OSTEOPOROSIS AND SARCOPENIA IN OLDER ADULTS

by

Didier Chalhoub

B.S. in Biology, American University of Beirut, Lebanon, 2007

M.D., University of Balamand, Lebanon, 2011

M.P.H., University of Pittsburgh, 2012

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This dissertation was presented

by

Didier Chalhoub

It was defended on

March 2nd, 2015

and approved by

Robert M. Boudreau, Ph.D.
Assistant Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Susan Greenspan, M.D.
Professor, Department of Internal Medicine
School of Medicine, University of Pittsburgh

Anne Newman, M.D. M.P.H
Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Joseph Zmuda, Ph.D.
Associate Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Dissertation Advisor
Jane A. Cauley, Dr.P.H.
Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Jane A. Cauley, Dr.PH

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Didier Chalhoub, Ph.D.

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ABSTRACT

The percentage of individuals older than 65 years of age is increasing. In 2008, approximately 506 million individuals worldwide were older than 65. This number is expected to double and reach 14% of the world's population by year 2040. With this increase, a higher number of older men and women are expected to experience deterioration in their bones and muscles leading to osteoporosis and sarcopenia respectively. Therefore, understanding the burden that osteoporosis and sarcopenia represent in older men and women could have major public health implications.

We studied the importance of areal and volumetric bone mineral density (vBMD) in fracture risk prediction in older men. We found that low areal BMD (aBMD) and (vBMD) were both associated with multiple sites of fracture. Nonetheless, low vBMD was not found to be a better predictor of major osteoporotic fractures (Hip, spine wrist, shoulder) compared to aBMD, except at the spine. Subsequently, in the same cohort of older men, we found that low appendicular lean mass was positively associated with central and peripheral bone skeletal size, density and strength parameters that have been previously related to fractures. On the other hand, grip strength was only associated with site specific radial strength and geometric parameters. There was no association between leg power and the skeletal size, density and strength of older men after adjusting for appendicular lean mass and grip strength. These findings highlight the more important role of the mechanical load of the muscles on bones, compared to the muscle strength and power. Finally, we were interested in examining whether sarcopenia with or without

osteoporosis is associated with an increased risk of non-spine fractures. In this third paper, we demonstrated that men with both sarcopenia and low BMD are at a much higher risk for non-spine fractures compared to men with either one or neither condition. On the other hand, low BMD with or without sarcopenia in older women was associated with an increased risk of fractures, suggesting that low BMD is the driving force of non-spine fractures in older women.

Future research should investigate further the crosstalk between muscle and bones. There are currently multiple sarcopenia definitions. Therefore, a consensus on the definition for sarcopenia should be reached, so that diagnostic and therapeutic tools can be developed. Furthermore, dual-energy X-ray absorptiometry (DXA) remains the gold standard diagnostic tool for fracture risk assessment.

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PREFACE

I am grateful to my advisor, mentor and role model, Prof Jane Cauley, for her patience, guidance, and for teaching me the importance of using diligence in conducting research. I would like to thank her for the freedom and trust she granted me during my training. I also would like to thank my dissertation committee for their invaluable feedbacks.

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1.0 INTRODUCTION – THE MUSCULOSKELETAL SYSTEM

The percentage of individuals older than 65 years of age is increasing. Back in 2008, approximately 506 million individuals worldwide were older than 65. This number is expected to double and reach 14% of the world's population by year 2040 [1]. With this increase in the older population, a higher number of older men and women are expected to experience deterioration in their bone and muscle leading to osteoporosis and sarcopenia respectively. A similar decreasing trend in bone strength (density and quality), lean mass, and muscle strength is observed with age [2]. Based on these findings, it is believed that muscles and bones share genetic, biological, and physiological processes that may be triggering this well synchronized decline in both tissues. This review will provide some insight about the muscle bone interaction and etiologies in an attempt to better understand the factors that mediate this cross talk. This is an emerging field of research and many attempts are being made to understand the etiologies shared by both tissues so that preventive measures and interventions could be targeted to both simultaneously. Furthermore, musculoskeletal disorders are a major cause of disabilities worldwide and represent a major economical burden. The cost spent on musculoskeletal disorders is greater than the cost of breast cancer, stroke, and cardiovascular diseases combined [3]. Therefore, it is of primary importance to understand the burden that osteoporosis and sarcopenia represent on older men and women.

The purpose of this dissertation will be to study the epidemiology of osteoporosis and sarcopenia. Specifically, the combined effects of sarcopenia and osteoporosis on health outcomes such as fractures and falls will be studied.

1.1 OSTEOPOROSIS

1.1.1 Definition

Osteoporosis is a condition defined as low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [4]. The World Health Organization (WHO) defines osteoporosis based on bone mineral density (BMD) alone, and previous fracture [5]. This definition does not take bone quality and bone microarchitecture into consideration, and therefore doesn't cover the full spectrum of bone strength. On the other hand, the National Institutes of Health (NIH) defines it as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture [6]. The term bone strength includes both bone density and bone quality. Bone density is a reflection of bone mass and is expressed by grams per area or per volume depending on the measurement tool used. Bone quality is a reflection of the architecture, damage accumulation, turnover, and mineralization of the bones [7].

The strength of bone is determined by both its material composition and geometric structure [7]. Bone geometry plays a major role in bone strength and hence, fracture risk [8]. As men and women age, the cross-sectional area of the medullary cavity increases, resulting in the reduction of the cortical area of bones. Furthermore, older individuals experience a thinning of

the bone cortex (poor geometry) because endocortical resorption exceeds periosteal apposition [9]. Another important geometric parameter is the distribution of cortical mass about the bone center. It has been shown that resistance of bones to compressive loads and to bending depend on the cortical area and the distribution of cortical mass about the center respectively [10]. These are important geometric parameters to consider while assessing bone strength.

Bone size, cortical thickness and porosity, trabecular number and thickness, and mineral content are all important factors in assessing bone strength [9]. A disruption in one or more of these factors could result in a decrease in bone strength and consequently, osteoporosis.

1.1.2 Pathophysiology

Normal and healthy bone is known to constantly remodel by osteoblast and osteoclast activity. The osteocytes, which represent 95% of all bone cells, are embedded in the matrix of bones and control the activity of osteoblasts and osteoclast located at the bone surface [11]. Continuous bone resorption followed by bone formation is necessary to maintain bone volume and calcium homeostasis [12]. During increased osteoclastic activity, the osteoblast formation also increases which indicates that these two processes may be coupled. The receptor activator of nuclear factor-kB ligand (RANKL), a tumor necrosis factor derived from osteocytes, was discovered and helped in clarifying how osteoblasts regulate osteoclast activity [13] [14] [15] [16]. Osteoclasts, under normal regulation, do not pathologically resorb bones. As a matter of fact, the osteoblast-derived factor RANKL is essential for osteoclast formation [17]. Osteoprotegerin (OPG), a decoy receptor, has the function of inhibiting the resorption by decreasing the differentiation and function of osteoclast. OPG prevents the osteoclast formation, attachment to bone, activation, and survival of osteoclasts. OPG inhibits the binding of RANKL to the receptor activator of

nuclear factor-kB (RANK) [18] [19] (Figure 1). RANK is a receptor located on the membrane of osteoclasts and osteoclasts precursors. Previous animal studies have shown that OPG deficient mice had increased osteoclast activity resulting in severe osteoporosis. In these mice, both trabecular and cortical porosity increased and parietal bone became thinner [20] [21]. The ratio of RANKL to OPG was shown to be an important determinant of bone resorption, with high RANKL and low OPG promoting bone resorption. As long as the RANKL to osteoprotegerin ratio is within the normal range, bone resorption remains under control [22]. The RANKL and OPG do not affect only BMD but also the geometry and strength of the bones [23] [24]. Changes in hormonal levels (estrogen, testosterone, etc.) and steroid intake were found to disrupt this balance by increasing the RANKL/osteoprotegerin ratio and consequently favoring osteoporosis and fractures.

1.1.3 Radiographic diagnostic tools

Based on the WHO approach, Dual-energy X-ray absorptiometry (DXA) is the gold standard diagnostic tool used to identify patients with osteoporosis [25] [26]. DXA was first introduced in the late 1980s early 1990s [27]. It's low cost, quickness, low radiation and precision made it popular and commonly used by researchers and clinicians. DXA relies on two dimensional scans to provide areal bone mineral density (aBMD) measurements. To diagnose osteoporosis, the aBMD of the femoral neck is used to calculate the T-score. T score is obtained by subtracting the mean aBMD of the young normal population from the measured femoral aBMD and dividing by the standard deviation of the normal population: *T-score= (Measured BMDa – Young adult mean BMDa)/ Young adult population SD.*

Subjects are considered to have normal BMD if their T-score is greater than or equal to -1. A T-score strictly below -1 is an indication of low bone mass: osteopenia is present if the T-score is between -1 and -2.5, and osteoporosis if T-score is below or equal to -2.5. Using the WHO approach, T-score is calculated using mean femoral neck aBMD obtained from the National Health and Nutrition Examination Survey III reference data [28]. Young Caucasian women are used as the reference population in both men and women as recommended by the International Society for Clinical Densitometry (ISCD) [29]. However there are some controversies regarding the usage of young Caucasian women as the reference group. Other working groups propose to use gender-specific and ethnic specific reference data [30] [31]. Osteoporosis, diagnosed based on bone density alone, seems to miss a large proportion of individuals with low bone strength. As a matter of fact, most fractures occur in non-osteoporotic individuals [32] . Only 20% of osteoporotic individuals, diagnosed only based on femoral BMD, experience fractures. This may be due to the fact that the population of osteopenic subjects is much larger and that bone quality is not being captured for proper bone strength assessment.

DXA has several limitations. Some trials have shown that the increase in aBMD does not explain the reduction in fracture risk [33] [34]. This may be because aBMD takes a long time to change despite earlier changes in bone turnover markers detected in the blood [35] [36]. Another limitation is that it relies on bone size to measure the aBMD which usually results in overestimation of BMD in subjects with large bones and underestimation in subjects with small bones [37] [38]. This contributes to some of the race/ethnic differences observed in aBMD. Moreover, DXA does not differentiate non-bone hyperdensities such as aortic calcifications and foreign bodies from actual bone which could result in overestimation of aBMD especially at the lumbar spine [39]. Also, DXA assumes that the soft tissue at the site of interest is homogenous.

However, soft tissues are a mixture of fat and muscle which don't have the same composition [40]. A final limitation is that monitoring aBMD changes to assess therapy efficacy is controversial. Despite these limitations DXA is still the gold standard imaging technique used to diagnose osteoporosis. One of the reasons is because BMD linearly correlates and accounts for 60-70% of bone strength [41] [42] [39].

As previously stated, DXA is currently the most widely used method to assess bone mass and diagnose osteoporosis. However, bones are three dimensional structures and using two dimensional scans to assess their density is limited. Additionally, DXA is an integrated measure of bone density without differentiating between the trabecular and cortical compartments. This 2 dimensional imaging technique does not capture the size, shape, and geometry of bones. Advances in technology are making it possible to assess bone quality (microarchitecture and geometry) and obtain volumetric measurements of trabecular and cortical compartments. Although not commonly used in clinical settings because of high cost and lack of diagnostic cutoff points, these novel imaging techniques are improving the bone research field and could be a linchpin for future therapeutic breakthroughs. Many imaging techniques, such as Magnetic resonance imaging and quantitative ultrasonography, are currently being explored. However, this review will focus on the Quantitative Computed Tomography (QCT).

QCT was first introduced in the late 1970s [39]. It was initially used for diagnostic purposes other than bones. The Quantitative Computed Tomography (QCT) is a more intuitive method of measuring bone density using a 3 dimensional approach. QCT is a 3 dimensional imaging technique that provides volumetric BMD (vBMD) instead of aBMD in which case size becomes irrelevant [43]. Furthermore, QCT can distinctively measure trabecular and cortical bones allowing a separate assessment of these bone compartments. This is an important

advantage since trabecular and cortical compartments have different metabolic activities [44]. Furthermore, QCT provides 3 dimensional geometric parameters and information about trabecular structure in central (Hip and Spine) and peripheral regions (radius and tibia) of the skeleton. It was designed to assess the BMD, bone size, shape of bones, as well as biomechanical measures. The parameters provide information about the resistance of bone to bending (cross sectional moment of inertia-CSMI), the bending strength (polar strength index-SSIp, axial strength index- SSIx), the torsional strength (section modulus-SM), and the ability of the bone to resist torsion (polar moment of inertia-PMI) [45]. The bone's polar moments of inertia provide information about the ability of bones to resist torsion, whereas the axial moments measures the distribution of cortical bone mass about the center of the cross-section of the tubular bone [46]. The polar or axial strength strains are a reflection of the torsional and bending rigidity of the long bone shaft [47]. The section modulus is a reflection of the resistance of the bones to stress. If high, it means that a higher load is needed to cause mechanical failure [48].

At the hip, QCT helps in differentiating between cervical and trochanteric fractures. It also provides more information about femoral geometry and hip structure which were found to be associated with hip fractures independently of BMD [49] [50] [51]. Other parameters such as the cross-sectional area and medullary volume could be obtained as well to better assess quality of bones [52]. Cross sectional area, neck axis length and cortical thickness have been associated with bone failure load [53] [50].

In the lumbar spine area, QCT provides information about the trabecular compartment of the vertebrae. For accurate reading of these scans, at least two vertebrae should be seen by the radiologist. This is done mostly to reduce the radiation exposure [39]. Since trabecular and cortical compartments have different patterns of deterioration, assessing the vertebrae with QCT

provides more compartment-specific information compared to DXA. Geometric parameters are also important for bone quality assessment in the spine. The endplate area, cross-sectional area, or vertebral surface area have been shown to improve the correlation of BMD with failure load [54] [55] [56]. On the other hand, cortical thickness is difficult to measure in spine because of spatial resolution [57].

Peripheral QCT measures BMD, bone size, and shape of the radius and tibia. At the distal sites, the cortical and trabecular bone mineral content (BMC), cross-sectional area, and BMD can be measured. However, on the shaft of the bones the trabecular component does not exist but cortical thickness, endosteal, and periosteal circumference can be measured [58].

In pQCT, the section modulus, moment of inertia, and the SSI were correlated with failure load [59] [60] [61]. Despite the fact that pQCT provides more information about bone quality and strength, it was not found to better predict failure load compared to DXA alone [62].

QCT also has its limitations. The radiation received by the patient is much higher compared to DXA and this might be of concern since the gonads are in the scan field for central QCT [38]. Also, the high cost of the equipment makes it less readily available, especially for the central QCT. In addition, QCT is less precise and highly variable. There are currently no clear cut-off points used in QCT imaging to diagnose osteoporosis. Future endeavors to find a standard population that could be used for diagnostic purposes could make the QCT the gold standard imaging tool of choice.

1.1.4 Epidemiology

Prevalence and incidence

Currently, about 54 million Americans above age 50 have osteoporosis and low bone mass (10.2 million have osteoporosis and 43.4 million have low bone mass). This number is expected to increase and with it the number of osteoporotic fractures. The National Osteoporosis Foundation (NOF) expects it to increase to 64.4 million in 2020, and 71.2 million in 2030 [63]. It is estimated that the lifetime risk of any fracture is 40% and 13% in US women and men respectively [64]. With this increase in prevalence of osteoporosis, a higher number of fractures are expected, leading to an increase in morbidity and mortality [65]. Back in 2005, approximately 2 million incident fractures occurred. This number is now on the rise since a larger number of the US population has low bone mass. Although many are not detected, vertebral fractures represents 27% of fractures. Wrist fractures accounts for 19% of fractures, hip fractures 14%, and pelvic fractures 7% [65].

There are gender and race differences in osteoporosis and fracture prevalence. Peak BMD and rate of BMD loss explain some of these disparities. Men have a higher peak BMD compared to women. As men and women age the average rate of hip BMD loss increases. Nonetheless, women tend to lose more bone than men especially after menopause [66]. In men, although the rate of BMD loss is moderate, those with low BMD at baseline experiences higher bone loss compared to men with normal BMD at baseline [67].

Race differences also exist [68]. In both genders, peak BMD is the highest in African Americans [69] [70] [71].

The BMD of Mexican American women is higher than the BMD of Caucasians, but lower than BMD of African Americans. Asian women tend to have the lowest BMD [72] [73].

These differences in older women could be attributed to the peak bone mass as well as the rate of bone loss. Indeed, white women lose twice more BMD than African American women. These differences in BMD result in different risks of fractures among ethnic groups [6].

As expected, African Americans experience the lowest rate of fractures. However, white women experience the higher risk of hip fractures compared to Asian women despite the fact that Asian women have a lower BMD [66] [74]. This may be due to poorer bone geometry and/or increase in fall frequency among Caucasian women.

The hip, vertebral, and distal radius regions are the sites with the highest percentage of trabecular bone and this why they are the most common sites of insufficiency fractures

Hip fracture

Hip fractures represent less than 20 percent of osteoporotic fractures worldwide with the large majority seeking medical attention [75]. Therefore, hip fractures are easy to track and are used to determine osteoporosis burden. Another reason why hip fractures are important to assess is because they are associated with poor outcomes such as deep vein thrombosis, urinary tract infections, nosocomial infections, disability, and eventually death. Hip fracture was found to be associated with more disability and mortality than all other fractures combined [76]. Furthermore, they account for most fracture related expenditures [77]. About 20% of patients who experience a hip fracture die within a year [78]. The risk of hip fracture has been shown to increase exponentially with age with the great majority occurring above age 70. It occurs mostly in older women since they live longer, with women to men ratio of approximately 2 [79]. Most hip fractures result from a fall [80]. Nonetheless, it is important to note that there is a high

variability in hip fracture incidence across the world with higher magnitudes in women compared to men [81].

In North America, hip fractures have been found to decrease between 1995 and 2005 in both men and women [82] [83]. In the US, white men and women continued to experience a decrease in incidence of hip fractures after 2005. Blacks and Asians didn't experience any changes while a small non-significant increase in hip fracture rate was seen in Hispanic women [84].

Northern Europe countries such as Iceland, Ireland, and Norway were found to have the highest risk of hip fractures. Countries around or below the equator were associated with a lower risk of hip fractures [85]. Globally, hip fractures follow more or less a similar trend in developed countries: increases in rates until the mid-1990s with a subsequent decrease after that. However, this is not the trend in Asian countries [81]. Cauley et al. hypothesized that this observed decrease could be due to one or more of these factors: release of bisphosphonate (1995), obesity epidemic, lifestyle changes and/or an increase in calcium and vitamin D intake [86].

Vertebral fracture

Vertebral fractures are the most common osteoporotic fracture with a prevalence of 15% in women aged 50-59 and 50% in women above age 85 [87] [88] [89]. Before age 65, prevalence of vertebral fractures is very similar or slightly higher in men compared to women. However, after age 65, the women to men ratio becomes close to that of hip fractures [90]. It has been found that vertebral fractures increase linearly with age and a good percentage of vertebral fractures occur in osteopenic older men and women [91]. These fractures are less well documented than hip fractures. To a lesser extent than hip fractures, vertebral fractures are

associated with an increased risk of death [92]. Vertebral fractures are important in individuals with osteoporosis because they tend to occur earlier and could indicate a decrease in bone strength perhaps because the vertebrae have more trabecular bone than cortical bone. Since trabecular bone is affected earlier than cortical bone in osteoporosis, vertebrae become at a high risk of fracturing [93].

There are specific risk factors associated with vertebral fractures such as increase age, smoking, low milk consumption during pregnancy, low physical activity, previous fall, and aluminum-containing acid usage [94]. The risk of hip fracture was noted to be high in subjects with vertebral fracture [95]. Vertebral fractures have clinical implications. If detected, it is usually an indication to start therapy even if the T score is not below -2.5.

Despite these important facts, most vertebral fractures are asymptomatic and are considered to be underdiagnosed. However, some anthropometric signs such as a decrease in height of more than 2 to 4 cm could hint to a possible spine fracture [96]. Worldwide, the prevalence of radiographic vertebral fracture is similar in men and women but clinical vertebral rates tend to be much higher than the hip fracture rates [81].

Distal forearm fracture

The incidence of forearm fractures is greater in women than in men with about half occurring after age 65 [97]. Forearm fractures follow a different pattern compared to the hip and vertebral fractures. It is believed to increase between ages 45 and 60 because of the nature of the fall. After age 60, wrist fractures plateau and even decrease slightly perhaps because women tend to fall backwards or sideways with no attempt to break the fall with an outstretched arm [98]. The incidence in men is low and remains low throughout life.

Fracture risk prediction tool (FRAX)

The WHO designed a country specific tool known as the fracture risk prediction tool (FRAX). FRAX has been shown to be a better predictor of fracture than T-scores alone. In 2008, the WHO added 11 risk factors to the femoral neck BMD as part of FRAX [99]. The 11 risk factors that were added are: age, sex, weight, height, previous fracture, parental history of hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and alcohol 3 or more units per day. These factors were added to help in clinical assessment of patients because several studies have shown the importance of both clinical risk factors and BMD in predicting fractures (Figure 2)[100]. Furthermore, age has been found to increase the risk of fractures by 11 folds compared to BMD [101]. FRAX is a country specific tool that takes the mortality and hip fracture rate of the country into consideration. It has been developed in approximately 50 countries so far [102]. Using a poisson regression, the country specific 10 year probability of a major osteoporotic (hip, proximal humerus, clinical vertebral, forearm) fracture and hip fracture in men and women between 40 and 90 years of age can be calculated [101]. The risk factors included in FRAX were based on 12 prospective cohorts. These risk factors were subsequently validated in 11 other cohorts [103]. Nonetheless, it is important to note that FRAX is most effective in patients who are not getting treated for osteoporosis. Another FRAX limitation is that it does not include risk factors for falls which are known to be independent risk factors for nonvertebral fractures. Also, FRAX considers BMD only at the femoral neck. Therefore, BMD at other sites, biochemical indices, and computed tomography could provide extra information to better predict fractures [101].

1.2 SARCOPENIA

1.2.1 Definition

Although the concept of age associated loss of muscle mass has been known for centuries, it was not until 1989 that Rosenberg coined the term “sarcopenia”. Sarcopenia was initially defined as the loss of muscle mass [104] [105]. The main purpose was to assign a name to this condition and promote research in the field. Many age related processes are believed to accelerate the loss of muscle mass. Nuclear apoptosis, oxidative stress, muscle fiber denervation, and reduction in satellite cell content and regenerative potential are some known etiologies [106] [107] [108]. Furthermore, sarcopenia has been linked to a decrease in functional capacity, increased risk of falls and fractures, inability to perform activities of daily living (ADL), loss of independence, and increase risk of death [109] [110] [111] [112]. Because of these age related consequences, some researchers and clinicians consider sarcopenia to be a geriatric syndrome.

Nonetheless, it is important not to confuse sarcopenia with other geriatric syndromes such as cachexia and frailty. Cachexia is defined as severe wasting as a result of diseases. It’s usually due to inflammatory processes, insulin resistance, and muscle breakdown [113] [114]. Most cachectic older men and women are sarcopenic, but not all sarcopenic older individuals are cachectic. On the other hand, frailty is more physiological in nature and affects multiple systems at once. In frailty, the accumulation of subtreshold levels makes it difficult for the body to withstand stress. A considerable overlap exists between frailty and sarcopenia [115].

In 2001, Morley et al. added muscle strength to the original definition of sarcopenia after numerous studies (mostly cross sectional) showed a relation between muscle mass and muscle strength [116] [117]. The main reason for adding muscle strength into the definition was because

lean mass, measured by DXA, underestimated the prevalence of sarcopenia [118]. Another reason is because muscle strength is associated with function and disability whereas muscle mass is not [119] [120] [121] [122]. Therefore, by adding muscle strength, sarcopenia becomes more clinically relevant.

Subsequently, new definitions emerged under the sarcopenia syndrome umbrella adding muscle strength and/or physical performance to the muscle mass. The European Working Group on Sarcopenia in Older People (EWGSOP), the Foundation for the National Institutes of Health (FNIH), and the International Working Group on Sarcopenia each has its working definition.

EWGSOP was founded in 2009 to come up with a clinical definition and diagnostic criteria for sarcopenia. This group defined sarcopenia as a syndrome characterized by the progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death [123] [124]. The European working group recognized in addition to low muscle mass that there are many other factors that may contribute. The EWGSOP added muscle strength to its' definition because the relationship between muscle mass and strength is not linear and therefore, considering muscle mass alone may not be of clinical relevance [124] [125].

Similarly to EWGSOP, the FNIH definition includes both muscle mass and strength in its' algorithm. The purpose of this group is to focus on the clinical aspect of sarcopenia. Therefore, FNIH put in place a project in order to identify criteria for clinically relevant weakness and low lean mass, and apply them to populations with high rates of functional limitations [126].

The international working group on sarcopenia, which consists of a group of geriatricians, met in 2009 and proposed an alternative definition to Sarcopenia. These scientists

agreed that sarcopenia should be assessed in older individuals exhibiting signs of decline in physical function, strength, or health status. The group defined sarcopenia as follows: “Sarcopenia is the age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjuction with increased fat mass” [127]. As seen in the definition, this group stressed the fact that increased fat mass should be part of the syndrome. Infiltration of fat into muscles results in a decrease in muscle quality and performance as seen in sarcopenic obesity. Even more, according to this group total body fat should be accounted for while evaluating muscle mass.

These working groups consider sarcopenia to be a geriatric syndrome. Nonetheless, other researchers believe that muscle mass, muscle strength, and physical function should be assessed separately because age-associated changes in muscle mass explain less than 5% of the variance in muscle strength change [128]. This indicates that there are other physiological factors other than muscle mass that could explain muscle weakness in older adults [129]. Manini et al. proposed to define loss of muscle mass and muscle weakness (dynapenia) independently since these two conditions have different etiologies [130]. Based on this concept, a dynapenia algorithm has been proposed. This algorithm is beyond the scope of this review.

1.2.2 Pathophysiology

Normal muscle is characterized by a homogenous distribution of type I and type II fibers. Type I fibers are more fatigue-resistance whereas type II fibers have glycolytic potential, lower oxidative capacity, and faster response [131].

As individuals age, they progressively experience a decrease in their muscle fiber size. This decrease has been shown to be fiber specific with larger decreases occurring in type II fibers

compared to type I [132]. Up to 40% of type II fibers are smaller in elderly subjects compared to younger subjects. Type I fibers do not change significantly with age [133] [134]. Despite a clear understanding of how the muscle fiber size changes with age, there is not enough evidence regarding the age associated loss of the number of muscle fibers [112]. Furthermore, the muscle fiber size becomes more heterogenous as men and women get older [135]. Extensive grouping of the same types of muscle fibers occur as seen under the microscope [136]. As part of the aging process, the muscle architecture deteriorates as well. For instance, muscle fascicles tend to be shorter and attach less obliquely to its tendon which may lead to lower force production. Such age-related changes in fiber size and muscle architecture are observed in sarcopenic individuals irrespective of the etiologies [137].

1.2.3 Diagnostic tools

Currently, a gold standard to diagnose sarcopenia does not exist because there is no consensus on the definition of sarcopenia. Several algorithms have been proposed by the different working groups to diagnose sarcopenia.

The EWGSOP algorithm relies on a low lean mass plus either slowness or weakness. This group also categorized sarcopenia into stages based on severity: presarcopenic (low muscle mass), sarcopenia (low muscle mass with either slowness or weakness), and severe sarcopenia (low muscle mass with slowness and weakness) [115].

On the other hand, the proposed algorithm of the International Working Group is based on having a low whole body or appendicular fat-free mass in combination with poor physical functioning. In other words, sarcopenia with limited mobility would be an indication for therapeutic intervention [127].

Irrespective of the algorithm used, there are many ways to measure muscle mass, muscle strength, and physical performance of older individuals. To measure muscle mass, anthropometric measures, computed tomography (CT), magnetic resonance imaging (MRI), dual energy X-ray absorptiometry (DXA), and bio impedance analysis are some available options [115]. Because CT and MRI distinguish fat from other soft tissues in the body, they are considered to be the gold standard for muscle mass assessment especially in research. However, the high radiation, high cost, and limited accessibility make it less used in clinical settings [115].

Anthropometric measurement is the simplest and cheapest method to assess body composition. It is achieved by measuring the height, weight, skin folds, waist circumference, etc. Using the height and weight, the body mass index (BMI) can be calculated to determine if individuals are underweight, normal, overweight, or obese. Although BMI is correlated with body fat, it does not provide information about body composition [115] [138].

Bioelectrical Impedance is another method used to assess body composition and muscle mass. Based on the concept that water conducts electricity and fat does not, total body water, fat-free mass, fat mass, percentage of body fat and appendicular skeletal muscle mass measurements can be obtained. Gender and ethnic specific prediction equations have been modeled for adults and elderly, and reference values have been established [139] [140] [141] [142]. However, in this method, prediction equations are not always accurate, especially in overweight older adults [143].

Dual-Energy X-Ray Absorptiometry (DXA) is currently the most common and reliable technique to evaluate body composition. The whole body DXA provides fat and lean mass data [144]. However, there is more than one approach to interpret the results obtained by DXA. The two most adopted methods for assessing low muscle mass are the appendicular skeletal muscle

mass index and the residuals method. The appendicular skeletal muscle index is calculated by dividing the appendicular lean mass by height squared (ALM/h2). Low muscle mass is considered present if the calculated values are below certain established sex specific cutoffs [123] [145] [146]. Although it takes height into account, this method doesn't adjust for total body fat. The residuals method is based on calculating the sex specific residuals of the regression of ALM (kg) on height (m) and whole-body total fat mass (kg). Participants with residuals below the 20^{th} percentile are considered to be sarcopenic [146]. The Framingham study published an article comparing these different methods. They found that the residuals method predicted the mobility limitations in both men and women better than simply dividing by height squared [147]. This seems to be in accordance with the International Working Group definition which includes total fat mass in its sarcopenia definition.

Muscle strength can be measured by handgrip strength or knee flexion/extension [115]. Handgrip strength is a good measurement of muscle strength. Previous studies have shown that it correlates well with lower extremity muscle power, knee extension torque, and calf cross-sectional muscle area [148]. It has also been associated with ADL and mortality [149] [150]. To determine muscle weakness, the EWGSOP recommended cutoffs of 30 Kg and 20 Kg for men and women respectively [148]. On the other hand, the FNIH project recommends the usage of 26 kg and 16 kg for men and women respectively [126]. These cutoffs were determined based on the muscle strength data of nine collaborating studies: 1) Age, Gene/Environment Susceptibility-Reykjavik Study [151], 2) Boston Puerto Rican Health Study [152], 3) Clinical Trials [153], 4) Framingham Heart Study [154], 5) Health, Aging, and Body Composition Study [155] 6) Invecchiare in Chianti [156], 7) Osteoporotic Fractures in Men Study [157] , 8) Rancho Bernardo Study [158], 9) Study of Osteoporotic Fractures [100]. Muscle strength could also be assessed by

the knee flexsion/extension. Although used in research settings, this method is not adopted in clinical practice because special equipment is needed [115]. This approach allows for isometric and isokinetic measurement of strength. Furthermore, muscle power which has been shown to be a better predictor of functional activities than muscle strength could be measured [159] [160] [161]. Nonetheless, more studies are needed in older people to establish clinical cutoffs.

Physical performance can be measured by Short Physical Performance Battery (SPPB), usual gait speed, timed get-up-and-go test, and stair climb power test. SPPB and usual gait speed will be discussed. The SPPB assesses balance, gait, strength, and endurance. The SPPB is based on 4 components: stand with feet together, semi-tandem and tandem positions, time to walk 8ft, and chair stands [162]. The maximum score is 12 and sex specific cut-off points have been established [163]. SPPB is recommended by the international working group on sarcopenia [164].

Usual gait speed is another commonly used measurement to assess physical performance. Gait speed, especially over a 6 meter course, has been linked to disabilities, adverse health events, and mortality [163] [165] [166]. The European and the international working groups on sarcopenia use 8m/s and 1m/s cutoffs respectively to determine slowness.

1.2.4 Epidemiology

The prevalence of sarcopenia varies based on the definition. Nonetheless, few studies have dichotomized sarcopenia based on specific criteria in order to calculate sarcopenia prevalence. For instance, using a cut-off point of two SD for the appendicular skeletal muscle mass index, the prevalence of sarcopenia ranged between 13% and 24% in those aged 65 to 70 years, and over 50% in those older than 80years. For individuals above age 75%, men had a higher

prevalence (58%) compared to women (45%) [145]. When total body fat was taken into account by using the residuals method, a higher prevalence of severe sarcopenia was observed in women compared to men. Severe sarcopenia was defined as a skeletal muscle mass index two standard deviations below young adult values [167]. Also, functional impairment and disability was greater in sarcopenic women compared to sarcopenic men [146] [167].

Loss of muscle strength is correlated with the loss of muscle mass. Nonetheless, these two follow different patterns of decrease with age. The cross sectional area of the muscle decreases by 40% between ages 20 and 60 [168] [169] [170]. The muscle mass reduction is accelerated after the age of 50 [171]. Men usually experience larger decreases (14.8%) in appendicular lean mass compared to women (10.8%) [172]. These gender specific changes in muscle mass have been suggested to be hormonal in nature [173]. The decrease starts to be noticeable after the age of 30. Muscle mass decreases by 3 to 8% per decade, with acceleration in muscle loss after age 60 [174]. On the other hand, muscle strength decreases by 20 to 40% with age and can reach up to 50% in the oldest of the old [175] [176] [177] [178]. Men have greater decrease in muscle strength compared to women which is usually explained by the fact that men have higher baseline values. The decline in muscle mass has been associated with a decline in muscle strength. However, the strength decline is more rapid than the mass decline suggesting that there is a decrease in muscle quality as individuals age [124].

Studies looking at longitudinal changes in muscle strength and mass are lacking. Goodpaster et al. followed older adults for a duration of three years. Findings showed that white and black men experience a 3.4% and 4.1% decline in muscle strength respectively. On the other hand, there is a 2.6% and 3.0% decline in muscle strength for white and black women respectively. Annualized change in lean mass was about 1% in older adults irrespective of

gender or race. In another study, Newman et al. studied the changes in weight and lean mass. Findings showed that older persons lose both lean mass and fat mass with age. However, more lean mass was conserved compared to fat mass with changes in weight. Furthermore, more lean mass is lost with weight loss favoring sarcopenia [179].

Sarcopenia is linked to many health outcomes such as loss in functional capacity, loss of independence, and falls [110] [111]. In this review, the main consequence of sarcopenia we are interested in studying, is its effect on the bone strength. Therefore, the common etiologies of muscle and bone deterioration as well as the crosstalk between these two tissues will be elucidated in the next section.

1.3 MUSCLE BONE ETIOLOGIES

Muscles and bones are neighboring tissues with close ties and are both derived from a common mesenchymal precursor [2]. Muscles contribute to bone development during embryogenesis [180]. Bones have been shown as well to play a role in fetal myoblast survival and limb muscle growth[181]. This crosstalk between muscles and bones does not occur only during fetal development but is a lifelong process [3]. Throughout life, muscles and bones seem to follow the same decreasing pattern. The loss of muscle mass and bone mass has been shown to be coupled and part of the same functional unit [182]. However, the etiologies behind this synchronized decrease in the bone and muscle tissues are not very well understood. Some of these risk factors are believed to be genetic in nature whereas others physiological and hormonal. Pleiotropy, mechanotransduction, and endocrine roles are the main etiologies responsible for the coordinated and progressive deterioration of the musculoskeletal system throughout life [3].

1.3.1 Pleiotropy

It is believed that genes could play a role in the simultaneous deterioration of muscles and bones. Efforts are being made to discover these pleiotropic genes with the hope of treating osteoporosis and sarcopenia together. The pleiotropic effect on the musculoskeletal system could be direct or indirect [183]. Direct pleiotropy is when one gene affects both bone and muscle phenotype. However, in most instances, the pleiotropy is indirect and impacts muscles and bones through systemic control factors[183].

Bone mass and geometry have been previously linked to genetic determinants [184-186]. Furthermore, muscle mass and strength has been shown to be under genetic control [187]. After finding a high genetic correlation between bone geometric parameters and muscle mass, scientists became interested in discovering genes that could explain the synchronized deterioration in bones and muscles [188].

Myostatin, coded by the Growth Differentiation factor gene (GDF8), is a member of the Transforming Growth Factor (TGF-B) superfamily. During muscle disuse, myostatin is secreted from skeletal muscle cells into the blood and act on neighboring tissues [189]. This systemic factor influences simultaneously bone and muscle metabolism. In animal models, myostatin deficiency was associated with greater cortical bone mineral content and with a hypermuscular phenotype [190].

Vitamin D receptor (VDR) gene is another pleiotropic gene that affects the musculoskeletal system. VDR is known to regulate bone metabolism and homeostasis. In addition to its action on the bones, few studies demonstrated that VDR is expressed in skeletal muscles. By binding to these receptors, vitamin D was shown to increase muscle strength[183]. The effect of the single-nucleotide polymorphisms (SNPs) within this gene were associated with

decreased vertebral area, increased risk of vertebral fractures, femoral neck width narrowing, and increased lean mass and muscle strength [191] [192] [193] [194].

The Insulin-like Growth Factor (IGF-1), coded by the IGF-1 gene, is a systemic hormone involved in the development and repair of bones. The mechanical load of muscles on bones results in an increase in IGF-1 leading to osteocytes differentiation and bone formation [195]. Therefore, with age, the decrease in IGF-1 leads to attenuated response of the bones to the mechanical load of muscles. Evidence of IGF-1 effect on cortical bones has been well established. The action of IGF-1 is not unidirectional. It also induces muscle hypertrophy by acting on its receptor [196].

Low density lipoprotein receptor related protein 5 (LRP5), coded by the pleotropic gene wnt, is another systemic factor that is linked to both bones and muscles. In addition to being associated with BMD in humans, LRP5 mutations in mice resulted in a greater skeleton strength [197] [198] [199]. Furthermore, the LRP5 knockout mice demonstrated a lack of response to mechanical stimuli [200]. Similarly to the growth hormone, LRP5 may play a role in the mechanical response of bones to muscles. Whereas IGF-1 plays a role in sensing the mechanical load of muscle on bones, LRP5 consists more of responding to the load by producing new periosteal bone [200]. Mechanotransduction will be discussed further in the next section.

1.3.2 Mechanotransduction

The bone is an organ that senses the mechanical pressure of muscles. The muscle load is important not only to maintain the strength of the bones but also for fracture repair [183] [201]. The anabolic effect on the bones could be explained by a direct process (mechanotransduction) or indirect one (endocrine regulation such as IGF1 and LRP5 discussed earlier) [2]. The pressure

of the muscles on the bones is sensed by osteocytes. The translation of this mechanical signal to a cellular one is known as mechanotransduction. Osteocytes form a network of cells which are interconnected. This network of cells have the capability of sensing the load of muscles [11]. As a result, osteocytes send signals to recruit other cells facilitating the bone remodeling as well as matrix formation [202, 203]. The osteocytes also stimulate the expression of molecules such IGF-1 as previously discussed [204, 205]. Also, osteocytes have been shown to regulate osteoblast and osteoclast activities [206, 207]. Initially, studies conducted on tennis players have shown that the dominant arm had a higher BMD [208-210]. This fact intrigued scientists, and subsequent studies were conducted showing associations between muscle mass and strength, and BMD. As discussed in the sarcopenia section, muscle mass and strength decrease throughout life. This decrease is believed to result in a concomitant decrease in BMD and quality.

In fact, a decrease in muscle mass and strength have been previously associated with low BMD[211] [212] [213] [214] [215] [216]. Other studies also showed that older individuals with sarcopenia had poorer quality of bones [217] [218].

1.3.3 Endocrine roles

Muscles and bones are endocrine organs that secrete paracrine hormones [3]. Humoral factors, such as IGF-1 and FGF-2, are believed to play a major role in the muscle bone cross talk. These growth factors secreted by the muscle have receptors on the periosteum which is located at the muscle bone interface [219]. Other myokines could also impact indirectly the bones. For instance, interleukin 6 (IL-6) and leukemia inhibitory factor (LIF) have been previously associated with resorption and formation of bones respectively. Il-6 is a cytokine produced at high levels by the muscles, especially after resistance exercise [220]. Initially, it was believed

that the mechanism by which Il-6 impacts is through insulin production. Insulin was thought to bind to receptors on the osteoblasts and blunt the resorptive activity of PTH [221] [222]. However, more recent in vitro studies showed that Il-6 inhibits IGF-1 production and consequently, decrease bone formation [223].

Growth hormone (GH) and IGF-1 discussed in the pleiotropy section, exert important anabolic effects on both muscles and bones. With age, the GH/IGF-1 signaling pathway decreases in efficiency. This results in a decrease in muscle size and strength, a reduction in protein synthesis, and increased cell apoptosis. Furthermore, abnormalities in the GH/IGF-1 signaling leads to a decrease bone formation due to impaired osteoblasts and bone cell apoptosis (Figure 3) [224].

Furthermore, some animal studies have found that the growth factor Indian hedgehog (Ihh) produced by chondrocytes is responsible for fetal myoblast survival and limb muscle growth Also, myogenic progenitor cells and muscle satellite colonization have the ability to differentiate into chondrocytes or osteoblast. [181]. This shows that the cross talk between muscles and bones starts early during fetal development and continues throughout life. Muscles and bones also act as endocrine target organs, which are under the influence of similar hormones such as testosterone and estrogen. Estradiol is the main sex steroid responsible for bone resorption in men and women, and is also responsible for enhancing the muscle contractions on bones [225] [226]. Androgens affect the muscle mass and strength as well as the trabecular bone formation [227]. Therefore, as men and women age, the decrease in testosterone and estrogen may put men and women at a higher risk for sarcopenia and osteoporosis.

The age-related decrease in hormones, the mechanotransduction effect of sarcopenia on bones, and pleiotropy are important etiologies of sarcopenia and osteoporosis combined. More research is needed in this field to elucidate the exact mechanisms responsible for both conditions.

Common risk factors to both osteoporosis and sarcopenia are not known. Furthermore, the effect of both osteoporosis and sarcopenia on fracture risk is unclear. The aims of this dissertation is to elucidate these gaps in order to have a better understanding of the common etiologies of sarcopenia and osteoporosis.

2.0 SPECIFIC AIMS

2.1 IMAGING DIAGNOSTIC TOOLS

2.1.1 Specific aim 1

We aim to: 1) assess the risk of various types of fractures in older men by areal and volumetric BMD at multiple sites and 2) compare the fracture predictability of the areal and volumetric femoral neck and spine BMD

2.2 MUSCLE BONE CROSSTALK

2.2.1 Specific aim 2

We aim to: 1) determine the association between appendicular lean mass and measures of skeletal size, density, and strength, and 2) study the association between grip strength, and peripheral and central QCT skeletal parameters and 3) compare QCT parameters of participants across leg power quartiles

2.2.2 Specific aim 3

We aim to show that:

1) men and women with sarcopenia alone are at higher risk of having non-spine fractures compared to normal men and that 2) the combined effect of low bone mass and sarcopenia puts older men and women at a much higher risk of having non spine fractures.

The Osteoporotic Fractures in Men (MrOS) study will be used to answer the first two aims. Data from the Study of Osteoporotic Fractures (SOF) and MrOS will be used to answer the third aim.

3.0 PAPER1: AREAL AND VOLUMETRIC BONE MINERAL DENSITY AND RISK OF MULTIPLE TYPES OF FRACTURE IN OLDER MEN

Didier Chalhoub, MD MPH[1]; Eric S. Orwoll, MD [2]; Peggy M. Cawthon, PhD MPH[3]; Kristine E. Ensrud, MD MPH[4]; Robert Boudreau, PhD[1]; Susan Greenspan, MD[1]; Anne B. Newman, MD MPH[1]; Joseph Zmuda, PhD[1] Douglas Bauer, MD[5]; Steven Cummings, MD[5]; Jane A. Cauley, DrPH[1]

for the Osteoporotic Fractures in Men (MrOS) Study Research Group.

[1]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA; [2]Oregon Health and Sciences University, Portland, OR; [3]California Pacific Medical Center, San Francisco, CA; [4]University of Minnesota, Minneapolis, MN; [5]University of California Medical Center, San Francisco, CA

Contact information (emails):

Didier Chalhoub: dic14@pitt.edu

Eric S. Orwoll: orwoll@ohsu.edu

Peggy M. Cawthon: pcawthon@sfcc-cpmc.net

Kristine E. Ensrud: ensru001@tc.umn.edu

Robert Boudreau: BoudreauR@edc.pitt.edu

Susan Greenspan: greenspn@pitt.edu

Anne Newman: NewmanA@edc.pitt.edu

Joseph Zmuda: zmudaj@edc.pitt.edu

Douglas Bauer: dbauer@psg.ucsf.edu

Steven Cummings: scummings@sfcc-cpmc.net

Corresponding author: Jane A. Cauley, DrPH, University of Pittsburgh, Graduate School of Public Health, Department of Epidemiology, 130 DeSoto Street, Crabtree A510, Pittsburgh, PA 15261. jcauley@edc.pitt.edu; tele, 412-624-3057; fax, 412-624-7397

3.1 ABSTRACT

Although many studies have examined the association between low bone mineral density (BMD) and fracture risk in older men, none have simultaneously studied the relationship between multiple BMD sites and risk of different types of fractures. Using data from the Osteoporotic Fractures in Men study, we evaluated the association between areal BMD (aBMD) by dual-energy X-ray absorptiometry (DXA) and volumetric BMD (vBMD) by quantitative computed tomography (QCT) measurements, and different types of fractures during an average of 9.7 years of follow up. Men answered questionnaires about fractures every 4 months (>97% completions). Fractures were confirmed by centralized review of radiographic reports; pathological fractures were excluded. Risk of fractures was assessed at the hip, spine, wrist, shoulder, arm, rib/chest/sternum, pelvis/coccyx, leg, hand/finger, skull/face, ankle/foot/toe, and any non-spine fracture. Age and race adjusted Cox proportional-hazards modeling was used to assess the risk of fracture in 3301 older men with both aBMD (at the femoral neck (FN) and lumbar spine) and vBMD (at the trabecular spine and FN, and cortical FN) measurements, with hazard ratios (HRs)

expressed per standard deviation (SD) decrease. Lower FN and spine aBMD were associated with an increased risk of fracture at the hip, spine, wrist, shoulder, rib/chest/sternum, arm, and any non-spine fracture (statistically significant HRs per SD decrease ranged from 1.24 – 3.57). Lower trabecular spine and FN vBMD were associated with increased risk of most fractures with statistically significant HRs ranging between 1.27 and 3.69. There was a statistically significant association between FN cortical vBMD and fracture risk at the hip (HR=1.55) and spine sites (HR=1.26), but no association at other fracture sites. In summary, both lower aBMD and vBMD were associated with increased fracture risk. The stronger associations observed for trabecular vBMD than cortical vBMD may reflect the higher rate of bone turnover in the trabecular compartment.

3.2 INTRODUCTION

With the increase in the average age of the world population, the number of osteoporotic fractures likely will increase [81]. Worldwide, the total disability adjusted life years (DALYs) lost attributed to fractures was about 58 million in 2008 [228].

Mortality and morbidity are two major consequences of osteoporosis, primarily due to hip fractures [65]. However, the public health impact of osteoporotic fractures is not limited to hip fractures. In Medicare enrollees, while hip fractures had the highest excess cost, many types of fractures were associated with higher health care expenditures[65] [229]. Low bone mineral density (BMD) is an established risk factor for fractures. Indeed, low BMD has been linked to most fractures in women except for the heel, ankle, and face [230]. To our knowledge, a similar analysis has not been carried out in older men. We previously showed that low areal BMD

(aBMD) was related to all non-spine fractures and hip fractures in older men [231] [232]. Furthermore, Black et al. reported the relationship between trabecular and cortical FN volumetric BMD (vBMD) and hip fracture [52]. However, the association between multiple measures of BMD and risk of different types of fractures remains unexplored.

Thus, the purpose of the current analysis was to assess the risk of multiple types of fractures in older men by aBMD and vBMD at multiple skeletal sites. A second aim was to compare fracture predictability of different BMD measurements.

3.3 MATERIALS AND METHODS

The Osteoporotic Fractures in Men study (MrOS) is a multicenter prospective cohort study designed to identify risk factors for osteoporosis and osteoporotic fracture. This study consists of 5,994 older men recruited from six sites across the United States (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA) from March 2000 to April 2002 [233] [157]. To be eligible, men needed to be age 65 years or older, be able to walk without assistance from another person, and have reported no bilateral hip replacement. Human subjects' approval was obtained at all sites with written informed consent obtained from all participants. The first 650 men and all nonwhite men enrolled at each clinical site were referred for quantitative computer tomography (QCT) scans of the hip and lumbar spine as part of their baseline visit, for a total of 3786 men (63% of the MrOS cohort). Out of these participants, 134 had unusable QCT images because of insufficient number of images, interference from metal, calibration standard not visible, or unrecorded cause. From the remaining participants, 3,305 had complete aBMD and vBMD measurements. We restricted

analyses to 3,301 after excluding 4 participants with pathological fractures. Except for a higher proportion of minorities (12.9% vs 10.5%), the characteristics of men in the vBMD subset were similar to the overall population of men.

Areal Bone Mineral Density (aBMD) measurement

Femoral neck (FN) BMD (g/cm^2) and lumbar spine (LS) (L1-L4) BMD (g/cm^2) were measured using dual-energy X-ray absorptiometry (DXA) with the Hologic QDR 4500 (Bedford, MA). Details of the measurement and densitometry procedures have been published elsewhere [234] [231]. Standardized procedures for positioning the participants and analyzing the scans were followed for all scans. All DXA operators were centrally certified based on an evaluation of their scanning and analysis techniques. Cross-calibration studies performed before the baseline MrOS visit found no linear differences across the scanners, and the maximum percentage difference in mean total LS BMD between scanners was 1.4%. To assess longitudinal performance of the scanners, an anthropometric spine phantom was scanned daily and a hip phantom weekly at each clinical center. The right hip was scanned unless there was a fracture, implant, hardware, or other problem, in which case the left hip was scanned. The T-score was calculated using the National Health and Nutrition Examination Survey III reference database [28]. Young Caucasian women were used as the reference population as recommended by the International Society for Clinical Densitometry (ISCD) [29].

Volumetric BMD measurement

Volumetric BMD (g/cm^3) of the LS and hip regions was measured using QCT [53, 235]. As previously described, images were acquired using a GE Prospeed (Birmingham), GE Hispeed Advantage (Minneapolis), Philips MX-8000 (Palo Alto), Siemans Somatom +4 (Pittsburgh),

Philips CT-Twin (Portland), Toshiba Acquilion (Portland) site, or Picker PQ-5000 (San Diego). All QCT scans were transferred to the University of California at San Francisco for processing and central review. Image processing was performed using published methods [53, 236]. Each participant's scan included a calibration standard of three hydroxyapatite concentrations (150, 75, and 0 mg/cm $^{3;}$ Image Analysis). Images were converted from the native scanner Hounsfield Units (HU) to equivalent concentration (g/cm3) of calcium hydroxyapatite contained in the calibrations standard.

QCT measurement of the LS was obtained using an anatomical region 5 mm above the L1 superior endplate to 5 mm below the L2 inferior endplate. LS images were acquired using a setting of 120 kVp, 150 mA, 1-mm slice thickness, and 512 x 512 matrix in spiral reconstruction mode. To derive trabecular vBMD, previously described analytical techniques were employed to orient the vertebrae so that the vertebral cross-sections were obtained in a plane parallel to the two endplates and to segment the vertebral body from the scans. Vertebral trabecular BMD was determined in a region containing most of the trabecular bone in the vertebral body. This QCT protocol has been described previously [237].

To measure vBMD at the femoral neck, a QCT scan of the pelvic region (from the femoral head to 3.5 cm below the lesser trochanter) was acquired at settings of 80 kVp, 280 mA, 3-mm slice thickness, and 512 × 512 matrix in spiral reconstruction mode [235].

Regions of interest (ROI) in the left proximal femur were identified in QCT images reformatted along the neutral axis of the FN. The periosteal boundary of the femur was determined with a threshold-based region growing algorithm. Using this boundary, the cross-sectional area in each slice along the neutral axis of the FN between the proximal FN and the lateral edge of the trochanter was calculated, and the minimum and maximum areas were

determined. The FN ROI was defined as the portions of the neck extending from the slice with minimum cross-sectional area (medial boundary) to a point 25% of the distance toward the maximal cross-sectional area. Integral volume of the ROI was computed as the total volume within the periosteal boundary. A trabecular volume of the ROI was obtained by applying an erosion process to the integral volume to retain the same shape in a region fully contained within the medullary space. The cortical volume was then defined by applying a threshold of 0.35 g/cm^3 to all voxels between the periosteal boundary and the outer boundary of the trabecular volume. Volumetric BMD for trabecular and cortical compartments was computed over all voxels in the respective volumes.

Clinical fractures ascertainment

Questionnaires were mailed to participants every 4 months to identify fractures, with more than 97% completion. If a fracture was reported, the participants were contacted to obtain a copy of the radiographic report. All clinical fractures were confirmed by central review of radiographic report during an average of 9.4 years (0-13.7) from study enrollment until February 2014. Clinical spine fractures were confirmed by radiologist review of clinical images (x-ray, MRI, etc.) and in comparison to study lateral spine radiographs collected at the baseline visit. Fractures due to any level of trauma (minimal, moderate, and severe) were included since they have been previously associated with low BMD [238]. Multiple fracture sites were studied including hip, spine, wrist, shoulder, pelvis/coccyx, rib/chest/sternum, skull/face, hand/finger, ankle/foot/toe, arm, and leg.

Statistical methods

The analytical cohort consisted of 3301 older men with both complete aBMD and vBMD measurements. Age and race adjusted Cox proportional hazards modeling with 95% confidence intervals (CI) was used to calculate hazard ratios (HR) per one standard deviation (SD) decrease in aBMD and vBMD. A logistic regression was used to study receiver operating characteristic (ROC) curves of different BMD measurements for the major osteoporotic fractures which consist of the hip, spine, shoulder, and wrist. The ability of BMD measurements to predict fracture risk was assessed by the area under the curve (AUC) or C statistics. Statistical comparison was conducted between different AUC curves to determine which one most strongly predicts fracture risk. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

3.4 RESULTS

The average age of the men was 73.5 years with a mean FN T-score of – 0.61 (Table 1). Over a mean of 9.7 years, 580 men experienced 748 fractures, 305 of which were major osteoporotic fractures. On average, men were overweight and primarily white race.

BMD and Fracture risk

Lower LS and FN aBMD were associated with a statistically significantly higher risk of fracture at the hip, spine, wrist, shoulder, rib/chest/sternum, and arm (Table 2). The HRs ranged from 1.31 (rib/chest/sternum) to 2.74(hip) per one SD decrease in FN aBMD, and between 1.24 (rib/chest/sternum) and 3.56 (spine) per one SD decrease in total spine aBMD. The associations with ankle/foot/toe (spine), hand/finger (FN), pelvis/coccyx (spine) were borderline significant.

There was no relationship between aBMD, and leg and skull/face fractures. For all non-spine fractures, one SD decrease in LS aBMD and FN aBMD was associated with a 31% and 53%, respectively, increase in fracture risk.

Trabecular vBMD of both the LS and FN were also related to many fractures, Table 2. In particular, one SD decrease in trabecular vBMD of the LS was associated with almost a 4-fold increase in clinical spine fractures. Lower trabecular vBMD at both the spine and hip was also associated with a higher risk of hip, wrist, shoulder, rib/chest/sternum, ankle/foot/toe, arm and leg fractures. The association between trabecular vBMD at the LS and FN and any non-spine fractures was similar in magnitude to the association between aBMD and any non-spine fracture. In contrast, FN cortical vBMD was statistically significantly associated with hip and clinical spine fractures, but there was no association between cortical vBMD and fractures at other fracture locations. There was a modest relationship between FN cortical vBMD and any non-spine fracture, HR=1.13 (1.04, 1.24)

There was evidence of site specificity where a strong relationship was found for LS aBMD and spine fractures (HR=3.57) and between FN aBMD and hip fractures (HR=2.74). Site specificity was present as well between LS vBMD and spine fracture (HR=3.69). The effect size was the highest for spine fracture and lower for other fracture types. On the other hand, specificity between FN vBMD and hip fracture was not as robust since the calculated effect sizes were similar if not identical, such as in the case of clinical spine (Table 2).

The results of the AUC comparisons are shown in Table 3. FN aBMD (AUC=0.76) had a higher predictability of hip fractures compared to cortical FN vBMD (AUC=0.69). Furthermore, FN aBMD had a better predictability of hip fractures compared to trabecular FN vBMD (AUC=0.72). Nonetheless, there was no difference in AUCs between trabecular and cortical FN

vBMD for hip fractures. Trabecular vBMD of LS had better predictability of spine fractures compared to spine aBMD.

3.5 DISCUSSION

The risk of most types of fractures is higher with lower areal and volumetric BMD. Stronger associations were seen with trabecular vBMD compared to cortical vBMD. Furthermore, there was high specificity between BMD site and fracture type, especially for aBMD. Several fracture types were for the most part unrelated to low BMD, including fractures that occurred at the hand or finger; pelvis or coccyx; skull or face. Results showed that FN aBMD is a better predictor of hip fractures compared to trabecular and cortical FN BMD. However, trabecular vBMD of LS had better predictability of spine fractures compared to areal spine BMD.

Both low aBMD and vBMD were associated with an increased risk of different types of fractures. A previous study conducted in women has shown an increase of almost all types of fractures with low aBMD [230]. With the exception of spine fractures, which have an apparently stronger association in men (HR=3.57 in men, HR=2.06 in women for one SD decrease in LS aBMD), the risks of different type of fractures were roughly the same across gender.

Areal BMD is a strong independent risk factor for fractures in men[67]. Our results are consistent with previous MrOS reports which found strong associations between hip BMD and nonvertebral fractures (especially hip) in older men [232] [239]. The current analysis extends these findings to most fracture types.

On the other hand, the relationship between trabecular and cortical vBMD with fracture risk is less well understood. We showed that trabecular vBMD of LS and FN were both

associated with many types of fractures. In contrast, cortical vBMD was related to hip and spine fractures only. Although hip fractures are attributed to both cortical and trabecular bone loss, very few studies have examined the association between vBMD and hip fractures [52] [93]. Our results for hip fracture are consistent with an earlier MrOS report with shorter follow-up.

The stronger associations observed for trabecular vBMD compared to cortical vBMD may be explained by the higher rate of bone turnover in the trabecular compartment compared with cortical compartment. Trabecular and cortical compartments have different metabolic activities with the former being more active contributing to greater rates of bone loss [93]. With age, trabeculae become thinner, the number of trabeculae decreases, and trabecular spacing increases. The cortical compartment also undergoes age-related changes such as increase in porosity, but we were unable to capture cortical porosity with our measurements [240]. Although both compartments demonstrate microarchitecture changes, the different effect sizes may be explained by the trabecular and cortical bone-specific proportions. For instance, the vertebral body consists of largely trabecular bone with a thin layer of cortical bone [93]. The majority of the vertebral body strength is maintained by trabecular bone. Therefore, this may explain why trabecular BMD was more highly associated with spine fractures compared to cortical BMD.

Cortical FN BMD was associated with only hip and spine fractures perhaps because cortical bone at least at the hip plays a key role at this site relative to the other fracture locations. Yoshikawa et al. demonstrated that the loss of bone occurs more on the superior aspect of the FN [241]. At the FN, the superior region of the cortical bone is thinner compared to its inferior region. With age, thinning of the superior region occurs, and compromises the capacity of the femur to absorb energy independently of osteoporosis. The thinning of this region with age may reflect a lower mechanical load. Since most hip fractures result from a fall, the impact on the hip

reverses the stress pattern leading to increase in compressive stress on the superior neck which is mainly cortical bone [242]. This may explain why low cortical FN was associated with an increased risk of hip fractures. Although loss of cortical bone occurs at other sites as well, the biomechanics of fractures as well as the proportion of cortical bone in individual bones may explain why we did not detect statistically significant associations with other fracture sites. Risk of spine fractures was also higher with lower cortical FN BMD. Although the trabecular bone is known to constitute the majority of the vertebra, the cortical thickness influences vertebral strength mostly when the trabecular bone volume gets low [243-245]. Since our cohort consists of elderly men with low trabecular spine BMD (0.11 g/cm^3), it is likely that the cortical bone influenced the vertebral strength and hence, spine fracture risk.

The risk of hip fracture was higher with low FN aBMD compared to the trabecular and cortical vBMD. Indeed, FN aBMD was a better predictor of hip fractures compared to trabecular and cortical FN BMD. This finding could be explained by the fact that areal FN aBMD is not compartment specific and comprises both trabecular and cortical bone. Areal BMD is known to highly correlate with and account for 60-70% of the bone strength [42, 246]. In agreement with our findings, a previous study showed that the QCT parameters' prediction of hip fracture was not improved compared to aBMD [52]. On the other hand, our findings showed that trabecular spine BMD was a better predictor of spine fractures compared to areal spine BMD. In their study, Wang et al also demonstrated that vBMD improved vertebral fracture risk assessment compared to aBMD [247]. Here, although areal spine comprises both compartments, the fact that the trabecular proportion of the vertebrae is much greater than the cortical proportion may explain the higher predictability of the trabecular vBMD at the LS. Furthermore, the artifacts seen on DXA scans may explain the lower predictability of areal spine BMD.

There are several strengths to our study. MrOS is a multicenter prospective study examining potential risk factors for fractures in a large population of older men. We were able to examine the association of both aBMD and vBMD including both the trabecular and cortical compartments and fractures risk in the same group of men. However, there are also several limitations. Most importantly, the men were primarily Caucasians and our results may not be generalizable to men of other race/ethnic groups. In addition, the number of specific fractures varied by site limiting our power to detect an association for fracture locations that were uncommon. To assess predictability of fractures, we used the widely used method of area under the curve. However, there are other methods based on the integrated sensitivity and specificity, and on reclassification tables that may provide additional information compared to AUC [248].

To conclude, low aBMD and trabecular vBMD were associated with an increased risk of most fractures. There was no evidence that trabecular vBMD was superior to aBMD in predicting hip fractures, which was not the case for spine fractures. Although QCT provides a compartment specific assessment of bone, it has several disadvantages such as its high cost, radiation exposure, and not being readily clinically accessible. With the exception of spine fractures, QCT does not appear to add additional information to fracture risk assessment once aBMD from DXA is known. Future studies might be needed to understand further the advantage of QCT over DXA in predicting spine fractures. In addition, screening for osteoporosis using DXA may help in preventing multiple types of fractures.

3.6 TABLES AND FIGURES

Table 3.6.1. Baseline characteristics

Characteristics	Values	Range
Age (yrs)	73.5(5.9)	65-100
BMI (kg/m^2)	27.3 (3.8)	17.2 – 50.7
Race, n(%)		
White	2,878 (87.7)	
African American	170 (5.2)	
Asian	121 (3.7)	
Hispanic	91 (2.8)	
Other	41(1.2)	
Previous fracture, n(%)	1791 (54.3)	
Areal BMD (g/cm^2)		
Total spine	1.07 (0.19)	0.51-2.10
Total hip	0.96 (0.14)	0.53-1.45
Femoral neck	0.78 (0.13)	0.35-1.49
Femoral neck T-score	-0.61 (1.06)	-4.25-5.27
Volumetric BMD (g/cm^3)		
Femoral neck		
Cortical bone	0.53 (0.06)	0.33-0.93
Trabecular bone	0.07 (0.04)	-0.06-0.29
Total femur		
Cortical bone	0.52 (0.05)	0.35-0.81
Trabecular bone	0.10(0.04)	-0.01-0.25
Total spine		
Trabecular bone	0.11 (0.04)	0.01-0.35

Table 3.6.2. Areal and volumetric BMD and risk of various types of fractures (FX): age and race adjusted hazard ratios (HR) and 95% confidence intervals (CI) HR per one SD decrease in BMD

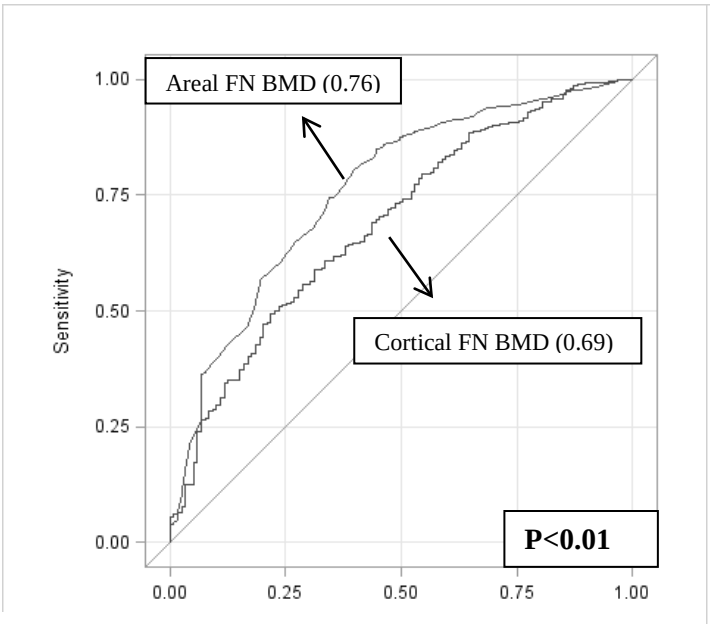
		Areal BMD		**Volumetric BMD**		
	N of FX	Total spine	Femoral neck	Trabecular spine	Cortical FN	Trabecular FN
Hip	119	**1.29 (1.07, 1.56)**	**2.74 (2.19, 3.42)**	**1.80 (1.43, 2.26)**	**1.55 (1.28, 1.87)**	**1.74 (1.41, 2.13)**
Clinical Spine	99	**3.57 (2.78, 4.58)**	**1.95 (1.54, 2.47)**	**3.69 (2.78, 4.90)**	**1.26 (1.02, 1.55)**	**1.74 (1.39, 2.18)**
Wrist	46	**1.43 (1.04, 1.97)**	**1.82 (1.30, 2.55)**	**1.46 (1.04, 2.05)**	1.28 (0.95, 1.72)	**1.74 (1.25, 2.43)**
Shoulder	41	**1.63 (1.17, 2.28)**	**1.88 (1.31, 2.70)**	**1.73 (1.18, 2.54)**	1.14 (0.83, 1.56)	**1.46 (1.05, 2.04)**
Rib/chest/sternum	141	**1.24 (1.04, 1.48)**	**1.31 (1.09, 1.57)**	**1.27 (1.05, 1.54)**	1.05 (0.88, 1.24)	**1.26 (1.06, 1.51)**
Ankle/foot/toe	91	1.21 (0.97, 1.51)	1.18 (0.94, 1.47)	**1.35 (1.06, 1.73)**	0.99 (0.80, 1.22)	**1.26 (1.01, 1.58)**
Arm	55	**1.68 (1.25, 2.27)**	**1.55 (1.14, 2.09)**	**1.75 (1.26, 2.44)**	1.09 (0.83, 1.43)	**1.35 (1.01, 1.81)**
Hand/finger	52	1.20 (0.89, 1.60)	1.30 (0.97, 1.76)	0.94 (0.71, 1.24)	1.08 (0.82, 1.43)	1.28 (0.95, 1.73)
Leg	43	1.22 (0.88, 1.68)	1.32 (0.94, 1.84)	**1.56 (1.08, 2.25)**	1.06 (0.78, 1.44)	**1.54 (1.10, 2.16)**
Pelvis/coccyx	34	1.38 (0.96, 1.99)	1.11 (0.78, 1.59)	1.45 (0.97, 2.17)	0.86 (0.62, 1.20)	1.29 (0.90, 1.85)
Skull/face	27	1.17 (0.78, 1.75)	1.09 (0.73, 1.63)	0.91 (0.61, 1.34)	1.08 (0.73, 1.59)	1.06 (0.71, 1.57)
Any non-spine fracture*	524	**1.31 (1.19, 1.43)**	**1.53 (1.38, 1.68)**	**1.39 (1.26, 1.54)**	**1.13 (1.04, 1.24)**	**1.34 (1.22, 1.47)**

Table 3.6.3. Age and race adjusted area under the curve (AUC) comparisons for all types of fractures

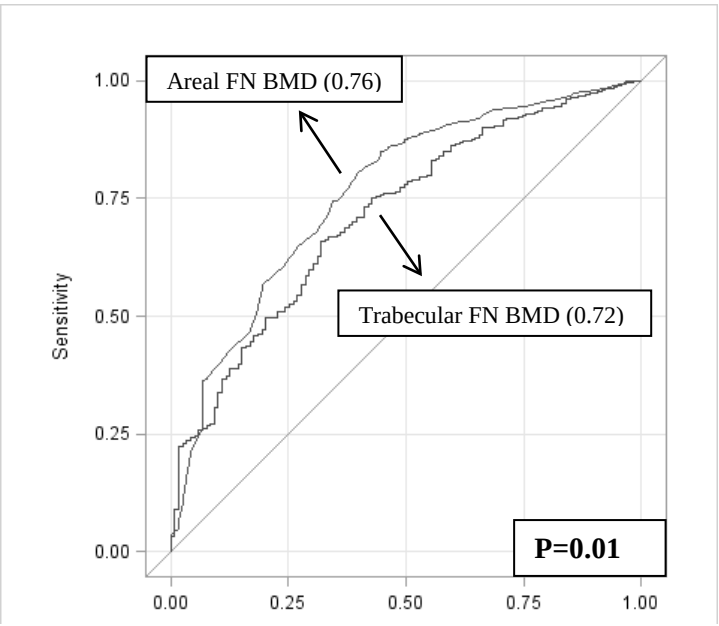
		Areal BMD		Volumetric BMD			
	N of FX	Total spine	Femoral neck	Trabecular spine	Cortical FN	Trabecular FN	p-value
Hip	119	0.67	0.76	0.71	0.69	0.72	a,b,d,e,f,g,
Clinical Spine	99	0.72	0.70	0.79	0.63	0.69	b,c,e,f,h,i,j
Wrist	46	0.51	0.58	0.59	0.57	0.64	d
Shoulder	41	0.74	0.75	0.75	0.72	0.74	
Rib/chest/sternum	141	0.62	0.59	0.61	0.59	0.60	
Ankle/foot/toe	91	0.59	0.58	0.60	0.59	0.62	
Arm	55	0.64	0.60	0.66	0.60	0.62	
Hand/finger	52	0.57	0.58	0.57	0.58	0.59	
Leg	43	0.58	0.61	0.64	0.59	0.65	
Pelvis/coccyx	34	0.69	0.66	0.68	0.66	0.67	
Skull/face	27	0.59	0.62	0.59	0.58	0.59	f
Any non-spine fracture*	524	0.60	0.61	0.62	0.59	0.62	b,d,f,h,j

Significant with $p<0.05$: **a** total spine vs femoral neck, **b** total spine vs trabecular spine, **c** total spine vs cortical FN, **d** total spine vs trabecular FN, **e** femoral neck vs trabecular spine, **f** femoral neck vs cortical FN, **g** femoral neck vs trabecular FN, **h** trabecular spine vs cortical FN, **i** trabecular spine vs trabecular FN, **j** cortical FN vs trabecular FN

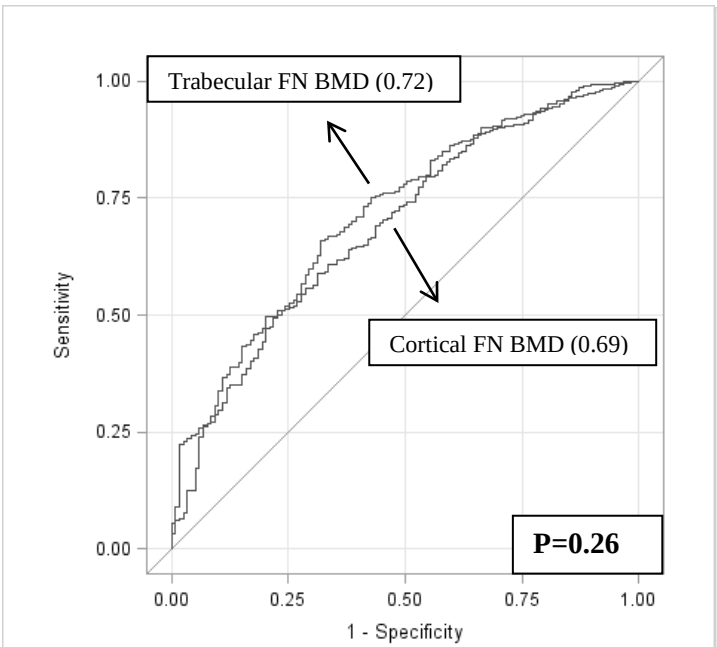
a) HIP FRACTURE



b) HIP FRACTURE



c) HIP FRACTURE



d) SPINE FRACTURE

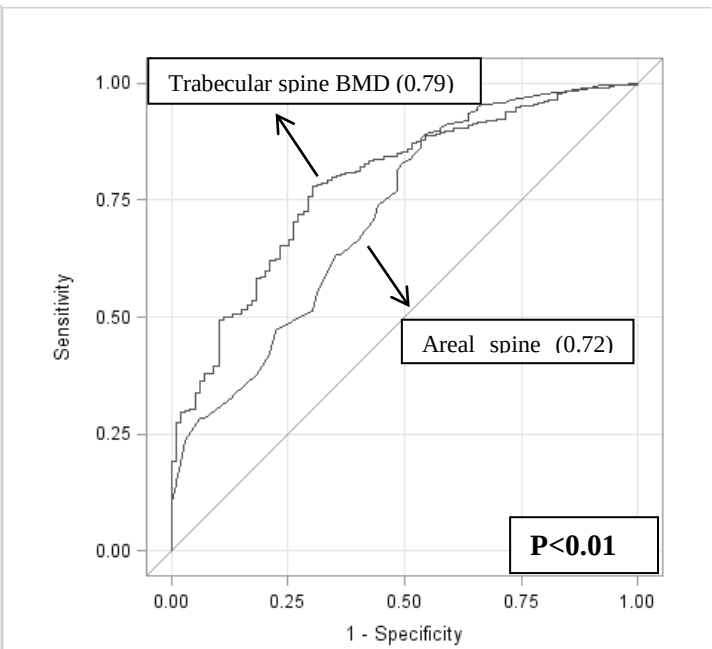


Figure 3.6.1. Receiver Operating Characteristic (ROC) curves comparisons of hip and spine fractures

4.0 PAPER 2: THE ASSOCIATION BETWEEN LEAN MASS, MUSCLE STRENGTH AND POWER, AND SKELETAL SIZE, DENSITY AND STRENGTH OF OLDER MEN

Didier Chalhoub, MD MPH[1]; Robert Boudreau, PhD[1]; Susan Greenspan, MD[1]; Anne Newman, MD MPH[1]; Joseph Zmuda, PhD[1]; Andy Hoffman, MD[2] ; Nancy Lane, MD[3]; Marcia Stefanick, PhD[2] ; Elizabeth Barrett-Connor, MD[4]; Tien Dam, MD[4,5]; Peggy Cawthon, PhD MPH[6]; Eric Orwoll, PhD[7]; Jane A. Cauley, DrPH[1]

for the Osteoporotic Fractures in Men (MrOS) Study Research Group.

[1]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA; [2]Stanford University School of Medicine, CA; [3]Department of Internal Medicine, University of California, Davis School of Medicine; [4]Division of Epidemiology, Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA; [5]Division of Geriatrics and Aging, Columbia University, New York, NY; [6]California Pacific Medical Center, San Francisco, CA; [7]Oregon Health and Sciences University, Portland, OR;

Contact information emails:

Didier Chalhoub: dic14@pitt.edu

Robert Boudreau: BoudreauR@edc.pitt.edu

Susan Greenspan: greenspn@pitt.edu

Anne Newman: NewmanA@edc.pitt.edu

Joseph Zmuda: zmudaj@edc.pitt.edu

Andy Hoffman: arhoffman@stanford.edu

Nancy Lane: nelane@ucdavis.edu

Marcia Stefanick: stefanick@stanford.edu

Elizabeth Barrett-Connor: ebarrettconnor@ucsd.edu

Tien Dam: td2265@columbia.edu

Peggy Cawthon: pcawthon@sfcc-cpmc.net

Eric Orwoll: orwoll@ohsu.edu

Corresponding author: Jane A. Cauley, DrPH, University of Pittsburgh, Graduate School of Public Health, Department of Epidemiology, 130 DeSoto Street, Crabtree A510, Pittsburgh, PA 15261. jcauley@edc.pitt.edu; tele, 412-624-3057; fax, 412-624-7397

Alternate corresponding author: Didier Chalhoub MD, MPH, email: dic14@pitt.edu

4.1 ABSTRACT

Studies examining the relationship between muscle variables and bone strength have been previously published. However, none have included all three muscle measurements and/or both central and peripheral parameters. The purpose of this study was to explore the relationship between lean mass, strength, and power, and skeletal size, density and strength. We studied the association between appendicular lean mass (ALM), grip strength and leg power, and peripheral and central quantitative computed tomography parameters in 3,245 men aged 65 or older. ALM, grip strength, and leg power were measured by dual-energy X-ray absorptiometry (DXA), Jamar dynamometer, and the Nottingham Power Rig, respectively. Data was presented as least squares means generated from linear regression models. A multivariable model adjusting for potential confounders including age, race, study site, BMI, and muscle measurements were developed. For the multivariable model, percent differences between the lowest and highest quartiles (Q) were reported. ALM was associated with central and peripheral QCT parameters with statistically significant percent higher values (Q4 vs Q1) ranging from 2.8% (cortical vBMD) to 36.8% (Medullary volume). Grip strength was only associated with radial parameters with statistically significant percent higher values (Q4 vs Q1) ranging from 2.5% (periosteal circumference) to 9.0% (Polar moment of inertia). There was no association between leg power, and central and peripheral QCT parameters. In older men, ALM was positively associated with central and peripheral QCT parameters. Higher grip strength was associated with higher radial strength and geometric parameters that have been previously related to non-spine fractures. Longitudinal studies are needed to further establish whether changes in lean mass, strength and power influence skeletal size, density and strength.

4.2 INTRODUCTION

Muscles and bones are neighboring tissues with close ties and are both derived from a common mesenchymal precursor [2]. Throughout life, the loss of muscle mass and bone mass has been shown to be coupled and has been hypothesized to be part of the same functional unit [182]. The association of muscle mass or strength with DXA measures of areal BMD is well established [214] [215] [213] [212] [211] [216]. Since many non-osteoporotic individuals experience fractures, it is thought that bone geometry not captured by DXA may also play a role in fracture risk [249] [250]. Because of its proximity to bone, skeletal muscle force generates bending moments on bone potentially affecting its geometry [251]. Peripheral and central QCT measures of bone geometry have been associated with fracture risk [52] [247] [45]. Therefore, identifying the risk factors affecting bone geometric parameters such as the size and shape of the trabecular and cortical bone compartments may identify potential targets for interventions to reduce fractures.

Few studies have examined the association between skeletal muscle mass, muscle strength and power, and bone geometry and strength properties. Available literature is limited to one or two muscle measurements, to specific skeletal sites, to younger individuals, to women only, or to a single technology [217, 218, 252, 253]. Of importance, these studies adjusted for potential confounders but not for other muscle mass measurements in their analyses.

In this paper, the purpose was to study the association between muscle mass, strength and power, and measures of skeletal size, density, and strength.

4.3 MATERIALS AND METHODS

The Osteoporotic Fractures in Men (MrOS) study is a multicenter prospective cohort study designed to identify risk factors for osteoporosis and osteoporotic fracture. This study consists of 5,994 older men recruited from six sites (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA) across the United States from March 2000 to April 2002 [157] [233]. To be eligible, men needed to be age 65 years or older, be able to walk without assistance from another person, and have reported no bilateral hip replacement. Human subjects' approval was obtained at all sites with written informed consent obtained from all participants.

Central QCT analytical cohort

Due to limitations on study resources, the first 650 men and all nonwhite men enrolled at each clinical site were referred for QCT scans of the hip and lumbar spine as part of their baseline visit for a total of 3786 men (63% of the MrOS cohort). Out of these participants, 134 failed because of insufficient number of images, interference from metal, calibration standard not visible, or unrecorded cause. From the remaining participants, 3,245 had complete whole body DXA and volumetric BMD measurements. Except for a higher proportion of minorities (12.9% vs 10.5%), the characteristics of men in the vBMD subset were similar to the overall sample of men in the cohort. The pelvic region from the femoral head to 3.5 cm below the lesser trochanter was scanned at settings of 80 kVp, 280 mA, 3-mm slice thickness, and 512 x 512 matrix in spiral reconstruction mode. Calibration standards containing known hydroxyapatite concentrations were included with the participant in every scan.

At the femoral neck, the following measures were obtained. The cross-sectional area (cm2) was computed as the area within the periosteal boundary at the minimum cross-section. Integral volume (cm3) was computed as the total volume of the ROI within the periosteal boundary. A trabecular volume was obtained by applying an erosion process to the integral volume to retain the same shape in a region fully contained within the medullary space. The cortical volume was defined by applying a threshold of 0.35 g/cm3 to all voxels between the periosteal boundary and the outer of the trabecular volume. Medullary volume was computed by subtracting the cortical volume from the integral volume. The percent cortical volume was computed as cortical volume divided by integral volume times 100%. vBMD (g/cm3) was computed as the concentration of calcium hydroxyapatite averaged over all voxels in the integral, trabecular, or cortical volumes. The spine parameters consisted of the total vertebral vBMD, cross sectional area, integral bone BMD, vertebral strength index L1-L2, and areal spine.

pQCT analytical cohort

Men who returned for their second exam an average of 4.7±0.3 years later (from March 2005 to May 2006) 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 a pQCT ancillary study and are included in the current analysis. A total of 657 men were deceased or terminated before being contacted for the second visit, and less than 1% declined to participate. This resulted in a return rate of 98% for the follow up visit. After excluding 8 men with missing or invalid information and 23 nonwhite men, this analysis

included 1143 subjects. Additionally, 58 participants were not included because whole body DXA was missing.

The pQCT parameters that we selected for this analysis were previously shown to be associated with non-spine fractures [45]. As previously described, slices were obtained (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 difference between the scanners is the granty 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% to 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. At the more cortical 33% radius and 66% tibia sites, we used Contour mode 2 (169 mg/cm3) for cortical bone properties. A threshold of 280 mg/cm3 was used to determine the polar strength strain index (SSIp). Polar strength strain index (SSIp, mm3) and section modulus (mm3) were calculated as estimates of bone bending strength. 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 (cousins ref). Similar precision values were reported at the Pittsburgh site. An anthropomorphic phantom was scanned daily for quality assurance at both sites.

We included parameters that estimate the resistance of bone to bending and torsional force as a result of inertial properties of mass distributed around the torsional or bending axis (cross sectional moment of inertia-CSMI) [254], the bone strength in bending and torsion based on distribution of density-weighted bone voxels from polar axis (polar strength index-SSIp, axial strength index- SSIx) [255], the ratio of the bone's resistance to bending and torsion to its maximally distributed distance about the bending or torsional axis (section modulus-SM) [256], and the ability of the bone to resist torsion (polar moment of inertia-PMI) [45]. The participants provided informed consent, and the study was approved by the institutional review board at each site.

Skeletal Muscle mass, strength and power measurements

Lean mass of the extremities and total body fat was obtained using the Hologic QDR 4500. Appendicular lean mass was calculated as the sum of lean mass in the arms and legs. Bone mineral content was removed from the lean mass calculation. Grip strength (kg) was measured twice using a Jamar dynamometer (Jackson, MI, USA) in both the right and left arms [257]. The maximum grip strength from all tries was used in our analysis. The Nottingham Power Rig was used to measure leg power extension in watts. [258, 259]. All clinic staff performing DXA, leg power and grip strength measures completed formal, centralized training and passed a certification test.

Other Measurements

Participants completed a questionnaire that collected information on demographics. Body weight was measured on balance beam scales (except for one site which used a digital scale). Height was measured on a Harpender stadiometer (DyFed, UK). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Physical activity was assessed with the Physical Activity Scale for the Elderly (PASE) with higher scores indicating a greater level of activity[260]. Information on previous fractures was obtained.

Statistical analysis

Baseline characteristics were compared across the groups using ANOVA for continuous variables and Chi Square for categorical ones. Pairwise comparisons of the baseline characteristics were calculated and p-values were included in Table 1. Central and peripheral QCT parameters were compared across quartiles of lean mass, strength and power quartiles. Multiple regression analysis was used to determine the association between quartiles of ALM, grip strength, leg power with measures of bone strength, geometry and volumetric density. All analyses were initially adjusted for age, study site, and race. The multivariable model included age, study site, race, BMI. Also, ALM, grip strength, and/or leg power were added to the MV model after testing for collinearity (variance inflation factor <5). Results were presented as least squares (LS) means. A trend test and pairwise comparisons were performed to compare the LS means of the QCT parameters. Statistical significance was set at $p<0.05$. For the multivariate model, percent differences between the lowest and highest quartiles (Q4 vs Q1) were reported. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA).

4.4 RESULTS

Baseline characteristics

Men with higher ALM, grip strength, and leg power were younger and more physically active. They also had higher BMI and total body fat. A greater percentage of men with high ALM and muscle power had a history of fractures. Men with high appendicular lean mass also had a strong grip strength and leg power (Table 1).

Bone outcomes

Femoral neck – Statistically significant differences in all QCT parameters were observed across ALM quartiles. In the multivariable model, percent differences (Q4 vs Q1) for statistically significant QCT parameters between the lowest and highest ALM quartiles ranged between 2.8% (cortical vBMD) and 27.4% (Medullary volume). Most QCT parameters were statistically different across grip strength and muscle power quartiles (Table 2). In the multivariable model, however, these associations lost their statistical significance. Areal FN BMD was positively associated with both ALM and grip strength (Figure 1).

Spine - Statistically significant differences in all spine QCT parameters were observed across ALM quartiles (Table3). In the multivariate model, percent differences for statistically significant QCT parameters between the lowest and highest ALM quartiles ranged between 3.1% (integral vBMD) and 21.9% (vertebral strength). Grip strength and leg power were associated with CSA and integral bone vBMD in the initial model. For grip strength, no association was seen after adjusting for additional confounders. However for leg power, there was a 3.3% and 11.5% interquartile decrease in CSA and vertebral strength respectively. After adjusting for

ALM and grip strength, areal FN BMD was positively associated with both ALM and grip strength (Figure 2).

Radius - Statistically significant differences in tibia QCT parameters were observed across ALM, grip strength, and muscle power quartiles (Table 3). In the multivariable model, percent differences for statistically significant pQCT parameters between the lowest and highest quartiles ranged between 9.2% (periosteal circumference) and 36.8% (PMI) for ALM, between 2.5% (periosteal circumference) and 9.0% (PMI) for grip strength. There was no association between leg power and radius pQCT parameters (Figure 3).

Tibia - Statistically significant differences in tibia QCT parameters were observed across ALM, grip strength, and muscle power quartiles (Table 4). In the multivariable model, percent differences for statistically significant pQCT parameters between the lowest and highest quartiles ranged between 15.6% (33% cortical BMC) and 35.6% (33% PMI) for ALM. There was no association between grip strength and leg power, and tibia pQCT parameters (Figure 4).

4.5 DISCUSSION

Findings of this analysis showed that ALM was positively associated with central and peripheral QCT parameters. These associations were independent of grip strength and muscle power. The relationship between ALM and all QCT parameters was stronger compared to that of grip strength and leg power. This positive association remained robust even after adjusting for the other muscle measurements. This suggests that the mechanical load of the lean mass on bone may contribute more to their size, density and strength than the muscle strength and power. At the femoral neck, ALM was associated with bone size parameters including CSA, medullary,

cortical and integral volumes. Cortical vBMD was the only density measurement related to ALM. No associations were observed between ALM, and trabecular and integral vBMD. In previous studies, the structural and biomechanical bone strength of the proximal femur has been associated with hip fracture risk independently of BMD [52] [261]. Specifically, Black et al. demonstrated that one SD decrease in cortical vBMD and volume was related to a higher risk of hip fracture independent of aBMD. FN trabecular vBMD did not however improve hip fracture prediction compared to FN areal BMD [52]. At the spine, we showed that the ALM interquartile percent differences were the highest for CSA and vertebral strength. This is an important finding since in older men, vertebral strength has been shown to be highly related to vertebral fracture risk in comparison to areal BMD [247]. Peripherally, ALM was associated with the bone strength and geometry of the radius and tibia. Although the MrOS study doesn't include microarchitecture measures of bones, it is important to note that ALM is related to the trabecular number and spacing of the radius. Furthermore, in another paper, the STRAMBO study research team found that muscle mass was associated with bone size of the forearm [218].

Grip strength was related only to areal BMD measurements centrally. Similar to our findings, low grip strength has been previously found to be associated with areal BMD at the spine and femoral neck [262]. However, despite its association with vertebral fractures, our results showed no relationship between grip strength and the size, volumetric BMD, and strength of the hip and spine. Furthermore, we found an association between grip strength and the geometry and strength parameters at the radius, but not at the tibia suggesting site specific effects. Concordantly, Kaji et al. demonstrated that grip strength is correlated with the vBMD, cortical area, cortical thickness, and polar strength strain index of the forearm. [263]. The STRAMBO study also showed that low grip strength was associated with poor cortical and

trabecular microarchitecture but not with the CSA of the radius in older men [218]. This reiterates the importance of the integrated nature of skeletal muscle and bone. The stronger associations found between grip and radius structural and geometric parameters may be explained by the muscle attachments on the bones. Muscles of the forearm such as the flexors originate from the epicondyle of the humerus (proximal to radius) and inserts on the wrist (distal to radius). Since grip strength is used to measure muscle strength, a high correlation with radius parameters is expected. We postulated that this may be why greater percent differences in radius parameters were observed between the lowest and highest grip strength quartiles. This is not the case for the hip, spine, and tibia. For instance, very few muscles cross the femoral neck with most muscles attaching more distally on the trochanter of the femur. Therefore, during muscle contractions skeletal muscles exert minimal strain on the neck of the femur.

Negative associations were seen between leg power and spine parameters (CSA and vertebral strength) after adjusting for BMI, ALM and grip strength. No association was found between leg power and peripheral QCT parameters. These results are contradictory with a previous study we conducted using the same MrOS cohort. In that study, we examined the relationship between muscle power and pQCT parameters and found an association between leg power and bone strength parameters (cross sectional area and the polar strength strain index) [252]. However, the multivariable model did not include lean mass and grip strength. Despite the fact that leg power explains 6.6% of the variance in bone-strength strain index and 8.9% of the variance in the section modulus (SM) at the tibial mid-shaft, we did not find any association between leg power and tibial strength parameters [253]. Furthermore, the previous variances were obtained from a study conducted in women, which may suggest some gender differences in the muscle power association with tibial bone parameters.

There are several strengths to our study. MrOS is a multicenter prospective study examining potential risk factors for fractures in a large population of older men. We were able to examine the association of lean mass, grip strength and leg power with central and peripheral QCT parameters. There are also several limitations to our study. Peripheral QCT measurements were available for a smaller number of MrOS men, and the peripheral and central parameters cohorts were not the same. Another limitation is that the Nottingham power rig is limited as a measure of power because it does not separate velocity from force. Also, since this is a cross sectional study, we were unable to establish a temporal relationship between the muscle measurements and QCT parameters.

In older men, the ALM was positively associated with central and peripheral QCT parameters. The ALM and grip strength were associated with peripheral strength and geometric parameters that have been previously related to non-spine fractures [45]. Additionally, the stronger relationship observed for ALM suggests that the mechanical load of the muscles on bones may contribute more to their size, density and strength compared to the muscle strength and power. Future efforts to increase muscle size may play a key role in improving density and quality of bones. Longitudinal studies are needed to further establish whether changes in ALM and strength improves the skeletal size, density, and strength.

4.6 TABLES AND FIGURES

Table 4.6.1. Baseline characteristics across appendicular lean mass, grip strength, and muscle power quartiles

	Characteristics	Q1	Q2	Q3	Q4	p-trend
Appendicular lean mass	Age	76.41 ±6.41	73.97 ±5.56	72.50 ±5.28	71.02 ±4.71	**<0.0001**
	Caucasian	668(84.03)	724(91.18)	727(91.68)	699(87.92)	**<0.0001**
	Height (m)	1.69 ±0.06	1.73 ±0.05	1.75 ±0.06	1.79 ±0.06	**<0.0001**
	Weight (kg)	69.86 ±7.41	78.76 ±7.50	86.03±8.00	96.11 ±11.17	**<0.0001**
	BMI (kg/m2)	24.57 ±2.62	26.40 ±2.76	28.05 ±3.15	30.06 ±3.88	**<0.0001**
	Total body fat (kg)	17.66 ±5.20	20.19 ±5.92	22.80 ±6.51	25.17 ±7.59	**<0.0001**
	PASE score	139.33±67.73	147.13 ±66.19	153.33 ±66.38	153.57 ±67.37	**<0.0001**
	Nottingham leg power (N)	163.29±45.26	197.01±49.45	218.95±54.52	249.88±66.50	**<0.0001**
	Appendicular lean mass (kg)	20.03 ±1.40	23.00±0.62	25.11±0.64	28.79 ±2.22	**<0.0001**
	Grip strength (kg)	36.41 ±6.88	40.78±7.21	43.26 ±7.29	46.91±8.77	**<0.0001**
	Previous fracture (N, %)	394(49.56)	433(54.60)	438(55.23)	456(57.36)	**0.015**
Grip strength	Age	77.03±6.45	74.37 ±5.47	72.64±5.25	70.47 ±4.39	**<0.0001**
	Caucasian	572(87.86)	745(88.27)	722(88.92)	740(89.81)	0.65
	Height	1.70 ±0.07	1.73 ±0.06	1.74 ±0.06	1.78 ±0.06	**<0.0001**
	Weight	78.11 ±12.63	81.02 ±12.79	83.26 ±12.59	87.67 ±12.05	**<0.0001**
	BMI	26.86±3.76	27.10 ±3.86	27.33 ±3.80	27.75±3.49	**<0.0001**
	Total body fat	20.80 ±6.64	21.38 ±6.93	21.50 ±7.17	22.06 ±6.95	**0.007**
	PASE score	131.63±64.05	143.37 ±64.39	152.33±70.54	162.33 ±66.71	**<0.0001**
	Nottingham leg power	162.72±52.51	188.92 ±50.08	214.26 ±55.35	251.83 ±58.64	**<0.0001**
	Appendicular lean mass	22.24 ±3.33	23.40 ±3.12	24.53 ±2.99	26.38 ±3.16	**<0.0001**
	Grip strength	30.36 ±3.92	38.23 ±1.65	43.86 ±1.64	52.57 ±4.32	**<0.0001**
	Previous fracture	363(55.76)	456(54.03)	441(54.38)	436(52.91)	0.75

Table 4.6.1. Continued

Muscle Power	*Age*	77.44±6.03	74.25±5.45	71.96±4.75	69.85±3.93	**<0.0001**
	Caucasian	639(87.90)	642(88.07)	647(89.00)	655(89.73)	0.66
	Height	1.71 ±0.07	1.73 ±0.06	1.75 ±0.06	1.77 ±0.06	**<0.0001**
	Weight	76.55±11.55	80.16±12.24	83.41±11.67	89.73±11.92	**<0.0001**
	BMI	26.13±3.57	26.78±3.63	27.19±3.50	28.58±3.53	**<0.0001**
	Total body fat	19.86±6.49	20.81±6.97	21.28±6.79	23.13±6.83	**<0.0001**
	PASE score	129.63±65.73	147.16±64.31	158.69±66.90	161.50±67.76	**<0.0001**
	Nottingham leg power	130.51±25.55	183.67±11.65	224.96±11.31	288.89±38.66	**<0.0001**
	Appendicular lean mass	22.06±3.10	23.34±2.85	24.66±2.88	26.76±3.13	**<0.0001**
	Grip strength	36.19±7.21	40.27±7.06	43.83±7.16	47.72±7.82	**<0.0001**
	Previous fracture	360(49.52)	391(53.64)	413(56.81)	412(56.44)	**0.019**

Table 4.6.2. Quartiles of appendicular lean mass, grips strength, and muscle power by central QCT parameters: Age, race and site adjusted

	Characteristics	Q1	Q2	Q3	Q4	p-trend	Pairwise
Appendicular lean mass	**Femoral neck**						
	Cross-sectional area (cm^2)	11.44	12.09	12.50	13.19	<0.0001	abcdef
	Percent cortical volume	45.12	45.25	46.07	45.74	0.016	bd
	Integral vBMD (g/cm^3)	0.290	0.294	0.303	0.305	<0.0001	bcde
	Cortical volume (cm^3)	8.03	8.65	9.28	10.06	<0.0001	abcdef
	Integral volume (cm^3)	17.90	19.30	20.41	22.29	<0.0001	abcdef
	Medullary volume (cm^3)	9.88	10.65	11.14	12.23	<0.0001	abcdef
	Cortical vBMD (g/cm^3)	0.517	0.522	0.530	0.537	<0.0001	bcdef
	Trabecular vBMD (g/cm^3)	0.076	0.079	0.085	0.086	<0.0001	bcde
	Femoral neck BMD (g/cm^2)	0.753	0.786	0.824	0.854	<0.0001	abcdef
	Spine						
	Total vertebral vBMD (g/cm3)	0.116	0.118	0.121	0.125	<0.0001	bcef
	Cross sectional area (cm2)	10.89	11.62	11.98	12.76	<0.0001	abcdef
	Integral bone BMD (g/cm3)	0.210	0.215	0.221	0.228	<0.0001	abcdef
	Areal spine (g/cm2)	1.01	1.05	1.08	1.13	<0.0001	abcdef
	Vertebral strength index L1-L2 (N)	0.261	0.287	0.313	0.353	<0.0001	abcdef
Grip strength	**Femoral neck**						
	Cross-sectional area (cm^2)	11.75	12.04	12.38	12.79	<0.0001	abcdef
	Percent cortical volume	45.52	45.63	45.41	45.69	0.819	
	Integral vBMD (g/cm3)	0.296	0.296	0.296	0.301	0.219	
	Cortical volume (cm^3)	8.557	8.741	8.989	9.422	<0.0001	bcdef
	Integral volume (cm^3)	18.91	19.35	20.00	20.87	<0.0001	bcdef
	Medullary volume (cm3)	10.36	10.61	11.01	11.45	<0.0001	bcdef
	Cortical vBMD (g/cm3)	0.523	0.524	0.524	0.529	0.160	
	Trabecular vBMD (g/cm3)	0.079	0.079	0.082	0.086	0.002	cef
	Femoral neck BMD (g/cm2)	0.784	0.789	0.803	0.826	<0.0001	bcdef
	Spine						
	Total vertebral vBMD (g/cm3)	0.118	0.119	0.120	0.121	0.455	
	Cross sectional area (cm2)	11.43	11.54	11.84	12.11	<0.0001	bcdef

Table 4.6.2. Continued

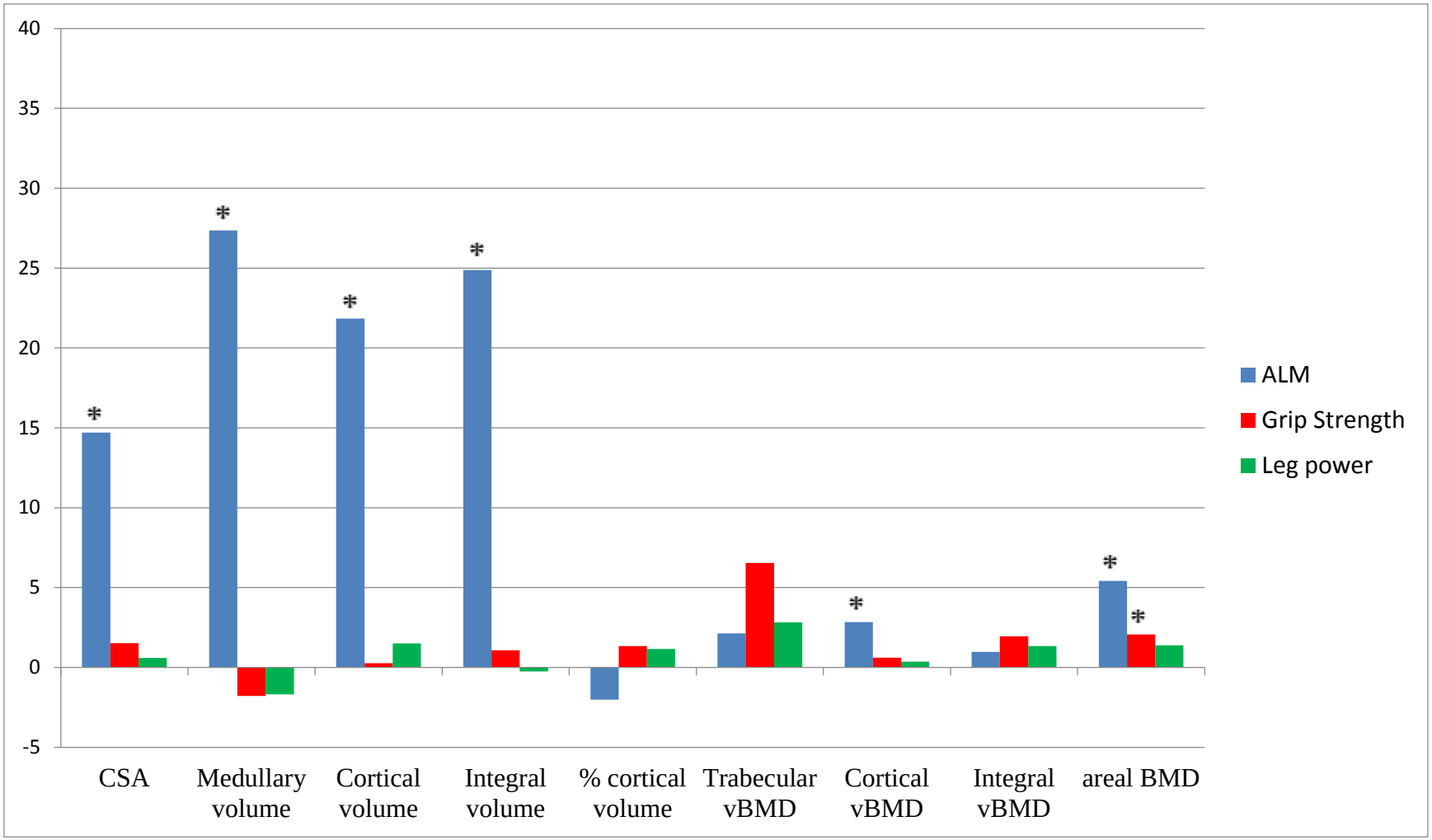
	Integral bone BMD (g/cm^3)	0.216	0.216	0.217	0.222	0.015	cef
	Areal spine (g/cm2)	1.040	1.046	1.066	1.091	<0.0001	bcdef
	Vertebral strength index L1-L2 (N)	0.297	0.290	0.299	0.315	0.069	e
Muscle Power	**Femoral neck**						
	Cross-sectional area (cm^2)	11.76	12.13	12.44	12.78	<0.0001	abcdef
	Percent cortical volume	45.42	45.35	45.81	45.92	0.320	
	Integral vBMD (g/cm3)	0.294	0.294	0.301	0.302	0.016	bcde
	Cortical volume (cm^3)	8.460	8.794	9.100	9.609	<0.0001	abcdef
	Integral volume (cm^3)	18.82	19.56	20.09	21.16	<0.0001	abcdef
	Medullary volume (cm3)	10.36	10.76	11.00	11.55	<0.0001	abcef
	Cortical vBMD (g/cm3)	0.520	0.522	0.528	0.528	0.037	bc
	Trabecular vBMD (g/cm3)	0.079	0.079	0.083	0.086	0.0054	bce
	Femoral neck BMD (g/cm2)	0.776	0.790	0.811	0.831	<0.0001	abcdef
	Spine						
	Total vertebral vBMD (g/cm3)	0.118	0.118	0.120	0.123	0.063	ce
	Cross sectional area (cm2)	11.45	11.62	11.77	12.03	<0.0001	bcef
	Integral bone BMD (g/cm3)	0.214	0.214	0.219	0.223	0.0002	bcde
	Areal spine (g/cm2)	1.041	1.051	1.068	1.086	0.0004	bce
	Vertebral strength index L1-L2 (N)	0.293	0.287	0.300	0.311	0.118	e

a: Q1 vs Q2**, b:** Q1 vs Q3**, c:** Q1 vs Q4, **d:** Q2 vs Q3**, e:** Q2 vs Q4**, f:** Q3 vs Q4

Table 4.6.3. Quartiles of appendicular lean mass, grips strength, and muscle power by peripheral QCT parameters: Age, race, and site adjusted

Characteristics	Appendicular lean mass				Grip Strength				Muscle power			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
FN aBMD	0.73	0.77	0.79	0.82	0.78	0.76	0.77	0.79	0.78	0.79	0.80	0.81
Tibia 4%												
Total BMC (mg/mm)	338.1	370.1	380.8	405.6	360.6	361.7	370.4	390.1	366.0	375.7	381.4	402.2
Trabecular BMC (mg/mm)	113.3	126.5	128.3	138.1	121.6	121.1	125.0	132.3	122.8	127.6	128.3	136.7
SSIx (mm3)	1125.6	1300.5	1337.7	1467.3	1257.6	1250.2	1295.0	1378.2	1286.2	1313.7	1350.1	1443.1
SSIp (mm3)	2109.5	2419.5	2528.0	2755.1	2350.7	2331.6	2408.1	2600.6	2406.0	2470.4	2549.0	2719.2
Radius 33%												
Total BMC (mg/mm)	121.3	130.3	136.4	144.0	125.3	130.0	133.1	141.4	128.8	131.8	134.9	140.0
Total CSA (mm2)	132.5	140.9	147.5	158.3	137.3	142.9	143.9	153.4	139.1	142.8	145.0	151.4
Cortical BMC (mg/mm)	112.8	122.3	127.6	134.5	116.5	121.0	124.8	132.5	120.4	123.2	126.4	131.3
Cortical CSA (mm2)	96.28	104.47	109.29	115.56	100.2	103.6	106.5	113.2	103.0	105.4	107.9	112.5
Periosteal circumference (mm)	40.72	42.01	42.98	44.52	41.43	42.27	42.43	43.82	41.70	42.26	42.60	43.52
CSMI (mm4)	1094.7	1262.5	1369.7	1549.0	1194.9	1265.5	1322.1	1472.4	1237.0	1283.3	1347.7	1447.2
PMI (mm4)	2536.6	2948.7	3204.4	3665.7	2774.0	2953.9	3079.7	3466.8	2867.4	3024.1	3129.8	3412.7
SM (mm3)	307.6	340.8	361.7	398.1	324.7	340.1	351.9	383.8	335.8	346.0	357.2	379.2
SSIx (mm3)	180.6	200.9	213.3	232.0	190.2	200.9	207.2	223.9	195.3	202.4	210.6	220.2
SSIp (mm3)	317.01	348.5	369.8	404.6	332.0	347.5	361.4	392.1	342.2	353.2	364.4	384.6
Tibia 33%												
Cortical BMC (mg/mm)	336.8	363.4	375.4	395.1	354.0	358.6	370.9	383.1	357.0	367.8	375.4	388.4
PMI (mm4)	27602.2	31446.4	33595.5	38764.7	31117.1	31751.8	32995.6	35589.1	31808.4	32385.6	34027.9	36188.3
SSIx (mm3)	1119.1	1230.5	1273.6	1409.9	1207.5	1228.8	1272.5	1337.1	1232.4	1239.8	1294.8	1350.2
Tibia 66%												
SM (mm3)	2955.2	3313.9	3479.5	3790.8	3204.4	3299.7	3383.4	3607.8	3271.8	3392.4	3508.2	3684.7
SSIp (mm3)	3015.7	3347.6	3489.8	3812.1	3233.2	3332.2	3427.0	3643.5	3311.9	3415.7	3506.0	3697.0

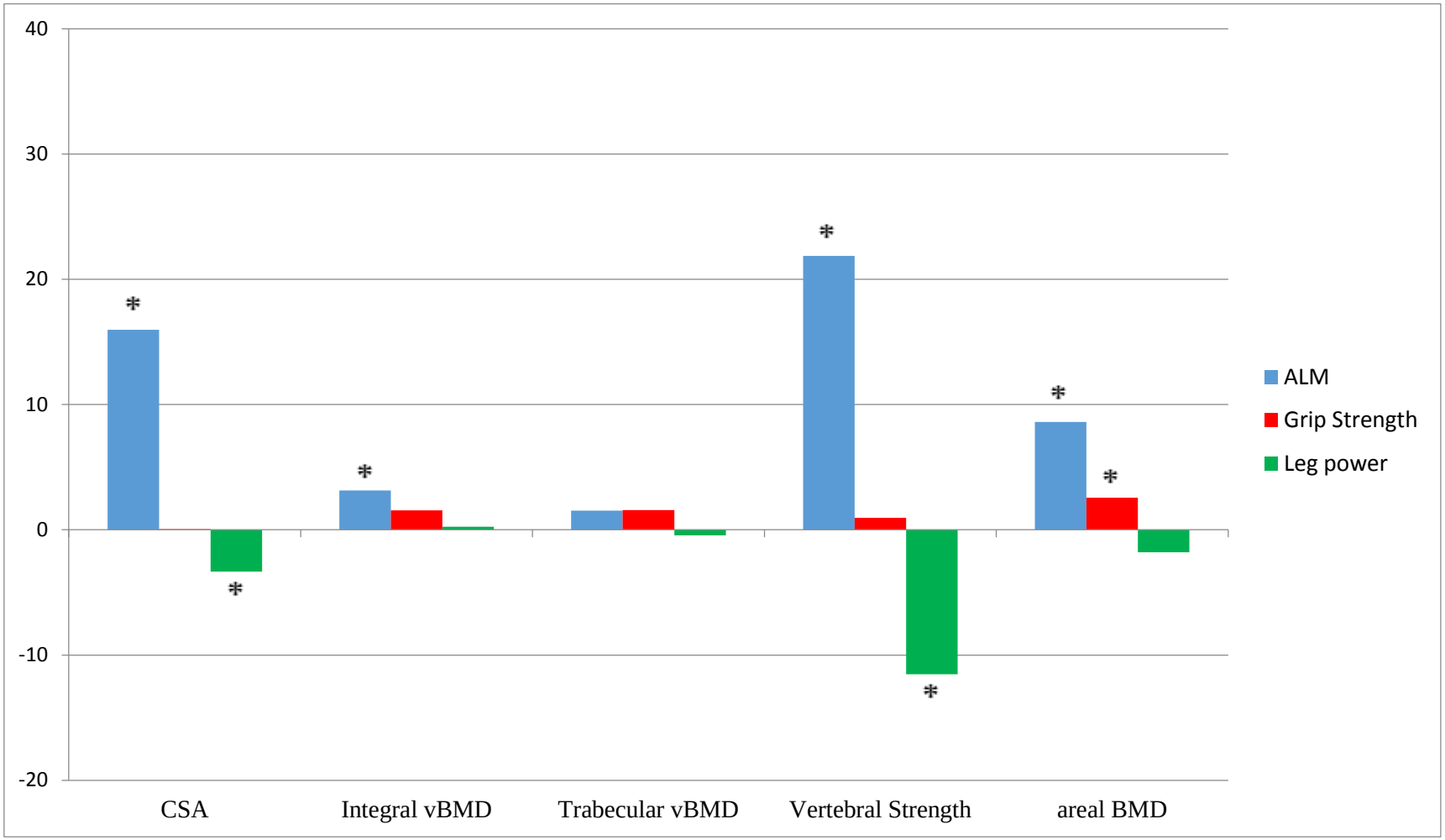
All p trends were statistically significant



*Statistically significant with p<0.05,

[a] adjusted for site, age, race, BMI, grip strength and leg power (for ALM), ALM and leg power (for grip strength), and ALM and grip strength (for leg power).

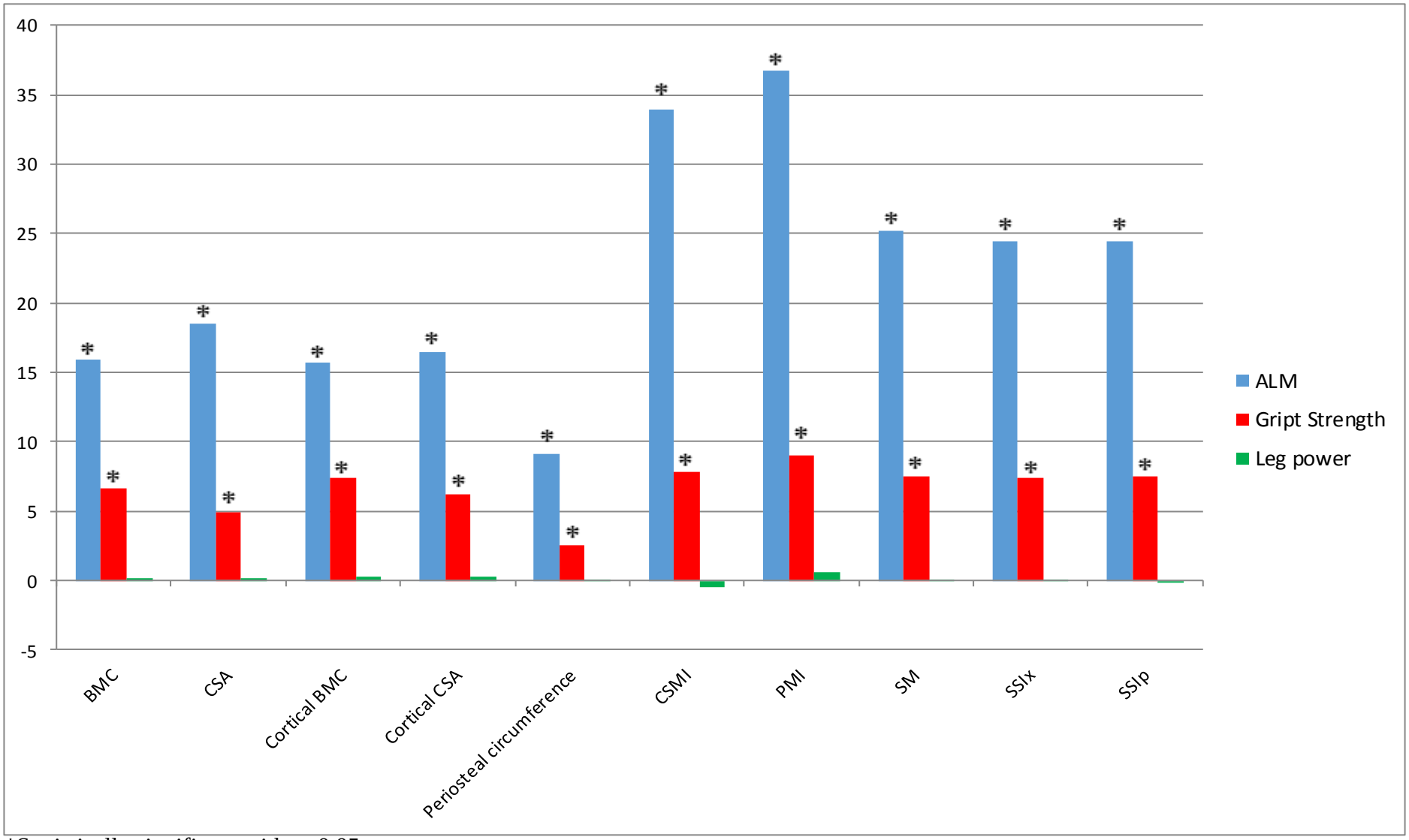
Figure 4.6.1. Percent difference in means of femoral neck parameters between 1st and 4th quartiles of ALM, grip strength, and leg power[a]



*Statistically significant with $p<0.05$

[a] adjusted for site, age, race, BMI; grip strength and leg power (for ALM); ALM and leg power (for grip strength); and ALM and grip strength (for leg power).

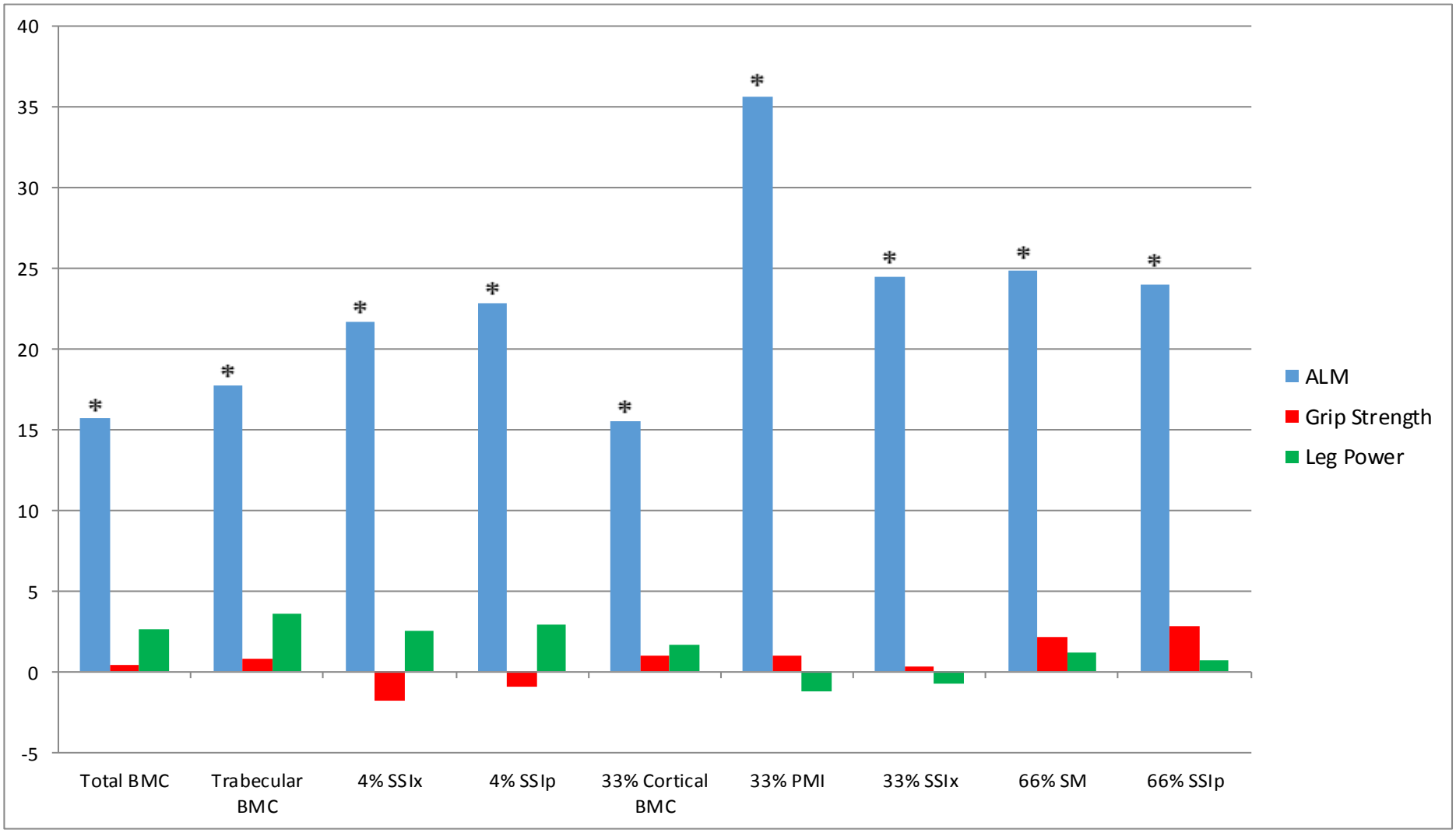
Figure 4.6.2. Percent difference in means of spine parameters between 1st and 4th quartiles of ALM, grip strength, and leg power[a]



*Statistically significant with p<0.05

[a] MV model site, age, race, BMI, grip strength and leg power (for ALM), ALM and leg power (for grip strength), and ALM and grip strength (for leg power).

Figure 4.6.3. Percent difference in means of radius QCT parameters between 1st and 4th quartiles of ALM, grip strength, and leg power[a]



*Statistically significant with $p<0.05$

[a] MV model site, age, race, BMI, grip strength and leg power (for ALM), ALM and leg power (for grip strength), and ALM and grip strength (for leg power).

Figure 4.6.4. Percent difference in means of Tibia QCT parameters between 1st and 4th quartiles of ALM, grip strength, and leg power[a]

5.0 PAPER 3: RISK OF NON-SPINE FRACTURES AMONG OLDER MEN AND WOMEN WITH SARCOPENIA, LOW BONE MASS, OR BOTH

Didier Chalhoub, MD MPH[a]; Peggy M. Cawthon, PhD MPH[b]; Kristine E. Ensrud, MD MPH[c]; Marcia L. Stefanick, PhD[d]; Deborah M. Kado, MD MS[e]; Robert Boudreau, PhD[a]; Susan Greenspan, MD[a]; Anne B. Newman, MD MPH[a]; Joseph Zmuda, PhD[a]; Eric S. Orwoll, MD [f]; Jane A. Cauley, DrPH[a]

for the Osteoporotic Fractures in Men (MrOS) Study Research Group.

[a]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA; [b]California Pacific Medical Center, San Francisco, CA; [c]Department of Medicine and Division of Epidemiology & Community Health, University of Minnesota, Minneapolis, MN; [d]Stanford University School of Medicine, Stanford, CA; [e]University of California, San Diego, La Jolla, CA; [f]Oregon Health & Sciences University, Portland, OR

Contact information (emails):

Didier Chalhoub: dic14@pitt.edu

Peggy M. Cawthon: pcawthon@sfcc-cpmc.net

Kristine E. Ensrud: ensru001@umn.edu

Marcia L. Stefanick: stefanick@stanford.edu

Deborah M. Kado: dkado@ucsd.edu

Robert Boudreau: BoudreauR@edc.pitt.edu

Susan Greenspan: greenspn@pitt.edu

Anne B. Newman: NewmanA@edc.pitt.edu

Joseph Zmuda: zmudaj@edc.pitt.edu

Eric S. Orwoll: orwoll@ohsu.edu

Corresponding author: Jane A. Cauley, DrPH, University of Pittsburgh, Graduate School of Public Health, Department of Epidemiology, 130 DeSoto Street, Crabtree A510, Pittsburgh, PA 15261. jcauley@edc.pitt.edu; tele, 412-624-3057; fax, 412-624-7397

5.1 ABSTRACT

The combined effect of age-related deterioration in bone and muscle manifested as low bone mineral density (BMD) and sarcopenia on fracture risk has not been reported. We examined whether men and women with both low BMD and sarcopenia have a higher risk of fracture than those with only one or neither condition. 5,544 men (mean age=73.7 years) from the Osteoporotic Fractures in Men study and 1,114 women (mean age=77.6 years) from the Study of Osteoporotic Fractures were followed up for 9 years and 8 years respectively. Sarcopenia was defined as low appendicular lean mass plus either slowness or weakness; and low BMD according to the World Health Organization definition of T-score<-1.0. Participants were classified as normal BMD and no sarcopenia (N=3367 men, 308 women); sarcopenic only (N=79 men; 48 women); low BMD only (N=1986 men; 626 women), and low BMD and sarcopenic (N= 112 men; 132 women). Men had 870 confirmed radiographic non-spine fractures, and women 272. Cox Proportionate Hazards Models were used to assess fracture risk.

Compared to men with normal BMD and no sarcopenia, the Hazard ratio [HR] for fracture was 3.79 (95% confidence interval [CI], 2.65-5.41) among men with low BMD and sarcopenia, 1.67 (95% CI: 1.45-1.93) among men with low BMD only, and 1.14 (95% CI, 0.62-2.09) among men with sarcopenia only (p-interaction=0.06). Women with low BMD and sarcopenia (HR, 2.27; 95% CI, 1.37-3.76), and women with low BMD alone (HR, 2.62; 95% CI, 1.74-3.95), but not women with only sarcopenia had increased risk of fracture compared to normal women. Our data indicate that men with both low BMD and sarcopenia are at especially high risk of fracture. Efforts to identify men with low BMD and sarcopenia may help prevent future fractures.

5.2 INTRODUCTION

Age-related deterioration in both bone and muscle manifested as low bone mineral density (BMD) and sarcopenia may contribute to fractures. It is well established that individuals with low BMD have an increased risk of fracture [76].

Falls and functional impairments, which are known to be associated with fractures, have been previously linked to sarcopenia[264] [167]. Furthermore, myosteatosis, which results in reduced muscle strength and function, has been associated with fractures [265] [266]. Hence, sarcopenia may increase risk of fractures.

Sarcopenia was initially defined as the loss of muscle mass [104]. However, more recent definitions of sarcopenia add components of muscle strength and/or physical performance, because the loss of muscle mass is not sufficient to characterize the sarcopenic syndrome [115]. Inclusion of these additional measures in the operational definition of sarcopenia may improve the prediction of clinical outcomes, such as fractures.

In 2009, the term “sarco-osteopenia” was coined to emphasize that both weak bones and weak muscles may contribute to fractures in the elderly [267]. To our knowledge, the combined effect of both sarcopenia, defined as low muscle mass and strength, and low BMD on fracture risk has not yet been studied.

The purpose of the current study was to compare the incidence of non-vertebral fractures among men and women based on both low BMD and sarcopenia. We hypothesized that individuals with both sarcopenia and low BMD will have the greatest risk of fracture compared to individuals with only one or neither condition.

5.3 METHODS

Study population

We examined data of 5,544 white and black men (mean age=73.7years) from the Osteoporotic Fractures in Men (MrOS) study and 1,114 white and black women (mean age=77.6 years) from the Study of Osteoporotic Fractures (SOF). The MrOS and SOF studies are both multicenter prospective cohort studies designed to identify risk factors for osteoporosis and osteoporotic fracture. In MrOS, 5994 older men were recruited from six sites (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA) across the United States from March 2000 to April 2002[157, 233]. In SOF, 9,704 women were recruited from four US sites (Baltimore, MD; Minneapolis, MN; Pittsburgh, PA; Portland, OR) between 1986-1988. The original SOF cohort was enhanced by the addition of 662 African American women recruited between 1997-98. To be eligible, both men and women needed to be age 65 years or older, be able to walk without assistance from another person, and have reported no

bilateral hip replacement. Human subjects approval was obtained at all sites with written informed consent obtained from all participants.

Body composition by whole body Dual Energy X-ray Absorptiometry (DXA) was available for the 5,544 white and black MrOS men at baseline and a subset of 1,114 white and black SOF women (when recruited for the year 10 exam). Women without whole body DXA were not included since sarcopenia cannot be assessed without appendicular lean mass.

Bone Mineral Density (BMD) measurement

In men, total hip BMD (g/cm^2) and femoral neck BMD (g/cm^2) were measured using DXA Hologic QDR 4500(Bedford, MA). In women, BMD was measured by DXA using Hologic 1000 and 2000 scanners. Details of the measurement and densitometry procedures have been published elsewhere [234] [231]. Briefly, certified technicians performed the DXA scans following a strict protocol. To assess longitudinal performance of the scanners, an anthropometric spine phantom was scanned daily and a hip phantom weekly at each clinical center. In both genders, the right hip was scanned unless there was a fracture, implant, hardware, or other problem, in which case the left hip was scanned. Individuals were classified as having low BMD according to the 1994 World Health Organization (WHO) recommendations if their femoral neck T-score was < -1 [268]. Subjects were considered to have normal BMD if their T-score was >= -1. The T-score was calculated using the National Health and Nutrition Examination Survey III reference database [28]. Young Caucasian women were used as the reference population in both men and women as recommended by the International Society for Clinical Densitometry (ISCD) [29].

Sarcopenia assessment

The definition of sarcopenia was based on the European Working Group on Sarcopenia in Older persons (EWSOP) [115]. Participants were classified as sarcopenic if they had low lean mass plus either slowness (classified by gait speed) or weakness (assessed by grip strength). Low lean mass was defined using the approach of Newman et al [146] to correct appendicular lean mass for height and fat mass. Linear regression was used to model the relationship between appendicular lean mass on height (meters) and fat mass (kg). The 20^{th} percentile of the distribution of residuals was used as the cutpoint for low muscle mass. Separate models were fit for men and women. We concentrated on the residual method because in the Health, Aging and Body Composition (Health ABC) and the Framingham studies, the residuals method was a better predictor of disability and mobility limitations in both men and women but other definitions of sarcopenia were not [123, 147]. Walking speed was calculated as the average two usual walking pace attempts over 6 meters and expressed as m/s. Slowness was defined as gait speed slower than 0.8 m/s. Grip strength was measured using a Jamar dynamometer (Jackson, MI, USA) in men and a handheld dynamometer (Sparks Instruments and Academics, Coralville, Iowa) in women. The maximum grip strength from all attempts was used in our analysis. Weakness was assessed by grip strength and characterized as less than 30 kg for men, or less than 20 kg for women. For each participant, height was measured on a Harpenden stadiometer (DyFed, UK). Lean mass of extremities and total body fat were obtained using the Hologic QDR 4500 and 2000 for men and women, respectively. Appendicular lean mass was calculated as the sum of lean mass in the arms and legs. Bone mineral content was removed from the lean mass calculation.

Subjects' classification

Men and women were classified into four groups based on their bone mass and sarcopenia status: 1) Individuals with normal BMD and no sarcopenia (N=3367, 61% men; 308, 28% women), 2) individuals with normal BMD and sarcopenia (N=79 men, 1% men; 48, 4% women), 3) individuals with low BMD and no sarcopenia (N=1986 men, 36% men; 626, 56% women), 4) and individuals with low BMD and sarcopenia (N= 112 men, 2% men; 132, 12% women).

Other Measurements

Covariates were assessed at baseline in men and at year 10 in women at the time of the whole body DXA. Participants completed questionnaires and interviews that collected information on demographics, lifestyle, medical history and a medication inventory. Participants were asked to bring all prescription and over-the-counter medications to the clinic for verification of use [269]. Smoking status was categorized as current or not (former, none) and alcohol consumption was assessed by the average number of drinks per week. Participants were asked if they walked as a form of exercise. Self-rated health was categorized as excellent/good vs fair, poor or very poor. Information on history of falls in the past year and previous fractures was obtained. Functional status was assessed by asking about difficulty with five instrumental activity of daily living (IADL) ("walking 2 or 3 blocks outside on level ground", "climbing up 10 steps without resting", "preparing meals", "doing heavy housework", and "shopping for groceries or clothes"). Weight was measured on balance beam scales (except for one of the MrOS site which used a digital scale). Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters.

Fracture Ascertainment

All non-spine fractures were identified through our mailed questionnaire follow-ups which were mailed every 4 months to ask if the participants had sustained a new fracture; these contacts were > 95% complete. Participants who reported a fracture were asked about the circumstances of the fracture. The degree of trauma was categorized into: "fall from a standing height or less" ;"fall on stairs, steps or curb", "fall from more than standing height", and traumatic. Traumatic fractures (minimal, moderate, and severe) were included since they have been previously associated with low BMD [238]. Pathological fractures were excluded. All fractures were confirmed by radiographic report and adjudicated centrally over a mean of 9 years for men and 8 years for women. These analyses included fractures that occurred between 2000 and 2012 in men, and between 1997 and 2009 in women. The follow-up time ended at the date of the first fracture, date of death, date of last contact or database lock. In sensitivity analyses, we excluded traumatic fractures (N=167, 19% in men; N=23, 8% in women).

Statistical analysis

Baseline characteristics were compared across the groups using ANOVA for continuous variables and Chi Square for categorical ones. Pairwise comparisons of the baseline characteristics were calculated and p-values were included in Table 1.

For the primary outcome, we initially adjusted for age. The incidence rates of non-spine fractures for each of the four groups were estimated using a Poisson distribution. Using Cox Proportional Hazards Models, the age and multivariable adjusted Hazard ratios (HR) and 95% Confidence Intervals were calculated. Participants with normal BMD and no sarcopenia formed the referent group. The multivariable-adjusted model included established risk factors for

fracture: age, race, fall history, previous fracture history, current smoking, glucocorticoids, rheumatoid arthritis, alcohol consumption, IADL impairments, and physical activity. We used backward elimination to drop all variables that did not reach a statistically significant level of $p<0.1$. The interaction term between low BMD and sarcopenia on fracture risk was assessed. Sensitivity analyses were conducted for different sarcopenia operational definitions. We also studied the association between low BMD and fracture risk adjusting for sarcopenia, and the association between sarcopenia and fracture risk adjusting for low BMD. In participants who experienced a non-spine fracture, pairwise comparisons were done to compare the circumstances of the fracture across the four groups.

Separate analyses were done for men and women using SAS 9.3 (SAS Institute, Inc., Cary, NC).

5.4 RESULTS

The majority of men were white with little difference in race across the groups. Sarcopenic men with or without low BMD were older than the other groups but there was little variability in smoking and alcohol consumption among the groups. A higher percentage of women with low BMD with or without sarcopenia were white and these women tended to be older. Total hip and femoral neck BMD were the lowest in the low BMD and sarcopenia group in men, and in the low BMD with or without sarcopenia groups in women. Unlike sarcopenic women, sarcopenic men had a higher number of IADL impairments, and a higher percentage of falls.

Men

A total of 870 (16%) men experienced a non-spine fracture: 402 (12%) normal; 11 (14%) sarcopenic; 421 (21%) low BMD; and 36 (32%) both low BMD and sarcopenia. The age-adjusted incidence of non-spine fracture was similar in normal men (13.2 per 1,000) and those with sarcopenia alone (15.1 per 1,000), but was much higher in men with both low BMD and sarcopenia (46.5 per 1,000) (Figure 1). Men with low BMD and sarcopenia had a 4-fold increased risk of fracture in comparison to normal men, HR= 3.75(2.64 to 5.32), Table 2. Men with sarcopenia alone did not have a statistically significant higher risk of fractures HR=1.19(0.65 to 2.17), however, the risk of fracture in those with low BMD alone HR=1.79(1.56 to 2.05) was intermediate between normal men and men with both conditions. These associations remained significant after adjusting for important covariates (Table 2). The interaction term between sarcopenia and low BMD was borderline significant (p=0.06). Low BMD was associated with fracture risk after adjusting for sarcopenia (HR, 1.97; 95% CI, 1.72-2.25). Similarly, sarcopenia was associated with fracture risk after adjusting for low BMD (HR, 2.25; 95% CI, 1.68-3.03). Exclusion of traumatic fractures showed somewhat similar results (Table 2b, p-interaction=0.11).

Women

Overall, 272 (25%) women experienced a non-spine fracture: 31 (10%) normal; 7 (15%) sarcopenic; 194 (33%) low BMD; and 40 (32%) both low BMD and sarcopenia. The age-adjusted incidence of fracture ranged from 13.9 per 1,000 in normal women to about 40 per 1,000 in women with low BMD or both low BMD and sarcopenia (Figure 1). Of interest, there was little gender difference in fracture incidence rates in subjects with low BMD and sarcopenia

(Figure 1). Women with low BMD with or without sarcopenia had an approximately 3-fold increased risk of fracture compared to normal women, HR= 2.80(1.72 to 4.58) and 3.09 (2.08 to 4.59) respectively (Table 2). The effect size decreased to 2.5 in both groups after adjusting for important covariates but remained statistically significant. Women with sarcopenia alone had a similar fracture rate as normal women. The interaction term between sarcopenia and low BMD was not statistically significant (p=0.37). Low BMD was associated with fracture risk after adjusting for sarcopenia (HR, 3.48; 95% CI, 2.47-4.90). However, sarcopenia was not associated with fracture risk after adjusting for low BMD (HR, 1.09; 95% CI, 0.79-1.49). Exclusion of traumatic fractures revealed similar results (Table 2b, p-interaction=0.38).

Circumstances of the fracture

Overall 80% of fractures in men and 90% in women involved a fall. In men with both low BMD and sarcopenia, 75% of their non-spine fractures involved a fall from a standing height or less. In comparison, fewer fractures in the other groups (between 56% and 64%) involved a fall from a standing height or less (Figure 2a.). Pairwise comparisons showed that differences were statistically significant between men with both low BMD and sarcopenia and men with low BMD alone, and between men with both low BMD and sarcopenia and men without both conditions.

Similarly, in women, a higher proportion of fractures in subjects with both low BMD and sarcopenia were due to a fall from < standing height (82%) compared to women with low BMD alone (75%), sarcopenia alone (67%), and normal women (78%). However, these differences were not statistically significant (Figure 2b).

5.5 DISCUSSION

The findings of this study show that men with both low BMD and sarcopenia have a 4-fold higher risk for non-spine fractures compared to men with normal BMD and no sarcopenia. In men, the borderline significance of the interaction term suggests that the effect of sarcopenia and low BMD on fracture risk may depend on each other. The risk of fracture was about 2.5-fold higher in women with both sarcopenia and low BMD as well as in women with low BMD alone. Sarcopenia alone was not an independent risk factor for fractures in men and women. Our findings illuminate a previously unrecognized and potentially strong role of sarcopenia in determining the risk of fractures among older men.

The coexistence of low BMD and sarcopenia in older men resulted in a much higher risk of fractures. Since, physical activity, IADL impairments, history of falls, and other mobility disorder risk factors were adjusted for in our analyses, this suggests that the increased risk of non-spine fractures in men with both low BMD and sarcopenia could be attributed to the crosstalk between muscles and bones. Mechanical stimuli, pleiotropy, and hormones are known to play major roles in this crosstalk possibly affecting bone strength [3]. Indeed, circumstances of fractures showed that these men had a higher proportion of fractures due to a lower degree of trauma compared to men with low BMD alone and normal men. Low muscle mass and strength have been associated with low BMD[211] [212] [213] [214] [215] [216] and poorer quality of bones [217] [218] which may be explained by the mechanical stimuli exerted by muscles. Muscles and bones share common genetic factors and are believed to be under the influence of pleiotropic genes responsible for the synchronized deterioration of both tissues with age [270]. Muscles and bones also act as endocrine target organs, which are under the influence of similar hormones such as testosterone and estrogen. Estradiol regulates bone resorption, and may also

enhance muscle contractile forces on bone [225] [226]. Androgens affect muscle mass and strength and trabecular bone formation [227].

Unlike our findings among men, the risk of non-spine fractures in women with low BMD alone and women with both low BMD and sarcopenia was similar suggesting that low BMD may be the driving force for non-spine fractures in women. Although the proportion of fractures due to a lower degree of trauma was higher in women with low BMD and sarcopenia, statistical significance was not met. Gender differences in fracture risk could be explained by the fact that muscle strength decline is generally two times greater in men compared to women [124]. In addition, low testosterone levels have been associated with a decrease in muscle mass and strength [271]. Since men lose more testosterone with age compared to women, this decline could play a role in the onset and severity of sarcopenia in older men [272]. Another possible explanation is the inadequate power to detect the risk of non-spine fractures in sarcopenic women due to their small sample size.

One of the strengths of this study is that the data were obtained from two very well established cohorts: MrOS and SOF, designed to understand the risk of fractures in older subjects. Another strength is that we adopted a unique approach in assessing the risk of non-spine fractures by classifying participants based on their bone and body composition. Additionally, the use of the residuals method to assess appendicular lean mass has been shown to be a good predictor of mobility limitations. Other appendicular lean mass assessment methods, such as the appendicular skeletal muscle index, do not account for total body fat [147] [146].

One main limitation of this study is that the definitions and algorithms of sarcopenia are still controversial [126]. For instance, the “International working group on sarcopenia” includes only the gait speed and the ratio of appendicular lean mass over height squared (ALM/height^2) in

its algorithm without assessing muscle strength [127]. On the other hand, the Foundation for the National Institutes of Health (FNIH) uses the ratio of appendicular lean mass over body mass index for muscle mass assessment as well as different muscle strength cutoffs (with or without physical performance assessment). The same analysis was repeated for the EWSOP (using ALM/ height^2 instead of the residuals method), the international working group, and the FNIH operational definitions. Although not shown here, the results were roughly the same for older men across all three definitions. In women, results were similar except for the FNIH definition which showed that participants with both low BMD and sarcopenia were not at a higher risk for non-spine fractures.

To conclude, men with both low BMD and sarcopenia had a much higher risk of fractures compared to men with only one or neither condition. This finding was not apparent in women suggesting gender differences in the role of sarcopenia on osteoporotic fractures. If our results are confirmed, assessment of sarcopenia status concomitantly with low bone mass status may assist in identifying men at the highest risk of future fracture. Development of treatments for sarcopenia management could potentially prevent fractures, especially in older men with both low BMD and sarcopenia.

5.6 TABLES AND FIGURES

Table 5.6.1.Baseline characteristics of older men by bone and body composition*

A) In Men

Characteristics	Normal BMD and no sarcopenia (N=3367)	Sarcopenia alone (N=79)	Low BMD alone (N= 1986)	Low BMD and Sarcopenia (N=112)	P value
Race					
White, n(%)	3173(94)	76(96)	1943(98)	111(99)	ac
Age (yr), mean ± SD	72.8±5.5	80.5±6.0	74.6±6.0	79.6±6.3	abcde
Body mass index (kg/m2), mean ± SD	28.3±3.8	26.4±3.5	26.2±3.4	24.5±2.7	abcef
Appendicular skeletal Mass (kg), mean ± SD	25.3±3.4	20.3±2.3	23.4±3.0	19.4±2.0	abcde
Current smoker, n (%)	114 (3.4)	1(1.3)	68(3.4)	8(7.1)	
Alcohol use (drinks/week), mean ± SD	4.7±7.3	5.7±10.9	3.8±5.8	3.0±5.0	acdf
Previous fracture, n(%)	1764(52.4)	43(54.4)	1228(61.9)	64(57.1)	a
Rheumatoid arthritis, n(%)	174(5.2)	9(11.4)	89(4.5)	9(8.0)	bd
Current oral and/or inhaled steroid user, n(%)	235(7.3)	12(16.9)	196(10.2)	267(24.8)	abce
Walks for exercise, n(%)	1660(49.3)	32(40.5)	1033(52.0)	52(46.4)	d
Excellent/Good Health Status, n(%)	2917(86.7)	61(77.2)	1718(86.6)	77(68.8)	bcde
Gait speed (m/s), mean ± SD	1.2±0.2	0.9±0.2	1.2±0.2	0.9±0.3	bcde
Grip strength (kg), mean ± SD	39.8.1±7.9	26.3±5.8	37.9±7.5	25.4±7.0	abcde
Functional status					
# of IADL impairments, mean ± SD	0.3±0.8	1.2±1.4	0.3±0.8	1.3±1.6	bcde
Any falls last 12 months, n(%)	693 (20.6)	37(46.8)	420(21.2)	32(28.6)	bcdf
2 or more falls last 12 months, n(%)	306(9.1)	21(26.6)	165(8.3)	18(16.1)	bcde
Total Hip BMD (g/cm^2), mean ± SD	1.03±0.11	0.97±0.09	0.84±0.09	0.79±0.10	abcdef
Femoral neck BMD (g/cm^2), mean ± SD	0.86±0.10	0.82±0.07	0.66±0.06	0.64±0.06	abcdef

Table 5.6.1. Continued

B) In Women

Characteristics	Normal BMD and no sarcopenia (N=308)	Sarcopenia alone (N=48)	Low BMD alone (N=626)	Low BMD and sarcopenia (N= 132)	P value
Race					
White, n (%)	65(21.1)	27(56.3)	393(62.8)	103(78.0)	bcef
Age (yr), mean ± SD	75.6±4.2	77.0±3.5	78.3±4.3	79.1±4.0	bcdf
Body mass index (kg/m2), mean ± SD	30.8±4.7	28.4±4.5	26.9±4.5	27.3±4.7	bcd
Appendicular skeletal Mass (kg), mean ± SD	17.0±2.7	13.3±1.9	15.0±2.3	12.6±1.5	bcde
Current smoker, n (%)	21(6.8)	4(8.3)	40(6.4)	11(8.3)	
Alcohol use (drinks/week), mean ± SD	0.7±1.8	1.5±3.6	1.1±2.8	1.0±2.9	ab
Previous fracture, n (%)	69(22.5)	9(18.8)	136(21.8)	24(18.2)	
Rheumatoid arthritis, n (%)	33(10.8)	5(10.4)	59(9.4)	6(4.6)	c
Current oral and/or inhaled steroid user, n (%)	15(4.9)	5(10.4)	28(4.5)	13(9.9)	ce
Walks for exercise, n (%)	119(38.8)	15(31.3)	272(43.7)	51(38.6)	d
Excellent/Good Health Status, n (%)	238(77.3)	37(77.1)	493(78.8)	104(78.8)	
Gait speed (m/s), mean ± SD	0.86±0.21	0.86±0.19	0.90±0.22	0.88±0.20	a
Grip strength (kg), mean ± SD	19.7±4.9	15.5±3.8	18.5±4.8	15.6±3.5	abcde
Functional status					
# of IADL impairments, mean ± SD	1.1±1.3	1.0±1.2	0.8±1.3	0.8±1.1	a
Any falls last 12 months, n (%)	91(29.6)	12(25.0)	189(30.2)	44(33.3)	
2 or more falls last 12 months, n (%)	31(10.1)	5(10.4)	79(12.6)	13(9.9)	
Total Hip BMD (g/cm^2), mean ± SD	0.93±0.3	0.91±0.12	0.70±0.11	0.71±0.09	acdf
Femoral neck BMD (g/cm^2), mean ± SD	0.85±0.11	0.83±0.09	0.60±0.08	0.61±0.08	acdf

Significance ($p<0.05$): **a** normal vs low BMD, **b** normal vs sarcopenic, **c** normal vs low BMD and sarcopenia, **d** low BMD vs sarcopenic, **e** low BMD vs low BMD and sarcopenia, **f** sarcopenia vs low BMD and sarcopenia. BMD: bone mineral density; SD: standard deviation; IADL: instrumental activity of daily living.

Table 5.6.2. Hazard ratio (95% confidence intervals) for non-spine fractures by sarcopenia, osteopenia/osteoporosis, and sarco-osteopenia/sarco-osteoporosis*

A) All fractures

Variable (unit)	Age adjusted HR (95% CI)	MV adjusted HR(95% CI)
Men		
Normal BMD and lean mass	1.00 (Ref)	1.00
Sarcopenia alone	1.19(0.65,2.17)	1.14(0.62,2.09)
Low BMD alone	1.79(1.56,2.05)	1.67(1.45,1.93)
Low BMD and sarcopenia	3.75(2.64,5.32)	3.79(2.65,5.41)
Women		
Normal BMD and lean mass	1.00 (Ref)	1.00
Sarcopenia alone	1.50(0.66,3.42)	1.26(0.55,2.90)
Low BMD alone	3.09(2.08,4.59)	2.62(1.74,3.95)
Low BMD and sarcopenia	2.80(1.72,4.58)	2.27(1.37,3.76)

Table 5.6.2. Continued

B) Traumatic fractures excluded (N=167, 19% in men; N=23, 8% in women)

Variable (unit)	Age adjusted HR (95% CI)	MV adjusted HR(95% CI)
Men		
Normal BMD and lean mass	1.00 (Ref)	1.00
Sarcopenia alone	1.26(0.67,2.38)	1.20(0.64,2.28)
Low BMD alone	1.88(1.61,2.20)	1.82(1.55,2.13)
Low BMD and sarcopenia	4.16(2.87,6.01)	4.08(2.79,5.96)
Women		
Normal BMD and lean mass	1.00 (Ref)	1.00
Sarcopenia alone	1.55(0.68, 3.55)	1.27(0.55,2.92)
Low BMD alone	2.95(1.97,4.42)	2.42(1.59,3.68)
Low BMD and sarcopenia	2.74(1.66,4.52)	2.14(1.27,3.58)

*MV model: adjustment included age, race, fall history, previous fracture, current smoking, steroids, rheumatoid arthritis, alcohol consumption, IADL impairments, and physical activity. BMD: bone mineral density; HR: hazard ratio; CI: confidence interval; IADL: instrumental activity of daily living

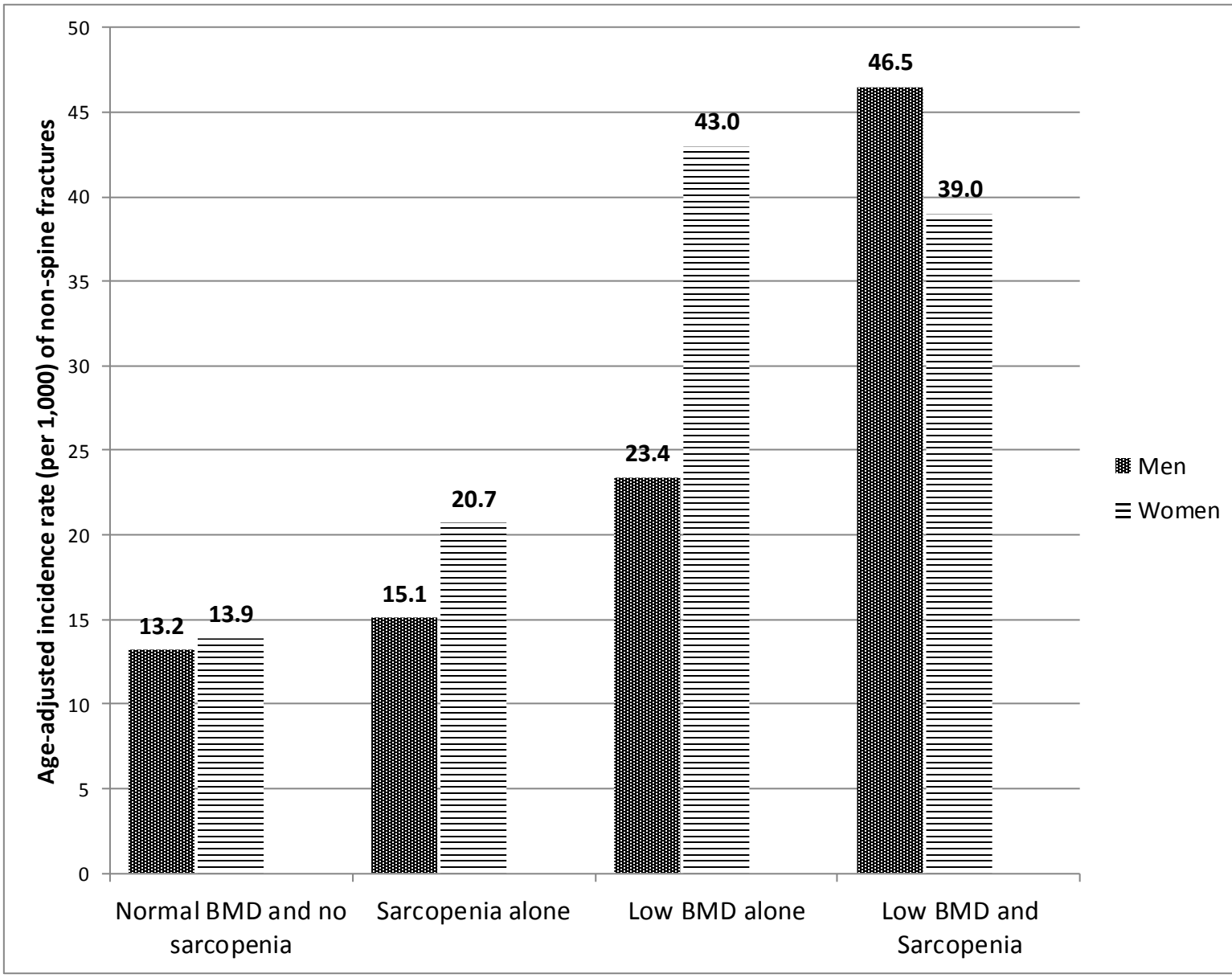
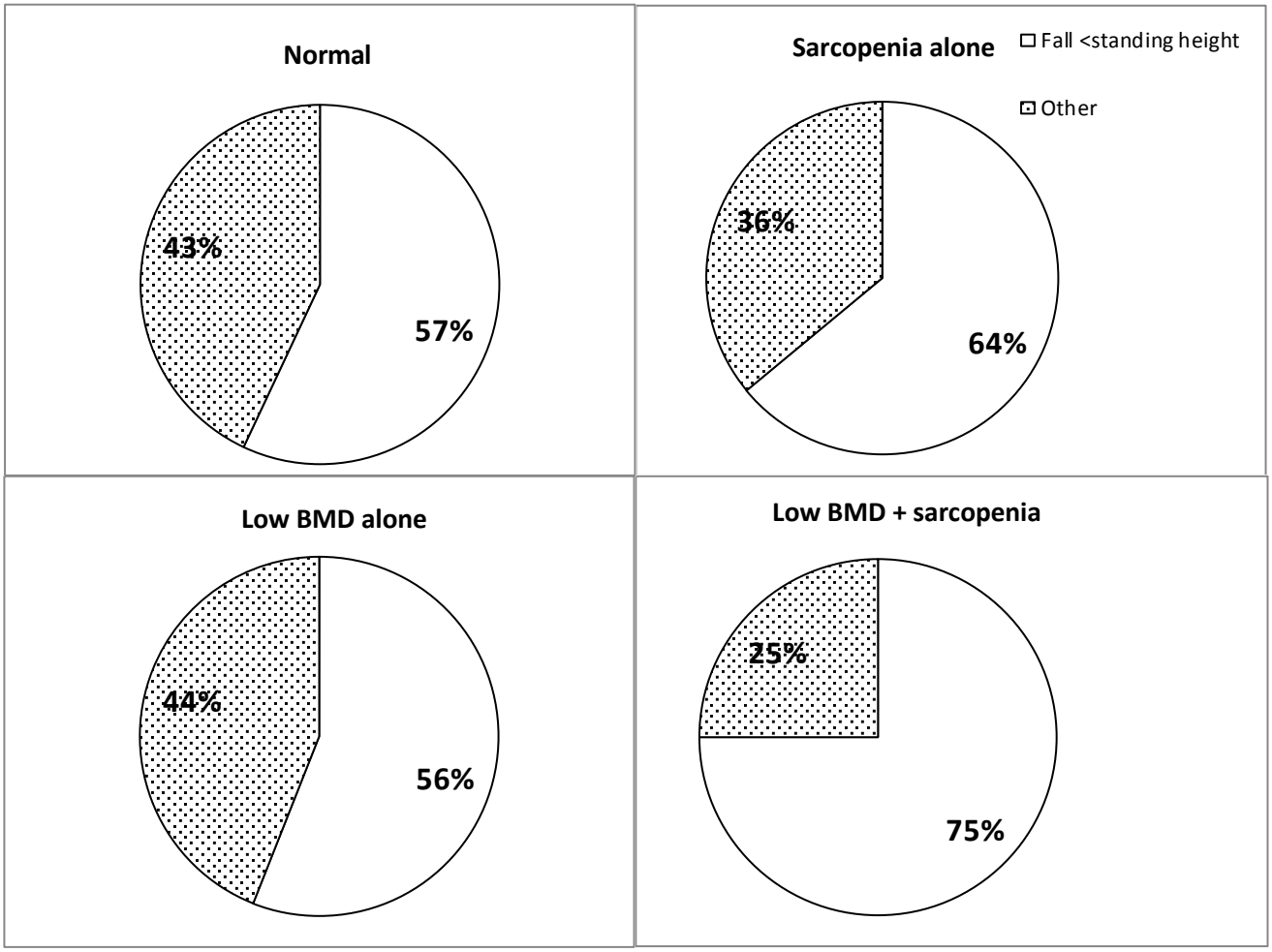


Figure 5.6.1. Age-adjusted incidence rate (per 1,000) of non-spine fractures by BMD and body composition

A) In Men


Normal
43%
57%
Sarcopenia alone
Fall <standing height
Other
36%
64%
Low BMD alone
44%
56%
Low BMD + sarcopenia
25%
75%

B) In Women

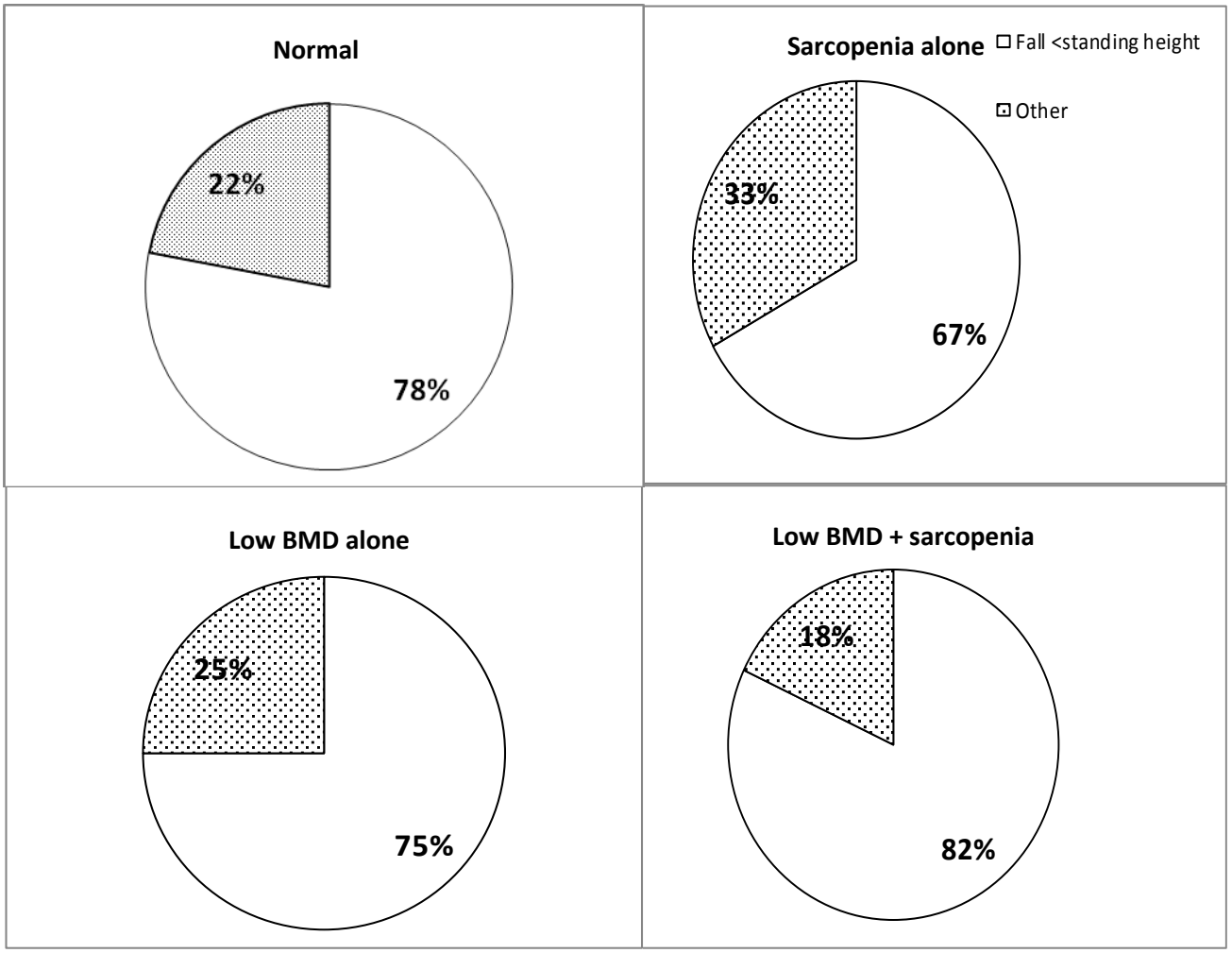


Figure 5.6.2. Proportion of fractures that were due to a fall from a standing height or less by low BMD and sarcopenia in older individuals

6.0 DISCUSSION

6.1 SUMMARY, CONCLUSIONS AND FUTURE RESEARCH

The primary aim of these three papers was to investigate the role of sarcopenia, osteoporosis, and osteoporotic fracture risk, and explore the muscle bone interaction. First, we were interested in comparing the importance of areal and volumetric BMD in fracture risk prediction. Areal BMD is the gold standard for clinical assessment of fracture risk but it is a two dimensional estimate of integrated cortical and trabecular BMD. We tested the hypothesis that a direct measure of trabecular and cortical volumetric BMD (vBMD) would improve fracture prediction. We found that low aBMD and vBMD are both associated with multiple sites of fracture risk, and that trabecular vBMD had stronger associations than cortical vBMD. Nonetheless, low vBMD was not found to be a better predictor of major osteoporotic fractures (hip, spine, wrist, and shoulder) compared to aBMD, except for spine fractures. Therefore, based on these results, DXA remains the diagnostic imaging technique of choice to assess fracture risk in older men. Future studies might be needed to understand further the advantage of QCT over DXA in predicting spine fractures.

Subsequently, in our second paper, we found that low appendicular lean mass (ALM) was associated with poorer measure of skeletal size, density, and strength as well as low spine and femoral neck aBMD. Although ALM was associated with all QCT parameters, grip strength

was related only to radius parameters. No relationship was found between leg power and QCT parameters. We postulated that the stronger relationship observed for ALM suggests that the overall mechanical load of lean mass on bones may contribute more to the skeletal size, density and strength than site specific measures of muscle strength and power. Future efforts to improve ALM may play a key role in improving density and quality of bones, and preventing fractures. Longitudinal studies are needed to further establish which changes in ALM and strength improves skeletal size, density, and strength. Taken together, these findings highlight that ALM was associated with strength and geometric bone parameters that have been previously related to fractures. The association between grip strength was limited to a site specific effect at the radius.

Finally, we were interested in examining whether sarcopenia with or without osteoporosis is associated with an increased risk of non-spine fractures. In this third paper, we demonstrated that men with both sarcopenia and low BMD are at a much higher risk for non-spine fractures compared to men with either one or neither condition. On the other hand, low BMD with or without sarcoepnia in women was associated with an increased risk of fractures, suggesting that low BMD is the driving force of non-spine fractures in older women.

The findings of these papers shed light on the cross talk between muscle and bones. In fact, the loss of muscle and bone mass has been previously shown to be coupled and part of the same functional unit [182]. One explanation to the observed higher risk of fractures in older men with sarcopenia and osteoporosis combined, may be that the low ALM and grip strength in these men contributed to lower skeletal size, density and strength. Therefore, assessing these muscle measurements concomitantly with bone strength may improve fracture risk assessment in older adults. Based on this concept, identifying and exploring the risk factors related to both muscle and bone deterioration instead of each one alone may lead to better assessments of fractures.

Pleiotropy, mechanotransduction, and endocrine roles are the main etiologies responsible for the coordinated and progressive deterioration of the musculoskeletal system throughout life [3]. This is an emerging field of research and many attempts are being made to understand the etiologies shared by both tissues so that preventive measures and interventions could be targeted to both simultaneously. Therefore, future studies should investigate further the role and importance of pleiotropy in the synchronized deterioration of both muscles and bones. In addition, more work is needed to understand the role that muscles and bones play as endocrine organs. Although, it is clear that muscles affect both the density [3][4][5][6][7] and quality of bones [8][9], the effect of the bones on muscles is less well understood and should be explored. Also, identifying and testing for muscle/bone loss biomarkers may help detect subclinical diseases which is essential for primordial prevention.

The World Health Organization (WHO) definition of osteoporosis relies on a femoral neck T-score of less than or equal to – 2.5 for osteoporosis diagnosis [10]. Despite the fact that this method is being widely used, only 20% of patients with osteoporosis experience fractures. In one of the papers, we compared the volumetric BMD with areal BMD without incorporating other bone structure and geometry parameters. We showed that vBMD was not better than aBMD but, future efforts should be made to incorporate other QCT bone parameters of size and strength with the ultimate goal of identifying individuals at a higher risk for fractures.

Furthermore, there is no clear consensus on the definition and diagnosis of sarcopenia. There are currently several operational definitions. The European working group, the international working group, and the FNIH have developed different algorithms to identify individuals with sarcopenia. These algorithms differ by whether or not to include physical function, as well as on different gait speed and muscle strength cutoffs [11]. Furthermore, several

methods exist to assess low muscle mass such as the appendicular skeletal muscle mass index (ALM/height2), the appendicular lean mass to BMI ratio (ALM/BMI), and the residuals method (linear regression of appendicular lean mass by height and total body fat) [12]. Future efforts should be made to have consensus on one operational definition, so that diagnostic and therapeutic tools can be developed.

6.2 PUBLIC HEALTH IMPLICATIONS

The percentage of individuals older than 65 years of age is increasing. In 2008, approximately 506 million individuals worldwide were older than 65. This number is expected to double and reach 14% of the world's population by year 2040 [1]. With this increase in the older population, a higher number of older men and women are expected to experience deterioration in their bones and muscles leading to osteoporosis and sarcopenia respectively.

Furthermore, musculoskeletal disorders are a major cause of disabilities worldwide and represent a major economical burden. The cost spent on musculoskeletal disorders is greater than the cost of breast cancer, stroke, and cardiovascular diseases combined [3]. Therefore, it is of primary importance to understand the burden that osteoporosis and sarcopenia represent in older men and women. Doing so would help in preventing future fractures and thus, poor health outcomes. In fact, mortality and morbidity are two major consequences of osteoporosis, primarily due to hip fractures [65]. Worldwide, the total Disability Adjusted Life Years (DALYs) lost attributed to fractures was about 58 million [228]. In Medicare enrollees, while hip fractures had the highest excess cost, multiple types of fractures were also associated with higher health care expenditures [229] [65].

The work included in this dissertation has important public health implications. Despite advances in technology, there was no evidence that trabecular vBMD was superior to aBMD. Therefore, DXA remains the gold standard for bone fracture assessment. Its' low cost, quickness, low radiation and precision makes the DXA a good screening tool that should be utilized more frequently to prevent fractures in community dwelling adults. Furthermore, diagnosing and preventing sarcopenia may also be important in preventing falls.

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