

The Effects of Physical Activity, Body Composition, Muscle Cross-Sectional Area and Sex Steroids
on Bone Volumetric Density, Strength and Geometry in Older Men

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Julie Cousins, August 2011

Dedication

This dissertation is dedicated to my wonderful parents – Robert and Joan Cousins. Thanks for everything! I love you!

Abstract

Introduction: Osteoporosis and related fractures are significant public health and economic burdens. Studies show that factors such as mechanical loading and sex steroids influence the bones of older women. In order to reduce the risk of osteoporosis in older men, it is important to understand what factors affect the strength of the bones of older men.

Aim: The primary aim of this study was to identify modifiable factors that influence bone volumetric density, bone geometry and estimates of bone strength in old men.

Methods: This cross-sectional study used data from the MrOS (n=1171) and Tobago Bone Health (n=500) studies. Dual Energy x-ray absorptiometry was used to assess areal bone mineral density, lean mass and fat mass. Peripheral quantitative computed tomography assessed volumetric bone mineral density, bone geometry, estimates of bone strength and muscle cross-sectional area.

Results:

After adjusting for age, clinic site, body weight, race and limb length, estimates of bone strength at the 4% and 66% site of the tibia were greater in the quartile of men with the greatest leg power compared to the least leg power and in the quartile of men that were the most physically active compared to the least active. Similar results were found at both the distal and midshaft of the radius when looking at physical activity and grip strength.

After adjusting for age, clinic site, limb length, and race, estimates of bone strength at the proximal and distal tibia and radius were positively associated with total body weight, BMI, lean mass and fat mass.

After adjusting for age, site, and tibia length, bone strength was positively associated with muscle cross-sectional area. Bioavailable testosterone and estradiol were positively associated with cortical vBMD while bioavailable estradiol was also positively associated with total and trabecular vBMD, bone compressive strength, cortical area and section modulus.

Summary: These findings suggest that greater physical activity, muscle strength, muscle power, lean mass, and muscle cross-sectional area (all surrogates of mechanical load) are important for bone strength. It may be important to utilize the role of muscle to prevent the natural loss of bone that occurs with aging. These findings are congruent with findings from previous studies conducted on older females.

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Chapter 1

Rationale, Specific Aims and Hypotheses

Rationale

Osteoporosis is commonly considered a disease that affects women, and therefore, the majority of research to date has studied the causes and means of prevention of osteoporosis in women. However, it has been estimated that one in four men over 50 years of age will suffer from an osteoporotic fracture in their lifetime [1]. To put this in perspective, the lifetime risk of experiencing an osteoporotic fracture is similar to the lifetime risk of developing prostate cancer [2]. Not only do men often go undiagnosed and untreated even though they are at risk for osteoporotic fractures, but there is also little information on the disease and its manifestations in men. Data exploring factors that influence bone strength in older men would provide information to help in identify risk factors for osteoporosis, and aid in the design of effective interventions. Given the substantial health and economic burdens associated with osteoporosis, men are an under-studied but important population to target for prevention to alleviate the public health and quality of life burden of this disease.

This dissertation uses data from the Osteoporotic Fractures in Men (MrOS) study and the Tobago Bone Health Study. Peripheral quantitative computed tomography (pQCT) will be used to compare tibial and radial bone volumetric density, total and cortical bone area, and estimates of bone compressive and bending strength in a subset of men (> 65 years) who participated in the multi-site MrOS study (n = 1171) and Tobago Bone Health Study (n=500).

The primary purpose of this cross-sectional study will be to examine the effects of physical activity, body composition, muscle cross-sectional area and sex steroids on the bone strength and geometry of the lower and upper extremities in older men.

The following specific aims are proposed:

Specific Aim 1: To examine the association between measures of physical activity, muscle strength and power and estimates of bone strength in community dwelling older men.

Hypotheses: We hypothesize that estimates of bone strength will be higher in men with higher levels of reported physical activity, muscle strength, and muscle power. We also hypothesize that

the higher bone strength among more active men or those with greater muscle strength and power will be due to differences in bone geometry rather than bone volumetric density.

Specific Aim 2: To explore the relationship between body weight (lean and fat mass and BMI) and bone strength and geometry in community-dwelling older men.

Hypotheses: We hypothesize that total body weight, BMI, lean mass and fat mass will be positively associated with estimates of bone strength at the tibia and radius. We further hypothesize that lean mass will account for the association between body weight, BMI and estimates of bone strength and that fat mass will not be associated with estimates of bone strength after adjustment for lean mass.

Specific Aim 3: Examine the interrelationships between mechanical loading (using muscle cross sectional area as a surrogate) and sex steroid hormones (testosterone and estradiol) on parameters of bone volumetric density, bone strength and geometry in older American and African men.

Hypothesis: We hypothesize that higher mechanical loading represented by larger muscle size will be positively associated with estimates of bone strength primarily due to higher periosteal apposition regardless of ethnic origin or sex steroid levels. Secondly, we hypothesize that higher levels of testosterone and estradiol will be associated with greater total bone area and volumetric BMD, but not overall bone strength.

Chapter 2

Introduction and Literature Review

Introduction

Osteoporosis is a significant public health problem

Osteoporosis is a skeletal disorder characterized by compromised bone strength that results in an increased susceptibility to fracture [3, 4]. It is a global public health burden and a serious concern for older adults. Over 1.5 million fractures are associated with osteoporosis each year. These fractures result in 500,000 hospitalizations, 800,000 emergency room visits, 2.6 million physician visits, 180,000 nursing home placements, and 13.7 to 18.3 billion dollars in direct healthcare costs each year [5]. Hip fractures are considered to be the most devastating consequence of osteoporosis as they are associated with severe disability and increased mortality [6]. It is estimated that over 200 million people worldwide currently have osteoporosis [7], and the prevalence is expected to increase with the increasing lifespan and aging population [1]. In the US alone, an estimated 44 million individuals (55 percent of the population over age 50) have low bone mass or osteoporosis. By the year 2020, it is predicted that 61.4 million Americans will suffer from osteoporosis [8]. More common in women, osteoporosis is also present in men, where it often goes undiagnosed and untreated.

Although osteoporosis is often considered to be a disease of older white women, 9-15 million men in the United States have low bone mass or osteoporosis [9]. Men sustain approximately 20-30% of all hip fractures and account for about 20% of the direct costs of osteoporosis [10]. Among those with osteoporotic hip fractures, men tend to suffer more morbidity and mortality than women. Wehren et al. (2003) found that men were twice as likely as women to die during the first two years following hip fracture [11]. By 2025, the projected number of hip fractures worldwide for men is approximately 1.16 million [12] versus the 0.5 million reported in 1990 [13]. These findings and projections suggest that there may be greater deaths in the future due to hip fractures and the complications associated with hip fracture in men.

Osteoporosis is a silent disease, whereby if not detected early, fracture may occur without prior warning. Much attention is placed on early prevention, detection, and treatment of osteoporosis. Therefore, it is important to identify factors that influence bone strength to aid in developing preventive measures to offset the individual and population burden of osteoporosis.

Studies in female populations have indicated important factors in the development of osteoporosis:

physical activity, body composition, muscle cross-sectional area and sex steroids are a few [14]. From a theoretical perspective, the findings regarding the first three factors, physical activity, body composition and muscle cross-sectional area, are congruent with well-established physiological mechanisms seen in bone biology. For example, it is well-known that bone is sensitive to its mechanical environment: it is able to adapt to changes in physical activity or inactivity by altering its mass and structure [15]. When bone is subjected to greater loads than usual, more bone is added to the existing skeletal structure. This increases bone strength in proportion to the environment's new mechanical demands. Therefore, physical activity, body composition (an important load on bone) and muscle cross-sectional area should be factors that influence the risk of osteoporosis in men as well as women. Nonetheless, this remains untested. Furthermore, estradiol has been demonstrated to play an important role in maintaining bone mass with advancing age in females. Estradiol and testosterone should play a similarly important role in regulation of bone metabolism in men. What also remains to be tested is whether there is a relationship between mechanical loading, sex hormones and risk of osteoporosis in older men.

Thus, the primary purpose of my dissertation was to examine the effect of physical activity, body composition, muscle cross-sectional area and sex steroids on bone volumetric density, bone geometry and estimates of bone strength of the lower and upper extremities in older men. Peripheral quantitative computed tomography (pQCT) was used to measure the bone parameters of older men. pQCT is a novel bone imaging technique. This dissertation is outlined in three parts. Part one describes the associations of muscular power, muscular strength and physical activity with pQCT-derived tibial and radial estimates of bone strength in older men. Part two describes the associations of body composition (weight, lean mass and fat mass) and BMI with bone volumetric density, bone geometry and estimates of bone strength in older men. Part three looks at the relationship of muscle cross-sectional area and bioavailable sex steroids with tibial estimates of bone strength, bone volumetric density and bone geometry in older men from the United States and the islands of Tobago and Trinidad.

The remaining portion of this chapter provides relevant background literature. This includes the theoretical framework for the dissertation, a review of physical activity, muscle power and strength and bone health, a review of body composition and bone health and a review of sex steroids and

bone health. Chapters three thru five provide the results from the three studies. Finally, chapter six will summarize the results and present conclusions.

2.1 – Overview and Theoretical Framework

Theoretical Framework: Bone is sensitive to its mechanical environment

Bone is a unique tissue with the primary mechanical function of supporting loads that are imposed on it. The skeleton is shaped to meet the loading requirements it faces throughout life. Over a century ago Roux [16] (summarized by Roesler [17]) theorized this relationship between physical loads and bone structure. It is commonly referred to as bone functional adaptation [18-21] and involves feedback loops that serve to maintain an “equilibrium” or “customary” strain level in the presence of bone strain [21]. This feedback loop was further developed by Frost’s mechanostat theory which endeavors to keep bone strain at an optimal level by adjusting bone structure. It refers to the concept of bone regulation according to certain thresholds while mechanotransduction is the physiological process that permits this to occur [15].

Mechanotransduction

Mechanotransduction is the process whereby the musculoskeletal system responds to imposed demands. Mechanotransduction involves four steps: 1) mechanocoupling, 2) biochemical coupling, 3) transmission of biochemical signal and 4) the effector response. Mechanocoupling is the process whereby a load is signaled to cells. Osteocytes and bone-lining cells detect that bone is being loaded through a process that is thought to be mediated by strain-induced interstitial fluid flow [22]. Signals are then transmitted from the osteocytes to mechanoreceptors within the cell membrane and cytoskeleton where a signaling cascade is initiated. Once the signal reaches the effector cells (osteoblasts and osteoclasts), bone remodeling begins and ultimately results in architectural changes that adjust bone structure to match the requirements of the mechanical environment [23].

Mechanostat theory

As stated before, the feedback loop was further described by Frost’s mechanostat theory. The mechanostat theory involves a control system in bone that is responsible for sensing changes in the mechanical demands placed on bone [15]. Frost proposed that bone responds to set-points

which control whether bone is added or taken away from the skeleton. According to the mechanostat theory, when bone is loaded above a set microstrain (which is greater than typical peak mechanical loads), modeling occurs via increased bone formation, effecting periosteal expansion and reduced endosteal resorption. This adaptive combination creates a bone that is more resistant to deformation. Thus, new bone is added in response to the mechanical demand which results in an increase in bone strength. In the trivial loading zone when there is virtually no mechanical stimulus to bone, bone is resorbed. It is resorbed by stimulation of intracortical and endosteal remodeling. Studies conducted during space flight[24, 25] reveal that this results in a net loss of bone over time. This substantial reduction in loading is associated with increased cortical bone porosity, expansion of the marrow cavity, thinning of the bone cortex, and, finally, a bone that is less resistant to strain. Thus, bone functional adaptation is regulated by the mechanostat.

Mechanostat theory has been verified in several animal experiments [26-29]. For example, in growing dogs, disuse osteopenia in the casted forelimb was the result of both reduced modeling on the periosteal surface (decrease in periosteal expansion) and increased remodeling on the endosteal surface (increased endosteal expansion) [28]. Remobilization of the dogs reversed both of these trends such that periosteal apposition increased and endosteal apposition was also restored.

The mechanostat theory of functional bone adaptation served as the theoretical framework for this dissertation. Bones are exposed to greater mechanical loads from physical activity, muscle power, muscle strength, muscle cross-sectional area and body composition. These loads may result in greater than typical peak mechanical loads which may lead to bone formation that increases bone strength.

Animal models of loading

Various animal models for studying the effects of mechanical loading on bone have been developed [30, 31]. Because of these models, it is known that the effects of mechanical loading are dependent upon the magnitude, duration and frequency of the mechanical stimulus applied [32]. A study by van der Wiel et al. (1995) studied the effects of running with and without a weighted backpack on female mice [33]. They found that short durations with a weighted backpack resulted

in greater total body bone mineral content than running without a backpack for longer durations [33]. The backpacks increased the peak strains during exercise.

Several studies of mechanical loading in animals of different age groups provide evidence of the effects of age on bones ability to sense mechanical loads. Steinberg et al. (1981) found that running had more of an anabolic effect on the bones of infant rats than mature rats [34]. Similar results were found in a study by Rubin et al. (1992) using the loadable functionally isolated ulna preparation in young and old male turkeys [35]. This study found that eight weeks of 300 cycles per day of loading resulted in greater cortical area, endosteal area and periosteal area between the loaded and unloaded ulnae of the young turkeys with no significant differences between ulnae of the older turkeys. These results suggest that older skeletons are less sensitive to mechanical loading.

Human models of loading

Mechanical loads are important for the growth and maintenance of bones. Gymnasts and runners provide excellent models of loading in the human body. Gymnasts can experience ground reaction forces more than 12 times their body weight, while runners only experience ground reaction forces of 3-5 times their body weight. A study by Robinson et al. (1995) found the areal bone mineral density (aBMD) of gymnasts at both the hip and the spine was 30-40% higher than in runners [36]. Another study of interest showed that during a training season, gymnast increase their aBMD while runner's aBMD does not increase [37]. One study found that during the off season, when gymnasts have not been training, their aBMD decreased significantly [38]. These studies highlight the adaptive response of bone to loading in the human skeleton.

Gaps in the literature with regard to the adaptive response of trabecular bone

The adaptive response to loading is complex and it is influenced by a number of properties within the loading environment. Less is known about loading properties that influence trabecular bone adaptation. This could be because of the difficulties associated with applying and controlling loads at trabecular sites [39, 40]. Previous studies in growing rats have demonstrated osteogenic effects of endurance exercise on trabecular bone formation [41, 42]; however, the differences in loading protocols were not assessed in these studies. van der Meulen et al. (2006) developed a device to

apply loads to the distal lateral femoral condyle of the rabbit [40]. The effects of the applied load on trabecular tissue resulted in the loaded limbs increasing their trabecular thickness and mineral apposition rates when compared to the control limb [40]. However, the researchers were unable to relate the bone formation to the properties of the mechanical environment such as the number of cycles. This was likely due to the small sample size. Thus, no conclusions could be made about the effects of load cycles on trabecular bone formation [40]. Future investigations with animal models will help to define other loading characteristics such as load magnitude and duration that influence trabecular bone functional adaptation.

The primary purpose of the skeleton is to be strong enough to support the loads that are typically placed on it. Bone exhibits a remarkable ability to adapt to changes in mechanical loading in order to best withstand future loads of the same nature. Thus, to optimize strength without overly increasing weight, bones accommodate the loads that are typically imposed upon them by undergoing alterations in mass and geometry. Therefore, it is important to measure both bone geometry and bone mass.

Bone geometry and volumetric trabecular BMD are important parameters to measure

A majority of studies that have explored the effects of mechanical loads on bone have used dual energy x-ray absorptiometry (DXA) aBMD or markers of bone turnover as primary outcomes. DXA is used because it is accessible, reliable, and allows for measurement of clinically relevant sites (proximal femur and lumbar spine); and bone turnover markers are used because they can provide some insight into systemic changes in bone metabolism that are apparent much earlier than any significant change in bone density as measured by DXA.

Although DXA is useful for measuring bone mass, traditional DXA outcomes do not consider the geometric properties of bone, and DXA is not able to assess cortical and trabecular bone compartments separately. These limitations are significant when exploring models of mechanical loading or unloading. Animal studies show that with increased loading, bone is laid down where strains are the highest, typically on the periosteal surface [43]. Small increases in bone mass, that may not be apparent in aBMD outcomes, can increase bone bending strength substantially [43, 44]. In animal models of unloading, bone is lost primarily from the endocortical and trabecular

surfaces of bone [45], allowing at least some of the bending strength to be maintained despite the loss of bone material.

Peripheral quantitative computed tomography (pQCT) is another technique used to measure bone. It measures bone mineral density (BMD) as volume of bone rather than areal measure made by DXA. Measurements with pQCT have been shown to be associated with bone strength and fracture risk, and allow determination of the geometry of the bone [46, 47]. Bone geometry includes the total area, cortical area, and trabecular area from a slice of bone. Unlike DXA, pQCT is able to differentiate between trabecular and cortical bone. Since trabecular bone is more metabolically active than cortical bone [48], the ability to measure trabecular bone separate from cortical bone may explain the better prediction of fracture risk with pQCT. Despite the advantages with pQCT, DXA remains the most commonly used technique to measure bone mineral content (BMC) and BMD.

Mechanical loading can influence bone size (dimensions) in ways that are not apparent in DXA aBMD, and small changes in geometry (particularly if bone is added to the periosteal surface) can lead to a substantial increase in bone strength. Therefore, it was worth exploring the relationship of physical activity, muscle power, muscle strength, body composition, muscle cross-sectional area, bioavailable testosterone and bioavailable estradiol on bone dimensions and volumetric density measured by pQCT.

2.2 – Physical Activity, Muscle Power, Muscle Strength and Bone Health

Physical activity and bone overview

Evidence from epidemiological, clinical and experimental exercise studies indicate that physical activity can be an effective intervention for increasing and maintaining bone mass and strength as well as decreasing the rate of bone loss, which may in turn reduce the risk of fracture [49]. Data from both adult and animal studies show that those who are more physically active have higher areal bone mineral density (aBMD) and a lower risk of osteoporotic fractures [50]. Most studies exploring the relationship between physical activity and bone health have used DXA-based bone mineral content or areal bone mineral density (aBMD) outcomes [51-53]. However, animal studies show that bone adapts its strength to changes in mechanical loading by preferentially increasing

bone size rather than mass/aBMD [54]. Technology such as peripheral quantitative computed tomography (pQCT) allows for assessment of volumetric bone density, bone geometry and estimates of mechanical strength at the tibia and radius – outcomes that may be more sensitive for assessing how bones respond to mechanical loading [55]. The first part of this section will discuss the studies of physical activity and bone strength and geometry in men according to study design. First, we will discuss cross-sectional studies, second longitudinal studies, third intervention studies, then the effect of physical activity on the skeleton with regards to fracture and falls, and finally, the effect of muscle power and muscle strength on bone parameters.

Cross-sectional studies of physical activity and bone strength and geometry among men

Cross-sectional studies can evaluate associations between bone strength and geometry and physical activity in a population at a defined place and time [56]. They provide less valuable information than randomized, controlled trials but they can provide specific information that is not yet available from other sources. This section is broken down by participant age group.

Children and adolescents

Studies in children and adolescents support the positive association of physical activity and bone strength and geometry [57, 58]. A recent study by McKay et al. (2010) noted a significant positive relationship between bone strength and impact physical activity among males and no relationship between nonimpact physical activity and bone strength [58]. In male participants, they also observed a significant positive relationship between total area and impact physical activity but no relationship with measures of bone architecture and impact or nonimpact physical activity [58]. A study of young male tennis players found that repetitive loading significantly increased bone mass by 17% and bone size by 12-21% in the playing arm compared with the nonplaying arm in pre-pubertal boys [57]. Peri-puberty boys also had significant exercise-induced bone gains when training was continued from pre- to peri-puberty [57]. There are a few peripheral quantitative computed tomography and physical activity studies of children. Ward et al. (2005) reported that physical activity enhanced bone geometry at diaphyseal sites in pre pubertal gymnasts and school children [59]. The previous studies provide evidence that physical activity positively influences bone strength and geometry in children and adolescents.

Adults and older men

Results from cross-sectional and retrospective studies have demonstrated that both current and past physical activity levels are associated with bone strength in men. In men over the age of 50, current participation in strenuous physical activity was associated with significantly greater femoral neck bone strength and cross-sectional area when compared to men who reported participation in light physical activity [60]. Lifetime physical activity was positively associated with greater subperiosteal diameter of the proximal femur [60]. According to Orwoll (2003), bone that is distributed further from its center of mass has greater bending strength [61]. Daly et al. (2006) noted that greater lifetime weight bearing physical activity was an important determinant of bone size, cortical area and strength at the mid-femur in older men [62]. These findings suggest that physical activity throughout the life is important for maintaining bone strength and geometry in men, specifically, in older men.

A couple studies have been conducted on male athletes. One study in former Finnish national tennis player found an increase in radius size but not volumetric density when compared to controls [63]. A study by Rantalainen et al. (2010) compared elderly volleyball players to elderly physically active control subjects [64]. The study found that volleyball players had larger tibial mid-shaft cross-sectional area and thicker cortex than controls [64]. Bone cross-sectional area was found to be larger in both sets of athletes compared to non-athlete controls. This suggests that activity may increase bone strength by increasing the size of the bone.

In conclusion, cross-sectional studies provide support that higher levels of physical activity promote greater bone strength and geometry compared with a sedentary or less active lifestyle. The size of this difference is dependent on the type and intensity of the activity, the age when the activity began and how many years the individual spent doing the activity.

Longitudinal, observational studies of physical activity and bone strength and geometry among men

Longitudinal, observational studies involve tracking the study population over a period of time [56]. Information is obtained from the same individual at more than one time. There are only a few

longitudinal studies looking at bone strength and geometry in boys and men. This section is broken down by participant age group.

Children and adolescents

In a seven year longitudinal study in adolescent boys aged 8-15 years, Forwood et al. (2006) found physical activity, measured by questionnaire, to be an independent predictor of cross sectional area and strength at the femoral neck [65]. Janz et al. (2007) conducted a six year longitudinal study in children aged 4-8 years [66]. This study found moderate to vigorous physical activity, based on accelerometry data, to have an independent effect on cross sectional area and strength of the femoral neck [66]. These studies support the idea that physical activity during the growing years is beneficial for bone strength and geometry. Macdonald et al. (2005), in a 20-month study using peripheral quantitative computed tomography (pQCT), found no significant differences in adjusted 20-month or percent change for any bone variable [67]. A major limitation of this study is that the sample size went from 26 boys at baseline to 8 boys at the 20-month follow-up. A longitudinal DXA study in adolescent boy found higher physical activity to be a predictor of greater bone mineral content [68]. These studies provide evidence that physical activity during childhood results in a positive effect on bone structural strength.

Adults and older men

No longitudinal studies in men were found looking at bone strength and geometry in older men. There was one longitudinal study found in older men using DXA based aBMD. In this ten year longitudinal study, Daly et al. (2008) found that habitually active elderly men have a decreased rate of bone loss compared with inactive elderly individuals [69]. In addition, the older men that maintained a moderate level of physical activity during the ten years had better balance than the inactive men, although, a physically active lifestyle was not found to be protective against fractures in this group of men.

Taken together, these longitudinal studies provide evidence for the important role of physical activity to ensure optimal bone strength and geometry during adolescents. The aBMD results provide evidence for the importance of maintaining an active lifestyle to prevent bone loss into old age. Longitudinal studies need to be conducted in men that are specifically designed to look at

bone strength and geometry. Next, the effects of physical activity on bone strength will be looked at in randomized controlled trials.

Randomized controlled trials of physical activity and bone strength and geometry among men

In the following section, findings will be discussed from randomized controlled trials of physical activity and bone strength and geometry. Randomized controlled trials are studies that involve an intervention designed to improve health that is applied to a population with an outcome assessed at baseline and follow-up [56]. It involves a treatment and a control group with participants randomly assigned to each group. Some of the difficulties with randomized controlled trials include subject recruitment and compliance associated with exercise intervention. This section is broken down by participant age group.

Children and adolescents

There have been four intervention studies using DXA-based hip structural analysis (HSA) [70-73] and two intervention studies using pQCT [74, 75] to look at bone strength and geometry in children and adolescent boys. After a 20 month intervention, Mackelvie et al. (2004) reported that, in boys, a high impact circuit training program demonstrated a significantly greater increase in femoral neck cross-sectional area when compared with controls [70]. This adaptation in their bone structure resulted in a significant greater change in the boy's femoral neck bending strength [70]. Weeks et al. (2008) found that 8 months of physical education jumping did not significantly increase estimates of bone strength at the femoral neck in boys [71]. Some possible reasons for the lack of intervention effect are insufficient stimulus, limitation of DXA, or the shorter duration of the study because it can take up to 6-12 months to see adaptations in bone or due to a small sample size. The results of the DXA-based HSA studies are mixed on whether exercise increased bone strength and geometry. One reason for the difference in results could be the different pubertal stages in each of the studies. Two intervention studies have been conducted using pQCT. Johannsen et al. (2003) found no difference in the pQCT related bone parameters between the intervention and control boys. Macdonald et al. (2009) found that the boys in the intervention group had 3% greater gains in estimated tibial bending strength when compared to the boys in the control group [75].

Adults and older men

Very few intervention studies have evaluated the relationship of exercise and bone health in men using DXA. Currently, no studies have evaluated bone strength and geometric adaptations to exercise in men using pQCT. In a meta-analysis of DXA-based aBMD studies, Kelley et al. (2000) concluded that site-specific exercises may help to improve or maintain aBMD at the femur and lumbar in older men [76]. Little change was seen in aBMD among younger men [76].

Additional randomized controlled trials need to be conducted in men to evaluate the relationship of exercise and bone strength and geometry. These studies in children show mixed results for a relationship of physical activity and bone strength and geometry. Some of the studies show an increase in bone strength and geometry, while others did not find an increase, although, no studies found a decrease in bone strength with exercise. Next, we will look at the effect of exercise on the skeleton for the prevention of falling and fracture.

Effect of exercise on the skeleton for falling and risk of fracture

The most unfortunate consequence of an imbalance between bone strength and the loads imposed on them is fracture. There is evidence from a meta-analysis of randomized controlled trials that exercise reduces fall risk by 17% or more in community-dwelling older adults [77]. Moayyeri (2008) in a meta-analysis found that moderate-to vigorous physical activity was associated with a 45% reduction in proximal femur fracture risk in men [78]. Another study found that adult who became more inactive with age doubled their risk of proximal femur fracture when compared with adults that remained moderately active [79]. These studies suggest that as men age, they should be encouraged to maintain a physically active lifestyle to help prevent the risk of falling and fracture. Finally, we will discuss the effects of muscle power and muscle strength on bone parameters.

Muscle power and muscle strength are important factors for optimizing bone health

A study by Dixon et al. (2005) found low grip strength to be significantly associated with reduced aBMD in the spine and the femoral neck in women [80]. The study also found that men with low grip strength had a lower aBMD of the spine and femoral neck but the confidence intervals around all estimates included zero [80]. Another study assessing the relationship of grip strength and bone strength at the radius found a significant association with SSIp in adults ranging in age from 18 to

80 years of age [81]. A study in men found a 7% increase in calcaneus BMD per standard deviation increase in grip strength [82]. The different hand grip dynamometers used in these studies may have influenced the different results. Thus, it is important to look at how bone strength is associated with grip strength in older men.

Few studies have examined the association of leg power with bone strength in an older population. A recent study in older women found leg power explained 6.6% of the variance in bone strength-strain index and 8.9% of the variance in the section modulus at the tibial mid-shaft but that muscle strength did not significantly predict bone parameters [83]. Therefore, it may be important to look at muscle power in addition to muscle strength in an older population of men.

Thus, there is evidence that weight-bearing physical activity plays an important role in bone health across the male lifespan. During childhood, impact activity helps to increase bone strength and enhance bone geometry. As men age, physical activity helps to maintain bone strength, while in older men it helps to diminish bone loss. The specific type and amount of activity needed to increase bone strength is not known but a combination of resistance training and impact exercise may promote bone health into older age and thus, reduce the risk of fracture. Finally, muscular strength and power may have important implications in the bone health of an older population.

Section 3.3 – Body Composition and Bone

The relationship between body weight and bone strength in older men is not well understood

It is estimated that 68% of the current US population is overweight or obese [84]. In the midst of this growing obesity epidemic, the relationship between body composition and bone strength is of interest, and is likely of greatest importance in the elderly where osteoporosis is most prevalent. However, the relationship between body composition and bone strength in older community-dwelling men is not yet well-understood. This section will review the current literature that looks at the effect of body composition on bone health. First, we will look at the relationship of body mass index and fracture risk. Second, the relationship of body composition and bone mineral density will be discussed in overweight and obese individuals. Third, the relationship of body composition with

bone strength will be considered in overweight and obese individuals. The final discussion will be on the relationship between body composition and bone strength in normal weight individuals.

Body mass index and fracture risk

Body mass index (BMI) is a widely used measure to determine overweight and obesity. BMI values over 25 kg/m² are used to define overweight and values over 30 kg/m² are used to define obesity. The advantages of BMI include that it is inexpensive and easy to administer; thus, making it a useful tool when studying large groups such as in epidemiological studies. BMI is a useful tool for defining body composition of large groups of individuals but it lacks accuracy when evaluating the body composition at the individual level. The major limitation of the BMI is that weight is not divided into fat-free mass and fat mass. This can be an issue in older adults because as individuals age, they tend to put on fat weight and lose fat-free weight.

Recent studies have looked at BMI as a predictor of fracture risk [85, 86]. A meta-analysis by De Laet et al. (2005) showed that individuals with a BMI of >25 kg/m² had significantly lower risk of osteoporotic, hip and all fractures [86]. Similar results were seen by Beck et al. (2008) for hip and central body fractures while upper extremity fracture incidence did not vary with BMI [85]. These studies suggest that a higher BMI may have a protective or no effect on the risk of fracture. However, a recent study casts doubt on this view with the observation of a high prevalence of low trauma fractures among obese postmenopausal women, most of whom had normal BMD by dual energy x-ray absorptiometry (DXA) [87]. Among older adults with similar hip BMD, heavier individuals may have a higher risk of hip fracture [88].

Body composition and bone mineral density

The majority of studies addressing the relationship of body composition or BMI and bone health have been conducted using DXA. The limitations of DXA are that it is unable to assess differences in bone geometry or to identify specific adaptations in cortical and trabecular bone compartments. DXA is also unable to identify small differences in bone dimensions that translate into substantial increases in bone strength.

High body weight or BMI has been associated with higher bone mineral density (BMD) values in both men and women [89, 90]. It is thought that a larger body weight imposes a larger mechanical load on bone which causes an increase in bone mass to accommodate the larger load. In older men, weight loss is associated with hip BMD loss, regardless of whether the weight loss is voluntary or involuntary [91], suggesting that a relationship between body weight and bone outcomes exists. Thus it is important to look at the relationship between body composition or BMI and bone health among older men.

DXA-based studies have found total body fat mass to be more closely linked with aBMD than lean mass. Reid et al. (1992) found in healthy post menopausal women that aBMD was closely related to body weight, BMI and fat mass and less closely related to lean body mass [92]. Fat mass was an independent predictor of aBMD at all sites [92].

Other DXA-based studies have found lean mass to be more closely linked with aBMD than fat mass. Kirchengast et al. (2001) noted that BMI and lean mass were positively associated with areal BMD (aBMD) in healthy older men, while aBMD increased with increasing fat mass this association was not statistically significant [93]. In a large population-based study of men aged 30-79, appendicular lean mass showed the most robust association with aBMD at the hip, wrist and spine [94]. The fact that appendicular lean mass was not only positively associated with the weight bearing hip and spine but also the wrist provides support for the idea that muscle forces rather than absolute mass contribute to BMD. The previous DXA-based studies have found conflicting results when looking at the relationship of aBMD to fat or lean mass. BMI appears in these DXA-based studies to be positively associated with aBMD. However, another study found that body weight was a much better predictor of aBMD at the three sites than BMI [95].

Furthermore, in a recent study of women, Beck et al. (2008), found higher femoral BMD, cross-sectional area (CSA), and bending strength (SI) with higher body mass index (BMI) using DXA based structure outcomes [85]. The positive relationship between bone outcomes and body mass were proportional to lean mass and not to fat mass in these women [85]. Similarly, Trivison et al. (2008) found lean mass to be more strongly associated with proximal femur strength than fat mass in older men [96]. Thus, in two men of the same weight and height, the man with higher percentage

body fat would likely have a lower bone bending strength because they would have less lean mass. A study done in elderly Afro-Caribbean men noted that leg lean mass was the strongest predictor of bone bending strength, cross-sectional area and aBMD [97]. This study also found total body fat mass negatively associated with all shaft bone parameters [97]. The previous three studies used hip structural analysis (HSA) to estimate the strength parameters from DXA measurements. Although HSA estimates bone strength at the clinically relevant femoral neck, deriving three-dimensional properties from two-dimensional DXA images has known limitations. The main limitation is that assumptions must be made regarding the symmetry of the bone cross-sections. Thus, HSA results must be interpreted with these in mind. In order to more accurately capture the relationship between body composition and bone strength a few studies have used pQCT.

Body composition and estimates of bone strength using pQCT

Few studies have used peripheral quantitative computed tomography (pQCT) to look at the relationship between body composition and estimates of bone strength. A study in male mice looked at the effect of obesity on bone parameter as measured by pQCT [98]. This study found heavier body mass was associated with increased total bone cross-sectional area, mineral content and bone strength at both the diaphysis and metaphysis [98]. Thus, obese mice had larger and stronger bones compared to lean mice. A study by Wetzsteon et al. (2008) reported a positive relationship between change in bone strength and change in lean mass and muscle cross-sectional area in children ages 9 to 11 [99]. In this study fat mass did not appear to be related to bone strength. Another study using pQCT by Xu et al. (2010) found fat mass, lean mass and body weight to be negatively associated with relative bone strength index in post-menopausal women. Therefore, body composition may be a more important factor in explaining bone geometry and strength than overall body weight in children and in older women. A study done on the Arizona population, observed that loss of lean mass is more rapid in men than in women after age 80 [100]. This finding could have important implication for bone loss in older men. Finally, there have been no studies looking at the effect of body composition on bone strength and geometry in older men using the novel technology of pQCT. Overall, there remains considerable controversy regarding whether fat mass has a direct and positive effect of bones.

The relationship of body composition and bone strength in normal weight individuals

According to the Frost's mechanostat hypothesis, bones adapt their strength to mechanical loads generated from dynamic loads rather than static loads [101]. Animal studies of mechanical loading support this theory of bone functional adaptation by consistently showing significant increases in the strength of loaded bones [102, 103]. Muscle forces place greater loads on bones than do gravitational forces associated with weight [104]. It takes more than 2 kg of muscle force on bone to move a kilogram of body weight [105]. Studies have demonstrated that >70% of the bending moments on a bone are transmitted by muscle force rather than body weight [106]. Given the important role of muscle force in bone functional adaptation, variables representing muscle mass or strength should be associated with bone strength.

A recent study in children found that, after adjusting for lean mass, overweight, obese and normal weight children had similar whole body aBMD and BMC [107]. This study suggests that the skeleton is adapted to lean mass in normal, overweight and obese children. Bone should be appropriately adapted to the loads that are placed on them. Since the majority of load comes from muscle pull we would expect that bone strength would be adapted to the lean muscle of an individual. Assuming that a recommended weight individual's lean mass is appropriately adapted to their body weight, they should have bone strength adapted to their weight and more importantly the lean mass that is associated with it.

Thus, the evidence with regards to the relationship of body composition and bone health is mixed. DXA-based studies have found body weight, BMI, fat mass and lean mass to be related to aBMD. The findings with fat mass were stronger with women than men. The studies using HSA found bone bending strength to be adapted to lean mass and not fat mass. Studies using pQCT are also mixed as to how the various components of body composition affect bone strength and geometry. These studies provide evidence that a relationship does exist between body composition and bone strength but the direction of these associations are uncertain. Therefore, future studies should examine the relationship of body composition and estimates of bone strength in males.

Section 3.4 – Mechanical Load, Sex Steroids and Bone

Overview

Sex steroids have been shown to play a key role in the development and maintenance of male bone health throughout life. Studies have shown that decreasing bioavailable sex steroid levels are related to bone loss in both postmenopausal women and elderly men [108]. Most studies indicate that estrogen concentrations are associated with bone mineral density, turnover and loss in aging men, while the impact of testosterone on bone health parameters is more uncertain. This section will review the effect of testosterone and estradiol on the male skeleton. First, a discussion about the effect of testosterone and estradiol on animal skeletons will be conducted. Second, the relationship between testosterone, estradiol and bone mineral density will be discussed. Third, the relationship of testosterone and estradiol with bone strength and geometry will be considered. Fourth, testosterone deficiencies and its effect on bone health will be examined. Finally, mechanical loading and sex steroids effect on bone health will be examined.

The effects of testosterone and estradiol on animal skeletons

Turner et al. (1990) conducted a groundbreaking study in male and female rats led to the concept that androgens in males stimulate and estrogens in females inhibit periosteal bone formation [109]. Further evidence for the stimulatory role of testosterone on the periosteal bone surface was provided by studies in mice with a mutation of the androgen receptor [110, 111]. In these animals, trabecular bone resorption was higher and there was reduced cortical bone mass acquisition due to impairment of the periosteal bone formation. However, these findings were all in young mice and rats and thus, may not be as crucial of findings for the older skeleton. A study in aged male rats showed that androgen withdrawal induced pronounced cortical bone loss [112]. This was due mainly to increased endocortical bone remodeling [112]. This study suggests that cortical bone may be an important endpoint when looking at testosterone and bone in the aged skeleton.

Testosterone, estradiol and bone mineral density in men

Conflicting data have been presented regarding the predictive value of testosterone for aBMD in elderly men. Studies have shown testosterone to be correlated with aBMD. A study by Greendale et al. (1997) found bioavailable testosterone was positively associated with aBMD at the ultradistal radius, lumbar spine and hip in older men [113]. In a study of healthy older men, van den Beld et

al. (2000) found total and free testosterone to be positively related to total body aBMD after adjustment for age [114]. Total and free testosterone levels were found to be predictors of aBMD of the whole body, arm, total hip, femoral trochanter and lumbar spine in older men [115]. The highest predictive value of free testosterone for aBMD was found at the bone sites with higher cortical bone content [115]. Khosla et al. (1998) also suggested that bioavailable testosterone may have a greater influence on aBMD in men at sites that are predominantly cortical bone than at sites that are predominantly trabecular bone [116]. These studies support the notion that testosterone may have more of an effect on cortical bone than trabecular bone.

Other studies have found no correlation between testosterone and aBMD. Using data from the MrOS study, Cauley et al. (2010) found no association between bioavailable testosterone and aBMD at baseline [117]. After 4.5 years, total hip aBMD declined overtime for all men, irrespective of their bioavailable testosterone [117]. In this study, testosterone levels were unrelated to aBMD or changes in aBMD. In a group of healthy, community-dwelling men over the age of 75, there was no association between aBMD and bioavailable testosterone [118]. In a diverse sample of men, Araujo et al. (2008) found neither total or free testosterone to be associated with aBMD at the proximal femur, wrist or lumbar spine of men aged 30-79 years [119].

Population studies in older men have reported positive associations with estrogen concentrations and aBMD, turnover and bone loss [114-116, 119-122]. This relationship was stronger for bioavailable estradiol than with total estradiol [114, 116]. Low bioavailable estradiol was associated with faster rates of bone loss in older men [117, 123, 124]. Khosla et al. (2001) found that men with low levels of bioavailable estradiol had significantly higher rates of bone loss and levels of bone resorption markers than men with higher bioavailable testosterone [123]. These studies lend support to the notion that bioavailable estradiol is positively associated with aBMD in older men.

Finally, most studies have found a positive association between estradiol and aBMD, some studies have found a positive relationship between testosterone and bone density in older men, while others have not found an association. These studies may have been limited by the use of the two dimensional measurements of bone (aBMD). The use of DXA does not provide information about

volumetric bone mineral density (vBMD) or bone geometry. The next section will discuss studies looking at sex steroids, bone geometry and strength.

Testosterone, estradiol and bone geometry and strength in men

Few studies have looked at the relationship of sex steroids and bone geometry and estimates of strength in men. One study, using pQCT, in young adult males found free testosterone to be an independent positive predictor of cortical cross-sectional area and periosteal circumference in both the radius and the ulna, while free estradiol was a negative predictor of cortical cross-sectional area, periosteal circumference and endosteal circumference and a positive predictor of cortical vBMD [125]. These findings are in agreement with the findings of Mellstrom et al. (2006) and Khosla et al. (1998) that testosterone may have a greater influence on cortical bone than trabecular bone [115, 116]. Travison et al. (2009) did not find a relationship between total or free testosterone and proximal femur strength in men aged 30-79 years [126]. In these men free estradiol was positively associated with proximal femur strength. This association was greatly decreased after the adjustment for age, height, lean mass and fat mass but it was not eliminated. The previous two studies used hip structural analysis (HSA) to estimate the strength parameters from DXA measurements. Although HSA estimates bone strength at the clinically relevant femoral neck, deriving three-dimensional properties from two-dimensional DXA images has known limitations. The main limitation is that assumptions must be made regarding the symmetry of the bone cross-sections. Thus, HSA results must be interpreted with the limitations in mind.

In order to more accurately capture the relationship between testosterone and estimates of bone strength the following study used the three-dimensional technique of quantitative computed tomography (QCT) and peripheral QCT (pQCT). In men over the age of 60 years, Khosla et al. (2005) found bioavailable testosterone to be associated with cortical vBMD at the femoral neck and distal tibia [120]. As for the structural parameter, at the distal radius, distal tibia and femoral neck total bone area and subendocortical area were inversely associated with bioavailable testosterone in older men, although, the inverse association with bone size went away after adjusting for estrogen [120]. The inverse association was somewhat surprising and brings up the possibility that bioavailable testosterone may not have the same stimulatory effects on the periosteum in the

elderly that has been found in young boys [127]. Thus, further studies are needed to assess the effects of bioavailable testosterone on the periosteum.

The study by Khosla et al. (2005) also found bioavailable estradiol to be positively associated with cortical and trabecular vBMD and cortical area [120]. They also found an inverse association with bioavailable estradiol and subendocortical area [120], which is similar to the finding in rats that estrogen has a suppressive effect on periosteal apposition [109]. The Khosla et al. study highlights the importance of not only studying BMD but also bone geometry.

These studies provide support for the effects of testosterone and estradiol on vBMD, bone geometry and bone strength in the aging skeleton. However, future studies are needed to determine the exact relationship between sex steroids and bone geometry and estimates of bone strength in older males.

Testosterone deficiencies and bone health

Complete androgen insensitivity (CAIS) may represent a natural model to assess the impact of androgen receptors on bone. A study by Bertelloni et al. (1998) found significantly reduced aBMD and vBMD in prepubertal and pubertal individuals with CAIS in comparison with controls and in comparison with the normal bone values for males and females [128]. These results support a direct androgen action on bone mineralization.

Male to female transsexual persons present a unique opportunity to study the effect of extreme changes in gonadal hormones concentration on bone health parameter. A study by Lapauw et al. (2008) found lower free and total testosterone, cortical bone area and estimates of bone strength (SSIp) at both the radius and tibia in male to female transsexual persons when compared to controls [129]. This was mainly due to a smaller periosteal circumference. Smaller cortical thickness and endosteal circumference were also noted in these individuals [129]. Neither total nor free estrogen levels were significantly different from control although there was a clear increase in estrogen exposure in the male to female transsexual persons. The surgical and pharmacological removal of testosterone may have contributed to the decrease in estimates of bone strength in these men.

These findings provide evidence that testosterone has an effect on bone. The smaller cortical bone findings in the male to female transsexual persons is similar to the findings of the androgen withdrawn aged male rats.

The relationship between mechanical loads and sex steroids on bone strength in older men has not been explored

According to the mechanostat hypothesis, bones adapt their strength to mechanical loads generated from voluntary mechanical usage [101]. Animal studies of mechanical loading support this theory of bone functional adaptation by consistently showing significant increases in the strength of loaded bones [102, 103]. How the force from physiologic mechanical loading is generated on bone has been debated [104]. However, studies have demonstrated that muscle force plays an important role in generating bending moments on bone [106]; and therefore, alteration in bone strength have been shown to follow alterations in muscle activity [130]. Given the important role of muscle force in bone functional adaptation, variables representing muscle mass or strength should be associated with bone strength.

Only a few studies have looked at the relationship between testosterone and mechanical loading. A couple of recent studies were conducted by Callewaert et al. (2010) in male mice and Ducher et al. (2009) in young males [57, 131]. In the male mice, there was an increased periosteal bone formation in response to loading in androgen receptor knockout mice and androgen/estrogen receptor knockout mice [131]. In pre- and peripubertal boys, the exercise-induced increase in periosteal expansion is greater than postpubertal boy [57]. A study done on growing male rats found that low dose estrogen treatment decreased the loading-induced gain in cortical area and moment of inertia due to suppression of periosteal bone formation [132]. These studies are consistent with the idea that bones become less sensitive to loading when testosterone or estrogen concentrations are higher.

Thus, the evidence with regards to the relationship of testosterone and bone health is mixed, while the relationship with estradiol and bone health is stronger. In the DXA-based studies, some report a positive relationship between testosterone and aBMD in older men, while other did not find a

relationship. Most studies found an association of estradiol and aBMD. HSA studies in young men found testosterone to be associated with cortical cross-sectional area and periosteal circumference. A study using pQCT found that testosterone was inversely associated with femoral neck, radius and tibia total bone area and subendocortical area and positively associated with vBMD in older men but the effects on area were removed once estrogen was controlled for. Finally, future studies are needed to determine the relationship that testosterone or estradiol and mechanical loading have on bone geometry and estimates of bone strength in older males.

Chapter 3

**Muscle power and physical activity are associated with
bone strength in older men: the osteoporotic fractures
in men study**

**MUSCLE POWER AND PHYSICAL ACTIVITY ARE ASSOCIATED WITH BONE STRENGTH IN
OLDER MEN: THE OSTEOPOROTIC FRACTURES IN MEN STUDY**

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Purpose: The purpose of these analyses was to explore whether physical activity score, leg power or grip strength were associated with tibia and radius estimates of bone strength, cortical density, or total bone area. **Methods:** Peripheral quantitative computed tomography (pQCT) was used to compare tibial and radial bone volumetric density (vBMD, mg/cm³), total (ToA, mm²) and cortical (CoA, mm²) bone area, and estimates of bone compressive strength (bone strength index, BSI) and bending strength (polar strength strain index, SSIp) in a subset (n = 1,171) of men (≥ 65 years) who participated in the multi-site Osteoporotic Fractures in Men (MrOS) study. Physical activity was assessed by questionnaire (PASE), leg power by Nottingham Power Rig, and grip strength by a hand held Dynamometer. Participants were categorized into quartiles of PASE, grip strength or leg power. The model was adjusted for age, race, clinic, weight, and limb length. **Results:** In the tibia, BSI (+7%) and SSIp (+4%) were highest in the most active physically quartile compared to the least active (p<.05). At the 4% site of the tibia, men with the greatest leg power had both greater ToA (+5%, p < 0.001) and BSI (+5.3%, p = 0.086) compared to men with the least leg power. At the 66% site of the tibia, the men with the highest leg power, compared to the men with the lowest leg power, had greater ToA (+3%, p = 0.045) SSIp (+5%, p = 0.008). Similar results were found at both the distal and midshaft of the radius. **Conclusions:** The findings of this study suggest the importance of maintaining levels of physical activity and muscle strength in older men to prevent bone fragility.

INTRODUCTION

Osteoporosis and related fractures are major public health and economic burdens. While men account for 29% of all osteoporotic fractures and 25% of osteoporosis-related costs in the United States [5], the majority of studies identifying determinants of bone density and strength have been conducted in female populations [133]. Therefore, it is important to identify determinants of bone strength in older men.

According to the mechanostat hypothesis, bones adapt their strength to mechanical loads generated from voluntary mechanical usage [101]. Animal studies of mechanical loading support this theory of bone functional adaptation by consistently showing significant increases in the strength of loaded bones [102, 103]. How the force from physiologic mechanical loading is generated on bone has been debated [104]. However, studies have demonstrated that muscle force plays an important role in generating bending moments on bone [106]; and therefore, alteration in bone strength have been shown to follow alterations in muscle activity [130]. Given the important role of muscle force in bone functional adaptation, variables representing muscle mass or strength should be associated with bone strength. However, as recently summarized by Barry and Kohrt [134] exercise effects on bone mineral density (BMD) in human studies are remarkably modest when evident at all, and some clinical studies in cyclists suggest that extreme exercise levels may have negative effects on BMD [134, 135].

Most studies exploring the relationship between physical activity and bone health have used DXA-based bone mineral content or areal density (aBMD) outcomes [51-53]. However, animal studies show that bone adapts its strength to changes in mechanical loading by preferentially increasing bone size rather than mass/aBMD [54]. Technology such as peripheral quantitative computed tomography (pQCT) allows for assessment of volumetric bone density, bone geometry and estimates of mechanical strength at the tibia and radius – outcomes that may be more sensitive for assessing the bone response to mechanical loading [55].

Therefore, the primary objective of this study was to examine the association between measures of physical activity, muscle strength and power and estimates of bone strength in community dwelling older men. We hypothesized that estimates of bone strength would be higher in men with higher

levels of reported physical activity, muscle strength, and muscle power. We also hypothesized that the higher bone strength among more active men or those with greater muscle strength and power would be due to differences in bone geometry rather than bone volumetric density.

METHODS

Participants

Men who were at least 65 years of age were recruited from six communities in the United States (Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego California) to participate in the prospective Osteoporotic Fractures in Men (MrOS) study [136]. From March 2000 through April 2002, 5,995 men with no history of bilateral hip replacement and who were able to walk without assistance of another person were enrolled in the baseline examination. The study design and recruitment methods used by the study have been published elsewhere [137]. The Institutional Review Boards at each center approved the study protocol, and written consent was obtained from all study participants.

Men who returned for their second exam an average of 4.7 ± 0.3 years later were invited to participate in an ancillary study involving pQCT at the Minneapolis and Pittsburgh clinical centers. Of the 1550 men who attended the second exam at the Pittsburgh and Minneapolis sites, 1171 (76%) completed the clinic visit and agreed to participate in the pQCT ancillary study and are included in this analysis. The Institutional Review Boards at Minneapolis and Pittsburgh sites approved this ancillary study and written informed consent was obtained from all participants for the pQCT substudy.

Physical Activity, Strength and Power

Physical activity was assessed with the Physical Activity Scale for the Elderly (PASE) [138] with higher scores indicating a greater level of activity. The Nottingham Power Rig was used to measure leg extension power (W) [139, 140]. Participants were given five trials for each leg on the rig and the maximum value from either leg, regardless of whether or not the participant completed all 10 trials, was used in this analysis. Grip strength (kg) was measured twice by a hand held

Dynamometer (Jamar) in both the right and left arms [141]. The maximum grip strength from either arm from two trials was utilized.

Health History, Lifestyle and Demographic Data

Height was measured using a Harpenden stadiometer (DyFed, UK) and weight was measured in indoor clothing without shoes using a calibrated beam scale. Body mass index (BMI = kg/m²) was calculated from participant's height and weight. Tibia and forearm length were measured to the nearest millimeter with an anthropometric tape measure. Tibial length was measured from the tibial plateau to the medial malleolus and forearm length was measured from the ulnar styloid process to the olecranon process. The mean of two measurements for each variable was used for the analysis.

Information on demographics, medical and family history and lifestyle were obtained by questionnaire and interview by trained clinical staff at each site. Information from the baseline exam was used to assess race/ethnicity.

Dual-Energy X-ray Absorptiometry

Dual-energy X-ray absorptiometry (DXA) scans (QDR 4500 W, Hologic Inc., Bedford, MA) were performed to measure areal bone mineral density of the femoral neck, total body lean mass and total body fat mass. Standardized procedures for participant positioning and scan analysis were used for all scans. All DXA operators were centrally certified on the basis of an evaluation of scanning and analysis techniques. A daily phantom scan was completed at each site to monitor machine performance [137]. To adjust for inter-clinic differences, statistical models include indicator variables for the individual scanners. Each clinic scanned a Hologic whole body phantom throughout the study to monitor longitudinal changes, and correction factors were applied to participant data as appropriate [137].

Peripheral Quantitative Computed Tomography Measurements

Peripheral quantitative computed tomography (pQCT) was used to obtain slices (2.3 ± 0.2 mm) at the 4% and 66% sites of the left tibia and at 4% and 33% of the non-dominant forearm (radius). Slices are taken as a percentage of limb length from the distal end of the relevant bone. The XCT 2000 device (Stratec Inc., Pforzheim, Germany) and the XCT-3000 (Stratec Inc., Pforzheim,

Germany) were used to obtain the scans in Pittsburgh and Minneapolis respectively. The only difference between the 2000 and 3000 scanners is the gantry size. The same acquisition and analysis software (version 5.5) was used to analyze scans at both sites. We performed a precision study using a European forearm phantom scanned 3 times at each site at 200, 100, and 50 mg/cc respectively. Values on the two instruments were similar and within <0.5% for total area at all mg/cc, and from 0.5-1.0% for total density.

Voxel size was 0.5 mm and the scan speed was 25 mm/s. The anatomic reference line (distal edge of the tibial plafond and proximal point of the distal radial joint surface) was determined by acquisition of a 30 mm planar scout view of the joint line. Data were analyzed according to the manufacturer specifications. At the trabecular 4% sites, Contour mode 2 (169 mg/cm³) and Peel mode 1 (45% area) were used. Distal sites were assessed for total bone cross-sectional area (ToA, mm²) and total density (ToD, mg/mm³). Bone strength index (BSI, mg/mm⁴) was calculated as $[ToA * ToD^2]/1,000,000$ as an index of bone compressive strength. At the more cortical 33% radius and 66% tibia sites, we used Contour mode 2 (169 mg/cm³) to determine whole bone properties and Cortmode 1 (710 mg/cm³) for cortical bone properties. A threshold of 280 mg/cm³ was used to determine the polar strength strain index (SSIp). At these cortical sites, we assessed total bone cross-sectional area (ToA, mm²), cortical area (CoA, mm²), and cortical density (CoD, mg/mm³). Polar strength strain index (SSIp, mm³) and section modulus (mm³) were calculated as estimates of bone bending strength [142]. SSIp is a “density weighted” section modulus value while section modulus includes only geometric properties. For the Minneapolis site, precision with repositioning was determined in adults (women n=11, men n=4, age 28.5±6.5 years) as a coefficient of variation (CV, %) and varied from 0.28 (TotBMD) to 1.20 (TrabArea) at the distal tibia and from 0.31 (CortBMD) to 0.41 (TotArea) at the shaft [143]. Similar precision values were reported at the Pittsburgh site [144]. An anthropomorphic phantom was scanned daily for quality assurance at both sites.

Statistical Analyses

Differences in characteristics by quartiles of physical function measures were analyzed by ANOVA for continuous variables and chi-square for categorical variables. Multiple regression analysis was used to determine the association between quartiles of grip strength, leg power and PASE score

with measures of bone strength, geometry and volumetric density. All analyses were adjusted for age, limb length, weight, race (non-Hispanic white/not) and clinic site due to between group differences and established relationships between these factors and bone outcomes. The 106 men who were physically unable or refused to complete the leg power test were placed into a separate category. The 19 men that were unable or refused to complete the grip strength test were not included in the analysis. Data presented are least squares means with 95% confidence intervals. A trend test was also completed. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SAS version 9.13 (SAS Institute, Cary, NC, USA).

RESULTS

Descriptive characteristics

A total of 1171 participants underwent pQCT scans and examinations at either Minnesota (n=540) or Pittsburgh (n=631) MrOS sites. Their mean age was 77.2 ± 5.1 years old and 98% of the men were non-Hispanic white. Characteristics of men by quartile of leg power are presented in table 1. Men with greater leg power (Table 1) and grip strength (data not shown) were in general, younger, taller and heavier ($p < 0.001$). They also had a higher PASE score, greater total body lean mass and a higher body mass index ($p < 0.001$ for all). The most physically active men by PASE score tended to be younger and have a greater leg power and grip strength ($p < 0.001$) as compared with men who were less physically active. Height and weight did not differ significantly by quartile of PASE (data not shown).

Table 1. Characteristics of participants by quartile of leg power.

	Unable/ refused n=106	Quartile 1 25.0-133.6 W n=213	Quartile 2 134.7-170.2 W n=215	Quartile 3 171.8-214.9 W n=210	Quartile 4 217.2-452.8 n=220	p-value
Age (years)	78.5 ± 5.7	80.6 ± 5.1	77.4 ± 4.5	75.7 ± 4.3	74.0 ± 3.7	<0.001
Caucasian (%)	97	98	99	98	98	0.759
Height (cm)	172.5 ± 7.4	170.9 ± 6.6	172.3 ± 6.8	173.6 ± 6.8	176.3 ± 6.1	<0.001
Weight (kg)	88.3 ± 17.8	78.5 ± 11.9	82.0 ± 11.8	83.2 ± 12.2	89.4 ± 12.8	<0.001
BMI (kg/m ²)	29.6 ± 5.1	26.9 ± 3.6	27.6 ± 3.5	27.6 ± 3.6	28.8 ± 3.6	<0.001
Total body fat mass (kg)	25.5 ± 8.7	21.5 ± 7.0	22.5 ± 6.7	22.3 ± 6.5	23.8 ± 7.1	<0.001
Total body lean mass (kg)	60.3 ± 9.3	54.6±6.6	56.7±6.5	58.0±7.2	61.6±7.0	<0.001
PASE score	105.5±56.7	131.0±64.9	154.1±69.0	153.0±63.8	152.5±61.6	<0.001
Maximum Nottingham leg power (watts)	171.2±108.8	108.5 ±20.4	152.2 ± 10.9	192.3 ±12.1	254.5 ± 34.1	<0.001
Maximum Grip Strength (kg)	36.6 ± 7.8	36.0 ± 6.2	39.6 ± 7.1	42.5 ± 6.5	46.4 ± 7.7	<0.001
Tibia length (mm)	400.3 ± 24.1	397.4 ±25.0	397.4 ± 27.5	402.8 ±24.9	410.6 ± 23.5	<0.001

Values are mean ± SD unless otherwise noted.

Bone Outcomes

Tibia. Significant differences in pQCT bone parameters were observed across quartiles of physical activity and leg power in models adjusted for age, race, tibia length and weight (Table 2 & 3). At the highly trabecular distal tibia (4%), lower levels of physical activity were associated with reduced compressive bone strength and reduced total area, but were not associated with total density. Compressive bone strength (BSI) was on average 7% higher in the most active compared with the least active quartile (p-trend = 0.025) because total area (ToA, +3%, p-trend = 0.008) was greater, despite no difference in total density (ToD) at this site across quartiles of physical activity (p-trend = 0.174).

Similarly, there was a significant association between reduced leg power and lower total area, but leg power was not associated with BSI or total density. More specifically, men in the highest leg power quartile tended to have a larger total bone area at the distal tibia (4%) (ToA, +5%, p-trend < 0.001) as compared with men in the lowest quartile, while total density (ToD) was similar across all four quartiles of leg power (p-trend = 0.572). The difference between BSI in men with the greatest leg power (quartile 4) compared to that among men the least leg power (quartile 1) did not achieve statistical significance (BSI, +5%, p-trend = 0.059). Table 2 includes the 106 men that were unable or refused to complete the leg power test. These results are not included in the p-trend tests.

At the cortical 66% site of the tibia, Polar strength strain index (SSIp, mm³) and section modulus (mm³) were more robustly associated with leg power than physical activity (see figure 1 and tables 2 & 3). Estimates were higher (+4%, p-trend = 0.014 for SSIp; +4%, p-trend = 0.006 for section modulus) in the most active quartile of men compared with the least active quartile, perhaps largely due to greater cortical area (+4%, p-trend = 0.006) and cortical density (+1%, p-trend = 0.004). Total bone area was not associated with physical activity at this site. SSIp (+5%) and section modulus (+6%) tended to be higher in the men with the greatest leg power compared with the least leg power (p-trend = 0.001 and p-trend < 0.001, respectively). Men with the highest leg power (quartile 4) also tended to have larger total bone area (+3%, p-trend = 0.070) and cortical area (+4%, p-trend = 0.003) when compared with the men with the lowest leg power (quartile 1). Cortical bone density was not different between leg power quartiles at this site.

Radius. Parameters of bone strength at the distal trabecular site (4%) were significantly associated with both grip strength and physical activity in models adjusted for age, clinic site, race, radius length and weight (Table 4 & 5). Greater BSI was found in the quartile with the highest activity level (+7%, p-trend = 0.012) and the quartile with the highest grip strength (+6%, p-trend = 0.016) when compared to the quartile with the lowest activity level or grip strength. This difference was primarily due to a greater total area between the highest and lowest quartiles of physical activity (+4%, p-trend = 0.045) and grip strength (+11%, p-trend < 0.001). No differences in total density were found in either the grip strength or activity quartiles.

At the 33% site of the radius, estimates of bone strength were again significantly higher for men in the highest quartile of physical activity (SSIp, +6%, p-trend < 0.001; section modulus, +6%, p-trend < 0.001) and grip strength (SSIp, +13%, p-trend < 0.001; section modulus, +12%, p-trend < 0.001) compared with the lowest quartile. Figure 1 and tables 4 and 5 illustrate these findings. A significantly larger total area and cortical area were found between the most active (ToA, +4%, p-trend < 0.001; CoA, +6%, p-trend < 0.001) or the highest grip strength (ToA, +8%, p-trend < 0.001; CoA, 11%, p-trend < 0.001) quartiles and the least active or lowest grip strength quartiles. Cortical density was significantly different between highest and lowest quartile of grip strength (p-trend < 0.001) but not between the most and least physically active quartiles (p-trend = 0.080).

DXA. DXA femoral neck aBMD results are presented in tables 2 and 3. At the femoral neck, aBMD was not significantly different between the quartile of men with the highest leg power and the quartile of men with the lowest leg power. Men with the highest physical activity had 4% greater aBMD than men with the lowest physical activity.

Table 2. Tibial bone volumetric density, geometry and strength in older men by quartiles of leg power.

	Unable/refused (n=106)	Q1 25.0-133.6 W (n=213)	Q2 134.7-170.2 W (n=215)	Q3 171.8-214.9 W (n=210)	Q4 217.2-452.8 W (n=220)	p- trend#
pQCT 4% Tibia						
BSI	106 (99-113)*	114 (109-119)	115 (110-120)	117 (112-121)	120 (115-125)	0.059
Total Area (mm ²)	1273 (1240-1306)*	1256 (1232-1280)**	1281 (1259-1304)*	1284 (1261-1307)*	1320 (1296-1343)	<0.001
Total Density (mg/cm ³)	286 (277-295)*	299 (292-306)	299 (292-305)	300 (294-307)	301 (295-308)	0.572
Trabecular Density (mg/cm ³)	220 (212-228)*	231 (225-237)	233 (227-238)	232 (226-237)	234 (228-239)	0.534
pQCT 66% Tibia						
SSIp (mm ³)	3283 (3179-3387)*	3300 (3225-3374)*	3357 (3287-3427)*	3408 (3337-3478)	3471 (3397-3545)	0.001
Section modulus (mm ³)	3237 (3130-3345)**	3277 (3200-3354)**	3352 (3279-3424)*	3431 (3358-3503)	3474 (3397-3551)	<0.001
Total Area (mm ²)	752 (734-771)	755 (742-768)*	762 (750-775)	764 (752-777)	775 (762-788)	0.070
Cortical Density (mg/cm ³)	1062 (1055-1070)	1061 (1056-1067)	1064 (1059-1069)	1068 (1063-1074)	1066 (1061-1072)	0.080
Cortical area (mm ²)	322 (311-333)*	328 (320-336)*	334 (327-341)	341 (334-349)	342 (334-350)	0.003
DXA Femoral Neck aBMD [□]	0.758 (0.734-0.783)*	0.787 (0.769-0.805)	0.793 (0.776-0.809)	0.801 (0.784-0.817)	0.799 (0.781-0.817)	

Values are adjusted for age group, clinic site, race, tibia length and weight.

[□] Values are adjusted for age, clinic site, race, height and weight.

#P for trend includes only quartiles 1-4.

Values are means (95% confidence intervals). Significantly different from quartile four; *p<0.05, **p<0.001

Table 3. Tibial bone volumetric density, geometry and strength in older men by quartiles of physical activity.

	Q1 0-93.57 (n=292)	Q2 93.68-138.25 (n=292)	Q3 139-178.96 (n=296)	Q4 179.25-434.36 (n=291)	p-trend
pQCT 4% Tibia					
BSI	111 (107-115)*	115 (111-119)	116 (112-119)	118 (114-122)	0.025
Total Area (mm ²)	1268 (1249-1287)*	1279 (1260-1298)*	1273 (1254-1292)*	1308 (1290-1327)	0.008
Total Density (mg/cm ³)	294 (288-299)	299 (293-304)	300 (295-306)	299 (294-304)	0.174
Trabecular Density (mg/cm ³)	228 (224-233)	230 (225-235)	232 (227-237)	232 (228-237)	0.185
pQCT 66% Tibia					
SSI _p (mm ³)	3330 (3269-3391)*	3378 (3319-3438)	3364 (3305-3424)	3448 (3388-3508)	0.014
Section Modulus (mm ³)	3322 (3259-3386)*	3362 (3300-3424)*	3373 (3311-3435)	3451 (3389-3513)	0.006
Total Area (mm ²)	761 (751-772)	769 (759-780)	763 (752-773)	773 (763-784)	0.225
Cortical Density (mg/cm ³)	1059 (1055-1064)*	1060 (1056-1065)*	1066 (1061-1070)	1067 (1063-1071)	0.004
Cortical area (mm ²)	330 (324-337)*	330 (324-337)*	335 (329-341)	342 (336-348)	0.006
DXA Femoral Neck aBMD [□]	0.770 (0.756-0.784)*	0.787 (0.773-0.801)	0.799 (0.785-0.813)	0.803 (0.789-0.817)	

Values are adjusted for age, clinic site, race, tibia length and weight.

[□]Values are adjusted for age, clinic site, race, height and weight.

Values are means (95% confidence intervals). Significantly different from quartile four; *p<0.05, **p<0.001

Table 4. Radius bone volumetric density, geometry and strength in older men by quartiles of grip strength.

	Q1 18-34 kg (n=284)	Q2 36-38 kg (n=211)	Q3 40-45 kg (n=337)	Q4 46-78 kg (n=320)	p-trend
pQCT 4% Radius					
BSI	47 (45-49)*	48 (46-50)	48(47-50)	50 (48-52)	0.016
Total Area (mm ²)	368 (360-377)**	379 (369-388)**	390 (383-398)*	408 (400-416)	<0.001
Total Density (mg/cm ³)	354 (346-363)	356 (346-365)	351 (344-358)	351 (344-359)	0.507
Trabecular Density (mg/cm ³)	197 (192-203)	198 (192-205)	198 (194-203)	195 (190-200)	0.592
pQCT 33% Radius					
SSIp (mm ³)	342 (334-350)**	351 (342-360)**	365 (358-372)**	387 (379-394)	<0.001
Section modulus (mm ³)	335 (327-342)**	343 (335-352)**	356 (349-362)**	378 (371-385)	<0.001
Total Area (mm ²)	140 (138-142)**	144 (141-146)**	144 (142-146)**	151 (149-153)	<0.001
Cortical Density (mg/cm ³)	1152 (1148-1156)**	1159 (1154-1163)	1163 (1160-1167)	1163 (1159-1167)	<0.001
Cortical area (mm ²)	100 (99-102)**	103 (101-105)**	106 (104-107)**	111 (109-112)	<0.001

Adjusted for age, clinic site, race, radius length and weight.

Values are means (95% confidence intervals). Significantly different from quartile four; *p<0.05, **p<.001

Table 5. Radius bone volumetric density, geometry and strength in older men by quartiles of physical activity.

	Q1 (n=292)	Q2 (n=292)	Q3 (n=296)	Q4 (n=291)	p-trend
pQCT 4% Radius					
BSI	46 (44-48)*	49 (47-51)	49 (47-51)	49 (47-51)	0.012
Total Area (mm ²)	383 (375-391)*	382 (374-390)*	387 (379-396)*	399 (391-407)	0.045
Total Density (mg/cm ³)	345 (337-353)	357 (349-364)	357 (349-365)	350 (343-358)	0.348
Trabecular Density (mg/cm ³)	192 (186-197)	199 (194-205)	201 (195-206)	196 (191-202)	0.230
pQCT 33% Radius					
SSIp (mm ³)	354 (346-362)**	360 (353-368)*	362 (354-370)*	374 (367-382)	<0.001
Section Modulus (mm ³)	346 (339-354)**	352 (345-360)*	353 (345-360)*	366 (359-374)	<0.001
Total Area (mm ²)	142 (140-145)**	145 (143-147)*	145 (143-147)*	148 (146-150)	<0.001
Cortical Density (mg/cm ³)	1156 (1152-1160)	1159 (1155-1162)	1163 (1159-1167)	1160 (1156-1164)	0.080
Cortical Area (mm ²)	102 (101-104)**	105 (103-107)*	106 (104-107)	108 (106-109)	<0.001

Adjusted for age, clinic site, race, radius length and weight.

Values are means (95% confidence intervals). Significantly different from quartile four; *p<0.05, **p<.001

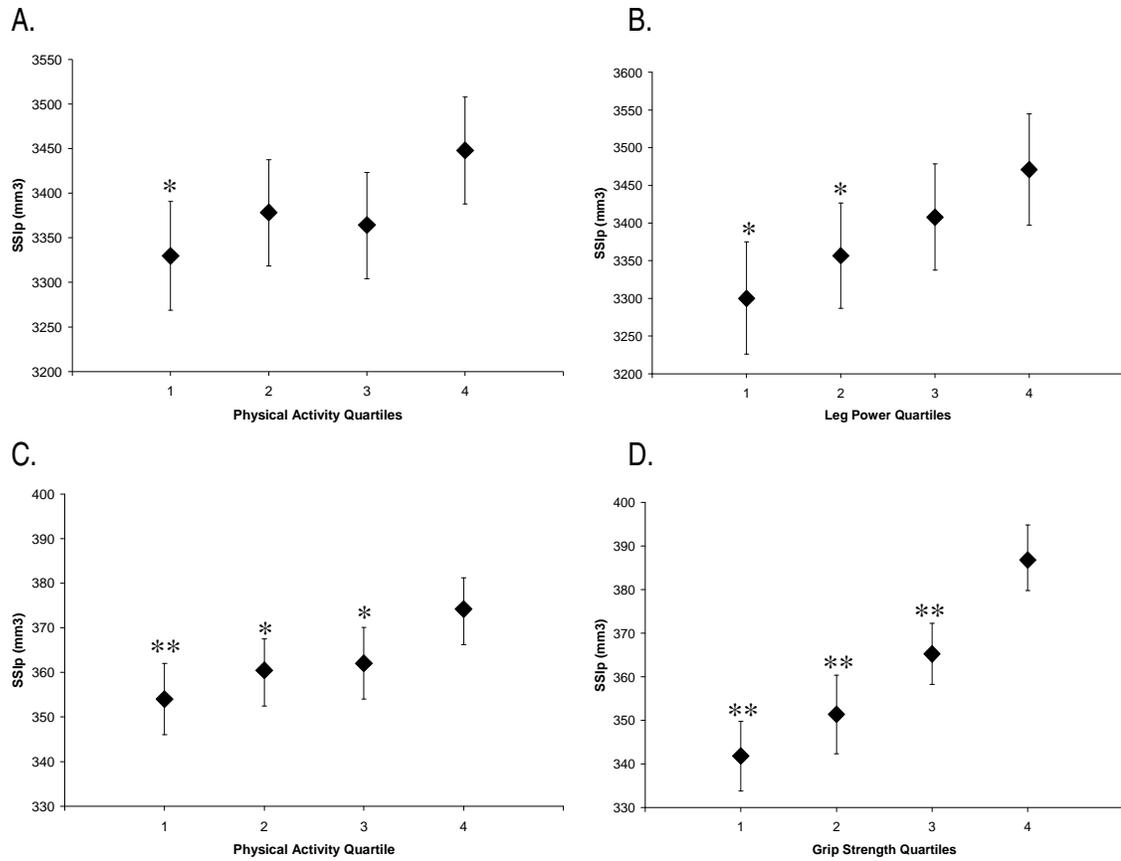


Figure 1. Estimated mean bone strength and 95% confidence intervals of the tibia 66% site by quartile of physical activity (A) and leg power (B). Estimated mean bone strength and 95% confidence intervals of the radius 33% site by quartile of physical activity (C) and grip strength (D). Values are adjusted for age, clinic site, race, limb length and weight. Significantly different from quartile four; * $p < 0.05$, ** $p < 0.001$

DISCUSSION

Our results suggest that older men with higher levels of reported physical activity and higher objective measures of leg power and grip strength have greater bone strength as estimated by pQCT measurements of the tibia and radius. Specifically, we found a 5% ($p < 0.05$) difference in estimates of bone strength between the lowest and highest quartiles of leg power, and a 4% ($p < 0.05$) difference between lowest and highest quartiles of physical activity. Furthermore, differences of 6% and 13% ($p < 0.001$) were observed at the cortical site of the radius between the lowest and highest quartiles of physical activity and grip strength, respectively. Moreover, differences were found in bone cross-sectional geometry rather than in volumetric density at cortical sites across quartiles of physical activity, leg power and grip strength—highlighting the importance of assessing

bone structure when evaluating these associations. These data suggest the importance for older men to maintain physical activity and muscle strength for prevention of bone fragility. We will discuss each of these points in more in detail below.

Physical activity (by questionnaire) tibial and radial bone strength

At both the midshaft and distal sites of the tibia and radius, estimates of bone strength were higher in the most active men as compared with that among least active men. These findings differ from those of a previous study that reported that PASE score was not significantly associated with areal bone mineral density (aBMD) in 1,543 older adults after controlling for isokinetic knee extensor strength, age, race, and sex [145]. Another study conducted in 690 older men found the physical activity index to be positively associated with femoral neck areal bone mineral density values before adjustment of age, body mass index, quadriceps strength, and dietary calcium. However, after adjustment, the association no longer remained statistically significant [146]. For more direct comparison to these previously published studies, we added leg power to our PASE models. Although differences between groups decreased slightly, the highest PASE quartile still had a 2.5% greater bone strength than the first quartile (data not shown). Thus, it is likely that differences between these previous studies and ours is largely explained by use of different bone outcomes. Notably, an increase in bone diameter due to mechanical loading would show up as a lower aBMD by DXA if mineral content remains the same.

Leg power and tibial bone strength

Few studies have examined the association of leg power with bone strength in an older population. A recent study in older women found leg power explained 6.6% of the variance in bone strength-strain index and 8.9% of the variance in the section modulus at the tibial mid-shaft but that muscle strength did not significantly predict bone parameters [83]. Similarly, among our cohort of older men, men in highest quartile of leg power compared to those in the lowest quartile had a 5% greater SSIp and 6% higher section modulus at the cortical site of the tibia. Similar muscle/bone associations were also detected at the radius.

Grip strength and radial bone strength

We also observed greater estimates of bone strength in both the midshaft and distal sites of the radius among men in the highest quartile of grip strength compared with men in the lowest quartile. This finding is in agreement with those reported by previous studies. One study assessing the relationship of grip strength and bone strength at the radius found a significant association with SSIP in adults ranging in age from 18 to 80 years of age [81]. Another study in men found a 7% increase in calcaneus BMD per standard deviation increase in grip strength [82]. These findings at both the tibia and radius highlight the site-specific association between muscle strength and power and bone outcomes.

Leg power and grip strength versus PASE score

In this study, we found a more consistent increase in bone strength between quartiles of leg power and grip strength than between quartiles of PASE score. Furthermore, PASE score was not strongly correlated with grip strength (Pearson $r = 0.153$) or leg power (Pearson $r = 0.106$). These findings suggest that evaluation of leg power and grip strength may be more helpful for identifying older men with lower bone strength than the PASE score when other clinical measures of bone strength have not been obtained or are not available. However, this remains to be empirically tested. Nevertheless, the significant difference in bone strength between the highest and lowest quartiles for physical activity, grip strength, and muscle power supports theories of functional adaptation of bone to implied mechanical demands [101, 147] and supports other studies that suggest interventions in older male populations should focus on maintaining muscle strength and power as well as increase levels of physical activity [148, 149]. Prospective randomized exercise intervention studies are needed in older male populations to test these theories and explore the relationship of exercise and fracture risk.

Bone density and geometry differences

In this study, we found that the association between bone strength and physical activity, muscle power and strength measures were attributable primarily to greater total bone area and not bone volumetric density at most sites. For example, we found a 3% difference in bone area, with no significant difference in bone volumetric density. Therefore, the 5% difference in estimated bone strength at this site is due primarily to a greater bone area, which is indicative of a greater

periosteal diameter. Small differences in aBMD were found with DXA. These data highlight the importance of assessing true volumetric bone mineral density as compared to the two-dimensional areal bone mineral density as measured by dual x-ray density. Congruent with other studies assessing volumetric bone mineral density, we saw no difference in vBMD across quartiles of physical activity, leg power, or grip strength. Rather, by detecting differences in bone geometry, these data highlight the importance of measuring both volumetric bone density as well as the structural underpinnings of bone strength differences.

Strengths and limitations

The findings of this study suggest the importance of maintaining levels of physical activity and muscle strength in older men to prevent bone fragility. There are several strengths to this study including the unique focus on older men, large sample size, use of validated measures such as the use of leg power as a measure of load on bone and use of pQCT to assess volumetric BMD, bone geometry and structural strength estimates in older men. There are also several limitations to this study worth noting. First, the majority of the men in this sample were Caucasian and generally healthy; therefore, we are not able to generalize the results to other populations. Another limitation is that activity was measured by self-report at one time point rather than over a longer period of time. A further limitation is that in addition to being mechanically linked, muscle and bone are genetically linked; therefore, individuals with increased muscle mass genetically may have enhanced bone measures. Finally, this analysis is limited by the cross-sectional nature of the data. Future longitudinal analyses including repeat pQCT measurements and fracture ascertainment are needed to confirm these associations. If these results are confirmed, findings should be used to direct design of intervention studies aimed at maintaining bone strength and lowering fracture risk in older adults.

Conclusions

In conclusion, these data suggest that in older men higher grip strength, leg power and levels of physical activity are associated with higher estimates of bone strength in the tibia and radius. Our findings add to previous DXA studies of physical activity in older men by showing that differences in bone strength are generally attributable to greater bone area rather than greater bone volumetric density and may help explain discrepant findings in studies using aBMD as outcomes. These

findings are congruent with findings in older women. They also suggest that it may be important for men to maintain muscle strength and power as well as physical activity with advancing age.

Chapter 4

Lean mass is associated with bone strength in older men: the osteoporotic fractures in men study

**LEAN MASS IS ASSOCIATED WITH BONE STRENGTH IN OLDER MEN: THE
OSTEOPOROTIC FRACTURES IN MEN STUDY**

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Purpose: The purpose of these analyses was to explore whether total body weight, body mass index, lean mass and fat mass were associated with tibia and radius estimates of bone strength, cortical density, and total bone area. **Methods:** Peripheral quantitative computed tomography (pQCT) was used to assess tibial and radial bone volumetric density (vBMD, mg/cm³), total (ToA, mm²) and cortical (CoA, mm²) bone area, and estimates of bone compressive strength (bone strength index, BSI) and bending strength (polar strength strain index, SSIp) in a subset (n = 1,171) of men (\geq 65 years) who participated in the multi-site Osteoporotic Fractures in Men (MrOS) study. Lean mass and fat mass were assessed by dual-energy X-ray absorptiometry. BMI was calculated from the height and weight of the men. The base model was adjusted for age, race, clinic, and limb length. **Results:** At the tibia 4% site, BSI was increased for each one kilogram increase in body weight (0.66 ± 0.08 , $p < 0.001$), lean mass (1.57 ± 0.15 , $p < 0.001$) or fat mass (0.49 ± 0.14 , $p = 0.007$). At the 66% tibia, SSIp was increased for each one kilogram increase in total body weight (12.3 ± 1.2 mm³, $p < 0.001$), lean mass (34.8 ± 2.2 mm³, $p < 0.001$) or fat mass (6.1 ± 2.3 mm³, $p = 0.007$). After lean mass and fat mass were added to the model, lean mass remained positively associated with estimates of bone strength while fat mass became negatively associated with estimates of bone strength in the tibia. Similar results were found at both the distal and midshaft of the radius. **Conclusion:** The findings of this study suggest the importance of maintaining lean mass in older men to prevent bone fragility.

INTRODUCTION

It is estimated that 68% of the current US population is overweight or obese [84]. In the midst of this growing obesity epidemic, the relationship between body composition and bone strength is of interest, and is likely of greatest importance in the elderly where osteoporosis is most prevalent. However, the relationship between body composition and bone strength in older community-dwelling men is not yet well-understood.

Most studies exploring the relationship between body composition and bone health have used DXA-based bone mineral content or areal density (aBMD) outcomes [92, 93]. Some of these studies have found total body fat mass to be more closely linked with aBMD than lean mass. Reid et al. (1992) found in healthy postmenopausal women that aBMD was closely related to body weight, BMI and fat mass and less closely related to lean body mass [92]. Fat mass was an independent predictor of aBMD at all sites [92]. Other DXA-based studies have found lean mass to be more closely linked with aBMD than fat mass. Kirchengast et al. (2001) noted that BMI and lean mass were positively associated with areal BMD (aBMD) in healthy older men, while aBMD increased with increasing fat mass this association was not significant [93]. The previous DXA-based studies have found conflicting results when looking at the relationship of aBMD to fat or lean mass. BMI appears in these DXA-based studies to be positively associated with aBMD. However, another study found that body weight was a much better predictor of aBMD at the three sites than BMI [95]. A recent study by Travison et al. (2008) used hip structural analysis (HSA) to estimate the strength parameters from DXA measurements. This study found lean mass to be more strongly associated with proximal femur strength than fat mass in middle-aged men [96].

Few studies have used peripheral quantitative computed tomography (pQCT) to look at the relationship between body composition and estimates of bone strength. A study in male mice looked at the effect of obesity on bone parameter as measured by pQCT [98]. This study found heavier body mass was associated with increased total bone cross-sectional area, mineral content and bone strength at both the diaphysis and metaphysis [98]. Thus, obese mice had larger and stronger bones compared to lean mice. One study by Wetzsteon et al. (2008) reported a positive relationship between change in bone strength and change in lean mass and muscle cross sectional

area in children ages 9 to 11 [99]. In this study fat mass did not appear to be related to bone strength. Another study using pQCT by Xu et al. (2010) found fat mass, lean mass and body weight to be negatively associated with relative bone strength index in post-menopausal women [150]. Finding from prior studies are inconsistent which may be in part due to the differences in study populations. Therefore, it may be important to look at the affect of lean mass and fat mass on bone strength in older men, in addition to BMI and total body weight.

The Osteoporotic Fractures in Men (MrOS) study is a multi-center prospective cohort study designed to study the risk factors for vertebral and all non-vertebral fractures in older men. The two sites (Pittsburg and Minneapolis) that have pQCT data are included in this analysis. This study presents a unique opportunity to enhance knowledge of how body composition affects estimates of bone strength and geometry in older men. The purpose of this paper is to explore the relationship between body composition (total weight, lean mass, fat mass and BMI) and bone strength and geometry in community-dwelling older men. We hypothesize that total body weight, BMI, lean mass and fat mass will be positively associated with estimates of bone strength at the tibia and radius. We further hypothesize that lean mass will account for the association between body weight, BMI and estimates of bone strength and that fat mass will not be associated with estimates of bone strength once lean mass has been taken into account.

METHODS

Participants

Men who were at least 65 years of age were recruited from six communities in the United States (Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego California) to participate in the prospective Osteoporotic Fractures in Men (MrOS) study [136]. From March 2000 through April 2002, 5,995 men with no history of bilateral hip replacement and who were able to walk without assistance of another person were enrolled in the baseline examination. The study design and recruitment methods used by the study have been published elsewhere [137]. The Institutional Review Boards at each center approved the study protocol, and written consent was obtained from all study participants.

Men who returned for their second exam an average of 4.7 ± 0.3 years later were invited to participate in an ancillary study involving pQCT at the Minneapolis and Pittsburgh clinical centers. Of the 1550 men who attended the second exam at the Pittsburgh and Minneapolis sites, 1171 (76%) completed the clinic visit and agreed to participate in the pQCT ancillary study and are included in this analysis. The Institutional Review Boards at Minneapolis and Pittsburgh sites approved this ancillary study and written informed consent was obtained from all participants for the pQCT substudy.

Health History, Lifestyle and Demographic Data

Height was measured using a Harpenden stadiometer (DyFed, UK) and weight was measured in indoor clothing without shoes using a calibrated beam scale. Body mass index ($\text{BMI} = \text{kg}/\text{m}^2$) was calculated from participant's height and weight. Tibia and forearm length were measured to the nearest millimeter with an anthropometric tape measure. Tibial length was measured from the tibial plateau to the medial malleolus and forearm length was measured from the ulnar styloid process to the olecranon process. The mean of two measurements for each variable was used for the analysis.

Information on demographics, medical and family history and lifestyle were obtained by questionnaire and interview by trained clinical staff at each site. Information from the baseline exam was used to assess race/ethnicity.

Dual-energy x-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) scans (QDR 4500 W, Hologic Inc., Bedford, MA) were performed to measure total body lean mass and total body fat mass. Standardized procedures for participant positioning and scan analysis were used for all scans. All DXA operators were centrally certified on the basis of an evaluation of scanning and analysis techniques. A daily phantom scan was completed at each site to monitor machine performance [137]. To adjust for inter-clinic differences, statistical models include indicator variables for the individual scanners. Each clinic scanned a Hologic whole body phantom throughout the study to monitor longitudinal changes, and correction factors were applied to participant data as appropriate [137].

Peripheral quantitative computed tomography

Peripheral quantitative computed tomography (pQCT) is a non-invasive technique that allows for three-dimensional assessment of estimates of bone strength, bone volumetric density, and bone geometry. pQCT was used to obtain slices (2.3 ± 0.2 mm) at the 4% and 66% sites of the left tibia and at 4% and 33% of the non-dominant forearm (radius). Slices are taken as a percentage of limb length from the distal end of the relevant bone. The XCT 2000 device (Stratec Inc., Pforzheim, Germany) and the XCT-3000 (Stratec Inc., Pforzheim, Germany) were used to obtain the scans in Pittsburgh and Minneapolis respectively. The only difference between the 2000 and 3000 scanners is the gantry size. The same acquisition and analysis software (version 5.5) was used to analyze scans at both sites. A precision study was performed using a European forearm phantom scanned 3 times at each site at 200, 100, and 50 mg/cc respectively. Values on the two instruments were similar and within <0.5% for total area at all mg/cc, and from 0.5-1.0% for total density.

Voxel size was 0.5 mm and the scan speed was 25 mm/s. The anatomic reference line (distal edge of the tibial plafond and proximal point of the distal radial joint surface) was determined by acquisition of a 30 mm planar scout view of the joint line. Data were analyzed according to the manufacturer specifications. At the trabecular 4% (distal) sites, Contour mode 2 (169 mg/cm³) and Peel mode 1 (45% area) were used. Distal sites were assessed for total bone cross-sectional area (ToA, mm²), total density (ToD, mg/mm³) and trabecular density (TrabD, mg/mm³). Bone strength index (BSI, mg/mm⁴) was calculated as $[ToA * ToD^2]/1,000,000$ as an index of bone compressive strength. At the more cortical 33% radius and 66% tibia sites, we used Contour mode 2 (169 mg/cm³) to determine whole bone properties and Cortmode 1 (710 mg/cm³) for cortical bone properties. A threshold of 280 mg/cm³ was used to determine the polar strength strain index (SSIp). At these cortical sites, we assessed total bone cross-sectional area (ToA, mm²), cortical area (CoA, mm²), and cortical density (CoD, mg/mm³). Polar strength strain index (SSIp, mm³) and section modulus (mm³) were calculated as estimates of bone bending strength [142]. SSIp is a “density weighted” section modulus value while section modulus includes only geometric properties. The strength strain index (SSI) is used as estimate of both geometric and material strength (although material properties can not be directly measured). The SSI has been shown to be an accurate and precise indicator of the structural properties of long bones tested in bending [142]. The SSI is more

strongly correlated with experimentally determined breaking force than either DXA measures of areal BMD, or CSMI or cortical volumetric BMD alone[142]. For the Minneapolis site, precision with repositioning was determined in adults (women n=11, men n=4, age 28.5±6.5 years) as a coefficient of variation (CV, %) and varied from 0.28 (total density) to 1.20 (trabecular area) at the distal tibia and from 0.31 (cortical density) to 0.41 (total area) at the shaft [143]. Similar precision values were reported at the Pittsburgh site [144]. An anthropomorphic phantom was scanned daily for quality assurance at both sites.

Statistical analysis

All bone and body weight/composition variables were checked for outliers and normality. Descriptive characteristics were analyzed by means and standard deviations. Multiple regression analysis was used to determine the association between total body weight, BMI, lean mass and fat mass with measures of bone strength, geometry and volumetric density. All analyses were adjusted for age, limb length, race (non-Hispanic white/not) and clinic site due to between group differences and established relationships between these factors and bone outcomes. Two additional models were run. In addition to adjusting for the above, model 2 adjusted for lean mass and model 3 adjusted for fat mass. Data presented are regression coefficient estimates with 95% confidence intervals. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Descriptive characteristics

A total of 1171 participants underwent pQCT scans and examinations at either Minnesota (n=540) or Pittsburgh (n=631) MrOS sites. Their mean age was 77.2 ± 5.1 years old and 98% of the men were non-Hispanic white. The MrOS men had a mean BMI of 28.0 ± 4.0 kg/m², height of 173.0 ± 6.9 cm, weight 83.9 ± 13.5 kg, fat mass 22.9 ± 7.1 kg, and lean mass 58.3 ± 7.5 kg. Sample characteristics are presented in Table 1.

Table 1. Descriptive Characteristics of the MrOS Men

	n	Mean	Standard Deviation
Age (years)	1169	77.2	5.1
Caucasian (%)	1169	98	
Height (cm)	1168	173.0	6.9
Weight (kg)	1169	83.9	13.5
BMI (kg/m ²)	1168	28.0	4.0
Fat mass (kg)	1163	22.9	7.1
Lean mass (kg)	1163	58.3	7.5
PASE score	1169	141.5	65.9
Maximum Nottingham leg power (watts)	866	177.3	58.8
Maximum grip strength (kg)	1150	40.6	8.0
Tibia length (mm)	1134	402.4	26.0
Radius length (mm)	1128	283.9	16.5
Tibia 4%			
Total Area (mm ²)	1135	1282.3	168.7
Total Density (mg/cm ³)	1135	297.9	46.9
BSI	1135	114.9	34.0
Trabecular Density (mg/cm ³)	1135	230.7	40.8
Tibia 66%			
SSIp (mm ³)	1135	3380.1	606.3
Total Area (mm ²)	1135	766.7	109.3
Cortical Density (mg/cm ³)	1135	1063.1	38.6
Cortical area (mm ²)	1135	334.5	56.7
Section Modulus (mm ³)	1132	3377.1	622.6
Radius 4%			
Total Area (mm ²)	1126	387.9	71.8
Total Density (mg/cm ³)	1126	352.1	68.2
BSI	1126	48.2	16.4
Trabecular Density (mg/cm ³)	1126	196.9	46.1
Radius 33%			
SSIp (mm ³)	1122	362.7	71.2
Total Area (mm ²)	1122	145.1	20.8
Cortical Density (mg/cm ³)	1122	1159.4	34.1
Cortical area (mm ²)	1122	105.3	15.9
Section Modulus (mm ³)	1122	354.3	69.9

Bone Outcomes

Tibia. At the highly trabecular distal site (4% tibia), total body weight, BMI, lean mass and fat mass were associated with bone compressive strength (BSI), total bone area, total density, and

trabecular density (table 2). For every one kilogram increase in body weight, lean mass or fat mass a 0.66 ± 0.08 ($p < 0.001$), 1.57 ± 0.15 ($p < 0.001$) or 0.49 ± 0.14 ($p = 0.007$) respective increase was seen in BSI. For every unit increase in BMI, BSI increased by 1.65 ± 0.26 ($p < 0.001$). When lean mass was added to the base model, every kilogram increase in fat mass was associated with a 0.38 ± 0.16 ($p = 0.02$) decrease in BSI (table 4). When fat mass was included in the model, BSI was associated with an increase of $1.79 \pm .018$ ($p < 0.001$) for every kilogram increase of lean mass. Similar findings were found for total area.

Similarly at the cortical 66% site of the tibia, total body weight, BMI, lean mass and fat mass were associated with bone strength strain index (SSIp), section modulus, total area and cortical area (table 2). A one kilogram increase in total body weight, lean mass or fat mass was associated with an increase in SSIp ($12.3 \pm 1.2 \text{ mm}^3$, $p < 0.001$; $34.8 \pm 2.2 \text{ mm}^3$, $p < 0.001$; $6.1 \pm 2.3 \text{ mm}^3$, $p = 0.007$, respectively). When lean mass was held constant fat mass became negatively associated with SSIp ($-15.0 \pm 2.4 \text{ mm}^3$, $p < 0.001$), while lean mass was associated with an even greater increase in SSIp ($43.4 \pm 2.6 \text{ mm}^3$, $p < 0.001$) when fat mass was held constant (table 3). Similar results were found with total area, cortical area and section modulus. As for cortical density, total body weight was not associated with it. BMI and fat mass were negatively associated with cortical density ($-1.0 \pm 0.3 \text{ mg/cm}^3$, $p = 0.001$, $-0.4 \pm 0.2 \text{ mg/cm}^3$, $p = 0.007$, respectively). Lean mass was positively associated with cortical density ($0.4 \pm 0.2 \text{ mg/cm}^3$, $p = 0.01$). The associations became stronger when lean mass or fat mass were added into the models.

Table 2. Tibial regression coefficient estimates of bone volumetric density, geometry and strength in older men.

	Weight	BMI	Lean Mass	Fat Mass
pQCT 4% Tibia				
BSI	0.66 (0.50-0.82)	1.65 (1.14-2.16)	1.57 (1.28-1.87)	0.49 (0.21-0.78)
Total Area (mm ²)	3.65 (2.88-4.42)	4.49 (1.93-7.05)	11.11 (9.72-12.51)	1.43 (0.02-2.84)
Total Density (mg/cm ³)	0.41 (0.19-0.63)	1.50 (0.80-2.21)	0.75 (0.33-1.17)	0.44 (0.049-0.83)
Trabecular Density (mg/cm ³)	0.41 (0.22-0.61)	1.08 (0.46-1.70)	0.86 (0.49-1.22)	0.38 (0.04-0.72)
pQCT 66% Tibia				
SSI _p (mm ³)	12.34 (9.93-14.74)	28.71 (20.79-36.63)	34.85 (30.50-39.19)	6.136 (1.72-10.55)
Section Modulus (mm ³)	14.42 (11.91-16.93)	33.40 (25.09-41.70)	38.98 (34.47-43.50)	8.69 (4.03-13.34)
Total Area (mm ²)	1.52 (1.10-1.94)	4.82 (3.45-6.18)	4.52 (3.74-5.30)	0.84 (0.08-1.60)
Cortical Density (mg/cm ³)	0.008 (-0.17-0.19)	-0.99 (-1.57- -0.42)	0.43 (0.086-0.77)	-0.44 (-0.75- -0.12)
Cortical area (mm ²)	1.36 (1.12-1.61)	2.65 (1.82-3.47)	3.45 (2.99-3.90)	0.96 (0.51-1.42)

Values are adjusted for site, age, race, object length. Values are regression coefficient estimates per 1 kg or 1 unit increase in each of the predictor variables (95% confidence intervals).

Table 3. Tibial regression coefficient estimates of bone volumetric density, geometry and strength in older men.

	Lean mass*	Fat mass#
pQCT 4% Tibia		
BSI	1.79 (1.44-2.14)	-0.38 (-0.70- -0.06)
Total Area (mm ²)	14.32 (12.71-15.93)	-5.53 (-7.00- -4.06)
Total Density (mg/cm ³)	0.69 (0.19-1.19)	0.10 (-0.36-0.56)
Trabecular Density (mg/cm ³)	0.88 (0.45-1.32)	-0.04 (-0.44-0.36)
pQCT 66% Tibia		
SSI _p (mm ³)	43.43 (38.41-48.46)	-15.03 (-19.67- -10.38)
Section Modulus (mm ³)	47.10 (41.86-52.34)	-14.24 (-19.08- -9.40)
Total Area (mm ²)	5.60 (4.69-6.52)	-1.90 (-2.74- -1.05)
Cortical Density (mg/cm ³)	0.94 (0.54-1.33)	-0.89 (-1.26- -0.53)
Cortical area (mm ²)	4.01 (3.48-4.54)	-0.99 (-1.48- -0.50)

*Values are adjusted for site, age, race, object length and fat mass. #Values are adjusted for site, age, race, object length and lean mass. Values are regression coefficient estimates per 1 kg increase in each of the predictor variables (95% confidence intervals).

Radius. Parameters of bone strength at the distal trabecular site (4%) were significantly associated with total body weight, BMI and lean mass (table 3). At the 4% radius, a one kilogram increase in body weight was associated with a 0.2 ± 0.04 ($p < 0.001$) increase in BSI, a 1.1 ± 0.2 mm² ($p < 0.001$) increase in total area, a 0.3 ± 0.2 mg/cm³ ($p = 0.03$) increase in total density and a 0.3 ± 0.1 mg/cm³ ($p = 0.003$) increase in trabecular density. For every one kilogram increase in lean mass, BSI increased 0.6 ± 0.1 ($p < 0.001$), total area increased 3.8 ± 0.3 mm² ($p < 0.001$), total density increased 0.6 ± 0.3 mg/cm³ ($p = 0.04$) and trabecular density increased 0.6 ± 0.2 mg/cm³ ($p = 0.003$). A unit increase in BMI was associated with an increase in BSI (0.6 ± 0.1 , $p < 0.001$), total area (1.5 ± 0.5 mm², $p = 0.006$), total density (1.4 ± 0.5 mg/cm³, $p = 0.007$) and trabecular density (0.9 ± 0.4 mg/cm³, $p = 0.008$). An association was not found between fat mass and parameters of bone strength and geometry at the 4% radius.

Estimates of bone bending strength (SSIp and section modulus) at the 33% radius were significantly associated with total body weight, BMI and lean mass but not fat mass (table 4). For every kilogram increase in total body weight or lean mass, SSIp is associated with an increase of 1.3 ± 0.2 mm³ ($p < 0.001$) or 4.3 ± 0.3 mm³ ($p < 0.001$), respectively. For every unit increase in BMI, SSIp is associated with an increase of 2.3 ± 0.5 mm³ ($p < 0.001$). Total area and cortical area are both positively associated with total body weight, BMI and lean mass. Cortical density is negatively associated with total body weight, BMI, lean mass and fat mass. When lean mass was held constant, fat mass was associated with lower SSIp (-2.5 ± 0.3 mm³, $p < 0.001$), lower total area (-0.6 ± 0.1 mm², $p < 0.001$), lower cortical area (-0.5 ± 0.1 mm², $p < 0.001$) and a lower section modulus (-2.3 ± 0.3 mm³, $p < 0.001$) (table 5). Lean mass was associated with higher SSIp (5.8 ± 0.3 mm³, $p < 0.001$), higher total area (1.6 ± 0.1 mm², $p < 0.001$), higher cortical area (1.3 ± 0.1 mm², $p < 0.001$) and a higher section modulus (5.9 ± 0.3 mm³, $p < 0.001$) when fat mass was held constant

Table 4. Radius regression coefficient estimates of bone volumetric density, geometry and strength in older men.

	Weight	BMI	Lean Mass	Fat Mass
pQCT 4% Radius				
BSI	0.22 (0.15-0.30)	0.56 (0.33-0.80)	0.63 (0.48-0.77)	0.13 (-0.01-0.26)
Total Area (mm ²)	1.10 (0.77-1.43)	1.49 (0.43-2.55)	3.81 (3.19-4.42)	0.21 (-0.38-0.81)
Total Density (mg/cm ³)	0.34 (0.03-0.66)	1.39 (0.38-2.39)	0.63 (0.016- 1.25)	0.39 (-0.18-0.96)
Trabecular Density (mg/cm ³)	0.33 (0.11-0.55)	0.93 (0.24-1.62)	0.64 (0.21-1.06)	0.39 (-0.0005-0.78)
pQCT 33% Radius				
SSI _p (mm ³)	1.28 (0.97-1.59)	2.32 (1.32- 3.32)	4.31 (3.75-4.88)	0.25 (-0.32-0.81)
Section Modulus (mm ³)	1.44 (1.14-1.74)	2.85 (1.88-3.83)	4.55 (4.00-5.09)	0.54 (-0.008-1.10)
Total Area (mm ²)	0.39 (0.30-0.48)	0.81 (0.52-1.10)	1.23 (1.07-1.40)	0.17 (0.002-0.33)
Cortical Density (mg/cm ³)	-0.30 (-0.46- -0.14)	-1.04 (-1.54- -0.54)	-0.36 (-0.67- -0.05)	-0.62 (-0.90- -0.34)
Cortical area (mm ²)	0.31 (0.24-0.38)	0.70 (0.48-0.92)	0.98 (0.85-1.11)	0.11 (-0.02-0.23)

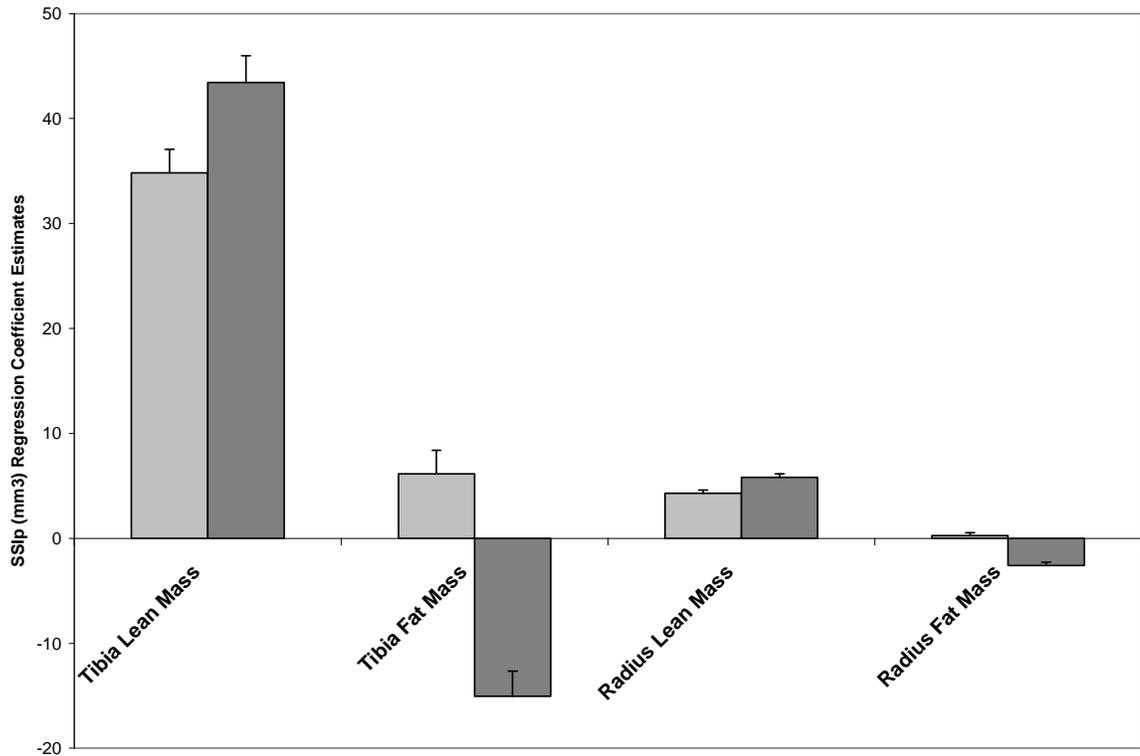
Values are adjusted for site, age, race, object length. Values are regression coefficient estimates per 1 kg or 1 unit increase in each of the predictor variables (95% confidence intervals).

Table 5. Radius regression coefficient estimates of bone volumetric density, geometry and strength in older men.

	Lean Mass*	Fat Mass#
pQCT 4% Radius		
BSI	0.77 (0.60-0.94)	-0.25 (-0.40- -0.10)
Total Area (mm ²)	5.13 (4.42-5.84)	-2.28 (-2.93- -1.63)
Total Density (mg/cm ³)	0.57 (-0.16-1.29)	0.11 (-0.55-0.78)
Trabecular Density (mg/cm ³)	0.57 (0.07-1.07)	0.11 (-0.35-0.57)
pQCT 33% Radius		
SSI _p (mm ³)	5.83 (5.18-6.474)	-2.59 (-3.18- -2.00)
Section Modulus (mm ³)	5.91 (5.29-6.54)	-2.34 (-2.91- -1.77)
Total Area (mm ²)	1.59 (1.40-1.78)	-0.61 (-0.78- -0.43)
Cortical Density (mg/cm ³)	0.001 (-0.36-0.37)	-0.62 (-0.95- -0.29)
Cortical area (mm ²)	1.28 (1.136-1.43)	-0.52 (-0.65- -0.38)

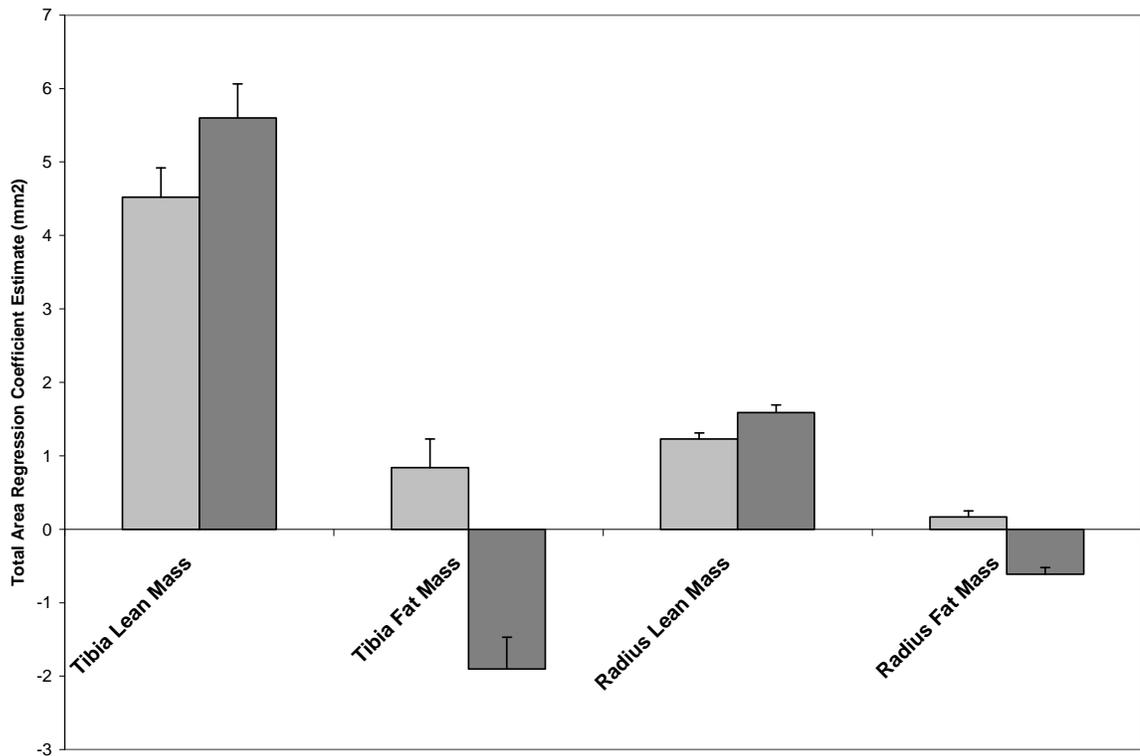
*Values are adjusted for site, age, race, object length and fat mass. #Values are adjusted for site, age, race, object length and lean mass. Values are regression coefficient estimates per 1 kg increase in each of the predictor variables (95% confidence intervals).

Figure 1. Strength Strain Index Regression Coefficient Estimates of the Tibia and Radius



The light gray bars represent the SSIP regression coefficient estimates from model 1 adjusted for age, clinic site, race, limb length for the tibia and the radius. The dark gray bars use either lean mass or fat mass as the predictor (listed under the x-axis). The dark gray bars represent SSIP regression coefficient estimates from model 2 (adjusted for age, clinic site, race, limb length and fat mass) when using lean mass as the predictor and model 3 (age, clinic site, race, limb length and lean mass) when using fat mass as the predictor.

Figure 2. Total Area Regression Coefficient Estimates of the Tibia and Radius



The light gray bars represent the total bone area regression coefficient estimates from model 1 adjusted for age, clinic site, race, limb length for the tibia and the radius. The dark gray bars use either lean mass or fat mass as the predictor (listed under the x-axis). The dark gray bars represent total bone area regression coefficient estimates from model 2 (adjusted for age, clinic site, race, limb length and fat mass) when using lean mass as the predictor and model 3 (age, clinic site, race, limb length and lean mass) when using fat mass as the predictor.

DISCUSSION

Consistent with previous studies in other populations, our results suggest that in older men higher total body weight and BMI are associated with increased estimates of bone strength. Our data further suggest that it is important to consider the components of that weight when using bone strength as an outcome. Among older men with similar lean mass those with higher fat mass have lower bone strength at the tibia and radius. Among older men with similar fat mass, those with higher lean mass have higher bones strength. Thus, when lean mass was held constant, a one kilogram increase in fat mass was associated with a decrease in the estimates of bone strength and when fat mass was held constant, every kilogram of lean mass was associated with a greater increase in the estimates of bone strength than when fat mass was not taken into account. Similar results were seen when lean and fat mass were entered into the weight and BMI models (data not

shown). These data, suggest the importance of looking at the individual components of body composition (lean and fat mass) rather than total body weight or BMI alone and support previous studies showing a strong relationship between muscle mass and bone strength [85, 96, 99, 151]. We will discuss these points in greater detail below.

Muscle bone relationship

Our findings are consistent with the mechanostat theory of functional bone adaptation that suggests that bone adaptation is driven primarily by changes in mechanical load [15]. The highest loads on bone are generated by muscle forces, rather than from body weight or fat mass. Although lean mass is a crude index of how bone adapts to muscle force, similar relationships to estimates of strength have been seen in other populations [85, 96]. Data from this study suggests that estimates of bone strength decreased with increasing fat mass. Thus, in two men of the same weight and height, the man with higher percentage body fat would likely have a lower bone bending strength because they would have less lean mass.

Previous studies have been conducted in older men and the MrOS cohort that lend support to the relationship between muscles and bones. A randomized controlled trial conducted in men aged 66 years found that the men who complete the 14 months of aerobic exercise training increased their radial BMD by 19% [152]. A previous study done on the MrOS cohort found that older men with the highest level of physical activity and muscle strength had significantly higher estimates of bone strength at the tibia and radius [153]. These studies demonstrate that maintaining a high level of physical activity and or muscle strength can help to preserve bone strength as men age.

Bone is positively associated with lean mass and negatively associated with fat mass

These data suggest that it may be important to look at the components of body composition in addition to total body weight and BMI. Lean and fat mass may play an important factor in explaining bone geometry and strength. At the midshaft and distal tibial, when the mechanical loading effect of lean mass is statistically removed, fat mass becomes negatively associated with estimates of bone strength (SSIp, Z and BSI), total area and cortical area. This suggests that fat mass may actually have a disadvantageous effect on bone. A study by Kichengast et al. found similar results to this study when looking at lean mass and aBMD but differing results in relation to

fat mass and aBMD in older men [93]. Their study found that aBMD increased with increasing fat mass although the association was not statistically significant [93].

Body composition and bone outcomes

Few studies have examined the association of body composition with bone strength in older men. A recent study in older women found higher femoral aBMD, cross-sectional area (CSA), and bending strength (SI) with higher body mass index (BMI) using dual energy x-ray absorptiometry (DXA) based structure outcomes [85]. The positive relationship between bone outcomes and body mass were proportional to lean mass and not to fat mass in these women [85]. This is similar to our finding in the MrOS cohort of older men. Total body weight, BMI, lean mass and fat mass were positively associated with distal and midshaft tibial estimates of bone strength, total area, cortical area, total density and trabecular density. The positive relationship between the bone outcomes and body composition became negatively associated with fat mass, BMI and total weight when lean mass was statistically removed from the model. When fat mass was controlled for in the model, lean mass, BMI and total weight were all positively associated with the bone outcomes. This suggests that the positive relationship between the bone outcomes and body composition may be due to lean mass rather than fat mass.

We observed a positive association of estimates of bone strength and lean mass but not fat mass in both the midshaft and distal sites of the radius. These findings are similar to the Chiu et al. (2009) finding in a large population-based study of men aged 30-79. They found a strong positive association between appendicular lean mass and wrist aBMD [94]. This study did not look at the relationship between fat mass and wrist aBMD. These findings provide support to the notion that muscle forces rather than absolute mass contribute to bone outcomes.

Strengths and limitations

The findings of this study suggest the body composition may be an important factor in explaining bone geometry and strength in older men. There are several strengths to this study including the unique focus on older men, large sample size, use of validated measure such as DXA to determine body composition and the use of pQCT to assess volumetric BMD, bone geometry and structural strength estimates in older men. There are also several limitations to the study worth noting. First,

the majority of the men in this sample were Caucasian and generally healthy; therefore we are not able to generalize the results to other populations. This analysis is limited by the cross-sectional nature of the data. Additionally, lean and fat mass are highly correlated, thus it is difficult to examine the interrelationship between these measures. Finally, we used DXA based lean mass as a surrogate for the muscle force. Although the two are closely related [154], we did not have a direct measure of muscle force on tibia or radius bone.

Conclusions

In conclusion, these data suggest that if you take two men with the same amount of lean mass, the man with lower fat mass will have higher estimates of bone strength. Thus, it may be important to look at body composition (lean and fat mass) in addition to total body weight or BMI. Our data suggest that, in order to maintain bone strength, muscle mass should be preserved in older men. Future longitudinal studies are needed to confirm these observations.

Chapter 5

Relationship of mechanical loads and bioavailable sex steroids to volumetric BMD, bone geometry and bone strength in older men

**RELATIONSHIP OF MECHANICAL LOADS AND BIOAVAILABLE SEX STEROIDS TO
VOLUMETRIC BMD, BONE GEOMETRY AND BONE STRENGTH IN OLDER MEN**

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Purpose: The purpose of these analyses was to explore whether muscle cross-sectional area, bioavailable testosterone and bioavailable estradiol were associated with tibia and radius estimates of bone strength, cortical density, or total bone area. **Methods:** Peripheral quantitative computed tomography (pQCT) was used to assess tibial muscle cross-sectional area, bone volumetric density (vBMD, mg/cm³), total (ToA, mm²) and cortical (CoA, mm²) bone area, and estimates of bone compressive strength (bone strength index, BSI) and bending strength (polar strength strain index, SSIp; section modulus, Z) in a subset of men (≥ 65 years) who participated in the multi-site Osteoporotic Fractures in Men (MrOS) Study (n = 275) and the Tobago Bone Health Study (n=500). Fasting morning serum samples were used to determine bioavailable sex steroids. The base model was adjusted for age, site, and limb length. **Results:** A one standard deviation increase in muscle cross-sectional area was associated with a BSI increase of 6.0 ($p < 0.001$), an SSIp increase of 152.5 mm³ ($p < 0.001$). Adjusting for bioavailable testosterone or estradiol slightly attenuated the results. At the 66% site of the tibia, bioavailable testosterone was associated with vBMD while bioavailable estradiol was associated with Z, vBMD and CoA. The association of bioavailable estradiol and section modulus was no longer statistically significant after adjusting for muscle cross-sectional area. **Conclusions:** The findings of this study suggest the importance of maintaining muscle cross-sectional area in older men to maintain bone strength.

Introduction

Sex hormones have been shown to play a key role in the development and maintenance of bone health throughout life. Studies have shown that decreasing bioavailable sex hormone levels are related to bone loss in both postmenopausal women and elderly men [108]. Most studies indicated that estrogen concentrations are associated with bone mineral density, turnover and loss in aging men, while the impact of testosterone on bone health parameters is more uncertain.

According to the mechanostat hypothesis, bones adapt their strength to mechanical loads generated from voluntary mechanical usage [101]. Animal studies of mechanical loading support this theory of bone functional adaptation by consistently showing significant increases in the strength of loaded bones [102, 103]. How the force from physiologic mechanical loading is generated on bone has been debated [104]. However, studies have demonstrated that muscle force plays an important role in generating bending moments on bone [106]; and therefore, alteration in bone strength have been shown to follow alterations in muscle activity [130]. Given the important role of muscle force in bone functional adaptation, variables representing muscle mass or strength should be associated with bone strength.

Only a few studies have looked at the relationship between testosterone and mechanical loading. A couple recent studies were conducted by Callewaert et al. (2010) in male mice and Ducher et al. (2009) in young males [57, 131]. In the male mice, there was an increased periosteal bone formation in response to loading in androgen receptor knockout mice [131]. In pre- and peripuberty boys, the exercise-induced increase in periosteal expansion is greater than postpubertal boys [57]. Both these studies are consistent with the idea that bones might become less sensitive to loading when androgen concentrations are higher.

The purpose of this study is to examine the interrelationship between mechanical loading (muscle cross-sectional area as a surrogate) and sex steroid hormones (testosterone and estradiol) on parameters of bone strength and geometry in older American and African men. We hypothesize that higher mechanical loading represented by larger muscle size will positively effect estimates of bone strength primarily due to higher periosteal apposition regardless of ethnic origin or sex steroid

levels. Secondly, we hypothesize that higher levels of testosterone and estradiol will be associated with greater total bone area and volumetric BMD, but not overall bone strength.

Methods

Participants

This cross-sectional study included 275 men from the Osteoporotic Fractures in Men (MrOS) study [136] and 500 men from the Tobago Bone Health Study [155] which is part of the Tobago Prostate Cancer Survey [156]. Details on the study participants and measurements have been published elsewhere [136, 155, 156]. Briefly men who were at least 65 years of age were recruited from six communities in the United States (Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego California) to participate in the prospective MrOS study. From March 2000 through April 2002, 5,995 men with no history of bilateral hip replacement and who were able to walk without assistance of another person were enrolled in the baseline examination. A stratified sampling design was used to select the MrOS participants whose fasting morning serum was used for measurement of sex steroids (n=2,623). The study design and recruitment methods used by the study have been published elsewhere [137]. The Institutional Review Boards at each center approved the study protocol, and written consent was obtained from all study participants.

Men who returned for their second exam an average of 4.7 ± 0.3 years later were invited to participate in an ancillary study involving pQCT at the Minneapolis and Pittsburgh clinical centers. Of the 1550 men who attended the second exam at the Pittsburgh and Minneapolis sites, 1171 (76%) completed the clinic visit and agreed to participate in the pQCT ancillary study. Of the 1171 men that completed the pQCT visit, 275 had sex steroid measurements. The 275 that were included were from the random sample of 1608 men from the entire MrOS cohort to be in a biomarker substudy in which sex steroid measurement were performed on fasting baseline serum. The Institutional Review Boards at Minneapolis and Pittsburgh sites approved this ancillary study and written informed consent was obtained from all participants for the pQCT substudy.

The Tobago Prostate Cancer Survey is an observational cohort study of prostate cancer prevalence and incidence in healthy men over the age of 40 years. Ambulatory, noninstitutionalized

and not terminally ill men from the islands of Trinidad and Tobago were enrolled in the baseline examination. Men who returned for their second exam between 2004 and 2007 were invited to complete a pQCT scan. A total of 2031 men returned (70% of survivors) and 451 new participants were recruited. Fasting morning serum was obtained from a random sample of 500 participants at least 65 years old. The current analysis includes men with pQCT and sex steroid measurements (n=447).

Anthropometric data

Height was measured without shoes using a wall-mounted stadiometer. Weight was measured in indoor clothing without shoes using a calibrated beam scale. Body mass index (BMI = kg/m²) was calculated from participant's height and weight. Tibia length was measured to the nearest millimeter with an anthropometric tape measure. Tibial length was measured from the tibial plateau to the medial malleolus. The mean of two measurements for each variable was used for the analysis. Information from the baseline exam was used to assess race/ethnicity.

Sex steroid measurement

For the MrOS samples, fasting morning serum was collected and stored at -70 C until assay. A combined gas chromatographic negative ionization tandem mass spectrometry and liquid chromatographic electrospray tandem mass spectrometry bioanalytical method was used to measure testosterone and estradiol (Taylor Technology, Princeton NJ). The ranges of detection for estradiol were 0.625–80 pg/ml and for testosterone were 2.5–320 ng/dl. Duplicate aliquots were assayed and averaged. The intraassay and interassay coefficients of variation (CV), respectively, were 2.5 and 6% for testosterone and 6.4 and 10.1% for estradiol. SHBG concentration was determined on an Immulite analyzer with chemiluminescent substrate (Diagnostic Products Corp., Los Angeles, CA). The standard curve ranged from 0.2–180 nmol/liter/l with intraassay CV of 4.6% and interassay CV of 5.8%. Bioavailable estradiol and testosterone were calculated using mass action equations described by Sodergard et al. [157].

For the Tobago samples, fasting morning serum was collected and stored at -80 C until assay. Hormone assays were completed using gas chromatography–liquid chromatography–mass spectrometry technique to measure total and bioavailable testosterone and estradiol. Standard

samples of several concentrations were included in all assay runs to ensure precision and accuracy. Details of the laboratory methods have been described [158, 159].

Dual energy x-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) scans (QDR 4500 W, Hologic Inc., Bedford, MA) were performed to measure total body lean mass and total body fat mass. Standardized procedures for participant positioning and scan analysis were used for all scans. All DXA operators were centrally certified on the basis of an evaluation of scanning and analysis techniques. A daily phantom scan was completed at each site to monitor machine performance [137]. To adjust for inter-clinic differences, statistical models include indicator variables for the individual scanners. Each clinic scanned a Hologic whole body phantom throughout the study to monitor longitudinal changes, and correction factors were applied to participant data as appropriate [137].

Peripheral quantitative computed tomography

Peripheral quantitative computed tomography (pQCT) is a non-invasive technique that allows for three-dimensional assessment of estimates of bone strength, bone volumetric density, and bone geometry. pQCT was used to obtain slices (2.3 ± 0.2 mm) at the 4% and 66% sites of the left tibia. Slices are taken as a percentage of limb length from the distal end of the relevant bone. The XCT 2000 device (Stratec Inc., Pforzheim, Germany) and the XCT-3000 (Stratec Inc., Pforzheim, Germany) were used to obtain the scans in Pittsburgh and Minneapolis respectively. The only difference between the 2000 and 3000 scanners is the gantry size. The same acquisition and analysis software (version 5.5) was used to analyze scans at both sites. A precision study was performed using a European forearm phantom scanned 3 times at each site at 200, 100, and 50 mg/cc respectively. Values on the two instruments were similar and within <0.5% for total area at all mg/cc, and from 0.5-1.0% for total density.

Voxel size was 0.5 mm and the scan speed was 25 mm/s. The anatomic reference line (distal edge of the tibial plafond) was determined by acquisition of a 30 mm planar scout view of the joint line. Data were analyzed according to the manufacturer specifications. At the trabecular 4% (distal) site, Contour mode 2 (169 mg/cm³) and Peel mode 1 (45% area) were used. The distal site was assessed for total bone cross-sectional area (ToA, mm²), total density (ToD, mg/mm³) and

trabecular density (TrabD, mg/mm³). Bone strength index (BSI, mg/mm⁴) was calculated as $[ToA * ToD^2]/1,000,000$ as an index of bone compressive strength. At the more cortical 66% tibia site, we used Contour mode 2 (169 mg/cm³) to determine whole bone properties and Cortmode 1 (710 mg/cm³) for cortical bone properties. A threshold of 280 mg/cm³ was used to determine the polar strength strain index (SSIp). At the cortical site, we assessed total bone cross-sectional area (ToA, mm²), cortical area (CoA, mm²), and cortical density (CoD, mg/mm³). Polar strength strain index (SSIp, mm³) and section modulus (mm³) were calculated as estimates of bone bending strength [142]. SSIp is a “density weighted” section modulus value while section modulus includes only geometric properties. The strength strain index (SSI) is used as estimate of both geometric and material strength (although material properties can not be directly measured). The SSI has been shown to be an accurate and precise indicator of the structural properties of long bones tested in bending [142]. The SSI is more strongly correlated with experimentally determined breaking force than either DXA measures of areal BMD, or CSMI or cortical volumetric BMD alone [142]. Muscle cross-sectional (MCSA, mm²) area was determined at the 66% of the tibia. For the Minneapolis site, precision with repositioning was determined in adults (women n=11, men n=4, age 28.5±6.5 years) as a coefficient of variation (CV, %) and varied from 0.28 (total density) to 1.20 (trabecular area) at the distal tibia and from 0.31 (cortical density) to 0.41 (total area) at the shaft [143]. Similar precision values were reported at the Pittsburgh site [144]. An anthropomorphic phantom was scanned daily for quality assurance at both sites.

The Tobago Bone Health Study used the XCT 2000 device (Stratec Inc., Pforzheim, Germany). A single axial slice of 2.5-mm thickness with a voxel size of 0.5mm and a speed of 20 mm/s was taken at all locations. The analysis software (version 5.5E) was used to analyze the scans. The Tobago study used the same sites and identical parameters for contour finding and separation of trabecular and cortical bone as the MrOS Study. All images were analyzed by a single Tobago Study investigator. Coefficient of variations were determined by repeating pQCT scans on 15 subjects with repositioning (CV ≤ 2.1%) [160].

Statistical analysis

All bone variables, sex steroids and muscle cross-sectional area were checked for outliers and normality. Differences in characteristics according to MrOS or Tobago study were compared using

t-tests. Multiple regression analysis was used to determine the association between muscle cross-sectional area and bioavailable sex steroids with measures of bone strength, geometry and volumetric density. All analyses were adjusted for age, tibia length and site. The Tobago location was entirely Afro-Caribbean and the Pittsburg and Minneapolis sites were almost entirely Caucasian; therefore, site was chosen to be included in the analysis because it also takes into account the differences between Pittsburg and Minneapolis. Bone parameters regression coefficient estimates were standardized to be interpreted on a standard deviation scale. Least-squared means procedure was used to estimate the mean (95% confidence interval) for each bone parameter by study location. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Descriptive characteristics

A comparison of the men in the MrOS and Tobago studies can be found in Table 1. The MrOS men were older (+5.5 years, $p < 0.001$) weighed more (+3 kg, $p = 0.006$) and had less lean mass (-2.5 kg, $p < 0.001$) and more fat mass (+4.8 kg, $p < 0.001$) than the Tobago men. The Tobago men had higher levels of bioavailable testosterone and estradiol than the MrOS men. Tibia length and muscle cross-sectional area were greater in the MrOS men. The MrOS and Tobago men were similar in height.

Table 1. Descriptive characteristics of the MrOS and Tobago men.

	MrOS n=274	Tobago n=500	p-value
Age (years)	77.1±4.8	71.6±6.0	<0.001
Height (cm)	172.7±6.6	172.2±6.7	0.797
Weight (kg)	82.8±13.7	79.8±14.5	0.006
BMI (kg/m ²)	27.7±4.0	26.9±4.4	0.104
Lean Mass (kg)	57.9±7.4	60.4±8.2	<0.001
Fat Mass(kg)	22.2±7.4	17.4±7.0	<0.001
Bioavailable Testosterone	208.5±62.6	228.8±8.4	<0.001
Total Estradiol	17.9±7.8	25.5±10.2	<0.001
Bioavailable Estradiol	12.0±5.0	15.9±6.2	<0.001
Tibia Length (mm)	401.4±24.3	392.6±53.9	0.002
Muscle Cross-Sectional Area (mm ²)	7519.1±1272.2	6831.6±1240.1	<0.001

Values are means ± standard deviations.

Muscle cross-sectional area's effect on vBMD, bone geometry and bone strength.

Muscle cross-sectional area was associated with bone compressive strength (BSI), total bone area and total density at the distal (4%) tibia (table 2). In the age, tibia length, and site adjusted model, BSI increased 6.0 ($p<0.001$) per standard deviation increase in muscle. This was largely due to an increase in total bone area (31.6 mm² per standard deviation increase in muscle, $p<0.001$). Further adjusting for bioavailable testosterone or bioavailable estradiol resulted in a slight change in BSI per standard deviation of muscle (5.7, $p<0.001$ and 5.5, $p<0.001$, respectively). Total density was positively associated with muscle cross-sectional area in the age, tibia length and site adjusted model. After adjusting for either bioavailable testosterone or bioavailable estradiol, they were no longer significantly associated.

At the cortical (66%) tibia, muscle cross-sectional area was positively associated with strength strain index (SSI_p), section modulus, total bone area and cortical area (table 2). Cortical density was negatively associated with muscle cross-sectional area. A one standard deviation increase in muscle cross-sectional area was associated with a 152.5 mm³ increase in SSI_p ($p<0.001$), a 165.8 mm³ increase in section modulus ($p<0.001$), a 25.1 mm² increase in total bone area ($p<0.001$), a 8.9 mm² increase in cortical area ($p<0.001$) and a 4.4 mg/cm³ decrease in cortical density ($p<0.001$). Adjusting for either bioavailable testosterone or bioavailable estradiol resulted in the slight attenuation of the associations.

Table 2. Muscle cross-sectional area

	Age, tibia length and site adjusted	Age, Tibia length, Site and Bioavailable Testosterone adjusted	Age, Tibia length, Site and Bioavailable Estradiol adjusted
pQCT 4% Tibia			
BSI	6.0 (3.0-8.9)	5.7 (2.7-8.8)	5.5 (2.5-8.4)
Total Area (mm ²)	31.6 (17.4-45.9)	30.9 (16.2-45.6)	31.0 (16.3-45.7)
Total Density (mg/cm ³)	4.6 (0.1-9.0)	4.3 (-0.3-8.8)	3.9 (-0.6-8.4)
Trabecular Density (mg/cm ³)	3.3 (-0.5-7.0)	2.7 (-1.1-6.5)	2.5 (-1.3-6.3)
pQCT 66% Tibia			
SSI _p (mm ³)	152.5 (101.1-203.9)	150.6 (97.5-203.6)	149.8 (96.7-202.8)
Section Modulus (mm ³)	165.8 (113.1-218.5)	164.1 (109.6-218.6)	162.4 (108.0-216.7)
Total Area (mm ²)	25.1 (15.9-34.3)	24.7 (15.2-34.2)	24.9 (15.4-34.4)
Cortical Density (mg/cm ³)	-4.4 (-7.3- -1.4)	-4.4 (-7.4- -1.3)	-4.7 (-7.7- -1.6)
Cortical area (mm ²)	8.9 (4.3-13.4)	8.8 (4.1-13.5)	8.6 (3.9-13.2)

Estimated cross-sectional differences (estimates from a multiple linear regression model) in tibia parameters per 1 standard deviation muscle cross-sectional area (95% confidence intervals).

Bold values indicate statistically significant effects.

Bioavailable testosterone and bioavailable estradiol's effect on vBMD, geometry and bone strength

At the highly trabecular distal tibia, bioavailable estradiol was positively associated with bone compressive strength, total bone density and trabecular density (table 3). Associations were not found between the bone variables and bioavailable testosterone at the distal site (table 3). In the model adjusting for age, site and tibia length, BSI increased 6.1 ($p < 0.001$), total density increased 8.2 mg/cm³ ($p < 0.001$) and trabecular density increased 5.9 mg/cm³ ($p < 0.001$) per standard deviation increase in bioavailable estradiol. These associations were slightly attenuated after adjusting for muscle cross-sectional area but remained significant.

Bioavailable testosterone was positively associated with cortical density at the 66% site of the tibia. Section modulus, cortical density and cortical area were all positively associated with bioavailable estradiol (table 3). In the model adjusted for age, tibia length and site, section modulus increased 51.2 mm³ per standard deviation increase in bioavailable estradiol ($p = 0.04$). Further adjusting for muscle cross-sectional area resulted in a 44.5 mm³ increase per standard deviation of bioavailable estradiol which was no longer statically significant ($p = 0.07$). For every one standard deviation increase in bioavailable estradiol, cortical density increased 3.8 mg/cm³ ($p = 0.005$) and cortical area increased 5.7 mm² ($p = 0.007$). After adjusting for muscle cross-sectional area, cortical density increased 3.9 mg/cm³ per standard deviation increase of bioavailable estradiol ($p = 0.004$) and cortical area increased 5.3 mm² per standard deviation increase in bioavailable estradiol ($p = 0.01$). Total estradiol resulted in similar finding to bioavailable estradiol (data not shown).

Table 3. Bioavailable testosterone and bioavailable estradiol

	Bioavailable Testosterone		Bioavailable Estradiol	
	Age, tibia length and site adjusted	Age, tibia length, site and muscle adjusted	Age, tibia length and site adjusted	Age, tibia length, site and muscle adjusted
pQCT 4% Tibia				
BSI	1.0 (-1.6-3.6)	1.2 (-1.4-3.7)	6.1 (0.6-1.4)	5.9 (3.3-8.5)
Total Area (mm ²)	-0.9 (-13.5-11.6)	-0.1 (-12.5-12.3)	-0.5 (-13.5-12.5)	-1.5 (-14.4-11.5)
Total Density (mg/cm ³)	1.3 (-2.6-5.1)	1.3 (-2.5-5.2)	8.2 (4.2-12.1)	8.0 (4.0-12.0)
Trabecular Density (mg/cm ³)	-0.4 (-3.7-2.8)	-0.3(-3.6-2.9)	5.9 (2.6-9.2)	5.7 (2.4-9.1)
pQCT 66% Tibia				
SSIp (mm ³)	-23.6 (-69.5-22.3)	-20.9 (-65.7-23.9)	32.6 (-15.0-80.2)	26.5 (-20.1-73.0)
Section Modulus (mm ³)	-19.4 (-66.6-27.9)	-16.7 (-62.7-29.3)	51.2 (2.4-100.1)	44.5 (-3.2-92.2)
Total Area (mm ²)	-5.9 (-14.1-2.3)	-5.4 (-13.4-2.7)	-1.2 (-9.7-7.3)	-2.1 (-10.5-6.2)
Cortical Density (mg/cm ³)	4.7 (2.1-7.2)	4.5 (2.0-7.1)	3.8 (1.1-6.4)	3.9 (1.2-6.5)
Cortical area (mm ²)	-0.5 (-4.5-3.4)	-0.4 (-4.4-3.5)	5.7 (1.6-9.8)	5.3 (1.2-9.3)

Estimated cross-sectional differences (estimates from a multiple linear regression model) in tibia parameters per 1 standard deviation bioavailable testosterone or bioavailable estradiol (95% confidence intervals).

Bold values indicate statistically significant effects.

Differences in vBMD, bone geometry and bone strength between the MrOS and Tobago Studies

Significant differences in pQCT bone parameters were observed between the MrOS and Tobago studies in models adjusted for age, site, tibia length and muscle (Table 4). At the distal tibia, the Tobago men tended to have a smaller total bone area (-4.2%, $p < 0.001$) but a higher total tissue density (+3.6%, $p = 0.02$). Differences were significant for total density before and after adjustment for bioavailable testosterone ($p = 0.01$) but did not remain statistically significant after adjustment for bioavailable estradiol ($p = 0.10$). At the cortical site, estimates of bone strength were on average +14.5% higher in the Tobago men when compared with the MrOS men ($p < 0.001$). MrOS men tended to have smaller cortical bone area (+16.0%, $p < 0.001$) and cortical density (+4.1%, $p < 0.001$). At the cortical site, the differences between the MrOS and Tobago men were only slightly attenuated and remained significant after adjustment for either sex steroid.

Table 4. Differences in bone geometry and strength between the MrOS and Tobago Studies.

	Muscle		Bioavailable Testosterone		Bioavailable Estradiol	
	MrOS	Tobago	MrOS	Tobago	MrOS	Tobago
pQCT 4% Tibia						
BSI	115.1 (110.5-119.7)	117.3 (114.0-120.6)	114.2 (109.4-118.9)	117.6 (114.3-120.9)	116.3 (111.5-121.1)	116.4 (113.1-119.80)
Total Area (mm ²)	1265.6 (1243.3-1287.8)	1214.1 (1198.2-1230.1)	1264.0 (1241.0-1287.1)	1212.9 (1196.6-1229.1)	1263.5 (1240.0-1287.1)	1213.1 (1196.7-1229.5)
Total Density (mg/cm ³)	299.4 (292.5-306.3)	310.3 (305.4-315.3)	298.5 (291.3-301.6)	310.9 (305.8-315.9)	301.3 (294.1-308.5)	309.3 (304.3-314.3)
Trabecular Density (mg/cm ³)	229.4 (223.6-235.2)	227.5 (223.3-231.7)	228.7 (222.7-234.7)	227.9 (223.7-232.2)	230.8 (224.7-236.9)	226.8 (222.5-231.0)
pQCT 66% Tibia						
SSIp (mm ³)	3320.4 (3240.1-3400.6)	3806.8 (3749.4-3864.3)	3305.2 (3222.0-3388.5)	3806.3 (3747.7-3864.9)	3316.8 (3231.9-3401.7)	3780.0 (3740.7-389.3)
Section Modulus (mm ³)	3323.9 (3241.4-3406.4)	3805.2 (3746.3-3864.1)	3313.1 (3227.5-3398.8)	3805.9 (3745.8-3866.0)	3330.8 (3243.7-3418.0)	3796.3 (3735.6-3856.9)
Total Area (mm ²)	742.8 (728.4-757.2)	760.5 (750.2-770.8)	740.7 (725.7-755.6)	760.3 (749.8-770.8)	740.4 (725.1-755.7)	760.4 (749.8-771.1)
Cortical Density (mg/cm ³)	1073.7 (1069.0-1078.3)	1117.7 (1114.4-1121.0)	1072.8 (1068.1-1077.6)	1117.5 (1114.2-1120.9)	1073. (1069.0-1078.8)	1116.9 (1113.6-1120.3)
Cortical area (mm ²)	338.0 (330.9-345.0)	392.0 (387.0-397.1)	337.6 (330.2-344.9)	392.4 (387.3-397.6)	339.5 (332.1-346.9)	391.4 (386.1-396.6)

Values are adjusted for site, age, object length, and muscle.

Values are means and 95% confidence intervals.

Bold values indicate statistically significant effects.

Discussion

In accordance with our hypotheses, these data suggest that in older men muscle cross-sectional area is positively associated with estimates of bone strength and geometry as estimated by pQCT measurements of the tibia. These associations were slightly attenuated after adjusting for bioavailable sex steroids but remain significant. Also in agreement with our hypotheses, bioavailable sex steroids were significantly positively associated with cortical vBMD. Bioavailable estradiol was also positively associated with total and trabecular vBMD, bone compressive strength, cortical area and section modulus. After further adjustment for muscle cross-sectional area, all associations remained significant except with section modulus. These relationships were consistent across both the Afro-Caribbean and US cohorts. However, we found that Afro-Caribbean men had greater total vBMD, strength strain index, section modulus, cortical vBMD and cortical area than Caucasian men after adjusting for age, tibia length, muscle and site. Each of these points will be discussed in more detail below.

Muscle bone relationship

Consistent with our hypothesis, we found that at both the midshaft and distal sites of the tibia, estimates of bone strength were higher in men with greater muscle cross-sectional area. On average, an increase of one standard deviation in muscle size was associated with approximately 4.2% greater mean bone strength. These data are consistent with animal and human studies that show a strong association between bone strength and muscle force [102, 103]. We used muscle cross-sectional area as a surrogate for muscle force as supported by recent studies in children and adults [161, 162]. Wezsteon et al. (2011) found muscle size, muscle strength, body weight and physical activity to be independently and significantly associated with bone geometry in healthy participants aged 5-35 year [161].

In agreement with the mechanostat, our data suggest that muscle force (as measured by muscle cross-sectional area) is associated with a beneficial adaptation of bone geometry and bone strength. A study in older male athletes found that volleyball players had larger tibial mid-shaft cross-sectional area and thicker cortex than controls [64]. Previous studies have found an association between physical activity and bone strength due primarily to greater total bone area in

older men [153, 163]. These studies suggest that activity may increase bone strength by increasing the size of the bone.

In an effort to give these data clinical relevance, the results were adjusted by a one standard deviation of muscle cross-sectional area. In an unadjusted model, in these data, each year was associated with an SSIp decrease of 32.8 mm³; therefore the SSIp mean increased 4.2% per one standard deviation increase in muscle cross sectional area which is similar to the effect of 4.7 years of aging on bone SSIp.

Bioavailable estradiol and vBMD, bone geometry and estimates of strength

A study conducted on older men found that estradiol prevented the increase in bone resorption markers suggesting that estrogen inhibits bone resorption [164]. Thus, estrogen should be positively associated with vBMD. Our results found bioavailable estradiol to be associated with cortical and trabecular vBMD. On average, a one standard deviation increase in bioavailable estradiol leads to a 0.3% increase in mean cortical vBMD and a 2.5% increase in mean trabecular vBMD. A study done on a diverse sample of middle-aged men found that total and free estradiol levels were positively correlated with aBMD and cross-sectional area of the intertrochanter region while a significant correlation was not found at the narrow neck or shaft in the model adjusted for age, lean mass, fat mass and height [126]. The association between bioavailable estradiol and vBMD in these men is consistent with previous data using DXA showing stronger associations between aBMD at multiple sites and bioavailable estradiol as opposed to bioavailable testosterone in older men [113, 116, 119, 121].

Bioavailable Testosterone and vBMD

Our results suggest that higher levels of bioavailable testosterone are positively associated with cortical vBMD in older men. Similarly, in men over the age of 60 years, Khosla et al. (2005) found bioavailable testosterone to be associated with cortical vBMD at the femoral neck and distal tibia [120]. As for the structural parameter, at the distal radius, distal tibia and femoral neck total bone area and subendocortical area were inversely associated with bioavailable testosterone in older men, although, the inverse association with bone size went away after adjusting for estrogen [120].

Although not statistically significant, our study found a negative association with structural parameter at the distal tibia (total area), and tibial midshaft (total and cortical area) and bioavailable testosterone. The inverse association was somewhat surprising and brings up the possibility that bioavailable testosterone may not have the same stimulatory effects on the periosteum in the elderly that has been found in young boys [127]. Thus, further studies are needed to assess the effects of bioavailable testosterone on the periosteum.

This study did not find bone geometry and estimates of bone strength to be significantly associated with bioavailable testosterone. This finding differs from a study done, using pQCT, in young adult males that found free testosterone to be an independent positive predictor of cortical cross-sectional area and periosteal circumference in both the radius and the ulna [125]. Our results are similar to a study done by Travison et al. (2009) [126]. They did not find a relationship between total or free testosterone and proximal femur strength in men aged 30-79 years [126].

Differences between MrOS and Tobago men vBMD, bone geometry and estimates of strength

When controlling for the differences in tibia length, age and muscle cross-sectional area, at the tibia, Tobago vs MrOS men had greater estimates of bone strength at the cortical site but not the trabecular site. Cortical vBMD at the midshaft and total vBMD at the distal tibia were also greater in the Afro-Caribbean men vs the MrOS men. This is similar to the Nam et al. (2010) finding age-adjusted mean aBMD measures at the hip, lumbar spine and femoral neck were 8-20% higher in the Afro-Caribbean men than the US Caucasian men [165].

Strengths and limitations

There are several strengths to this study including the unique focus on older men, large sample size, the inclusion of Afro-Caribbean and Caucasian men, and the use of pQCT to assess vBMD, bone geometry and structural strength estimates in older men. There are also several limitations to this study worth noting. First, the men in this sample were ambulatory Afro-Caribbean and Caucasian and generally healthy; therefore, we are not able to generalize the results to other populations. Another limitation is the precision of the sex steroid assays. A further limitation is the calculation of the bioavailable sex steroids which are indirect measurements of these

concentrations. Finally, this analysis is limited by the cross-sectional nature of the data. Future longitudinal analyses including repeat pQCT measurements and fracture ascertainment are needed to confirm these associations. If these results are confirmed, findings should be used to direct design of intervention studies aimed at maintaining bone strength and lowering fracture risk in older men.

Conclusions

In conclusion, these data suggest that in older men muscle cross-sectional area is positively associated with estimates of bone strength and geometry while bioavailable estradiol is positively associated with vBMD. These results suggest that it may be important for older men to preserve their muscle size in order to maintain bone strength. These results contribute to the understanding of vBMD, estimates of bone strength and geometry in older Afro-Caribbean and Caucasian men. Future studies are needed to confirm these observations.

Chapter 6

Summary and Conclusions

Summary

In summary, the purpose of this dissertation was to explore the effects of various types of loading and sex steroids on bone volumetric density, bone geometry and estimates of bone strength in older men. The results presented in chapters three through five help define how loading influences bone outcomes in older men. The work from this dissertation contributed to the literature in several ways. First, we used a novel assessment tool (pQCT) to assess bone volumetric density, estimates of bone strength and bone geometry. Additionally, we provided further insight into the muscle-bone relationship in older men. Finally, there is a unique focus on older men. Below is a summary of the findings from each paper with respects to the three studies.

Muscle power and physical activity are associated with bone strength in older men: the osteoporotic fractures in men study

Summary:

Tibia

- At the distal tibia, lower levels of physical activity were associated with reduced compressive bone strength and reduced total area, but were not associated with total density.
- There was a significant association between reduced leg power and lower total area, but leg power was not associated with BSI or total density at the 4% site of the tibia.
- At the 66% site of the tibia, estimates of bone strength (SSI_p and Z) were higher in the most active quartile of men compared with the least active quartile, perhaps largely due to greater cortical area and cortical density.
- SSI_p and section modulus tended to be higher in the men with the greatest leg power compared with the least leg power. This was largely due to greater total bone area and cortical area rather than cortical bone density.

Radius

- At the radius, greater compressive bone strength, strength strain index and section modulus were found in the quartile with the highest activity level and the quartile with the highest grip strength when compared to the quartile with the lowest

activity level or grip strength. This difference was primarily due to a greater total area.

Conclusions:

- These data suggest the importance for older men to maintain physical activity and muscle strength/power for prevention of bone fragility.
- They also suggest that it may be important for men to maintain muscle strength and power as well as physical activity with advancing age.

Lean mass is associated with bone strength in older men: the osteoporotic fractures in men study

Summary:

Tibia

- At the highly trabecular distal tibia, total body weight, BMI, lean mass and fat mass were associated with bone compressive strength, total bone area, total density, and trabecular density.
- Similarly at the cortical 66% site of the tibia, total body weight, BMI, lean mass and fat mass were associated with bone strength strain index, section modulus, total area and cortical area.
- Among men with similar lean mass, those with higher fat mass will have lower estimates of bone strength. Among older men with similar fat mass, those with higher lean mass have higher estimates of bone strength.

Radius

- Parameters of bone strength (BSI, SSIP and section modulus) at the radius were significantly associated with total body weight, BMI and lean mass but an association was not found with fat mass.
- At the distal and midshaft of the radius, among men with similar lean mass, those with higher fat mass will have lower estimates of bone strength. Among older men with similar fat mass, those with higher lean mass have higher estimates of bone strength.

Conclusions:

- It may be important to look at body composition (lean and fat mass) in addition to total body weight or BMI
- In order to maintain bone strength, muscle mass should be preserved in older men.

Relationship of mechanical loads and bioavailable sex steroids to volumetric BMD, bone geometry and bone strength in older men**Summary:**

- Muscle cross-sectional area was associated with bone compressive strength, total bone area and total density at the distal tibia.
- At the 66% site of the tibia, muscle cross-sectional area was positively associated with strength strain index, section modulus, total bone area and cortical area while cortical density was negatively associated with muscle cross-sectional area.
- At the distal tibia, bioavailable estradiol was positively associated with bone compressive strength, total bone density and trabecular density while associations were not found between the bone variables and bioavailable testosterone at the distal site.
- Bioavailable testosterone was positively associated with cortical density at the 66% site of the tibia while section modulus, cortical density and cortical area were all positively associated with bioavailable estradiol.

Conclusion:

- These results highlight the importance of preservation of muscle size in older men in order to maintain their bone strength.
- Bioavailable estradiol may be an important variable to consider when determining the bone volumetric density of older men.

In conclusion, in order to maintain their bone strength, older men should remain or increase their physical activity to try to preserve the size and mass of their muscles. Although, future longitudinal studies are needed to confirm the results from the previous three studies.

Chapter 7

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