, similar or greater lumbar aBMD among post-bariatric women was shown in comparison to groups matched to post-surgery BMI, rather than pre-surgery BMI, likely explaining the observed differences.

Cross-sectional studies: Radius

Unlike the proximal femur, radius bone outcomes primarily demonstrate significant differences in favor of bariatric patients in cross-sectional studies. Among men and women who had undergone RYGB a mean of 10.8 months earlier, total and one-third radius aBMD was 5.2 – 7.3% *greater* in bariatric patients compared to morbidly obese controls[80]. Likewise, Periera et al[77] found 23.7% greater distal radius aBMD in a small sample premenopausal bariatric patients compared to non-obese premenopausal controls approximately 9.8 months post surgery. While early work by Parfitt et al[145] demonstrated 15 – 20% lower radius bone mineral density in women nearly seven years post jejunoileostomy compared to age-matched normal women, BMI and menopausal status of the groups were not reported. In addition, differing surgical procedure and time since procedures may have contributed to the contrasting outcomes among studies. Nonetheless, recent cross-sectional studies suggest current-day bariatric patients ostensibly

maintain greater bone density at the forearm, particularly compared to non-obese premenopausal women.   It is possible these results could be explained by a greater absolute lean mass in bariatric patients. Compared to healthy weight counterparts, greater absolute lean mass is observed in overweight and obese individuals (+23 – 35%) [57, 81]. A number of studies support the theory that bone mass and strength follow closely with lean mass rather than body weight [56, 81-83] including cross-sectional data showing a positive linear association between lean mass and radial bone mass[84]. A number of studies suggest that appendicular lean mass remains unchanged compared to pre-bariatric surgery controls[85, 86] and that absolute lean mass is greater in post-bariatric patients compared to their normal weight counterparts[87] - which could explain the higher aBMD at this site[49].

Cross-sectional and retrospective studies: Summary

In summary, the majority of cross-sectional and retrospective studies found similar or greater bone mineral density up to four years following bariatric surgery at the femoral neck, lumbar spine, and radius compared to control groups matched by post-surgery BMI. Two of five studies that examined the femoral neck found non-significantly lower femoral neck aBMD among post bariatric women. Further, one study reported lower lumbar spine aBMD in men nearly 15 years post gastric bypass[78]. With the exception of Coates et al[80], studies compared bariatric groups to controls whose mean BMI ranged from 26.7 to 33 kg/m². Interestingly, bariatric cohorts remained obese and so it is not particularly surprising that bone density was greater than non-obese cohorts. Small sample sizes in these studies may have also contributed to the lack of significant differences. Additionally, comparing outcomes among heterogeneous patient populations does not allow for conclusions to be drawn for specific populations, such as premenopausal or postmenopausal women or men. Nevertheless, based on cross-sectional studies the notion of accelerated bone loss and increased risk of fragility fracture subsequent to bariatric surgery remains unfounded, particularly in RYGB-operated women.

Table 3-1. Cross-sectional and retrospective bariatric surgery and bone density studies

Study	Design	Surgery	Population	Primary Outcomes	Results
Gomez et al [154]	Cross-sectional	RYGB	**Pre-surgical group:** 25 women, *mean age 48y, mean BMI 44.5* **Post-surgical group:** 41 women, *mean age 46y, mean pre-surgery BMI 45.1, mean post-surgery BMI 31*	aBMD (DXA): TB	NS difference between groups
Valderas et al [155]	Cross-sectional	RYGB	**Surgical group:** 26 Hispanic postmenopausal women, *mean 3.5 years post surgery, mean age 58y, mean pre-surgery BMI 43.6, mean post-surgery BMI 29.6* **Control group:** 26 Hispanic *age- and BMI-matched postmenopausal women, mean age 57.5, mean BMI 29.2*	aBMD (DXA): FN, LS	NS differences between groups
Pereira et al [77]	Cross-section of a prospective cohort	VBG/ RYGB	**Surgical group:** 16 premenopausal women, *mean 9.8 months post surgery, mean age 38y, mean post-surgery BMI 33.4* **Obese group:** 12 women, *mean age 32y, mean BMI 47.7* **Non-obese control group:** 11 premenopausal women, *mean age 37y, mean BMI 26.7*	aBMD (DXA): DR, FN, LS	**Surgical:** ↑13.4% DR and ↑15.6% LS, NS FN vs. Non-obese control; ↑23.7% DR vs. Obese **Obese:** NS radius vs. Non-obese controls

Study	Design	Surgery	Population	Measures	Results
Abbasi et al[156]	Retrospective, *mean 54 months post surgery*	BPD-DS	136 Patients *(123 female, 13 male), mean age 43.8y*	*T-*, *Z-*scores (DXA): FN, LS; Osteoporosis Incidence	*T-*scores: -0.439 FN, -0.710 LS *Z-*scores: 0.023 FN; -0.285 LS Osteoporosis Incidence: 12.5%
Vage et al[157]	Retrospective, *>25 years post surgery*	JIB	**Postmenopausal women:** 18 Intact shunt, *mean age 56.7y, mean BMI 33* 4 Reversed shunt, *mean age 58.3y, mean BMI 39.2*	*Z-*scores (DXA): LS, FN, TH; Osteoporosis Incidence	*Z-*scores: NS different than mean of normal subjects Osteoporosis incidence: 16.7% Intact, 50% Reversed
Goode et al[79]	Cross-section of a prospective cohort	RYGB	**Surgical group:** 44 women, *mean 4 years post surgery; 23 premenopausal, mean 4 years post surgery, mean age 41y; 21 postmenopausal, mean age 54; mean BMI 33* **Control group:** 65 women; *23 premenopausal, mean age 43y; 42 postmenopausal, mean age 53y; mean BMI 33*	aBMD (DXA): LS, FN	LS NS difference between groups ***Premenopausal:*** LS NS difference between groups ***Postmenopausal:*** ↑10.3% LS vs. Control; LS NS difference between groups
Coates et al[80]	Cross-sectional	LRYGB	**Surgical group:** 25 patients *(16 female, 9 male), mean 10.8 months post surgery, mean age 51y, mean BMI 32* **Control group:** 30 obese controls *(24 female, 6 male); mean age 49y, mean BMI 48*	aBMD (DXA): TR, UD, DR	↑5.2% TR, NS UD, ↑7.3% DR vs. Control
Bano et al[75]	Cross-sectional	JIB and BPD	**5 Groups,** *mean 14.8 years post surgery***:** **5 premenopausal women** (BPD), *mean age 41.2y* **13 postmenopausal women**; *mean age 55.9y* **7 postmenopausal taking HRT**, *mean age 53.1y* **5 men**, *mean age 51.4y* **6 postmenopausal women with surgical reversal 7yrs prior**, *mean age 53.8y*	aBMD, T-, Z-scores (DXA): LS, FN; Osteoporosis Incidence	FN NS difference between groups, LS ↓13.5% men vs. surgical reversal *T-*score: LS men (-2.08) and postmenopausal (-1.21) vs. surgical reversal group (0.87) *Z-*score: LS men (-1.62) vs. surgical reversal group (0.96) Osteoporosis Incidence: 15.4% of postmenopausal women

Ott et al[78]	Cross-sectional	RYGB	**Surgical group:** 26 women, *mean 10 years post surgery, mean age 45y, mean body weight 98.5kg* **Dietary weight loss control group:** 7 women, *mean age 46y, mean body weight 80.8kg*	aBMD (DPA): FN, WT, Tr, LS; Weight Loss	FN NS difference; LS ↑18.2% vs. Control Weight Loss: 41.2 kg Surgical vs. 9.8 kg Control
Parfitt et al[145]	Cross-sectional	JC and JI	**Surgical group:** 21 women, *mean 7 years post surgery, mean age 44.7y* **Control group:** 40 women, *mean age 47.8y*	aBMD (PA): Radius	↓15.4% proximal radius; ↓20.1% distal radius vs. Control
Halverson et al[158]	Retrospective, *mean 37 months post surgery*	JIB	8 patients *(7 female, 1 male)* with low circulating 25(OH)D levels, mean age 42y	Metacarpal radiographs; Osteopenia/osteoporosis Incidence: mid-radius	All hand radiographs normal Osteopenia/Osteoporosis Incidence: 50% osteopenia

All reported differences significantly different from control (at least P < 0.05), unless noted as NS.

BPD = biliopancreatic diversion; **JC** = jejunocolostomy; **JI** = jejunoileostomy; **JIB** = jejunoilieal bypass; **LAGB** = laparoscopic adjustable gastric band; **RYGB** = Roux-en-Y gastric bypass;

VBG = vertical banded gastroplasty; **aBMD** = areal bone mineral density; **BMI** = body mass index; **DXA** = dual energy x-ray absorptiometry; **DR** = distal radius; **FN =** femoral neck; **LS** =

lumbar spine; **TB** = total body; **TH** = total hip; **TR** = total radius; **Tr** = trochanter; **UR** = ultradistal radius; **WT** = Ward's triangle; **NS** = not significant; ↑ = higher; ↓ = lower

II. Prospective Studies

Prospective studies that assess bone change within the same patients for several months after bariatric procedures provide a higher level of evidence for change in bone density with surgery-induced weight loss. Malabsorptive (including restrictive/malabsorptive) procedures prospective studies focused primarily on the Roux-en-Y gastric bypass (RYGB) and restrictive procedures studies included laparoscopic adjustable gastric banding (LAGB) and vertical banded gastroplasty (VBG). With one exception, all studies included a baseline pre-surgical measurement with post-surgical followups varying from six months to approximately 10 years. Six studies were limited to homogenous samples of women or premenopausal women, and all other studies included a heterogeneous sample of men and women of ages ranging 30 to 64 years and samples ranging from nine to 233 participants. It is understood that weight loss differs between surgery types, with malabsorptive surgeries resulting in greater weight loss. In the prospective studies that observed aBMD changes following bariatric procedures, weight loss outcomes were congruent with those reported in previous studies[60]. Among malabsorptive procedures, one-year post-surgical weight loss reductions ranged from 34 – 42% while restrictive procedures resulted in losses of approximately 25% from baseline. Studies are summarized in Table 3-2 and discussed below by bone region.

Prospective changes at hip sites

Studies exploring bone change after bariatric restrictive and malabsorptive procedures suggest that bone loss appears to preferentially affect the hip region[88, 89], including the trochanter[80, 90, 91] and femoral neck[77, 92-94]. While research in premenopausal women indicates that bone loss may appear as early as six months after adjustable gastric banding (AGB)[94, 95], evidence clearly supports bone loss at the first post-operative year when the majority of weight loss has occurred (body weight reductions of 25% for restrictive procedures and 32 - 42% for malabsorptive procedures). However, the degree of aBMD loss varied substantially from 2.1 – 14.1% at the proximal femur. Giusti et al[94] found that trochanter and femoral neck aBMD significantly declined 2.1 – 2.3% one year following LAGB in premenopausal women. However, more dramatic one-year declines of 10.5 – 14% in proximal femur aBMD (including femoral neck, trochanter, and Ward's triangle regions) were observed by Guney et al[90] in VBG-operated patients after 25% body weight

reduction, which was significantly greater bone loss than the diet-restricted weight loss group whose hip aBMD declined 9 – 10% after 15% loss of body weight.

Greater overall magnitudes of one-year bone loss are observed following malabsorptive procedures (32-42% weight loss) with reductions of 9.2 – 10.9% at the femoral neck and 8 – 10.5% at the total hip. Vitamin D and calcium are administered to patients in most studies due to the intestinal bypass of key absorption sites for these nutrients. Nonetheless, significant aBMD loss is observed regardless of supplementation. As an example, Vilarrasa and colleagues[92] observed one-year 10.9% femoral neck declines from pre-surgical levels following a 34% weight loss in vitamin D and calcium-supplemented women. In another study, outcomes from thirteen patients (who did not exceed DXA weight maximums of 300 lbs pre-surgery) of a larger RYGB cohort (age range 20 – 64 years) had lost 9.2% and 8% bone mass at the femoral neck and total hip, respectively[93].

It appears that loss of bone mass at hip sites may persist beyond the first post-surgical year, at least following restrictive procedures. Two studies report additional 24-month declines of 3.5% of femoral neck aBMD and up to 4.4% additional trochanter aBMD loss when body weight further declined from 25% to 33%[91, 94]. In contrast, singular evidence following malabsorptive procedures reported one-year total hip aBMD declines congruent with other authors (9.3%), but described no further decline after the second and third years, suggesting that bone loss may subside after the first post-surgical year[89]. However, these long-term outcomes were derived from a small subset (n = 3) of a larger cohort (n = 233), which may not provide adequate data to detect significant changes. Further, weight changes were not reported so it is unknown if weight loss also subsided around the time of the first measurement.

Prospective findings clearly suggest that hip bone mass is lost following both restrictive and malabsorptive bariatric procedures. Mixed restrictive/malabsorptive procedures comprise the bulk of surgical weight loss treatment with RYGB as the "gold standard" technique. Hence, there is greater published data evaluating the prospective effects of malabsorptive-type procedures in contrast to restrictive procedures on bone mass. One explanation for the wide range of aBMD loss at this weight-bearing site may be the variability of weight loss and resulting reduction in skeletal loading. Greater weight loss following RYGB and BPD procedures appears to result in a greater degree of bone loss at hip sites compared to restrictive procedures (Figure 3-1). The magnitude of change in aBMD has previously been associated with change in body weight[88, 93]. As one example,

the 4% trochanter aBMD decrease in VGB patients reported by Cundy et al[91] when body weight dropped a mean 25% from pre-surgical levels was significantly greater in those patients who had lost the most weight at six months (>25% body weight) compared to those who had lost less than 21% body weight at one year. Further, a study of 37 LAGB patients exhibited significant six-month reductions in aBMD from pre-surgery values at the femoral neck (-1.6%) with 16.4% weight lost, further 12-month reductions at the femoral neck and trochanter (-2.3% and -2.1%, respectively) as weight decreased 25% from baseline, and continued 24-month losses from pre-surgery levels of femoral neck and trochanter aBMD (-5.8% and -6.5%, respectively) when weight loss reached 33.4%[94]. Moreover, differing bone outcomes may be partly attributed to study design, sample size, or population of interest. Whereas four of eleven authors studied homogenous populations of premenopausal women, others included men and women in varying stages of aging.

Prospective changes at the spine

Vertebral bone changes following bariatric procedures are less clear than hip sites and differ by procedure type. The majority of research examining changes in vertebral aBMD following restrictive procedures reported either no change or slight gains in lumbar spine aBMD[90, 94-96]. For example, one study of premenopausal LAGB women reported lumbar spine aBMD gains of 2.4% beginning six months post surgery to a total of 3.5% at the first year, which then stabilized at the second year[94]. In two studies lumbar spine aBMD trended higher in the first two years but did not reach significance[95, 96]. Mean lumbar spine aBMD outcomes among VGB patients either did not change or slightly decreased (non-significant) at any post-operative time point[90, 91].

Unlike the stability in density observed following restrictive procedures, vertebral density begins to decline as much as 3% nine months following RYGB[80], extending to a 4% loss observed ten years after biliopancreatic diversion[159]. With only one exception[90], one-year aBMD outcomes illustrate vertebral declines from 3.6 – 8%. While Fleischer et al[93] described no change in lumbar aBMD, possibly attributable to the small sample (n = 13) and wide range of patient ages (20 – 64 years), research in non-menopausal calcium and vitamin D-supplemented women found significant vertebral aBMD declines of 3.6 - 8%[88, 92, 103]. We are unable to confidently conclude whether vertebral bone loss persists since only two known studies described lumbar spine aBMD declines of 12.8%[96] and 4%[159] at 24 months and 10 years, respectively, post bariatric surgery. Albeit small,

these studies provide support for short-term lumbar spine bone density loss among non-menopausal women undergoing malabsorptive bariatric procedures.

The majority of malabsorptive prospective studies provide evidence for short-term lumbar spine bone density loss among non-menopausal women, but outcomes following purely restrictive procedures remain equivocal. One possible explanation for the procedure-specific differences may again be attributed to the differences in degree of weight loss (Figure 3-2). Additionally, metabolically active trabecular bone in the spine may be more responsive to changes in hormonal milieu[107, 160] that accompany RYGB procedures[161] and contribute to differing outcomes. For example, the discovery that leptin-deficient mice have high vertebral bone mass despite being hypogonadal and obese has implicated the adipokine in the regulation of bone mass[107]. While circulating leptin is proportional to fat mass and therefore high in obese individuals, they also exhibit leptin resistance[161, 162]. Significant reduction in plasma leptin occurs following RYGB procedures[163] and is correlated with increased bone turnovers markers[108], citing its possible influence over changes in vertebral bone mass.

Prospective changes at the radius

Based on evidence from only two known malabsorptive and restrictive/malabsorptive prospective studies, bone change following bariatric surgery at the radius remains inconclusive. In their 12-month observation of 23 RYGB patients Fleischer et al[93] found no significant aBMD change at the distal radius. However, small but significant one-year aBMD declines in the total forearm (-0.55%) and increases at the radius (+1.9%) were found in a larger cohort of BPD and RYGB patients[89]. Total forearm aBMD continued to decline in the second and third year following surgery (-3.62% and -1.83%, respectively) while radius aBMD was no longer significantly different from pre-operative values. Based on these two studies it is unclear of the effect of malabsorptive or restrictive/malabsorptive procedures on forearm bone density. While both groups were systematically supplemented with calcium, Vitamin D, or a multivitamin, the heterogeneous nature of the samples may have contributed to the conflicting outcomes.

Prospective studies: Summary

Bone loss following both malabsorptive and restrictive procedures preferentially affects the hip. Evidence supporting vertebral aBMD reduction subsequent to malabsorptive procedures has not been observed following restrictive procedures. Further, effects on the total body and non weight-bearing sites such as the forearm are less clear. Evidence exists that aBMD declines as much as 15% at hip sites one year following bariatric procedures. Micronutrient supplement did not mitigate observed reductions in bone density. With the exception of continued declines (-5.8 - 6.5%) observed two years post surgery in premenopausal women, long-term changes were not examined so it remains unclear if femoral bone loss persists following restrictive procedures. Moreover, since studies were mainly limited to short-term observations the long-term effects of weight loss on bone induced by bariatric malabsorptive procedures have not been established.

While aBMD reductions at the hip region may, in part, be attributable to decreased loading, differing changes by bone region must be interpreted with caution in light of inaccuracy associated with DXA measurement of aBMD in obese populations. Variability of aBMD significantly increases beyond tissue depths of 25 cm[113], and excess fat around bone overestimates aBMD[114]. Therefore, preoperative aBMD may have been falsely high and actual losses may be less than observed. In addition, study samples were small (<37), which may have precluded observation of significant differences. Nutritional supplementation and dietary intake were either not controlled or reported so it is unknown what effect post-operative dietary and supplementation protocols may have had on bone outcomes.

Table 3-2. Prospective bariatric surgery and bone density studies

Study	Design	Surgery	Population	Primary Outcomes	Results
Tsiftsis et al. [103]	Prospective, 12-month	BPD – LL	**Group A:** 26 premenopausal women, *mean age 30.3y, mean BMI 49.4* **Group B + Calcium (2g/day):** 26 premenopausal women, *mean age 34.8y, mean BMI 53.7*	aBMD (DXA): LS; *T*-, *Z*-scores; Body Weight; BMI	**Group A:** aBMD ↓ 8%; *T*-score pre 0.862 vs. post 0.003; *Z*-score pre 0.715 vs. post -0.123; Body Weight ↓42%; BMI ↓38% **Group B:** aBMD ↓7%(NS); *T*-score pre 0.851 vs. post 0.181; *Z*-score pre 0.726 vs. post -0.356; Body Weight ↓39%; BMI ↓39%
Vilarrasa et al. [92]	Prospective, 12-month	RYGB	62 women, *mean age 45.3y, mean BMI 43.9*	aBMD (DXA): FN, LS; *T*-scores; Osteoporosis Incidence; BMI	aBMD: ↓10.9% FN; ↓3.6% LS; NS TB; T-scores: FN pre 1.1 vs. post 0.13; LS pre 0.68 vs. post 0.25 Osteoporosis Incidence: 1.6%; BMI ↓34%
Carrasco et al. [88]	Prospective, 12-month	RYGB	42 premenopausal women, *mean age 37.7y, mean BMI 45*	aBMD (DXA) TH, LS, TB; Osteoporosis Incidence; Body Weight, BMI	aBMD: ↓10.5% TH; ↓7.4% LS; ↓3.0% TB Osteoporosis Incidence: 0%; Body Weight ↓34.4%; BMI ↓34.4%
Mahdy et al. [115]	Prospective, 12-month	RYGB	70 Patients *(49 female, 21 male), mean age 45y, mean BMI 48.1*	aBMD (DXA): TB; Body Weight; BMI	aBMD: ↓3.2% TB; Body Weight ↓32%; BMI ↓32%
Fleischer et al. [93]	Prospective, 12-month	RYGB	23 Patients *(18 female, 5 male), age range 20-64y; mean BMI 47.0*	aBMD and BMaD (DXA): FN, TH, LS, DR; Body Weight; BMI	aBMD (n = 13): ↓9.2% FN; ↓8% TH; NS LS; NS DR; BMaD ↓5.6% FN; NS LS; Body Weight ↓34%; BMI ↓34%
Pereira et al. [76]	Prospective, 12-month	VGB and RYGB	Subset of 8 chosen from each group, *mean 9.8 months post surgery*: **OGg:** 16 VBG / RYGB premenopausal women; age 37.8y **OG:** 12 obese women, mean age 32y **CG:** 11 non-obese premenopausal controls; mean age 37y	aBMD (DXA) LS, FN, DR, Body Weight	aBMD: OGg: ↓11.7% LS; ↓11.7% FN; ↓4.2% DR vs. OG; Body Weight: 1yr post-op ↓34%; 2yr post-op ↓29.7%

Johnson et al. [89]	Prospective, 4-year	RYGB and BPD	7 BPD and 226 RYGB patients *(187 female, 46 male), mean age 38.6y and 43.4y, mean BMI 49.6 and 54.4*	aBMD (DXA): TH, LS, R, TF; Osteoporosis Incidence	aBMD **1y:** ↓9.3% TH (n = 22); ↓4.5% LS (n = 21); ↓0.55% TF (n = 91); ↑1.9% R (n = 23); **2y:** NC TH; NC LS; NC R; ↓3.6% TF (n = 14); **3y:** No change for all bone outcomes Osteoporosis Incidence: 0%
Giusti et al. [94]	Prospective, 24-month	LAGB	37 pre-menopausal women, *mean age 37y; mean BMI 43.7*	aBMD (DXA): TB, LS, FN, Tr; Body Weight	aBMD **6m:** ↑1.4% TB; ↑2.4% LS; ↓1.6% FN; NS Tr; **12m:** NS TB; ↑3.5% LS; ↓2.3% FN; ↓2.1% Tr; **24m:** NS TB; NS LS; ↓5.8% FN; ↓6.5% Tr; Body Weight: **6m:** ↓16.4%; **12m:** ↓25.2%; **24m:** ↓33.4%
Von Mach et al. [96]	Prospective, 2-year	RYGB and AGB	**Patients:** 4 RYGB women, *mean age 44.5y, mean BMI 42.7* 9 AGB (6 female, 3 male), *mean age 41.1y, mean BMI 41* **Obese controls:** 6 (4 female, 2 male), *mean age 49y, mean BMI 41.2*	aBMD (DXA) TB, V; Body Weight; BMI	aBMD TB: ↓3.5% RYGB; ↑3.0% AGB; NC Control; V: ↓12.8% RYGB; ↑4.1% AGB; NC Controls; Body Weight: ↓28.6% RYGB; ↓16.0% AGB; NC Controls; BMI: ↓28.6% RYGB; ↓17% AGB; NC Controls
Coates et al. [80]	Prospective, 9-month	LRYGB	15 Patients (12 female, 3 male), *mean BMI 48*	aBMD (DXA): LS, FN, TH, Tr, TB; Body Weight; BMI	aBMD (n= 12): ↓3.3% LS; ↓5.1% FN; ↓7.8% TH; ↓9.3% Tr; ↓1.6% TB; Body Weight ↓27%; BMI ↓27%
Guney et al. [90]	Prospective, 12-month	VGB	**Surgical Patients:** 16 (14 female, 2 male), *mean ages 33 and 41yrs, mean BMI 46.4* **Obese dietary controls** (low calorie diet ~1200kcal/day): 65 *(53 female, 12 male), mean ages 40 and 51yrs, mean BMI 36*	aBMD (DXA): FN, Tr, WT, LS; BMI	**Surgical:** aBMD ↓13.5% FN; ↓10.5% Tr; ↓14.1% WT; NS LS; BMI ↓25% **Control:** ↓9.9% FN; ↓9.2% Tr; ↓9.6% WT; NS LS; BMI ↓15%
Pugnale et al. [95]	Prospective, 12-month	AGB	31 premenopausal women, *mean age 36y, mean BMI 43.6*	aBMD (DXA): TB, FN, Tr, LS; Body Weight; BMI	NS changes for all bone outcomes; Body Weight: **6m:** ↓16%; **12m:** ↓23%; BMI: **6m:** ↓15%; **12m:** ↓23%

Strauss et al. [158]	Prospective, 2.5-year	AGB	17 Patients (15 female, 2 male), *mean age 43.2y, mean BMI 40.4*	aBMD (DXA): TB; *T*-score; Body Weight; BMI	aBMD: NS change TB; *T*-Score: NS (pre 0.51 vs. post 0.83); Body Weight ↓22%; BMI ↓21%
Marceau et al. [159]	Prospective, 10-year	BPD	33 Patients (26 female, 7 male), *mean age 35.8y, mean BMI 44.6*	aBMD (DXA): FN, LS; *T*-score; Body Weight; BMI	aBMD 4yr: NS FN; NS LS; 10yr: NS FN; ↓4% LS *T*-scores: FN NS (pre 0.98 vs. 4yr 1.16 vs. 10yr 0.8); LS NS (pre 1.06 vs. 4yr 0.94 vs. 10yr 0.88); Body Weight ↓31%; BMI ↓32%, both 4yr
Cundy et al. [91]	Prospective, 2-year	VBG	**Patients:** 18 *(16 female, 2 male), mean age 37y, mean BMI 43.4* **Controls:** 18 *(16 female, 2 male); mean age 37y, mean BMI 23.3*	aBMD (DXA): FN, Tr, WT, LS; Body Weight; BMI	aBMD **1yr:** FN NS; ↓4% Tr; WT; LS NS; **2yr:** FN NS; ↓4.8% Tr; ↓3.9% WT; LS NS; Body Weight: **6m:** ↓21%; **1yr:** ↓25%; **2yr:** ↓21%; NC Controls
Rickers et al. [160]	Prospective, 54-month	JI	10 patients (9 female, 1 male), *mean age 33y*	BMC (DPA): Distal Forearm	BMC (expressed as % of baseline): Baseline: 101.3% of age- and sex-matched normal mean; 6m ↓1.5%; 12m ↓1.6%; 54m ↓9.6%
Rickers et al. [161]	Prospective, 12-month	JI	**Group 1:** 11 Current Surgical Patients *(9 female, 2 male), mean age 33y* **Group 2:** 12 Male post-surgical patients (m*ean 3.5 years post surgery), mean age 34y*	BMC (DPA): Distal Forearm; Overweight (%)	BMC (expressed as % of age- and sex-matched normal mean): **Group 1:** 102.6% baseline vs. 100.8% 12m (NS) **Group 2:** 103.9% baseline vs. 103.8% 12m (NS) Overweight (%): *(significance not reported)* **Group 1:** 114% baseline vs. 38% 12m **Group 2:** 48% baseline vs. 43% 12m

All reported differences significantly different from control (at least *P* < 0.05), unless noted as NS.

AGB = adjustable gastric band; **BPD-LL** = biliopancreatic diversion - long limb; **JI** = jejunoileostomy; **LAGB** = laparoscopic adjustable gastric band; **LRYGB** = laparoscopic Roux-en-Y gastric bypass; **RYGB** = Roux-en-Y gastric bypass; **VBG** = vertical banded gastroplasty; **aBMD** = areal bone mineral density; **BMaD** = bone mineral apparent density; **BMC** = bone mineral content; **BMI** = body mass index; **DPA** = dual photon absorptiometry; **DXA** = dual energy x-ray absorptiometry; **DR** = distal radius; **FN** = femoral neck; **LS** = lumbar spine; **TB** = total body ; **TH** = total hip; **TR** = total radius; **Tr** = trochanter; **UR** = ultradistal radius; **V** = vertebral; **WT** = Ward's triangle; **NC** = no change; **NS** = non-significant; ↓ = decrease; ↑ = increase
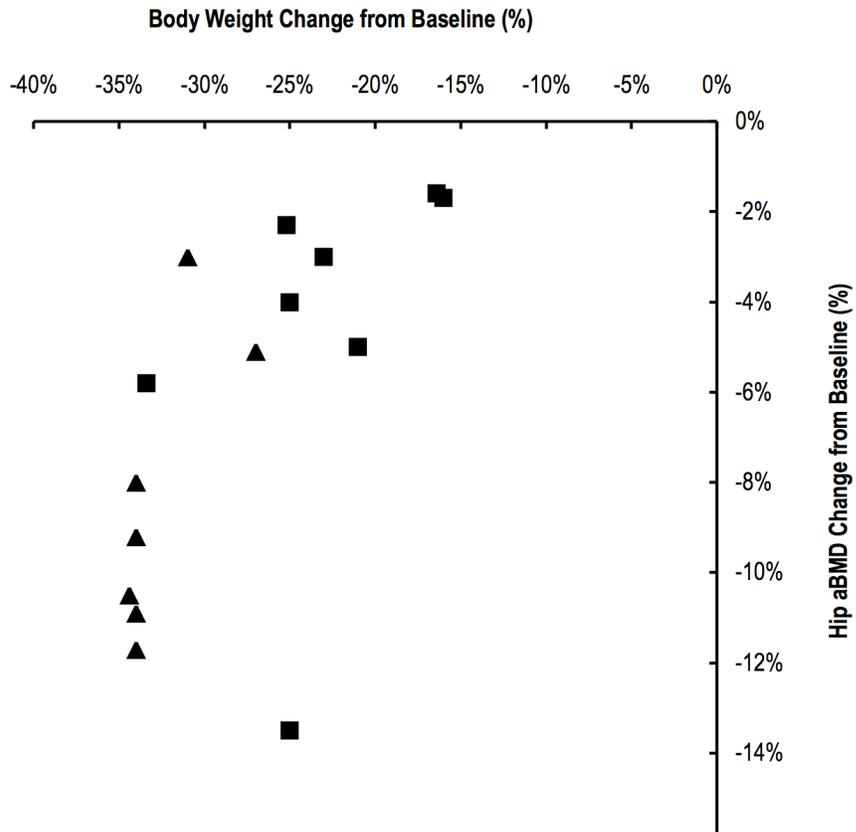
Figure 3-1. Prospective studies. Percentage change in body weight from baseline (pre-surgery) levels plotted against percentage change in hip areal bone density (aBMD) (i.e., femoral neck, trochanter, Ward's triangle, and total hip). Malabsorptive and restrictive/malabsorptive procedures (triangles); restrictive procedures (squares).
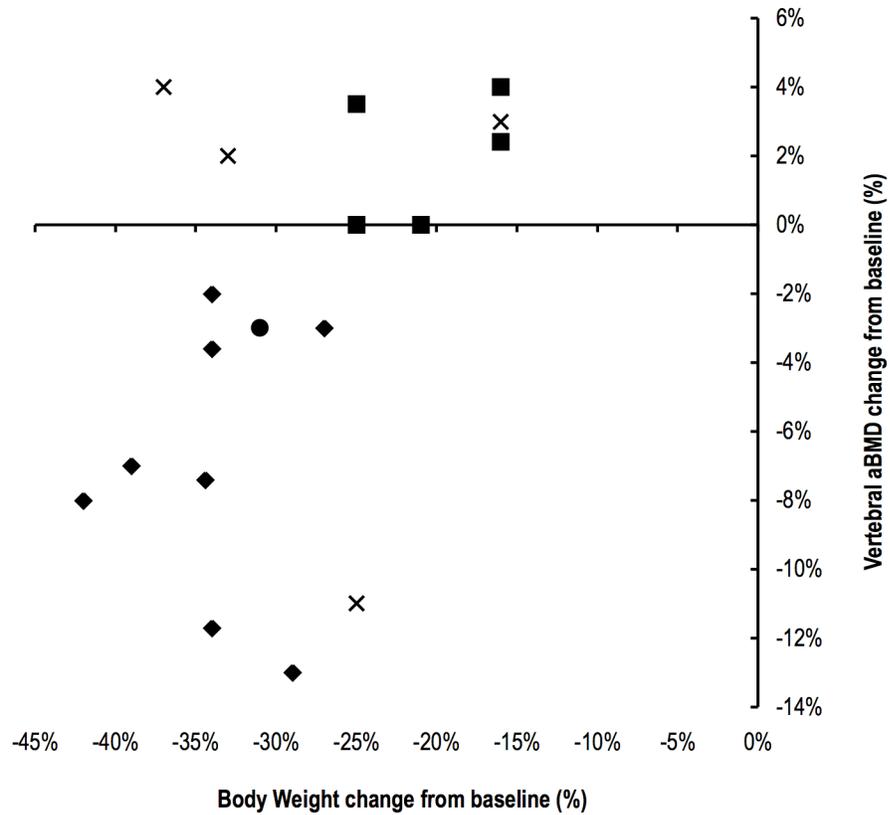
**Figure 3-2.** Prospective studies. Percentage change in body weight from baseline (pre-surgery) levels plotted against percentage change in vertebral areal bone mineral density (aBMD). Malabsorptive and restrictive/malabsorptive procedures (diamonds); restrictive procedures (squares); non-significant malabsorptive and restrictive/malabsorptive procedures (filled circles); non-significant restrictive procedures (cross-hatches).

Bariatric Surgery: Osteoporosis and Fracture Incidence

Little is known about the relationship between current bariatric techniques and osteoporosis and fracture incidence. Clinically, osteopenia and osteoporosis are defined as DXA-measured *T*-scores (aBMD relative to young adult norms) of less than -1.0 S.D. and -2.5 S.D., respectively. Cross-sectional and retrospective studies have not consistently reported *T*- or *Z*-(age- and sex-matched) scores of bariatric patients to assess osteoporosis incidence. Bano et al [74] investigated the incidence of osteoporosis among five groups who had undergone JIB or BPD approximately 15 years prior. Femoral neck *T*-scores did not differ among groups, but compared to the surgical reversal group (0.87) lumbar spine *T*-scores were significantly lower in men aged 51.4 years (-2.08) and post-menopausal women (mean age 55.9 years) not taking hormone therapy (-1.21). More recently, a cohort of 136 patients (mean age 43.8 years) who had undergone BPD-DS approximately 54 months earlier had mean lumbar spine and femoral neck *T*-scores of -0.71 and -0.44, respectively[155]. Further, mean *Z*-scores at the same sites were -0.29 and 0.02, respectively, indicating that bone loss, if any, had not exceeded healthy counterparts. As well, Vage et al[156] found that while 22.7% of post-menopausal women were osteoporotic 25 years after JIB, mean *Z*-scores were not low or significantly different from normal subjects within one-year age groups. Together, this would suggest that long-term incidence of osteoporosis is evident in some men and post-menopausal bariatric patients, but overall mean lumbar spine and femoral neck *Z*-scores do not differ from what would be expected for age and gender. While causality and temporality cannot be concluded, a strong association between bariatric surgery and osteoporosis is not supported.

Not unlike cross-sectional and retrospective studies, the prospective effect of bariatric surgery on osteoporosis development remains unknown and few researchers have measured or reported change in *T*- or *Z*-scores, or osteoporosis and fracture incidence. Some early prospective changes in *T*- and *Z*-scores, mainly at the total body and spine, have been reported after both restrictive and malabsorptive procedures. Strauss et al[158] found no change in total body *T*-scores in AGB patients a mean 2.5 years following surgery (pre 0.51 vs. post 0.83). Similarly, hip and spine *T*-scores did not change significantly from baseline values at four and 10 years post-operatively in BPD patients with mean 10-year hip and spine *T*-scores of 0.84 and 0.88, respectively[159]. Fractures were reported in eight patients at follow-up (two ankle, rib, wrist, toe, finger, tibia, and spine), including six who had fractured prior to weight loss surgery. In contrast, Tsiftsis et al[103]

reported significant 12-month declines in lumbar spine *T*-scores among premenopausal women who underwent BPD whether they were calcium-supplemented or not (pre 0.851 vs. post 0.181 and pre 0.862 vs. post 0.003, respectively). *T*-scores still remained well above the level diagnostic of osteopenia or osteoporosis, and final mean *Z*-scores were -0.356 and -0.123 (supplemented and non-supplemented, respectively). Two studies reported that mean spine and pelvis *T*-scores significantly declined in women 12 months after undergoing RYGB as well, but remained within normal range (0.25 and 0.13, respectively)[88, 92]. Nonetheless, 16.1% - 19.3% developed osteopenia at the femoral neck and lumbar spine, and one patient became osteoporotic at the lumbar spine in the study by Vilarrasa and colleagues[92], whose sample included women at various stages of menopause. But among non-menopausal women osteopenia or osteoporosis did not develop at the spine, and only 9% developed osteopenia at the hip in the initial six months post surgery. Further, Johnson and colleagues[89] reported that no RYGB/BPD patients had or developed osteoporosis at follow-up measurements. All together, reductions in *T*-scores are ostensibly commensurate with bone loss at the hip and spine, but it is not clear if bone loss has clinical relevance regarding the incidence of osteoporosis and/or fracture rates in patients who have undergone surgery for obesity. Bariatric patients generally remain overweight, despite substantial weight reduction, and thus may continue to benefit from greater aBMD afforded by high skeletal loading.

Discussion

Our review summarized the literature exploring the association between bariatric surgery and changes in bone density (Tables 3-1 and 3-2). According to cross-sectional and retrospective research there is no appreciable difference in aBMD at the hip region, but greater aBMD at the spine and radius, in post-surgical bariatric patients compared to obese or overweight populations. Further, *Z*-scores do not indicate that age-related bone loss among bariatric patients is greater than would be normally expected for age and gender. However, these studies are unable to capture the dynamic nature of bone tissue from measurement at a single time point and so causality and temporality cannot be established.

There does appear to be a relationship between declining bone density and bariatric surgery. Prospective investigations provide evidence of bone loss that preferentially affects the hip

region and, to a lesser degree, the spine in women. While bone loss occurs among patients who undergo all bariatric procedures, declines were most dramatically described following procedures with a malabsorptive component (e.g., RYGB and BPD). Studies reporting mean *T*- and *Z*-scores or osteoporosis incidence reveal that these patients have normal range *T*-scores and have not, in large measure, developed osteoporosis. However, prospective investigations have mainly examined small cohorts of bariatric patients and analyzed heterogeneous samples of men and women, or women at various stages of menopause, or diverse surgical techniques. There was also inconsistency among measured bone regions, limiting comparisons across studies. Further, few studies examining restrictive procedures reported supplementation protocols among patients. Nearly all malabsorptive procedures studies, albeit inconsistent, reported calcium and vitamin D supplementation protocols, which may have confounded aBMD outcomes. The majority of prospective studies additionally lacked control groups for comparisons of post-operative outcomes. These limitations restrict the conclusions that may be drawn regarding the skeletal effects of bariatric surgery except in well-designed and controlled studies.

The contribution of factors influencing bone changes, including body composition, dietary intake and micronutrient status, endocrine and sex hormones, and lifestyle factors such as physical activity can only be speculated this review. For example, rapid and substantial weight loss differentially effects fat and lean tissue components[166] and regional compartments[85] of body composition, both of which impact skeletal loading. In a recent review of fat-free mass changes during significant weight loss, Chaston and colleagues[110] reported lean mass reductions, on average, represented 30%, 28%, and 17% of total weight loss following RYGB, BPD, and LAGB, respectively, which may shed light on the association between reduction in body weight and bone changes at the hip. Moreover, changes in physical activity, not reported in these studies, have the potential to mediate the interaction between body composition and bone mass. Vitamin D deficiency is also reported in up to 80%[167] of bariatric patients preoperatively with many patients remaining deficient up to 10 years postoperatively[168]. In none of the reviewed studies were patients supplemented to become replete prior to surgery so the influence of vitamin D deficiency and the effect of non-systematic supplementation on bone status remain unclear. Finally, evidence supporting alterations in adipokines such as leptin and adiponectin following surgically induced weight loss likely influences the skeleton in ways not yet fully understood[154, 163-165].

Future Directions

Although increasing evidence supports a link between hip and spine bone loss and bariatric and metabolic surgery for obesity, the magnitude of this effect and the underlying mechanisms are unclear. In addition, the clinical significance of these changes remains to be elucidated until large-scale investigations are conducted. Future investigations should focus on outcomes by separately studying gender, age, race, and surgical procedure to better understand the relationships between bariatric surgery and bone health, particularly the clinical significance of declining *T*-scores and risk for future fractures. Evaluating bone changes in women at different stages of menopause will be important for delineating age-related declines in bone loss from those subsequent to substantial weight loss. Moreover, bone loss subsequent to procedures with differing weight loss outcomes (e.g., Roux-en-Y gastric bypass vs. adjustable gastric band procedures) are needed to clarify the proportionality of the relationship that appears to exist. Little research has studied alterations in body composition as a factor influencing changes in bone after bariatric surgery. Further, the role of physical activity as a primary influence on mechanical loading needs to be prospectively evaluated. Finally, it remains to be determined if technological limitations are falsely inflating observed outcomes. DXA accuracy is limited in morbidly obese individuals and, in addition, is not able to distinguish bone compartment-specific changes. Using novel technology, such as quantitative computed tomography, provides data regarding differential changes in trabecular and cortical bone, along with bone architectural changes that will be necessary to more fully quantify the skeletal effects of bariatric surgery. Future well-designed research will ameliorate the current limited knowledge by identifying high-risk populations and may have implications for future therapeutic targets.

4

Bone Geometry and Strength in Obese and Healthy Weight Women

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Abstract

The relationship between bone strength and body weight in adult women remains unclear. Research has shown that overweight women exhibit greater absolute bone strength compared to healthy weight women, but existing studies have included mostly overweight, but not the severely obese adults. **Purpose:** To describe tibial and radial bone geometry, volumetric density, and estimates of bone strength in obese women. Bone geometry and strength were assessed by peripheral quantitative computed tomography (pQCT) in obese (mean BMI 38.0 (SD 11.0) kg/m^2, n = 34) and healthy weight (mean BMI 21.6 (SD 1.5) kg/m^2, n = 74) women. Total volumetric bone mineral density (ToD, mg/mm^3), total bone area (ToA, mm^2), and bone compressive strength (bone strength index (BSI)) were assessed at the distal (4%) sites of the tibia and radius. ToA and cortical bone area (CoA, mm^2), cortical volumetric density (CoD, mg/mm^3), cortical thickness (CoTh, mm), and bone bending strength (polar strength strain index (SSIp), mm^3) were measured at the midshaft sites of the tibia (66%) and radius (50%). **Results:** Compared to healthy weight females, bone strength was higher (+1.6 – 15%) in the obese women at all sites except the distal radius. The greater bone strength was due primarily to a greater ToA (+3.4 - 11%). Interestingly, CoD was significantly lower in obese women at the proximal sites (-2.9 – 3.4%, $P < 0.001$). Adjusting for body weight, bone strength was lower (-5 –19%) in obese women at all midshaft sites. Further, bone strength was lower (-10 –13%) in the obese women at the tibia, but not radius, after adjusting for MCSA. **Conclusions:** Obese women had greater bone strength compared to healthy weight women, due to greater bone area, at both weight bearing and non-weight bearing sites. However, these differences reversed at cortical bone regions after adjusting for and body weight. Similar to findings in pediatric studies, these data suggest that bone strength may be low for body weight in obese women. Future studies should further explore the relationship of body weight, and its components, to parameters of bone strength in obese populations.

Introduction

Obesity is a significant public health concern and is associated with numerous chronic conditions including hypertension, dyslipidemia, diabetes, and osteoarthritis[169]. The notion that obesity exerts a protective effect on the skeleton is secondary to widely accepted evidence supporting a positive association with high body weight and BMI and an elevated areal bone mineral density (aBMD, g/cm^2) as assessed by DXA[121, 122]. While several researchers report a lower risk of osteoporotic fracture in overweight adults compared to their normal weight counterparts[122], others report a higher incidence of extremity fractures in overweight individuals[81, 170].

Obese individuals possess excess body fat relative to their height and weight (e.g., body mass index). A positive association between body mass index (BMI) and body fat, along with concomitant increases in aBMD with BMI, have led some authors to conclude that excess body fat is a determining factor of bone strength[119, 125, 126, 128]. While studies including pre- and postmenopausal women have demonstrated positive associations between total body fat and aBMD at sites throughout the skeleton[125, 127], little is known about the separate effects of components of body weight on bone strength in obese individuals. The relative contributions of fat and lean mass on bone strength remain the focus of investigation.

Several lines of evidence suggest that bone strength may be adapted to lean mass rather than body weight and/or fat mass[56, 57, 82, 137, 141]. Intuitively, this is a plausible explanation given that muscle forces exert the greatest physiological load on bone[49, 171], and that overweight individuals generally have higher absolute lean mass to move their higher body weight by generating greater muscle forces during locomotion[7]. For example, proximal femoral structural geometry is more robust in overweight individuals[81], and that corresponding strength indices are primarily adapted to lean mass rather than body weight in children[57], young adults[56], and older women[81]. In addition to the contribution of body composition to bone strength, it is important to consider bone strength relative to the loads imparted by the prevailing loading environment. Since muscle force is highly correlated to muscle size, muscle cross-sectional area (MCSA) from peripheral quantitative computed tomography (pQCT) and total lean mass from dual energy x-ray absorptiometry (DXA) are surrogates to assess bone strength relative to lean mass or body weight[56, 172].

There is an implicit assumption that the high aBMD associated with high body weight shown in DXA-based studies connotes greater bone mechanical strength. But the planar nature of DXA is unable to consider the three-dimensional properties of bones, providing little information about the relative contribution of cortical and trabecular compartments and overall geometry to indices of bone strength. PQCT provides outcomes of volumetric bone density (vBMD, g/cm^3) and mechanically meaningful measures of bone geometry, such as bone cross-sectional area, from which estimates of bone strength are derived[149].

To further the current knowledge base of bone strength in obese individuals, we conducted a cross-sectional analysis to evaluate the differences in indices of bone strength assessed by pQCT between obese women and normal weight younger women. Our purpose was to compare bone geometry, density, and estimates of bone strength and their association with muscle CSA and body weight in obese and normal weight women.

Materials and Methods

Study Design and Participants

This was a cross-sectional study examining bone health among obese and normal weight women living in the Minneapolis-St. Paul area. Extremely obese participants (N = 34, mean age 45.4 years), awaiting bariatric surgical treatment for obesity, were mainly recruited from the University of Minnesota Weight Management Clinic. Overweight and obese participants were also recruited from community-based nutritional weight management classes, before weight loss. A majority of participants were classified as obese (n = 21; 62%) with only 13 (38%) being overweight. As the majority were obese and the mean BMI of this group (44.6 kg/m^2) considered "extremely obese", we grouped overweight and obese participants together and refer to this group as "obese" throughout the manuscript. Normal weight female controls (N = 74, mean age 25.8 years) were drawn from baseline data of the Women in Steady Exercise Research study[173], an exercise intervention study of sedentary women aged 18 – 40 years. Women were excluded from the study if they were pregnant at the time of study, had been diagnosed with osteoporosis, or were taking any medication known to influence bone metabolism.

Details of the study and testing procedures were explained to each participant and a written informed consent was obtained before data collection. Upon informed consent, participants

completed a general health and medical history. The Institutional Review Board of the University of Minnesota approved this study.

Anthropometry

A wall-mounted stadiometer (Model 242; Seca, Hanover, MD) was used to measure height to the nearest 0.1 cm. An electronic scale (Model 840; Seca, Hanover, MD) was used to measure body weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. Women were classified as healthy weight (BMI 18.5 – 24.9), overweight (BMI 25.0 – 29.9), or obese (BMI ≥ 30). Tibia length was measured with an anthropometric tape measure to the nearest millimeter from the tibial plateau to the medial malleolus. The forearm was similarly measured, from the olecranon to the ulnar styloid process.

Bone Measurements

PQCT (Norland/Stratec XCT-3000; Orthometrix, Inc. White Plains, NY) scans were acquired using a 2.3-mm slice at the distal (4%) and proximal (66%) sites of the left tibia, and the distal (4%) and midshaft (50%) sites of the non-dominant radius. A 30-mm planar scout view was obtained over the joint line for placement of the anatomic reference line. Based on bone length, the tibia distal (4%) and proximal (66%), and radius distal (4%) and midshaft (50%) locations were identified by the scanner. A scan speed of 25 mm/s and sampling resolution (voxel size) of 0.4 mm were used. Total scan time for each limb did was approximately five minutes. One trained operator (L.S.) performed the measurements and analyzed all scans. Analysis modes and thresholds for outcomes were chosen based on manufacturer's recommendations. Precision with repositioning was determined in our laboratory in adults (women n = 11, men n = 4; mean age = 25 ± 6.5 years) as a coefficient of variation (CV, %) and varied from 0.28% to 1.2% for all measurements. Quality assurance was performed by daily scanning a manufacturer-provided anthropometric phantom.

The distal (4%) tibia and radius sites were assessed for bone geometry (ToA, total cross-sectional area, mm^2), total bone volumetric density (ToD, mg/mm^3), and an estimate of bone compressive strength (bone strength index (BSI), mg/mm^4 = ToA X ToD^2/100,000). Bone outcomes assessed at bone the radius midshaft (50%) and tibial proximal (66%) sites included the geometric parameters ToA, cortical area (CoA, mm^2), cortical thickness (CoTh, mm), and cortical volumetric density (CoD, mg/mm^3). Estimated indices of bone bending strength obtained from

midshaft and proximal sites included section modulus (Z, mm^3) and polar strength-strain index (SSI_p, mm^3). Muscle cross-sectional area (MCSA, mm^2) was also obtained at the radius (50%) and the tibia (66%).

Statistical Analyses

All data were analyzed using SPSS (v17.0) for Windows. Independent sample *t*-tests were used to compare descriptive statistics between groups, with means ($\pm$ S.D.) reported for each outcome. Differences in bone and muscle outcomes between obese and normal weight groups were assessed using analysis of covariance (ANCOVA). To control for differences in body size, we adjusted the model for tibial and ulnar length at their respective sites. Since age differed significantly between groups, we also adjusted for age in all of the analyses. We conducted analyses on two additional models. Given the significant difference in body weight between the obese and normal weight groups, we added body weight as a covariate in a second model, along to determine whether differences in bone outcomes and muscle area remained after holding weight constant. In a third model, we added MCSA, along with bone length and age, as a covariate to assess whether differences in bone outcomes between groups remained after controlling for MCSA. Alpha for the two-sided hypotheses was set at 0.05. For all outcomes, differences were considered significant if $P < 0.05$. Means and 95% confidence intervals are reported for bone parameters and MCSA.

Results

Descriptive variables for both groups are presented in Table 4-1. Obese women were older, heavier, and had greater BMI than normal weight control women. While ulna length was not different between the groups, tibia length was 11.9 mm shorter in obese women compared to controls. Muscle cross-sectional area (MCSA) at the proximal tibia was significantly greater in obese women (6728.4 vs. 4889.7 mm^2, $P < 0.001$), but no different than controls at the midshaft of the radius.

Bone outcomes

Tibia. Tibia bone outcomes are shown in Table 4-2. Compared to normal weight controls, obese women had significantly higher values of estimated bone strength at both tibia sites, after

controlling for tibia length and age. At the distal (4%) tibia, obese women had significantly higher bone compressive strength (BSI) (+15%, $P < 0.01$) due to greater ToA (+1%, $P < 0.05$), despite no significant group differences in ToD. At the proximal (66%) tibia, estimates of bone bending strength (Z and SSIp) were significantly greater in obese women compared to normal weight women (+13% and 14%, respectively, $P < 0.001$), as a result of greater bone area (ToA, +11%, $P < 0.001$; and CoA, +22%, $P < 0.001$) and CoTh (+20%, $P < 0.001$). While obese women exhibited significantly lower cortical volumetric density (CoD, -3%, $P < 0.001$) at the proximal site, more robust bone geometry resulted in greater bone strength. Compared to normal weight women, muscle cross-sectional area was significantly greater at the proximal tibia in obese women (+28.8%, $P < 0.001$).

After adding body weight as a covariate in the second model, distal (4%) BSI remained significantly greater in obese compared to normal weight women (+10.7%, $P < 0.01$). At the proximal (66%) tibia, results reversed with obese women exhibiting significantly lower estimates of bone strength (Z and SSIp) compared to normal weight women (-6.8% and -3.5%, respectively, $P < 0.001$) (Figure 1). Muscle cross-sectional area remained significantly greater in obese women (+4.8%, $P < 0.001$) when adding body weight to the model.

For the third model, we added leg MCSA as a covariate to the first model (Figure 4-1). Compared to normal weight women, all estimates of bone strength were significantly lower in obese women. At the distal tibia, BSI was significantly lower (-0.4%, $P < 0.01$) in obese women. At the proximal tibia, bone strength estimates (Z and SSIp) were significantly lower (-12.8% and -10.3%, respectively, $P < 0.001$) among obese women compared to controls.

Radius. Radius bone outcomes for model 1 are shown in Table 4-2. Compared to normal controls, estimates of bone strength were significantly greater at the radial midshaft after adjusting for ulna length and age, but did not differ at the distal site. Despite the lack of difference in estimated compressive strength (BSI) at the distal (4%) site, obese women had significantly greater ToA (+7.1%, $P < 0.01$), but no difference in ToD. At the midshaft (50%) site, obese women had significantly greater estimates of bending strength (Z and SSIp) compared to normal weight women (1.6% and 8.1%, respectively, $P < 0.001$) as a result of greater bone area (ToA, +4% and CoA, +2.5%, both $P < 0.05$). While obese women exhibited significantly lower CoD (-3.4%, $P < 0.001$) at the radial midshaft, greater bone area resulted in greater bone bending strength.

Again, when body weight was added for the second model bone strength differences remained unchanged at the distal radius. At the midshaft site, estimates of bone strength (Z and SSIp) became significantly less (-19% and -11.4%, respectively, both $P < 0.001$) in obese compared to normal weight women when body weight was controlled (Figure 4-2).

For Model 3, forearm MCSA was added as a covariate to Model 1 (Figure 4-2). Bone strength parameters were significantly greater in obese participants compared to controls at both trabecular and cortical sites, yielding 3% greater ($P < 0.05$) estimated bone compressive strength (BSI) in obese women at the 4% site and estimates of bone strength (Z and SSIp) were 3% and 7% greater, respectively, at the midshaft (50%) site (both $P < 0.001$).

Table 4-1. Descriptive characteristics

	Overweight/Obese BMI > 25	Healthy Weight BMI 18.5 – 24.9
N	34	74
Age (years)	45.4 ($\pm$12.4)**	25.8 ($\pm$5.9)
Height (cm)	164.3 ($\pm$7.5)	164. ($\pm$7.7)
Weight (kg)	102.3 ($\pm$29.7)**	58.6 ($\pm$6.9)
Body Mass Index (kg/m^2)	38.0 ($\pm$11.0)**	21.6 ($\pm$1.5)
Tibia Length (mm)	354.1 ($\pm$24.4)*	366.0 ($\pm$28.6)
Ulna Length (mm)	262.2 ($\pm$15.3)	260.4 ($\pm$15.5)
Tibia 66% MCSA (mm^2)	6728.4 ($\pm$1082.2)**	4889.7 ($\pm$630.3)
Radius 50% MCSA (mm^2)	2473.1 ($\pm$387.1)	2518.0 ($\pm$2242.0)

Values are presented as mean ($\pm$SD).
Significant differences between groups (*P < 0.05; **P < 0.001).

Table 4-2. Radius and tibia bone outcomes by group

Site	Outcome	Overweight/Obese	Normal Weight	Difference
Radius				
4%		(*n* = 33)	(*n* = 63)	
	ToD (mg/mm^3)	373.9 (340.4 – 407.4)	381.8 (360.2 – 403.5)	- 2.0%
	ToA (mm^2)	283.6 (261.5 – 305.7)	264.9 (250.6 – 279.2)	+ 7.1%**
	BSI (mg·mm^{-4}/100,000)	389.3 (342.8 – 435)	379.5 (349.7 – 409.6)	+ 2.3%
50%		(*n* = 34)	(*n* = 74)	
	ToA (mm^2)	106.9 (100.4 – 113.4)	103.1 (99.2 – 107.0)	+ 4%*
	CoD (mg/mm^3)	1159.8 (1147.5 – 1172.1)	1200.3 (1193.0 – 1207.7)	+ 3.4%***
	CoA (mm^2)	83.5 (78.8 – 88.2)	81.5 (78.7 – 84.3)	+ 2.5%*
	CoTh (mm)	3.1 (3.0 – 3.3)	3.1 (3.1 – 3.2)	--
	Z (mm^3)	223.3 (203.5 – 243.1)	219.8 (207.7 – 231.9)***	+ 1.6%***
	SSIp (mm^3)	222.1 (203.3 – 240.9)	205.4 (193.9 – 216.9)***	+ 8.1%***
Tibia				
4%		(*n* = 34)	(*n* = 53)	
	ToD (mg/mm^3)	325.6 (307.5 – 343.8)	307.3 (293.8 – 320.8)	+ 6%
	ToA (mm^2)	934.8 (865.9 – 1003.6)	928.4 (877.2 – 979.6)	+ 1%*
	BSI (mg·mm^{-4}/100,000)	299.3 (268.7 – 329.9)	261.1 (228.3 – 283.8)	+ 15%**
66%		(*n* = 34)	(*n* = 73)	
	ToA (mm^2)	551.0 (535.6 – 576.4)	495.8 (480.4 – 511.3)	+ 11%***
	CoD (mg/mm^3)	1119.9 (1109.1 – 1130.8)	1151.9 (1145.3 – 1158.4)	- 3%***
	CoA (mm^2)	324.5 (307.8 – 341.0)	267.6 (257.6 – 277.7)	+ 22%***
	CoTh (mm)	4.8 (4.5 – 5.0)	4.0 (3.9 – 4.2)	+ 20%***
	Z (mm^3)	2584.5 (2417.5 – 2751.4)	2289.2 (2188.7 – 2389.9)	+ 13%***
	SSIp (mm^3)	2407.9 (2250.3 – 2565.5)	2106.7 (2011.9 – 2201.6)	+ 14%***

Values are presented as means after adjustment for bone length and age (95% confidence interval). Significantly different from normal weight *P < 0.05; **P < 0.01; ***P < 0.001
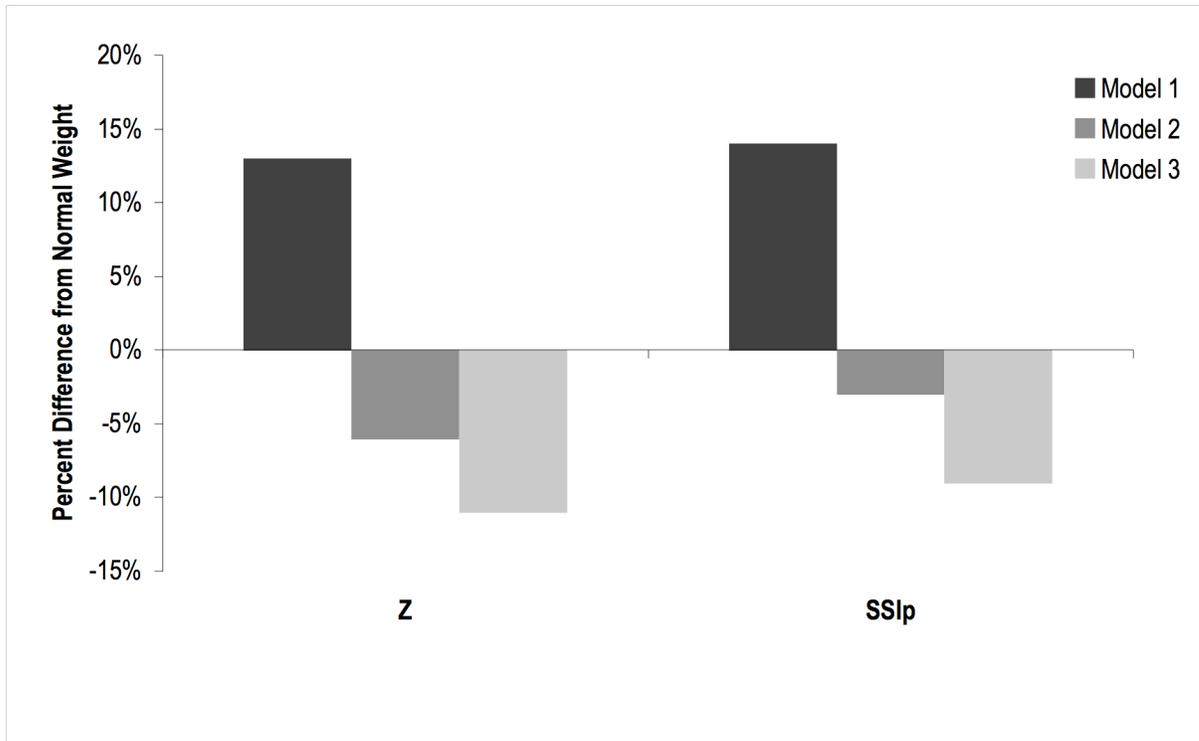
Figure 4-1. Tibia proximal (66%) bone strength differences from normal weight women. Outcomes adjusted for: Model 1: tibia length and age; Model 2: Model 1 + body weight; Model 3: Model 1 + tibia 66% MCSA. All *P* < 0.001 vs. normal weight.
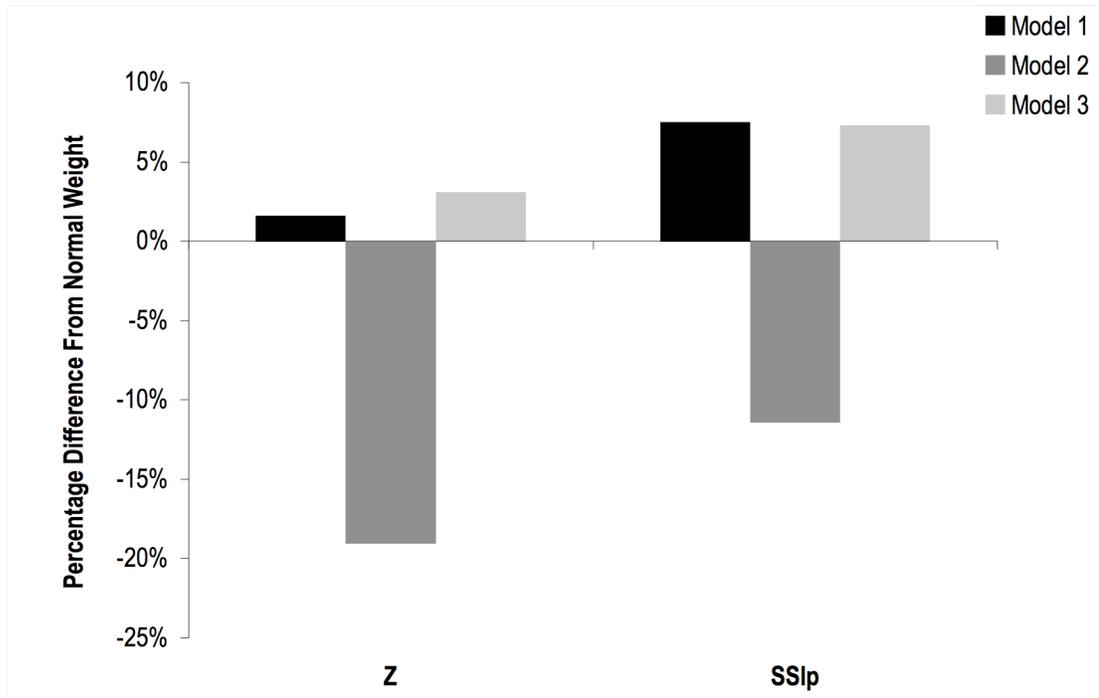
Figure 4-2. Radial midshaft (50%) bone strength differences from normal weight women. Outcomes adjusted for: Model 1: ulna length and age; Model 2: Model 1 + body weight; Model 3: Model 1 + radius 50% MCSA. All $P < 0.001$ vs. normal weight.

Discussion

This cross-sectional study explored differences in bone strength in obese women compared to young healthy-weight women. Results of this study support existing adult literature regarding the association between high body weight and bone strength. Consistent with previous studies, we demonstrated that absolute bone strength is higher in obese women at both weight bearing and non-weight bearing sites (except the distal radius). These differences in bone strength were associated with differences in bone geometry, rather than density. That is, obese women had wider, thicker bones compared to their normal weight counterparts. In contrast, cortical bone volumetric density was lower in obese women. Based on previous studies in overweight children and adults, we hypothesized that bone strength would be adapted to muscle size but low for body weight. While bone strength was low for body weight, it was also low for muscle size in this population of obese women. We discuss these aspects of our data below.

Absolute bone strength and geometry were higher in obese women

Our findings show that overweight women had greater absolute bone strength as evidenced by higher midshaft strength indices (Z and SSIp) at both weight bearing and non-weight bearing sites. With the exception of the distal radius, we showed that absolute bone strength in overweight/obese women was 13 – 14% greater at tibia sites and up to 8% greater at the radial midshaft. Importantly, these strength differences were due to greater total bone area at all sites and thicker cortices at weight-bearing sites. These findings are consistent with pQCT data in overweight children that found 14% greater tibia BSI and 15% greater SSIp, due to greater bone area (+6 - 10%)[57]. Other studies using hip structural analysis (HSA) in children and adolescents[56, 174], young adults[82], and adult women[81] also report greater absolute proximal femur strength as a result of greater cross-sectional area (up to 10%) and as much as 9% thicker cortices. In a study of 4,642 women, Beck et al[81] found 7 – 15% and 8 – 16% greater femoral neck and shaft strength indices (i.e., section modulus and cross-sectional area), respectively, in women (BMI 25 – 35 kg/m^2) compared to normal weight women. More robust bone geometry and strength in obese women is consistent with evidence that overweight adults have lower rates of hip fractures[122, 175]. In contrast, recent evidence suggests that overweight women have higher rates of peripheral fractures (distal radius and ankle/foot)[81, 170]. These seemingly contradictory data may be explained

by the lower bone strength relative to muscle size and body weight and lower cortical vBMD in overweight women.

Bone strength relative to body weight and MCSA

The mechanostat and related theories of functional adaptation suggest that bone strength is adapted to typical peak voluntary loads[40]. Since muscles produce the greatest load on bone, we theorized that bone strength in overweight/obese women would be higher due to greater absolute lean mass, but low for body weight. Our results are congruent with this theory, particularly at weight bearing sites. In our study, overweight/obese women had ~27% greater tibia muscle cross-sectional area and 11 – 13% greater tibia bone strength indices. The findings support the notion that absolute bone strength increases with body weight. However, we found that increased strength in the obese women was not proportionate to their higher body weight. After adjusting for body weight, bone strength in obese women was as much as 5% lower at the tibia midshaft and 11 – 19% lower at the radial midshaft, supporting the notion that excess body weight may be detrimental to the skeleton. Previous longitudinal studies in children[57] and cross-sectional studies in children and adolescents[56], and adults[81, 131, 137] have shown that bone strength was adapted to greater lean mass in the overweight, rather than body weight. As an example, in a study of 200 Chinese adults by Wu et al[137] showed that overweight individuals possessed 14% greater absolute femoral neck bone strength than the control group, but differences no longer remained after adjusting for total body lean mass, suggesting that that bone strength is appropriately adapted to lean mass.

Findings from our muscle-adjusted model depart from the current literature, particularly at the tibia. After holding MCSA constant obese women had significantly lower Zp and SSIp at the tibia (-13% and -10%, respectively), while radius midshaft strength differences remained similar to unadjusted outcomes. In our study, both body weight and MCSA were positively associated with bone strength indices at the tibia midshaft (all P < 0.001). However, when adjusting for MCSA, body weight was no longer correlated with strength parameters. In previous studies that have controlled for the mechanical loading effect of muscle cross-sectional area or lean mass in children[57], athletes[138, 176] and postmenopausal women[81], bone strength parameters have normalized to lean mass compared to healthy weight groups. In contrast, whereas moderate and extremely obese women in the study by Beck et al[81] did not differ in section modulus at the femoral

neck from healthy weight women, aBMD and CSA were 10% and 8%, respectively, lower than healthy weight values. While other studies did not examine populations at the extremes of obesity, it may be that strength differences observed in our study are due to the high BMI of our obese women (38 ±11 kg/m^2). While a positive linear relationship between muscle and bone geometry is consistent with mechanostat theory of bone functional adaptation[40], it is plausible that bone strength may plateau at the highest levels of lean mass, particularly given relatively unchanged strength differences at the radius where MCSA was similar.

Despite epidemiologic evidence showing increasing aBMD with BMI[121, 122], the notion that obesity is protective of bone is not supported in our study. While several studies have found a positive association between fat mass and bone mass and aBMD[120, 125-127], a growing body of evidence supports lean mass as the predominant factor influencing bone mass and strength. Zhao and colleagues[134] demonstrated that when controlling for the mechanical loading effect of body weight, fat mass (or percentage fat mass) were negatively correlated with bone mass. In a large cohort of Chinese adults, Hsu et al[135] showed higher risk of non-spine fractures (OR = 1.3 – 3.0, *P* = 0.002), independent of body weight, for individuals in the highest quartile of fat mass. Moreover, other studies found that when controlling for lean mass, associations between fat mass and proximal femoral geometry and strength parameters were unchanged or diminished in men[83, 84, 177] and older women[81, 131]. The higher risk of extremity fractures in obese adults could be explained by the low bone strength relative to body weight found in our study. That is, although bone strength is higher in an absolute sense, bone strength in obese women may not be high enough to withstand the high impact forces in the case of a fall in this population.

Lower cortical vBMD

Our findings show that obesity in women is associated with greater bone strength as evidenced by higher midshaft strength indices (Z and SSIp) at both weight bearing and non-weight bearing sites. Traditionally, increasing BMI has been associated with greater bone mass and a decreased risk of osteoporosis and fracture[121, 122], but a dearth of research has examined the influence of high BMI separately on cortical and trabecular bone compartments. We found that cortical volumetric bone mineral density (vBMD) was significantly lower (~ 3 – 3.5%) in overweight/obese women. Consistent with our results, Sukumar et al[124] recently showed 2.2% lower tibia cortical vBMD in obese compared to normal weight premenopausal women. Previous

studies have shown no difference in cortical vBMD at the tibia in young women[178] and children[179], but these studies didn't include individuals at the extremes of obesity. It is possible that the lower cortical density observed in our study illustrates an effect of moderate to extreme obesity on bone. Several reasons may exist for this finding. One possibility is the association between obesity and hormones such as parathyroid hormone that may negatively influence cortical vBMD. Although not measured in this study, the presence of high parathyroid hormone subsequent to secondary hyperparathyroidism increases bone turnover and increases cortical porosity[180]. In contrast, obesity has been associated with lower rates of bone formation, particularly type I collagen among postmenopausal women[181]. A second possibility is that greater mechanical loading in obesity leads to microdamage, turnover of damaged bone and an increase in porosity. Because vBMD measured by pQCT includes bone porosity, a higher prevalence of microdamange would lower cortical vBMD outcomes. A third explanation for the lower cortical vBMD among overweight/obese individuals observed in our study and others may be related, in part, to increasing evidence regarding the mesenchymal stem cell link between bone and fat cells. Recent research has demonstrated an association between increased visceral adiposity and increased vertebral bone marrow fat in obese women[182], and impaired bone health[183]. Further study is needed to validate these data and explore the underlying mechanisms.

Limitations and Future Directions

Few existing studies have compared bone geometric and densitometric parameters among extremely obese populations using novel pQCT technology. However, there are several limitations of this study. First, this study is limited by its cross-sectional design, which does not allow causality or temporality to be inferred. In addition to our relatively small sample size, we compared older women to younger healthy-weight women. Although our analyses adjusted for participant age, future studies should compare women matched by age and menopausal status to account for differences secondary to age-related bone loss. Given that we measured peripheral sites at the tibia and radius, our findings may not be generalizable to a larger population of overweight and obese individuals. Despite this our outcomes showing low tibia bone strength for body weight has also been demonstrated at the clinically-relevant femoral neck in overweight children[56] and women[81]. Further, we used MCSA as a surrogate measure of the dynamic loading forces to which bones adapt their geometry and strength. While MCSA is associated with muscle strength, future

studies should include direct measures of muscle force at the bone region of interest. Finally, our study primarily addressed differences in bone strength, but did not examine genetic, hormonal, nutritional, or other lifestyle factors that may have influenced bone geometry and density. Future cross-sectional and longitudinal studies that address the role of fat and lean mass components of body composition among extremely obese populations are needed.

Conclusion

In conclusion, our data show that overweight and obese women exhibit greater absolute bone strength at both weight bearing and non-weight bearing peripheral sites. Further, these differences are primarily due to great total bone area and thicker cortices. Our data also showed that despite lower cortical volumetric bone density, absolute bone strength remained greater that healthy weight women. After controlling for body weight, radius and tibia midshaft bone strength indices were significantly lower among overweight and obese women compared to healthy weight women. After controlling for muscle cross-sectional area, bone strength was only significantly lower at the tibia midshaft in overweight and obese women, while radius bone strength indices were significantly greater compared to healthy weight women. This study suggests that bone strength in overweight and obese women may be low for their high body weight, and, in turn, may help explain the increased risk of extremity fractures in this population.

5

Short-term Bone Strength is Preserved Following Bariatric Surgery: A Pilot Study

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Abstract

There is an increasing concern that bariatric surgery necessitates excessive bone loss, as evidenced in studies that use areal bone mineral density (aBMD) by dual energy x-ray absorptiometry as an outcome. However, few have explored the effect of bariatric surgery on bone from a mechanical strength perspective. **Purpose:** To prospectively examine the effects of bariatric surgery on body composition and estimates of bone strength in morbidly obese adults at baseline (pre surgery), 3 and 6 months post surgery. Bone geometry and strength were assessed by peripheral quantitative computed tomography (pQCT) in 21 morbidly obese adults (mean BMI 45.7 (SD 6.8) kg/m^2). Total volumetric bone mineral density (ToD, mg/mm^2), total bone area (ToA, mm^2), and bone compressive strength (bone strength index (BSI)) were assessed at the distal (4%) sites of the radius and tibia. ToA and cortical bone area (CoA, mm^2), cortical volumetric density (CoD, mg/mm^3), cortical thickness (CoTh, mm), and bone bending strength (section modulus (Z, mm^3) and polar strength strain index (SSIp, mm^3)) were measured at the midshaft sites of the tibia (66%) and radius (50%). Body weight (kg) and body composition (fat mass (kg) and fat-free mass (kg)) were assessed using air displacement plethysmography. Participants were divided into tertiles (High, Medium, and Low) of percentage weight loss at 6 months post surgery. Results: Participants in all three tertiles lost significant weight by 6 months post-surgery (mean loss - 5% to -30%, all $P < 0.05$). Fat mass was significantly reduced in all three tertiles at 6 months (mean loss – 9% to -51%, all $P < 0.05$), but only the High tertile lost significant amounts of fat-free mass following surgery (-8%, $P < 0.05$). Estimates of bone strength at the radius and tibia sites did not change at either post-surgical time point regardless of weight loss. Results: Bariatric surgery resulted in significant weight loss across all tertiles, which was primarily due to loss of fat mass rather than loss of fat-free mass. Contrary to DXA-based aBMD outcomes in the current literature, these results suggest that bone strength was preserved up to 6 months following bariatric surgery. Future longer-term studies exploring bone strength and geometry are needed to confirm these findings.

Introduction

Given the failure of traditional behavioral approaches, bariatric surgery has become an increasingly popular therapeutic approach to morbid obesity. In the last decade the number of bariatric surgical procedures performed worldwide increased over 700%[58]. Bariatric surgery produces substantial and durable weight loss up to 62% and 47% of excess weight, respectively[60], and attenuates or resolves obesity-related comorbidities including diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea in up to 80% of patients[60, 142]. Despite significant improvement in weight and comorbid conditions, there is growing concern that bariatric surgery may exert a negative effect on the skeleton by accelerating bone loss, thereby increasing bone fragility[143]. Among individuals who lose weight without surgery, epidemiological evidence supports increased rates of hip bone loss in older individuals, irrespective of body mass index (BMI)[3, 4], and an increased risk for hip fracture in middle-aged and older women[5].

A growing body of research suggests that marked weight loss following bariatric surgery leads to dramatic bone loss. Studies examining bone density changes following all types of surgical procedures (e.g., gastric banding, Roux-en-Y gastric bypass, biliopancreatic diversion) have demonstrated 12-month areal bone mineral density reductions up to 15% at hip sites[90] and up to 8% at the spine[103]. That surgery-associated weight reduction results in accelerated bone loss is the prevailing consensus in the bariatric literature. Areal bone mineral density (aBMD, g/cm^2) by dual energy x-ray absorptiometry (DXA) has been the primary outcome to measure changes in bone in post-bariatric patients. However, changes must be interpreted with caution in light of inaccuracy associated with DXA measurement of aBMD in obese populations. Variability of aBMD significantly increases with increasing tissue depths[184], and excess fat around bone overestimates aBMD[113]. Further, the planar nature of DXA is not able to characterize bone geometric parameters that underpin indices of bone strength. Peripheral quantitative computed tomography (pQCT) provides outcomes of volumetric bone mineral density (vBMD, g/cm^3) and mechanically meaningful measures of bone geometry, including bone cross-sectional area, from which estimates of bone strength are derived.

Recent research that examined bone strength following diet-induced weight loss showed that a 15% weight reduction did not compromise pQCT-based bone strength outcomes after one year[79]. No known studies have used pQCT technology to examine changes in bone strength

following bariatric surgery. The purpose of this pilot study was to explore the short-term effects of bariatric surgery on changes in bone strength indices in a morbidly obese adult population.

Methods

Study Design and Participants

We prospectively investigated 27 participants (age range 21 to 61 years), who underwent a bariatric surgery for weight loss at the University of Minnesota Weight Loss Surgery Center, between November 2009 and July 2010. Participants were recruited and enrolled in the study at the Weight Loss Surgery Center. Participants were eligible for the study if they had a body mass index (BMI, kg/m^2) of at least 40 or those of at least 35 with serious co-morbidities[185], but were excluded is they were taking medications or had conditions known to influence bone and/or bone metabolism. Surgical procedures included laparoscopic adjustable gastric band, Roux-en-Y gastric bypass and biliopancreatic diversion with and without duodenal switch. Details of the study and testing procedures were explained to each participant and a written informed consent was obtained before data collection. Upon informed consent, participants completed a general health and medical history. The Institutional Review Board of the University of Minnesota approved this study.

Outcome Measures

All study participants completed initial baseline measurements (mean 7.4 (SD 7.7)) days prior to surgery) and were measured again at 3 and 6 months post-operatively. All study measurements were conducted in the Laboratory of Musculoskeletal Health at the University of Minnesota. Study visits coincided with regularly scheduled postoperative care appointments at the Weight Management Clinic.

Body Composition and Anthropometry

Air-displacement plesthymography (BodPod, Life Measurement, Concord, CA) was used to obtain measures of body composition[186] and body weight, which was measured to the nearest 0.1 kg using the plethysmograph's electronic scale.   This method has been previously validated for use in extremely obese participants [187, 188]. Body composition outcomes were calculated by the BodPod's software. The instrument and scale were calibrated daily and, according to

manufacturer's instructions for measurements, participants wore compression shorts, job bra tops, swimsuits, or undergarments, and a Lycra-style swim cap. A wall-mounted stadiometer was used to measure height to the nearest 0.1 cm. Tibia length was measured with an anthropometric tape measure to the nearest millimeter from the tibial plateau to the medial malleolous. The forearm was similarly measured, from the olecranon to the ulnar styloid process.

Bone

Peripheral quantitative computed tomography (pQCT; Norland/Stratec XCT-3000; Orthometrix, Inc., White Plains, NY) scans were acquired using a 2.3 mm slice at the distal (4%) and proximal (66%) sites of the left tibia, and the distal (4%) and midshaft (50%) sites of the non-dominant radius. A 30-mm planar scout view was obtained over the joint line for placement of the anatomic reference line. Based on bone length, the distal and midshaft sites of the tibia and radius were identified by the scanner. A scan speed of 25 mm/s and sampling resolution (voxel size) of 0.5 mm were used. Total scan time for each limb was approximately five minutes. One trained operator (L.S.) performed the measurements and analyzed all scans. Analysis modes and thresholds for outcomes were chosen based on manufacturer's recommendations. Precision with repositioning was determined in our laboratory in adults (women n = 11, men n = 4; mean age 25 ± 6.5 years) as a coefficient of variation (CV, %) and varied from 0.3% to 1.2% for all measurements. Quality assurance was performed by daily scanning a manufacturer-provided anthropometric phantom.

The distal (4%) tibia and radius sites were assessed for bone geometry (ToA, total cross-sectional area, mm^2), total bone volumetric density (ToD, mg/mm^3), and an estimate of bone compressive strength (bone strength index (BSI), mg/mm^4 = ToA X ToD^2/100,000). Bone outcomes at the radius midshaft (50%) and the proximal tibia (66%) sites included the geometric parameters ToA, cortical area (CoA, mm^2), cortical thickness (CoTh, mm), and cortical volumetric density (CoD, mg/mm^3). Estimated indices of bone bending strength obtained from midshaft sites included section modulus (Z, mm^3) and polar strength-strain index (SSIp, mm^3). Muscle cross-sectional area (MCSA, mm^2) was also obtained at the radius (50%) and the tibia (66%).

Statistical Analysis

All data were analyzed using SPSS (v17) for Windows. Statistical significance was defined at $P < 0.05$ (two-tailed) for all analyses. All data were checked for skewness, kurtosis, outliers, and Shapiro-Wilks test of normality was checked for each dependent variable. Exploratory analysis for changes from baseline (pre-surgery) to 3 and 6 months post-surgery in body composition, resting metabolic rate, and bone variables was done using paired *t*-tests. Wilcoxon Signed Rank test was used for non-normally distributed data. Pearson product-moment correlations were used to compute correlation coefficients to determine the relationship between changes in body weight, fat mass, fat-free mass, and muscle area from pre-surgery (baseline) and post-surgery (3 and 6 month) body composition, resting metabolic rate, and bone variables. With skewed data, Spearman rank order relationships between changes in body weight, fat mass, fat-free mass, and bone variables were computed.

The group was divided into tertiles (High, Medium, and Low) based on the percentage reduction in body mass from pre-surgery (baseline) values. Paired *t*-tests were used to compare within-group changes in body composition variables from baseline to 3 and 6 months post-surgery. Between-group changes in body composition variables were compared using analysis of covariance (ANCOVA) at 3 and 6 months post-surgery, adjusting for baseline values. Post-hoc between group comparisons were performed using Sidak's adjustment for multiple comparisons.

Results

Of the 27 participants who enrolled, baseline characteristics of the 21 participants who completed the study are summarized in Table 5-1. Several reasons existed for those (n = 6) participants who did not complete the study. One participant did not undergo surgery for insurance reasons, and attrition of the others was based on scheduling conflicts and lack of interest. The majority of subjects were Caucasian (n = 19; 90%) and others (n = 2; 10%) were African-American. Of the women 10 (67%) were pre-menopausal and 5 (33%) were postmenopausal.

Body Composition

Exploratory analysis showed statistically significant overall mean changes in all body composition variables, including resting metabolic rate, at three and six months post-surgery (data not shown). At the third post-operative month, body weight and BMI were reduced a mean 13% from pre-surgery levels, fat mass (kg and %) declined 21% and 10%, respectively (all $P < 0.001$),

fat-free mass declined 4.5% ($P < 0.05$), and percentage fat-free mass increased by 11% ($P < 0.001$). Further, muscle cross-sectional area (MCSA) at the forearm (radius 50%) and lower leg (tibia 66%) were also reduced 7.4% and 6.5%, respectively (both $P < 0.01$), at three months post surgery. With the exception of fat-free mass and resting metabolic rate, continued declines were observed in all body composition variables at the sixth post-operative month. Weight loss ranged from -1% to -36% from baseline (pre-surgery) with a mean 6-month loss of 18.1%. Final mean BMI was 37.2 (SD 7.5) kg/m^2, reduced from 45.7 (SD 6.8) kg/m^2 at baseline. Changes from baseline for fat mass (kg and %) were -31% and -17%, respectively (both $P < 0.001$). Fat-free mass loss (-4.6%, $P < 0.005$) and percentage fat-free mass gain (+11.6%, $P < 0.001$) at six months were significantly different from baseline, but remained similar to 3-month changes. Finally, MCSA reduction at the forearm (radius 50%) and lower leg (tibia 66%) was significantly lower than baseline at 6 months (both – 8%, $P < 0.001$), but were not dramatically different from losses observed at 3 months.

The group was divided in High (> 20%), Medium (10 – 19.99%), and Low (< 10%) tertiles based on percentage reduction in body weight at 6 months post surgery. Body composition (including resting metabolic rate) baseline characteristics and mean changes in variables based on at 3 and 6 months are shown in Table 5-2. Mean percentage weight reduction (±SD) for each group was 31.1% (±5.5), 15.2% (±3.0), and 4.6% (±2.7), respectively. Percentage weight loss for the High tertile ranged from -37.3% to -20.4%, -19.2% to -10.6% for the Medium tertile, and -7.4% to -0.7% for the Low tertile. Body weight significantly declined in both the High and Medium tertiles at three months post surgery, 20.6% and 11.2%, respectively, and the baseline adjusted change in weight was greater in the High tertile (- 26.9 kg, 95% CI –30.9, -22.9) compared to the other two (Medium -14.7, 95% CI -19.1, -10.4 and Low -6.2, 95% CI -11.3, -1.0). However, significant 6-month reduction was observed across all tertiles, with the greatest change in weight occurring in the High (-39.1 95% CI –43.9, -34.4) and Medium (-19.9, 95% CI -25.1, -14.8) tertiles (Figure 5-1).

Fat mass (kg and %) declined significantly in the High and Medium groups at both post-operative time points, but only 3-month baseline-adjusted losses in the High tertile were significantly greater than the other tertiles (-21.8 kg (95% CI -26.1, -17.5 High vs. -11.9 kg (95% CI -16.5, -7.3) Medium and -6.9 kg (95% CI -12.3, -1.5) Low) (Figure 5-2). At 6 months baseline-adjusted losses in fat mass were significantly different between all tertiles (-34.5 kg (95% CI -39.6,

-29.4) High vs. -17.6 kg (95% CI -23.0, -12.2) Medium vs. -6.1 kg (95% CI -11.9, -0.3) Low). Only in the High tertile fat-free mass was significantly reduced at 3 and 6 months (-8.0% and -7.4%, respectively, both $P < 0.05$). Between-group differences in baseline-adjusted fat-free mass changes were evident at 3 months post surgery between only the High (-5.0 kg (95% CI -6.9, -3.2) and Medium (-2.8 kg (95% CI -4.8, -0.7) tertiles. Excepting the Low tertile, significant losses in peripheral lean mass occurred at both post-operative time points (Figure 5-3). At the forearm, MCSA significantly declined from baseline at three months in both the High and Medium tertiles (-15% and -5.3%, respectively), and those baseline-adjusted changes in the High tertile (-466.6 mm^2 (95% CI -550.7, -382.4)) were significantly greater than the Medium (-131.3 mm^2 (95% CI -217.2, -45.4)) and Low (-59.2 mm^2 (95% CI -158.3, 39.8)) tertiles. Reduction in forearm MCSA at 6 months remained significantly different from baseline in both the High and Medium tertiles, but appeared to have stabilized in the High tertile (-15.8%) and continued to decline slightly in the Medium Tertile (-7.2%). Between-group differences in baseline-adjusted loss of forearm MCSA differed between all groups at the sixth post-surgical month (-469.3 mm^2 (95% CI -533.9, -404.6) High vs. -209.4 mm^2 (95% CI -276.2, -142.7) Medium vs. -38.1 mm^2 (95% CI -108.5, 32.3) Low). Similarly, progressive losses in lower leg MCSA were evident at both post-operative time points in the High tertile (-12.3% and -15.1%, respectively) and Medium tertile (-4.5% and -7.9%). Further, between-group differences were significant between the High and Low tertiles at both 3 months (-959.8 mm^2 (95% CI -1312.1, -607.5) High vs. 56.0 mm^2 (95% CI -510.2, 398.3) Low) and 6 months (-1162.1 mm^2 (95% CI -1502.6, -821.5) High vs. 56.4 mm^2 (95% CI -467.9, 355.1) Low).

Bone Strength, Geometry and Volumetric Density

Overall mean baseline values, and 3 and 6-month mean changes in radius and tibia bone variables are presented in Figure 5-4. Exploratory analysis revealed little to no change in bone variables at either post-operative time point from pre-surgery values. At the distal (4%) sites, there were no significant changes in bone compressive strength (BSI), density (ToA), or geometry (ToA) parameters at either 3 or 6 months post bariatric surgery. Radius midshaft (50%) measures of bone strength (Z and SSIp), density (CoD), or geometry (ToA, CoA, and CoTh) did not significantly change from baseline at 3 or 6 months post surgery. At the proximal tibia (66%) there were also no differences in structure or density parameters. Bone strength (SSIp) significantly increased 1.1% ($P < 0.05$) at 3 months, but the difference was no longer evident at 6 months. Radius and

tibia bone strength baseline and 6-month values by tertile weight loss are presented in Table 5-3. There were no significant pre- to post-surgery differences in bone strength parameters among weight loss tertiles. For example, despite slight inceases in Z in across all three tertiles at the proximal (66%) tibia, changes from baseline or between-groups were not significant.

Table 5-1. Descriptive characteristics

	Mean $\pm$ SD
N	21
Age (years)	45.3 ($\pm$12.7)
Gender: Female (%)	15 (71.4%)

Surgery Type:
    Restrictive (%)
    Malabsorptive/Combination (%)
	
	9 (43%)
	12 (57%)

Body Weight (kg)	129.1 ($\pm$23.6)
Body Mass Index (kg/m^2)	45.7 ($\pm$6.8)
Fat Mass (kg)	67.4 ($\pm$16.4)
Body Fat (%)	52.0 ($\pm$6.3)
Fat-Free Mass (kg)	61.8 ($\pm$12.4)
Fat-Free (%)	48.0 ($\pm$6.3)
Tibia 66% MCSA (mm^2)	7673.3 ($\pm$1229.7)
Radius 50% MCSA (mm^2)	3024.9 ($\pm$771.4)
Resting Metabolic Rate (kcal/day)	1865.7 ($\pm$346.5)
Tibia Length (mm)	368.8 ($\pm$25.8)
Ulna Length (mm)	262.2 ($\pm$15.3)

Values are presented as mean ($\pm$SD).

Table 5-2. Baseline characteristics and changes in body composition from baseline. Mean ($\pm$ SD)

	High (>20%)	Medium (10 – 19.9%)	Low (<10%)
	n = 8	n = 7	n = 6
Age (years)	42.1 (12.5)	47.9 (13.5)	46.7 (13.4)
Gender (female:male)	(6:2)	(4:3)	(5:1)
Surgery Type			
Restrictive (n)		3	6
Malabsorptive/Combination (n)	8	4	
BMI (kg/m²)			
Baseline (Pre-surgery)	45.4 (6.4)	47.9 (21.2)	43.4 (7.1)
3 Month	35.9 (5.3) [a]	42.6 (6.1) [a]	42.4 (8.0) [a] , n = 5
6 Month	31.1 (3.9)[a]	40.6 (6.1)	41.4 (7.6)[a]
Weight (kg)			
Baseline	130.3 (15.8)	134.8 (24.9)	121.0 (31.7)
3 Month	103.5 (15.2) [a,b,c]	119.7 (21.2)[a,b]	120.28 (31.9) [b] ,n = 5
6 Month	91.1 (13.9)[a,b,c]	114.2 (20.2) [a,b]	115.4 (32.5) [a,c]
Fat Mass (kg)			
Baseline	67.9 (10.2)	69.5 (18.9)	64.0 (21.5)
3 Month	35.9 (12.8)[a,b,c]	57.5 (15.5)[a]	60.4 (22.6)[a], n = 5
6 Month	33.4 (10.7) [a,b,c]	51.5 (12.9) [a,b]	58.4 (22.5) [a,c]
Body Fat (%)			
Baseline	52.2 (5.1)	51.3 (8.9)	52.4 (5.0)
3 Month	44.1 (8.3)[a]	47.7 (7.9)[a]	49.6 (7.7), n = 5
6 Month	36.3 (8.4) [a,b,c]	45.4 (7.4) [a,b]	50.0 (6.6) [a,c]
Fat-Free Mass (kg)			
Baseline	62.3 (10.3)	65.3 (14.5)	57.0 (12.8)
3 Month	57.3 (9.0)[a,c]	62.2 (11.9)	59.9 (14.5), n = 5
6 Month	57.7 (9.3) [a]	62.1 (12.0)	56.9 (13.8)
Fat-Free (%)			
Baseline	47.8 (5.1)	48.7 (8.9)	47.6 (5.0)
3 Month	55.9 (8.3)[a]	52.3 (7.9)[a]	50.4 (7.7), n = 5
6 Month	63.7 (8.4) [a,b,c]	54.7 (7.4) [a]	50.0 (6.6)[a]
Radius 50% MCSA (mm²)			
Baseline	2877.3 (594.6) , n = 7	3369.8 (866.2)	2794.8 (822.3)
3 Month	2439.9 (544.6)[a,b,c] , n = 7	3190.3 (723.0)[a]	2859.8 (733.1), n = 5
6 Month	2421.5 (591.0) [a,b,c], n = 7	3128.8 (730.3) [a,b]	2777.8 (782.6) [c]
Tibia 66% MCSA (mm²)			
Baseline	7686.9 (500.37)	8205.6 (1666.2)	7034.3 (1216.5)
3 Month	6744.2 (577.9)[a,c]	7815.4 (1430.7)[a]	7365.7 (1066.2), n = 5
6 Month	6523.0 (542.6) [a,c]	7554.8 (1425.9)[a]	7061.2 (1327.1)
RMR (kcal/day)			
Baseline	1882.0 (274.6)	1964.6 (389.3)	1728.5 (410.6)
3 Month	1687.9 (243.0)[a,c]	1836.4 (324.3)[a]	1789.6 (423.5) (n = 5)
6 Month	1620.8 (244.7)[a,b,c]	1812.3 (327.1)[a]	1704.3 (415.6)

[a] Significant changes from baseline (Paired t-test)
[b] Significant ($p < 0.05$) between-group differences compared to Low group (ANCOVA; Sidak adjusted post-hoc test); [c] compared to Medium Group
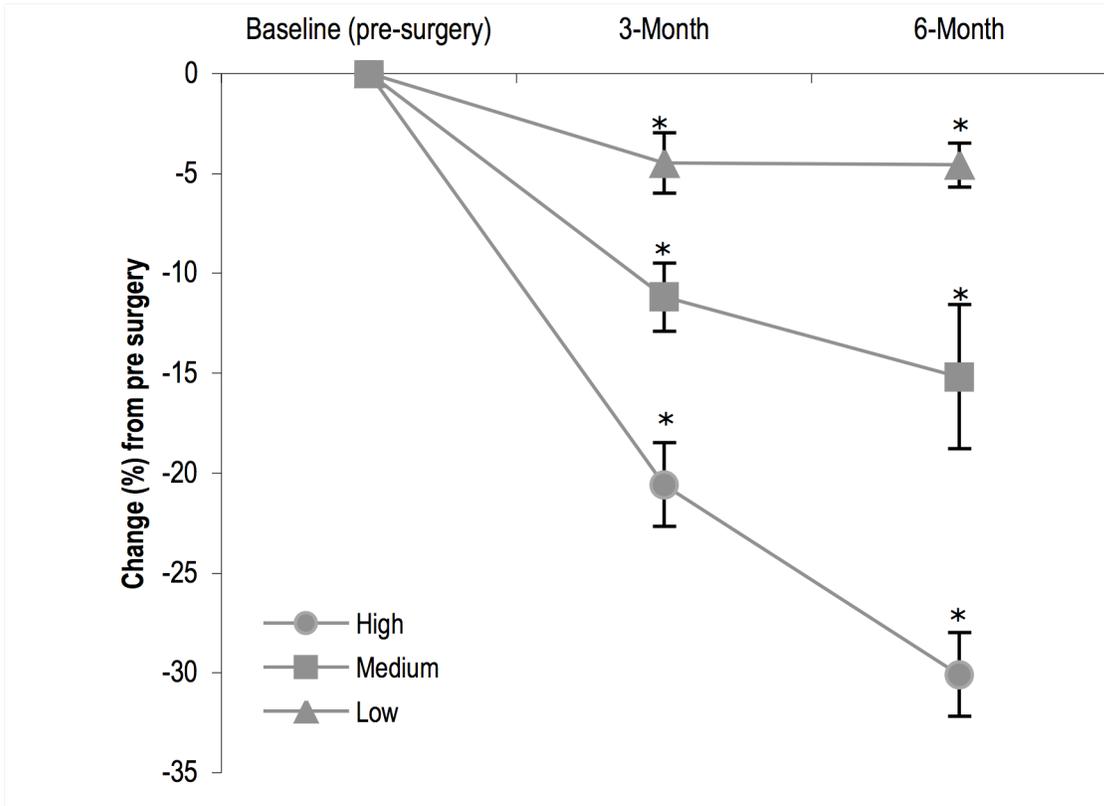
Figure 5-1. Mean percentage change ($\pm$ SD) in body weight by tertile of weight loss. Baseline adjusted between-group differences: *$P < 0.05$.
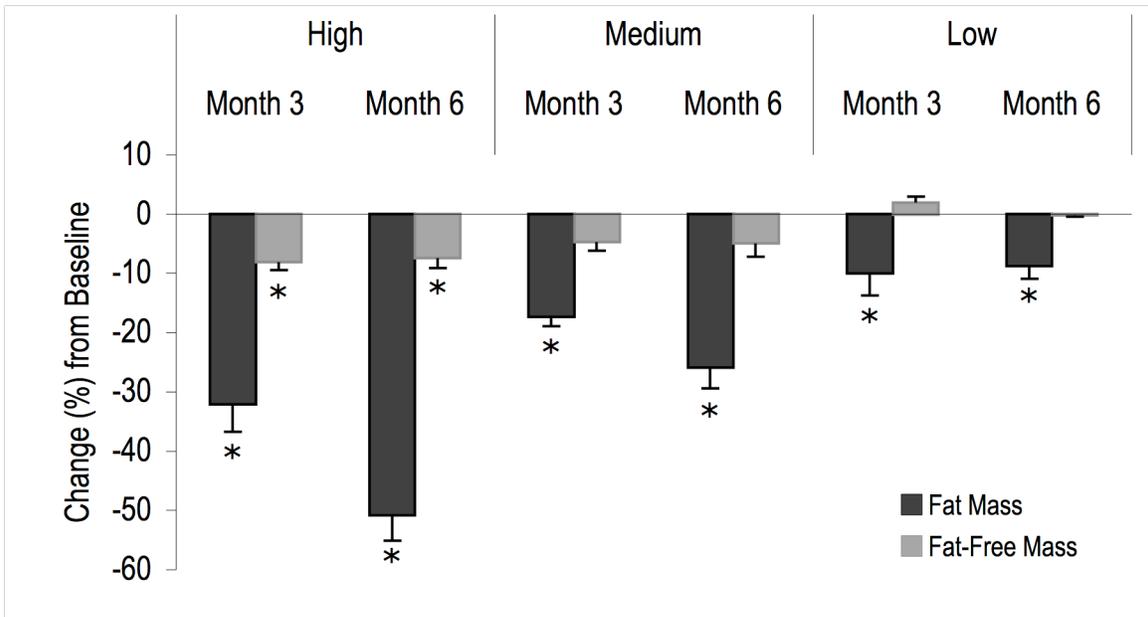
Figure 5-2. Mean percentage change (±SD) in fat mass and fat-free mass from baseline (pre-surgery) by tertile of weight loss. Significantly different from baseline: *P* < 0.05.
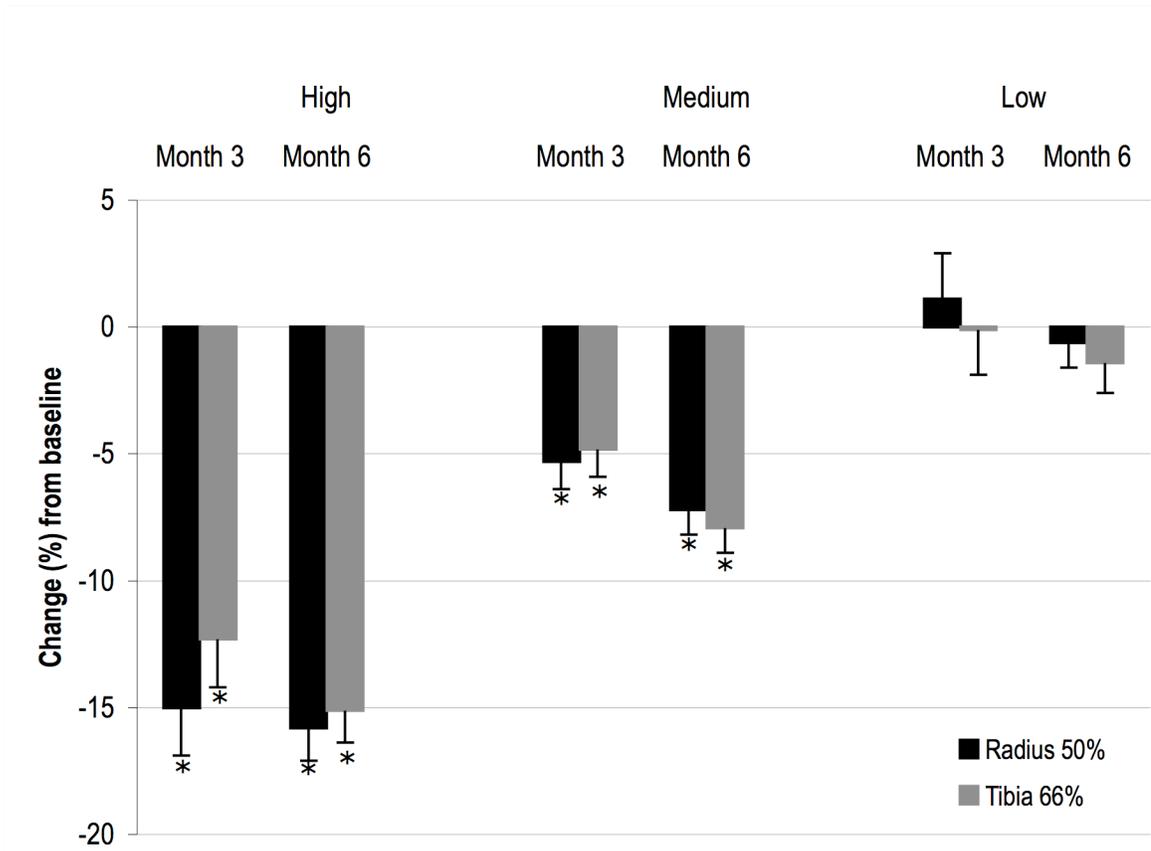
Figure 5-3. Mean percentage change (±SD) in tibia and radius MCSA from baseline by weight loss tertile. Signficantly different from baseline: *P < 0.05.
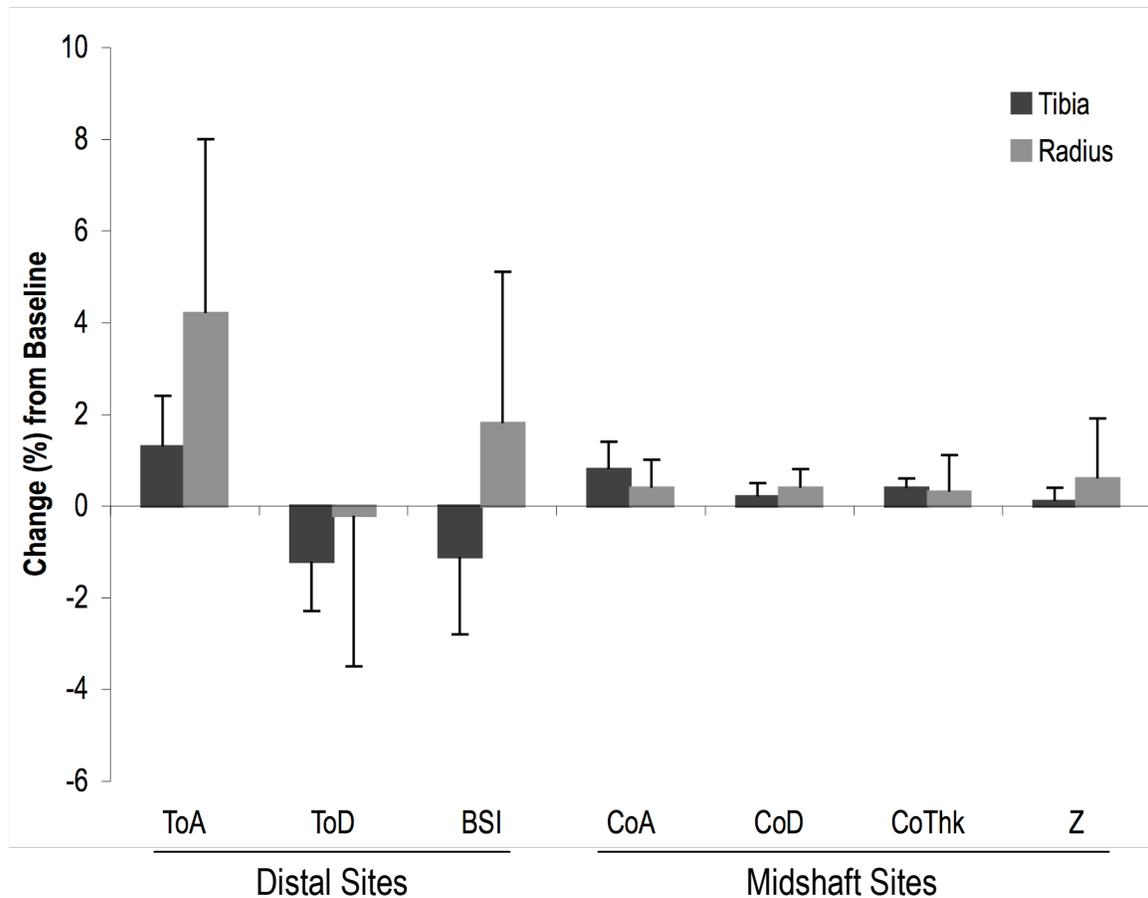
Figure 5-4. Overall bone parameter mean 6-month percentage change (±SD) from baseline at radius distal (4%) and midshaft (50%), and tibia distal (4%) and proximal (66%) sites.

Table 5-4. Baseline and 6-month bone variables by weight loss tertile. Mean (±SD)

	High (>20%)	Medium (10 – 19.9%)	Low (<10%)
	n = 8	n = 7	n = 6
Radius 4% Site			
BSI (mg/mm^{-4}/100,000)			
Baseline	44.8 (13.5)	59.5 (14.7)	45.1 (9.2), n = 4
6 Month	47.6 (15.3)	56.5 (12.2)	45.9 (8.6), n = 4
Radius 50% Site			
Z (mm^3)			
Baseline	287.7 (72.6), n = 7	319.9 (111.2)	277.4 (112.7)
6 Month	282.7 (61.0), n = 7	338.3 (104.5), n = 6	283.7 (117.4)
SSIp (mm^3)			
Baseline	283.2 (68.3), n = 7	313.9 (100.7)	280.3 (113.1)
6 Month	281.9 (61.5), n = 7	316.1 (110.4)	281.3 (111.2)
Tibia 4% Site			
BSI (mg/mm^{-4}/100,000)			
Baseline	110.5 (29.3), n = 7	131.6 (29.3)	116.3 (22.4)
6 Month	104.6 (35.4), n = 7	133.7 (28.4)	118.4 (22.8)
66% Site			
Z (mm^3)			
Baseline	2909.2 (714.8)	3194.7 (932.9)	2760.3 (934.5)
6 Month	2962.8 (720.5)	3215.2 (926.2)	2766.4 (940.9)
SSIp (mm^3)			
Baseline	2851.6 (696.7)	3105.3 (858.4)	2702.1 (894.3)
6 Month	2886.8 (687.8)	3119.6 (835.0)	2659.1 (844.7)

No significant within-group or between-group changes.

Discussion

This is the first known study to examine changes in bone strength using pQCT technology in a bariatric population. In the present study, we showed that morbidly obese adults lost significant body weight in the six months following bariatric surgery, primarily through a reduction in total body fat mass. However, in contrast to our hypothesis, indices of bone strength at the tibia and radius remained largely unaffected by the rapid and substantial change in body weight. While our results are consistent with previous pQCT-based weight loss studies, they are in contrast to DXA-based studies that reported significant loss of bone mineral density following bariatric surgical procedures. We discuss aspects of these data below.

Body Composition

As expected, we showed that body weight was significantly reduced among morbidly obese adults who underwent bariatric surgery for weight loss, and that most weight loss occurred in the first months following surgery. Interestingly, six of the 21 participants (Low tertile), who underwent adjustable gastric banding (restrictive) procedures, reduced their weight less than 10% by six months. These results are similar to outcomes following traditional diet and physical activity interventions[59], but are in contrast to studies that showed 6-month body weight reductions of 16 – 21% following restrictive procedures, including adjustable gastric banding[91, 94, 95]. However, weight loss in the High and Medium tertiles (-31%, and –15%, respectively) was consistent with 16 – 28% 6-month weight loss outcomes across all bariatric procedures[88, 94]. While weight loss continued to the sixth post-surgical month across all tertiles, a majority of the weight loss occurred in the first three months following surgery. Similarly, two other studies showed the greatest rate of weight loss in the first three months following both gastric bypass and gastroplasty procedures[85, 189].

The consensus regarding body composition changes following bariatric surgery remains equivocal, with concern over the detrimental effect of excessive lean mass loss, in this case, on skeletal integrity. Research in bariatric populations has shown total body fat mass reductions of 35 – 45% from baseline in the first post-operative year, but reductions in lean mass have ranged broadly from 3 – 30%[85, 115]. Our results showed that, only in the highest weight loss tertile, fat-free mass was significantly reduced from pre-surgery levels. Further, changes at 3 and 6 months were

similar (nearly -8%), suggesting that fat-free mass loss stabilized in the first post-operative trimester while fat mass progressively reduced 32% at 3 months and 51% at 6 months (Figure 5-2). The ratio of fat/fat-free mass loss at 6 months in the High, Medium, and Low tertiles (8:1, 6:1, and 6:1, respectively), further demonstrates the preferential loss of fat mass in our population. Zalesin showed that bariatric patients with the most rapid weight loss (e.g. gastric bypass procedures) experienced accelerated loss of both fat and lean mass, compared to slower weight loss procedures (i.e. restrictive) that preserved lean mass[109]. Similarly, our High tertile had the greatest rate of weight loss and most reduced fat-free mass, while the Low tertile marginally gained fat-free mass.

Safe ranges of lean mass loss relative to weight loss have not been identified, but some have noted that lean tissue losses should not exceed 22% of total weight loss[112]. In the present study, fat-free mass constituted only 12% of total weight loss in our High tertile - much less than the 18 – 31% of total weight loss reported by Chaston and colleagues[110] and more recent 6-month relative lean mass reductions of 23%[88], 30%[85], and 33%[111] reported following gastric bypass procedures. Furthermore, studies comparing one-year post-bariatric measures of fat and lean body mass (total body, trunk or appendicular) have found no difference from BMI-matched[85, 86] or lean[87] cohorts, suggesting that even seemingly excessive losses produce no deleterious deficit in lean mass.

Bone Strength, Geometry and Volumetric Density

Contrary to the majority of studies that observed dramatic losses of DXA-based aBMD at the hip (up to - 15%) and spine (up to - 8%) reported following bariatric surgery procedures, we found virtually no change in bone geometry, volumetric density, or indices of bone strength in both cortical and trabecular-rich radius and tibia sites. When considered as a group, bending strength (SSIp) at the tibia midshaft increased marginally (+1%) only at the third month, and was no longer different from baseline at the sixth month. Further, no changes in indices of bone strength at either the radius or tibia were evident when separated by tertile of weight loss (%). Consistent with our results, Uusi-Rasi et al[79] reported a lack of one-year changes in bone strength, geometry and volumetric density at both radius and tibia sites among participants who lost the most weight (-13.5 to - 19%) following an intensive 3-month diet-restricted intervention. Despite our conflicting results

with hip and spine outcomes, DXA-based cross-sectional studies found up to 24% greater radius aBMD in bariatric patients compared to both obese and overweight controls nearly one year after surgery[76], and prospective investigations reported either no significant change or slightly increased (+2%) radius aBMD 12 months following bariatric procedures [89, 93]. Several reasons for our results are discussed below.

Decreased mechanical loading has been proposed as a possible explanation for bone loss observed in DXA-based bariatric studies. While overall mechanical loading (i.e., body weight) in the present study was reduced 5 – 30%, static loading in the form of fat mass constituted a majority of the load reduction. The mechanostat theory of bone adaptation states that bone strength is adapted to the prevailing loading environment. Evidence in children[57], adolescents[56], women[81, 137], and men[83] indicate that bone strength is primarily adapted to lean mass. Since muscles produce the greatest physiological load on bone, a disproportionate loss of lean mass would have resulted in lowered bone strength, particularly at the weight-bearing tibia. As a percentage of total weight loss, our 12% fat-free mass loss was much less than 26 – 31% losses reported by Chaston et al[110] following similar procedures. Also, MCSA at the forearm and lower leg was reduced 7 – 15% in the Medium and High tertiles. Compared to healthy weight individuals, greater absolute lean mass is observed in obese individuals (+15 - 35%)[81], so our small observed decreases in fat-free mass and MCSA may not have been enough to affect bone parameters. Given that small amounts of fat-free mass were lost and bone strength did not change, our results appear congruent with mechanostat theory.

Massive weight loss may have made movement and activities of daily living less cumbersome and, thereby, increased physical activity. Physical activity is believed to have positive effects on bone health directly through dynamic loads imparted by the activity (e.g. walking or running), or indirectly through its positive effect on muscle mass and strength [7, 46]. Only about 4.5% of individuals awaiting bariatric surgery meet the weekly recommended levels of moderate to vigorous intensity physical activity[190], but spend over 80% of their time in sedentary behaviors[191]. Moreover, this level of physical activity may not significantly increase according to accelerometer-based data that showed only 5% of post-bariatric surgery patients actually meet recommended physical activity levels despite self-reported increases in activity[192].   Physical activity was not

assessed in this study so it remains unclear if increased physical activity in the months following bariatric surgery may have confounded bone strength outcomes.

Limitations of DXA technology may also contribute to the disparate findings from pQCT-based studies. Variability of areal bone mineral density (aBMD) significantly increases beyond tissue depths of 10 cm[184, 193], and excess fat around bone overestimates aBMD as much as 5.5%[113]. Moreover, work by Bolotin and colleagues suggests that changing fat/lean mass ratios further contribute to DXA aBMD inaccuracy[114, 116]. Even in light of varying degrees of lean mass lost following bariatric surgery, a significant portion of weight lost is attributed to changes fat mass (35 – 45%)[80, 88, 92, 94, 115]. Loss from the central body (trunk), rather than the peripheral body, constitutes the majority of weight loss[87]. Where the preponderance of tissue change occurs are also the same regions focused upon in DXA-based bariatric research (e.g., lumbar spine and hip regions). Thus, as the fat/lean mass ratio decreases so follows the DXA aBMD values[114], without a concurrent change in the true aBMD – mistakenly leading previous investigators to conclude that significant bone loss followed bariatric surgery. For example, the 9 -11% decreases in femoral neck DXA aBMD at the first year following RYBG surgery [93, 154] may have been erroneously attributed to changes in true aBMD, but were actually due to changes in extraosseous fat and lean tissue without any change in true aBMD. Thus, preoperative aBMD may have been falsely high and actual losses, if any, may have been less than observed.

Limitations and Future Directions

No known studies have examined changes in bone geometry and estimates of bone strength following bariatric surgery in morbidly obese adults using pQCT technology. However, there are several limitations of this study. First, weight loss following bariatric surgery is known to persist for at least 12 months and our study examined only short-term changes in bone parameters, so it is unclear if bone loss congruent with DXA-based aBMD outcomes will be evident in the future. In addition to our relatively small sample size, participants ranged in age from 21 to 61 years and included both men and women. Future studies should track homogenous cohorts to account for differences secondary to age-related bone loss, gender, and effect of surgery type on body composition and bone outcomes. Further, objective measures of physical activity before and

after bariatric surgery should be used to account for the confounding mechanical loading effect of physical activity on bone strength. Given that we measured peripheral sites at the tibia and radius, our findings may not be comparable to DXA-based outcomes at the clinically-relevant hip and spine. Given the widespread use of DXA technology in research and clinical settings, future studies should consider other methods, including Hip Structural Analysis, to assess geometric and strength parameters at the femur. Further, we assumed fat-free mass and MCSA as a surrogate measure of the dynamic loading forces to which bones adapt their geometry and strength. While fat-free mass and MCSA are associated with muscle strength, future studies should include direct measures of muscle force at the bone region of interest. Finally, our study primarily addressed changes in estimates of bone strength, but did not examine genetic, hormonal, nutritional, or other lifestyle factors that may have influenced bone geometry and density. Future longitudinal studies that address bone strength in bariatric patients are needed.

Conclusion

In conclusion, our data show that short-term bone geometry, density and bone strength are preserved following bariatric surgery, despite 6-month reductions in body weight up to 31% from baseline. The majority of weight loss consisted of fat mass across all tertiles, with a six to eight-fold greater loss of fat mass relative to fat-free mass. Our data also showed that while the High tertile lost significant fat-free mass, it constituted only 12% of total weight loss, which was significantly less than that observed in earlier studies. Preservation of lean mass appeared to play a role in the maintenance of bone strength in this population of bariatric patients.   This study provides an interesting, alternative approach to address the concern over accelerated bone loss following bariatric surgery.

6

Summary

The purpose of this dissertation was to explore the effect of mechanical loading via body weight and its components on bone in obese cohorts. The results presented in Chapters 3 – 5 helped to explain the effects of obesity and weight loss subsequent to bariatric surgery on bone health, and each chapters contributes uniquely to the current literature. This dissertation is novel in four specific ways. First, bone geometric and strength parameters were explored in severely obese adult cohorts. Moreover, using pQCT as measurement tool is important in describing the bone volumetric density and structure outcomes necessary for estimating bone strength, particularly among severely obese adults. Next, summarizing the relationship between bariatric surgery and bone health is significant from both a clinical and public health perspective. Further, quantifying bone structure and strength outcomes following surgery-induced weight loss plays an important role in assessing the risk of skeletal fragility. Finally, the interpretation of results based on mechanostat and theories of bone functional adaptation is novel in the bariatric and bone density literature. The findings of each paper relative to the specific aims and hypotheses are summarized below.

Specific Aim 1 was to comprehensively review the association between bariatric surgery, bone mineral density and osteoporosis incidence by summarizing and interpreting studies reporting bone mineral density and osteoporosis outcomes in the bariatric surgery literature.

As shown in Chapter 3, DXA-based cross-sectional studies demonstrated that, in general, bone density did not differ significantly in post-bariatric surgery patients compared to overweight and obese controls. Prospective DXA-based studies showed that significant bone density loss occurs in the first year following bariatric surgery. Bone loss preferentially affects hip sites after all procedure types and the spine following malabsorptive and mixed procedures. Further, mean T- and Z-scores remained within normal ranges up to 25 years post surgery. Despite the bone loss observed at hip sites in prospective studies, the concern over osteoporosis incidence or increased risk of fracture is not supported. The limitations of DXA in obese populations and the dearth of long-term prospective studies that include control populations highlight at need for further research, particularly to provide conclusive evidence regarding fracture outcomes in this population.

Specific Aim 2 was to examine the effect of body weight and lean mass (muscle cross-sectional area) on differences in bone volumetric density, bone geometry, and estimates of bone strength in obese and healthy weight women. I *hypothesized* that obese women would have greater absolute estimates of bone strength, due to greater bone area, compared to healthy weight women. Further, I *hypothesized* that estimates of bone strength in obese women would be low relative to their body weight.

The results in Chapter 4 are consistent with the hypothesis. The cross-sectional analysis showed that absolute bone strength was higher in the obese women at all midshaft sites and the distal tibia compared to the healthy weight women, but was not different at the distal radius. The greater absolute bone strength was primarily due to larger total bone area. However, cortical volumetric density was lower in obese women at both radius and tibia midshaft sites. After adjusting for body weight, estimates of bone strength were lower in obese women at the midshaft sites. Interestingly, estimates of bone strength were lower in the obese women at the tibia, but not the radius, after adjusting for muscle cross-sectional area. These results stress the importance of interpreting bone strength in obese populations relative to components of body composition.

Specific Aim 3 was to prospectively examine the effect of bariatric surgery on body weight, body composition (fat mass, fat-free mass, and muscle cross-sectional area), bone volumetric density, bone geometry, and estimates of bone strength in a morbidly obese adults cohort. I *hypothesized* that body weight would be significantly reduced, primarily due to a reduction in fat mass, in the 6 months following bariatric surgery for weight loss. I also *hypothesized* that bone strength would decrease, secondary to substantial and rapid weight loss, following bariatric surgery.

In Chapter 5, the body weight and body composition results were consistent with the hypothesis. The prospective analysis showed that bariatric surgery produced significant 6-month reductions in body weight in morbidly obese adults. Weight loss was primarily due to significant reductions in fat mass, rather than fat-free mass. Only among participants who lost the most weight was fat-free mass significantly reduced. Bone results were not consistent with the secondary hypothesis. The prospective analysis showed that bone volumetric density, bone geometry and estimates of bone strength did not significantly change six months following bariatric

surgery. These results were evident at both distal and midshaft sites of the radius and tibia, demonstrating that short-term bone strength is preserved in adults following bariatric surgery. Moreover, these findings suggest the need for future longer-term studies to assess bone geometry and strength following bariatric surgical procedures.

7

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