ETHNIC AND GENDER DIFFERENCES IN THE CORRELATES OF BONE MINERAL DENSITY

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ABSTRACT

Osteoporosis is an important public health concern because of the significant morbidity and mortality associated with osteoporotic fractures. It is well established that ethnic and gender differences influence osteoporosis risk, but the etiology of these differences is not well studied. The goals of this research were to examine correlates of hip bone mineral density (BMD) and rates of bone loss among persons of African ancestry in three complementary analyses.

In the first analysis, correlates of BMD were identified for 1,784 Tobagonian males, aged 40-84 years. BMD was inversely associated with age, height, and history of a broken bone. Lean mass, working on a fishing boat, and diabetes were positively associated with BMD. Correlates explained 25% of the variability in hip and femoral neck BMD.

Correlates of BMD were also identified for 340 postmenopausal Tobagonian females, aged 50-94 years. BMD was positively associated with weight, thiazide diuretics, aspirin, recent back pain, and diabetes. BMD was inversely associated with age, thyroid medication, family history of fracture, and beta-blockers. Correlates explained 37% - 38% of the variability in hip and femoral neck BMD.

Lastly, ethnic differences in rates of bone loss within gender were investigated among 457 Caucasian and 121 African American males and females, aged 65-87 years. Baseline and follow-up BMD was measured four years apart. African American males lost significantly less

hip BMD compared to Caucasian males (-0.04% vs. -0.45%), after adjusting for covariates. Longitudinal changes in lean and fat mass explained more variability in rates of bone loss than weight, after adjustment for covariates.

In conclusion, BMD was approximately one standard deviation higher among Tobagonians, despite gender, compared to NHANES data for African American males and females. Correlates of BMD were similar across gender among Tobagonians. Interestingly, older African American females had rates of bone loss that were comparable to Caucasian females, while African American males experienced significantly lower rates of hip bone loss.

With our aging society and longer life expectancies for persons of African ancestry, the public health significance of this research is that osteoporosis may have a greater impact among minorities in the future.

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1. Introduction

This body of research focuses on ethnic and gender differences in the correlates of bone mineral density (BMD). Chapter 2 of this document is a review of the literature on the natural history of osteoporosis, BMD, and well-known correlates of BMD. Special emphasis is placed on ethnic and gender differences and gaps in the literature. To address the paucity of literature on the ethnic and gender differences in the risk of developing osteoporosis, three separate analyses were undertaken to evaluate the correlates of BMD and changes in BMD over time among persons of African ancestry.

In chapters 3 and 4 we examined the interrelationships between BMD and demographic, lifestyle, anthropometric, and health-related factors among Tobagonian males and females, respectively. In the first analysis, correlates of total hip and femoral neck BMD were examined in a population-based study of 1,784 Tobagonian males, aged 40 years and older (Chapter 3). A similar analysis was undertaken to identify correlates of total hip and femoral neck BMD among 340 postmenopausal Tobagonian females, aged 50 years and older. Because the analyses with Tobagonian males and females were cross-sectional, we then examined longitudinal changes in total hip and femoral neck BMD among older African American (n=121) and Caucasian American (n=457) males and females. The objective of this final analysis was to evaluate ethnic differences in rates of bone loss within gender (Chapter 4). Factors associated with rates of bone loss were also examined (Chapter 4). Findings from these three complementary analyses are summarized in the final section of this document (Chapter 5).

2. Literature Review: Epidemiology of Osteoporosis

2.1. Disease Burden

Osteoporosis (OP) is a metabolic bone disease that affects the entire musculoskeletal system. (1) OP is characterized by reduced bone mineral density (BMD) and microarchitectural deterioration of bony tissue. (1, 4, 5) These age-related changes in bone contribute to decreased skeletal strength, which is a precursor for fragility and increased fracture risk. In the U.S., OP is clinically recognized by low trauma fractures at the proximal femur (hip), proximal and distal forearm (wrist), vertebrae (spine), and other skeletal sites. (1, 5-8)

2.2. Public Health Impact

OP is a major public health problem, especially among older persons. OP afflicts females more often than males, affecting approximately 44 million females in the United States and another 200 million females worldwide. (2) While OP can affect people of all ethnic groups and both genders, this disease is more prevalent in Caucasian females. (3)

An estimated 1.5 million osteoporotic fractures are reported annually in the US. (2) Osteoporotic-fractures cause significant morbidity and mortality. (1, 5, 9, 10) In 2001, over 17 billion dollars was spent on treatment for osteoporotic fractures and 7% of these costs were used to treat non-Caucasian males and females. (2) Hip fractures have significant economic costs and cause more disability than other osteoporotic fractures. (1) The incidence rate of hip fractures increase exponentially with age. (6, 11) Approximately 50% of people who sustain a hip fracture will have permanent functional disability greater than before hip fracture. Hip fractures are associated with a 15-20% increase in mortality, especially among older persons. (3, 12)

The number of hip fractures worldwide is expected to increase three-fold, from 1.7 million in 1990 to 6.3 million by 2050. (1, 13) One reason for this projected rise in hip fractures

is the increasing life expectancy for persons over the age of 65 years. For example, the number of older minorities is expected to double. (9) Minorities will comprise a larger proportion of the worldwide population and since OP primarily affects older persons, there may be dramatic increases in hip fracture risk among males and minorities. The incidence rate of hip fracture among minorities is lower than Caucasians. (2)

2.3. Background

2.3.1. Bone Biology

The skeletal system is comprised of cartilage and bone. (1, 14, 15) Bone is a living connective tissue consisting of cells and extracellular matrix. (14, 15) Connective tissue of bone has mechanical, protective, and metabolic functions. The extracellular matrix of bone tissue encompasses organic and inorganic components. Collagen fibers are the primary constituents of the organic extracellular matrix. Sixty-five percent of the extracellular matrix is inorganic matter, consisting of calcium and phosphate. Calcium and phosphate deposits are arranged into hydroxyapatite crystals that adhere to collagen fibers.

Bone is comprised of 70% calcium, 22% protein, and 8% water. Bone is also the main mineral repository of calcium, where 98% of the body's calcium is stored and maintained. (14, 15) Calcium is responsible for many biological functions such as bone mineralization, blood clotting, and membrane stability at the extracellular level.

Bone is often classified by its shape and structure. Axial and appendicular are just two types of bone shapes. Long bones are enchondral and provide structural support and include the humerus, radius, and hip. (14, 15) Flat bones are membranous and include the sternum, ribs, and vertebral bodies. (14, 15) Cortical and trabecular are bone structures. Cortical bone is approximately 80% of the skeletal mass and represents the external (periosteal) structure of bone

that is formed by dense (compact), calcified tissue. (14, 15) Cortical bone provides mechanical and protective support. (14, 15) Trabecular bone is made of chancellors and/or spongy tissue that is responsible for metabolic function. (14, 15) The appendicular skeleton (i.e., forearm or heel) is comprised mostly of cortical bone while the axial skeleton (i.e., hip, ribs or spine) is made up of both cortical and trabecular bone. Trabecular bone mass makes up 25% of whole body mass and the surface area of trabecular bone exceeds cortical bone. The spine and hip contain both cortical and trabecular.

Osteocytes, osteoblasts, and osteoclasts are three types of cells in mature bone tissue. Osteocytes originate from osteoblasts that are trapped during bone formation and mineralization. Osteocytes maintain bone matrix and are integral in bone homeostasis. Osteoblasts are bone forming cells that produce and secrete collagenous, non-collagenous, and regulatory factors. Osteoclast activity is the mechanism by which old bone is resorbed and removed. Conversely, osteoblast activity rebuilds new bone using collagen. Osteoblast cells secrete a bone matrix that encapsulates cells that form osteocytes.

2.3.2. Phases of Bone Growth

Skeletal health is largely determined by peak bone mass (PBM). (16-19) PBM is the quantitative amount of bony tissue accumulated from uterine life through the end of skeletal maturation. (16-19) the timing of PBM acquisition differs for axial and appendicular bone. It is estimated that in the second decade of life, the axial skeleton has achieved PBM. For the appendicular skeleton, it is estimated that the rate of bone growth slows considerably during late adolescence and PBM is attained earlier at the axial skeleton. Once skeletal maturation or PBM is achieved, bone mass does not increase any further. Approximately 90% of PBM is acquired by age 18 years. (18-20)

Bone mass acquisition and loss occurs in three phases across the life cycle for both males and females. The first phase is during early childhood when bone is acquired. Throughout adolescence, 50% of peak adult bone mass is acquired. The second phase is bone stabilization in the third decade until late fourth or early fifth decade. During this phase, there is virtually no bone loss and the final phase of bone growth occurs in the fifth decade. (21) PBM may be influenced by a number of factors including hormonal, physical activity, lifestyle, and nutritional factors. (19, 22) Nearly 60% of the risk of developing OP among older persons is explained by PBM acquisition. (17, 22)

Gender Differences in PBM

At birth until puberty, gender differences in bone mass are almost non-existent. (18) The onset of pubertal maturation accompanies gender differences in bone mass. Biochemical markers of bone formation and resorption are higher among males compared to age-matched females, resulting in rapid mineral accrual among males. Pubescent males have a longer bone growth period compared to females resulting in a greater increase in bone size and cortical thickness for males. (18, 19, 23)

Ethnic Differences in PBM

Research has shown that AA children develop higher PBM than Caucasian children, and this difference in PBM partially explains the lower risk of fracture among adult AAs. (24) A small study of 28 adolescent females found that AA adolescents absorb and retain calcium more efficiently than Caucasians, which favors bone accretion. Ethnic differences in calcium metabolism may account for higher BMD that has been observed in AA adults. (24) Another study of young adults showed that PBM was higher among AAs compared to Caucasians, and these ethnic differences did not vary by gender. (25) Higher bone mass among AAs compared to

Caucasians is related, in part, to larger bone size that has been observed in AAs. Within ethnicity, AAs achieve higher PBM compared to native Africans and these differences are attributed to nutritional and health-related factors.

2.3.3. Bone Metabolism

Healthy bone is constantly remodeling through a controlled process that is necessary for bone growth and repair. (14) The bone-remodeling pathway is initiated by signal transduction from osteocytes stimulating bone resorption (osteoclast activity), which triggers bone osteogenesis/formation (osteoblast activity). A synergistic relationship exists between bone formation and bone resorption and this relationship is controlled by calcitropic hormones, namely vitamin D metabolites (25 hydroxyvitamin D and one, alpha 25 dihydroxyvitamin D [25OHD and 1, 25$(OH)_2D_3$, respectively]), calcitonin, and parathyroid hormone (PTH). Bone remodeling is influenced by mechanical stimuli, hormonal changes (estrogen deficiency or hyperthyroidism), growth factors, and inflammation (rheumatoid arthritis or periodontal disease) that cause pathological alterations in bone tissue. Throughout the third decade of life, bone remodeling is in a state of equilibrium where bone resorption is coupled by bone formation. Around age 40, osteoblast activity is reduced and subsequent imbalances in remodeling contributes to small deficits of bone.(14) This imbalance between bone resorption and bone restoration causes skeletal fragility (i.e., low BMD), elevated excretion of urine metabolites (measured by biochemical assays), subsequent bone loss, and the gradual onset of OP later in life.(14)

<u>Calcitropic Hormones</u>

Dietary calcium and protein are essential for normal bone metabolism. Calcium regulates cell growth and low dietary calcium intake negatively influences bone metabolism by initially

depleting serum (circulating) calcium. The body will attempt to restore normal levels of serum calcium by releasing parathyroid hormone (PTH) which causes the kidney to convert inactive 25(OH)D to an active metabolite of 1, $25(OH)_2D_3$. Increased bone resorption is caused by 1, $25(OH)_2D_3$. When elevated PTH levels combine with 1, $25(OH)_2D_3$, this leads to increases in bone resorption.(14) Small increases in levels of PTH over time are associated with decreased vitamin D and increased levels of biochemical markers of bone turnover resulting from continued loss of BMD.(26,27)

25(OH)D has been shown to decrease with age, while PTH increases.(28-31) Secondary hyperparathyroidism (HPTH) results, in part, from vitamin D deficiency but is also related to sustained elevations in PTH levels.(32) The sustained elevations in PTH levels cause a continued state of high bone turnover, which usually reduces approximately 10 years following menopause in females.(26,31) HPTH causes higher rates of bone turnover, accelerated cortical bone loss, low BMD, and increased risk of fracture.(26,31,32) Research examining the ethnic differences in HPTH, increased bone turnover, and subsequent lower BMD is conflicting.(26,33) Since AAs have higher rates of PTH and low levels of 25OHD, there is some concern that secondary HPTH is more prevalent in AAs compared to Caucasians.(27,32-35) Some research suggests that AAs have skeletal resistance to the bone resorbing effects of PTH since bone turnover is lower, BMD is higher, and fracture rates are lower in AAs, despite elevated levels of PTH.(32,35) Conversely, other studies have identified normal PTH levels in AAs compared to Caucasians.(31,36)

Markers of Bone Turnover

Serum osteocalcin (OC) and urinary N-telopeptide of type I collagen (NTX) are just two of the biochemical markers of bone formation and bone resorption, respectively.(26) OC is a small, hydroxyapatite-binding protein made by osteoblasts that measures osteoblast function, and

levels of OC correlate with bone formation rates.(37) NTX is a degradation fragment that reflects osteoclast activity and is considered one of the best indices for assessing bone resorption.(37)

Biochemical markers of bone turnover are higher in children compared to adults because of the skeletal maturation phase that occurs during adolescence. Certain medications, medical conditions, menstrual cycle, time of day, season, exercise, nutritional factors, and physical immobility all affect biochemical markers of bone turnover.(37) For example, biochemical markers are elevated up to one year following a fracture but OC levels decrease substantially during pregnancy.(37) In the 3rd and 4th decades of life, biochemical markers of bone turnover are higher in males compared to females but at older ages, levels are higher in females than males.(37) One explanation for higher levels of biochemical markers in older females is that during menopause, these markers increase substantially and remain elevated for 10-15 years post menopause. Among perimenopausal females, declines in estrogen are accompanied by increased rates of skeletal remodeling, resulting in bone loss. This bone loss is related, in part, to diminished osteoblast activity that is unable to fully restore bone removed by osteoclasts during the resorption phase of skeletal remodeling.

In adult males, biochemical markers typically do not change with age.(37,38) Mechanisms of bone turnover are essential for understanding the pathogenesis of OP because changes in biochemical markers of bone turnover reflect alterations in skeletal metabolism like bone loss.

Biochemical markers of bone turnover are representative of rates of bone resorption and formation in the entire body and therefore, biochemical markers of bone turnover may provide additional insight into age-related changes in BMD since alterations in marker levels are parallel with declines in BMD.(37,38)

Ethnic Differences in Rates of Bone Turnover

Comparative studies of AA and Caucasian children as well as adults have demonstrated that biochemical markers of bone turnover were lower in AAs compared to Caucasians.(22,34,36,37) Several studies have also identified higher OC levels in Caucasians compared to AAs suggesting more bone remodeling activity among Caucasians.(31,36,39,40) Even though dietary calcium intake is lower in AA females compared to Caucasian females, calcium efficiency is the same in these two groups.(35) For example, Kleerekoper et al. studied the relationship between BMD, calcitropic hormones, and biochemical markers of bone turnover in 112 AA and 250 Caucasian postmenopausal females aged 55-75 years who were enrolled in a health maintenance organization.(40) In this study, biochemical markers of bone formation and resorption were significantly lower in AAs compared to Caucasians, indicating lower rates of bone remodeling for AAs.(40) Although serum PTH levels were significantly higher in AA females, mean BMD was also higher than Caucasians. This finding suggests that AA females may have greater skeletal resistance to PTH because of lower bone remodeling rates in the presence of elevated PTH and lower OC levels.(40) In another study with AA and Caucasian males, researchers also suspected mild skeletal resistance to PTH in AA males because of elevated PTH in the small sample examined.(33)

A community-based, multi-site study of 2,313 peri- and premenopausal multiethnic females demonstrated that Caucasian females had the highest mean serum OC levels compared to AA, Chinese, and Japanese females, even after adjustment for covariates.(41) Similar results were observed for mean urinary NTX levels after adjusting for covariates, thereby indicating higher biochemical markers of bone turnover in Caucasian females compared to AA and Chinese females in this study.(41) Data from cross-sectional and prospective studies support the premise

that bone turnover indices, serum calcidiol levels, and urinary calcium excretion are lower in AA males and females compared to Caucasian males and females.(26,31,35,36,40,41) Research suggests that AAs have lower levels of 1, $25(OH)_2D_3$, an indicator of reduced bone remodeling/turnover, compared to Caucasians, but mean BMD values are higher and the risk of fracture is lower among AAs.(26,31,35,36,40,41)

Endogenous Sex Hormones

Adequate levels of serum estradiol are necessary for PBM acquisition in both males and females, control of bone remodeling during reproductive years for females, and at older ages for males.(18,42) Estrogen promotes BMD by reducing bone resorption activity of osteoclasts. A positive relationship exists between serum estradiol and BMD in older females at all skeletal sites as well as males, depending on the skeletal site.(42) Review of the sex hormone literature suggests that estradiol was the dominant sex hormone that regulates bone resorption in males and females. Sex hormones maintain stable rates of bone turnover, thereby preserving BMD. (22,38,42) An inverse relationship exists between age and both serum estradiol and testosterone in males and females.(34,42)

Gender Differences in Sex Hormones

Gonadal sex steroid hormones may contribute to gender differences in BMD and both males and females experience age-related changes in testosterone and estradiol.(22,38) Females with hormonal dysfunction have low serum estradiol and elevated gonadotropin levels. (38) Males with hormonal dysfunction experience low testosterone levels commonly referred to as hypogonadism, which is a condition that manifests from testicular dysfunction and results in reduced levels of free testosterone.(38) Research has shown that low BMD was associated with hypogonadism in elderly males and 20-30% of bone loss can be contributed to

hypogonadism.(43) Among females circulating estradiol was reduced by 90% during menopause and this decline in estrogen is associated with increased bone resorption and decreased BMD. The available research proposes a causal link between low estradiol levels, accelerated bone loss, and low BMD in both males and females. Variations in serum estradiol partially accounted for gender differences in the rate of bone loss.(18,42)

Ethnic Differences in Sex Hormones

Gonadal sex steroid hormones may also contribute to ethnic differences in BMD.(22) A study of 402 AA and Caucasian males and females between the ages of 25 and 36 years, demonstrated that younger AAs have higher mean serum testosterone levels compared to younger Caucasians, but there were no ethnic differences in estradiol levels among younger females.(22) Serum testosterone and estradiol levels are typically higher in pre- and postmenopausal AA females compared to Caucasian females. While Cauley et al. demonstrated that serum estrone levels were higher among older AA females in a study of 273 Caucasian and 86 AA females, which was largely explained by obesity, but serum testosterone levels were similar.(44) A study of 33 AA and Caucasian males also demonstrated that AA males had higher circulating estradiol concentrations, which may lead to greater secretion of growth hormone and higher bone mass in AAs.(45) Research suggests that AAs have higher levels of estradiol and/or testosterone throughout all phases of life and this disparity may provide insight into ethnic differences in BMD.(22,44-46) Growth hormones and insulin growth factor I are other sex hormones that may influence bone metabolism, BMD, and bone loss. Sex hormones will not be studied or reported in this research.

2.3.4. Genetics

BMD heritability ranges from 50 to 90% at all ages.(47) Research suggests that genetic factors contribute to 80% of the variability in PBM and genetic differences in bone metabolism account for ethnic differences in BMD.(22) Genetic markers also provide insight to age-related changes in BMD and hip fracture risk.(47,48) This research will not directly assess genetics and its relationship to ethnic and gender differences in BMD.

2.4. Bone Mineral Density

BMD is a strong determinant of fracture risk and bone strength.(12,49) Bone strength encompasses the amount of bone tissue, architectural arrangement of bone, the presence of bone matrix or mineralization abnormalities, and the presence of microfractures.(50) Bone mass accounts for 70-80% of bone strength and is primarily determined by PBM acquisition and age-related bone loss.(16,51) Areal BMD is measured by dual-energy x-ray absorptiometry (DXA) and this device is the gold standard for measuring BMD at the hip and spine.(52) BMD is an estimated calculation of bone mineral within a specific scanned area (bone mineral content) divided by the projected area in the same region commonly referred to as areal density.(53) Areal BMD is a two-dimensional measurement that is based on bone length and width, which may be confounded by bone thickness.(53) Estimated volumetric BMD, defined as bone mineral apparent density (BMAD), is a calculation that partially adjusts for bone size and addresses potential confounding in areal BMD measures.(53)

The World Health Organization (WHO) diagnostic criteria for OP among postmenopausal Caucasian females is defined as hip, spine, or distal forearm BMD that lies 2.5 standard deviation (SD) or more below the young normal mean (T-score) of females aged 25-30 years.(1,53-56) Low BMD, a precursor to OP, is defined as BMD ranging between 1.0 to 2.5 SD below the young normal mean (T-score) at any one of the three skeletal sites previously

mentioned. Whether these diagnostic criteria are applicable to males and non-Caucasian females is unclear.

Low BMD is the best asymptomatic predictor of fracture risk. The lower the BMD, bone strength is diminished and less trauma is required to cause a fracture.(55-57) BMD can be measured at any skeletal site but areal hip BMD is a reliable surrogate for bone fragility that can be used to predict hip fracture risk.(1) Each SD decrease in BMD increases the risk of hip fracture two- to three-fold.(55-57) BMD varies by age, gender, and ethnicity and there is an age-related decrease in BMD across genders and ethnic groups.(58) PBM and patterns of bone loss determine BMD in older persons. Factors that influence PBM acquisition and patterns of bone loss have been discussed earlier.(16)

Gender Differences in BMD

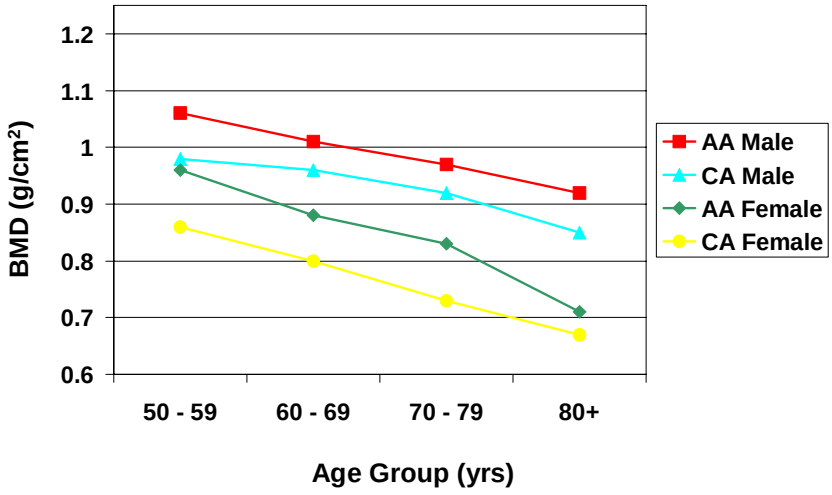
Males acquire a greater amount of bone during skeletal maturation than females, such that males have a larger skeleton, which may confound areal BMD values.(16,51) Areal hip BMD is higher in males than females because males have a wider and longer femur than females.(16,51) Additional explanations for higher BMD in males compared to females include greater PBM acquisition, bone size, and slower rates of bone loss. Looker et al. examined gender differences in BMD using data from the Third National Health and Nutrition Survey (NHANES III). Before adjusting for body size, males had significantly higher BMD than females. After adjusting for body size, gender differences in BMD attenuated.(59)

Ethnic Differences in BMD

The National Osteoporotic Foundation provides estimates for the prevalence of OP and low BMD for US males and females aged 50 years and older. (2) According to these estimates, 4% of AA males are osteoporotic compared to 7% for Caucasian males. Nineteen percent of AA

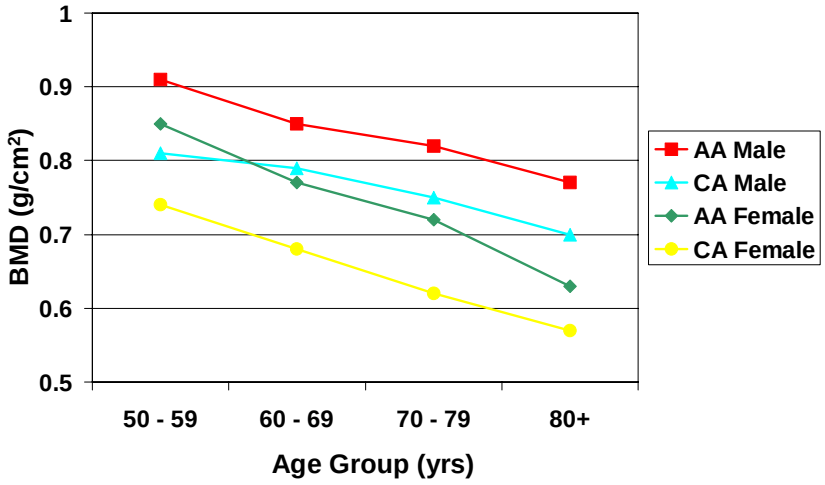
males are estimated to have low BMD compared to 35% of Caucasian males. Among AA females, 5% are osteoporotic compared to 10% of Caucasian females. An additional 35% of AA females and 49% of Caucasian females have low BMD. These estimates show that even though BMD is higher among persons of African ancestry, the risk of developing OP still exists. The ratio of low BMD measured at the femoral neck for African and Caucasian American females has been reported to be 1:7 at age 50 but at age 70, this ratio decreases considerably to 1:2.(35)

Mean total hip and femoral neck BMD data from the NHANES III are presented in figures 1 and 2 for non-institutionalized adults, aged 50 years and older in the US, by gender and ethnicity. (58) NHANES III data confirmed that AA males and females had greater hip and femoral neck BMD compared to Caucasians, and the greatest ethnic difference was observed for hip BMD. (58) Indeed, mean BMD values for AA females, aged 50-59 years, were comparable to mean BMD in Caucasian males of the same age. (58) Among males, AAs had mean total hip BMD that was 5% higher than Caucasians. These findings have been confirmed in other studies of AA and Caucasian males aged 23-80 years where AA males had 20% higher femoral neck and 8% higher whole body BMD compared to Caucasians. (64,65)



Looker et al. *Osteoporosis International* 1998; NHANES III

Figure 2-1. Mean total hip BMD (g/cm^2) by gender and ethnicity, NHANES III, US 1988-1994



Looker et al. *Osteoporosis International* 1998; NHANES III

Figure 2-2. Mean femoral neck BMD (g/cm^2) by gender and ethnicity, NHANES III, US 1988-1994

NHANES III data also demonstrated that AA females had 10% higher total hip BMD than Caucasian females of the same age. Despite ethnic differences in mean BMD, 28% of AA females had low hip BMD, which increases the risk of hip fracture.(66) Major strengths of the NHANES III data are the inclusion of both males and females from two ethnic groups, older persons, and the generalizability of the data. These data represent the most comprehensive, population-based reference values of BMD in U.S. males and females by ethnicity.(66)

Higher BMD among AA females compared to Caucasian females has been reported in other prospective, large studies with minorities. Siris et al. confirmed that AA postmenopausal AA females had higher BMD than Caucasian females, but the inclusion criteria was very strict such that females who were previously diagnosed with OP, used therapeutic agents to preserve BMD, and recently had a DXA exam were excluded from the study.(3) Because these study participants do not mirror the general population, their findings may not be generalizable to all postmenopausal females since rates of low BMD and fracture risk may be underestimated.(3)

Most of the ethnic disparity in BMD is related to differences in skeletal growth and maturation. Persons of African ancestry do not necessarily have higher BMD compared to Caucasians.(67-69) Studies examining ethnic differences BMD in persons of African ancestry and Caucasians have been primarily conducted in US females.(40,70-72) Few studies have examined ethnic differences in BMD among males, and all have consistently shown higher BMD among AA males compared to Caucasian males.(65,73-77) A study with only 34 AA males and 160 Caucasian males, aged 23-80 years, found that AA males had higher BMD the Caucasian males at every site measured.(65) Femoral neck BMD was 20% higher for AA males than Caucasian males, but with only 34 AA males, these results should be confirmed in a larger sample of AA males.(65) Another small study compared BMD of Gambian males (n=12) living

in the UK to Caucasian males (n=10). The study population was young (aged 18-48 years) and Gambian males had 21% higher femoral neck BMD compared to Caucasian males, but BMD was not higher among Gambian males at other sites measured.(74) George et al. compared BMD among older AA (n=191) and Caucasian (n=503) males. Older AA males had 10% higher femoral neck BMD compared to older Caucasian males, even after adjusting for covariates.(75) In most of these studies, researchers suggested that body size partially accounted for the higher BMD observed in AA males, which could be a function of higher PBM. Dibba et al. suggested that lean mass, rather than body size, explained the higher femoral neck BMD among Gambian males compared to Caucasian males. (74)

Gender and ethnic differences in BMD persist even after adjusting for important covariates, which suggests that these differences in BMD cannot be completely explained by body size, clinical and biochemical variables.(44,64) Adjusting for bone size still does not eliminate, possibly minimizes, gender or ethnic differences in BMD because males have greater BMD than females, due to greater bone width. AAs have higher BMD compared to Caucasians because of thicker trabecular bone. (22,62,78) Based on this information, the underlying mechanism(s) of gender and ethnic differences in areal BMD and subsequent hip fracture risk are not clearly understood.

As mentioned previously, BMD also differs among persons of African ancestry living in different geographical locations, which suggests BMD heterogeneity and that caution should be exercised when considering persons of African ancestry as a homogenous group.(67,69,74,79) Different lifestyle factors may to contribute to geographical differences in persons of similar ancestry. It has been speculated that both native Africans and AAs have genetic characteristics for superior BMD compared to Caucasians, but the potential for high BMD is not realized in

African because of lifestyle factors and that BMD is not preserved with advancing age even though trauma fractures are minimized. (67,79)

A limited number of studies have examined determinants of BMD in persons of African ancestry, and these studies have been primarily conducted in the US and among females. (3,6,60-62) AA males and females, both young and older, have 3-20% higher BMD at all skeletal sites compared to Caucasian males and females. (34,58,62,63)

Correlates of BMD

Extensive examination of anthropometric and lifestyle correlates of BMD have been studied in Caucasian males and females. (7,11,12,80-92) Results from population-based studies of middle-aged and older Caucasian males and females consistently found that age, low body mass index (BMI), inadequate dietary calcium intake, current cigarette smoking, and physical inactivity were risk factors for low BMD. Other risk factors for low BMD include medical history (personal history of fracture, osteoarthritis, gastrectomy, and etc.) and anthropometric factors (shorter height, lower weight, lower grip strength, and etc.)

Few studies have examined risk factors associated with lower BMD among AA males and females. (60,70,75) In a population-based study of AA males and females, low BMI, cigarette smoking, and physical inactivity (males only) were risk factors for low BMD.(70) Furthermore, the presence of one or more of these risk factors increased the risk of low BMD 2-fold for AA females and 3-fold for AA males, after adjusting for the effects of age.(70) A recent study by Robbins et al. examined correlates of BMD among 302 AA and 1289 Caucasian males and females in the Cardiovascular Health Study.(60) Older age and female gender were associated with lower BMD and interestingly, weight explained 21 and 27% of the variability in hip BMD for females and males, respectively.(60) Robbins et al. did not find a significant

association between smoking, physical inactivity, alcohol consumption and BMD among this small sample of older AAs, perhaps due to inadequate power.(60)

George et al. examined correlates of BMD among 191 older AA males, aged 65+ years, and found that taller height, higher weight, and physical activity were positively associated with BMD measured at the femoral neck and smoking was inversely associated with BMD. (75)

Age

Each decade of life translates to a 1.4 to 1.8-fold increase risk of fracture in both males and females because of substantial decline in BMD, gradual weakening of bone, declines in neuromuscular function, and increased risk of falls.(1,50,93) Aging is related to a curvilinear decline in musculoskeletal mass, linear decline in lean mass, and increase in fat mass.(94-96) Low BMD, lifestyle factors, falls, elevated cytokines, and reduced osteoblastic activity are common manifestations of aging that may lead to increases in fracture risk for both males and females. Older age alone increases risk of fracture such that an older person with the same mean BMD as a younger person is at higher absolute risk of fracture. Females in the eighth and ninth decade of life experience accelerated rates of bone loss greater than the immediate postmenopausal period. (1,93)

Anthropometry

Several studies have demonstrated that body weight and/or BMI is positively associated with BMD and that both are important predictors of BMD.(60,85,86,91,97,98) The protection from body weight stems from mechanical force that is exerted on to the skeleton, increased sex steroid levels, and growth factors.(99) Body weight is comprised of several components, including fat mass and lean mass, commonly referred to as body composition.(100,101) Lean mass combines muscle, visceral and connective tissue, glycogen, and body water. Fat mass is a

measure of adiposity. Estimates of soft-tissue lean mass and fat mass are calculated from whole body DXA. The contribution of lean and fat mass to BMD remains unclear because some studies report that lean mass was a stronger determinant of BMD (64,84,102), other studies report fat mass was stronger(103-105), and then it was reported that both were important determinants of BMD.(106) Research confirms that there is a progressive decline in lean mass and a progressive increase in fat mass with increasing age for both males and females. The age-related decrease in lean mass is associated with disability (80,96,107,108), but ethnic differences in age-related changes in body composition are not well established.

Anthropometric Gender Differences

Body weight is typically greater among males than females. Females who experience weight loss during perimenopause typically have higher rates of annualized BMD loss at the hip and spine.(109) Few studies examining the interrelationships between body composition and BMD have included minorities.(34,62,71,110,111) Research has shown that lean mass is greater in males compared to females and that fat mass is higher in females than males, especially in postmenopausal females.(112) Fat mass appears to be associated with BMD among postmenopausal females and lean mass is a strong predictor of BMD among males.(83)

Anthropometric Ethnic Differences

Anthropometric differences exist between AAs and Caucasian as demonstrated by AAs being heavier and taller, which is due in part to obesity and a larger musculoskeletal system in AAs, which may contribute to higher BMD among AAs.(34,64,106,113) AAs are thought to have genetically greater skeletal mass compared to Caucasians, which adds stress on the bone and results in greater BMD.(111,113) A comparative review of body composition in AA and Caucasian males and females substantiated ethnic differences in lean mass for these two groups,

and showed that AAs had significantly more lean mass.(113) Studies have also confirmed higher fat mass and lean mass in AA females compared to Caucasian females.(34,63)

Taaffe et al. examined the effects of lean mass and fat mass on BMD in a cohort of 2619 older Caucasian and AA males and females.(62) In this large study, they found that lean mass was a significant determinant of BMD for Caucasian males and AA males and females. Among females, fat mass was also significantly associated with BMD. Barondess et al. addressed the effect of body composition on BMD in healthy AA and Caucasian males aged 33-64 years.(64) They found that lean mass was an important determinant of BMD in males despite no ethnic differences in height, body weight, or BMI. Perry et al. demonstrated that the correlations between lean and fat mass were much weaker in Caucasian females compared to AA females aged 20-90 years. (34) There is some suggestion that fat mass, not lean mass, partially explains why AA females have greater BMD compared to Caucasian females. (113)

Within ethnicity, there may be differences in body composition based on geographical location as suggested in a study of 1,054 males and females of African ancestry residing in Nigeria, Jamaica, and the U.S. (114) Researchers found that for both genders, height, weight, waist and hip circumferences, percent body fat, and BMI were highest in the U.S. followed by Jamaica and then Nigeria.(114) Our research will further examine this notion by comparing several anthropometric variables in AA and Tobagonian males and females, which should provide additional insight into the contribution of body composition variables to ethnic differences in BMD (Chapters 3-5).

Falls

Mild trauma falls occur more often with advancing age and we believe the age-related increases in hip fracture incidence are directly related to a higher risk of falling.(7,8,93,115-118) Falls can

lead to permanent disability, increased mortality, and hip fracture. Ninety percent of falls sustained by older persons occur at standing height or lower, and these falls account for over 330,000 hospitalizations in the U.S. annually. (1) The frequency of falls, direction of falls, and characteristics of falls all affect hip fracture risk. (50,93,115) Of particular note is the increased risk of hip fracture resulting from landing on or near the hip/thigh after a fall.(50) Interestingly, the same mild trauma fall that causes fracture in older persons does not cause fracture in healthy adults because BMD and bone strength are greater in younger persons.(93) This finding supports the notion that BMD is also an important determinant in the risk of falling. For example, physical inactivity is also related to an increased risk of falling by accelerating bone loss, which contributes to lower BMD. Physical activity has osteogenic effects on bone, which improves coordination, BMD, and bone strength. (119)

Females aged 45-49 years have a 20% risk of falling and after the age of 80, the risk of falling is 50% in older females and 33% in older males. (1) A study by Means et al. compared history of falls and fall-related injuries among 280 ambulatory, community-dwelling AA and Caucasian females aged 65 and older.(120) They reported similar number of recent falls between AA and Caucasian females even though AA females had poorer balance and mobility, suggesting that higher BMD among AAs may be protective against sustaining a fall, even in the presence of fall-related risk factors.(120) Since BMD and lifestyle factors can attenuate the risk and impact of falling, we will further examine patterns of recent falls in Tobagonian males (Chapter 3) and females (Chapter 4).

Personal/Family History of Fracture

Personal history of fracture increases the risk of subsequent fracture 1.7 to 7-fold.(1,5,12,121) Sustaining a fracture at an earlier age and number of previous fractures

substantially increases the risk of future fracture(s), which results from lower BMD.(1,5,12,93,121) A longitudinal study of nearly 10,000 Caucasian females aged 65 and older from the Study of Osteoporotic Fractures (SOF) demonstrated that females who experienced a premenopausal fracture had a 30% greater rate of fracture following menopause.(122) The SOF did not report findings for minority participants so we cannot be certain that these findings are relevant to minority females. A case-control study of older AA females by Grisso et al. identified heavier body weight at age 50, calcium supplement use, and prednisone use as risk factors for subsequent fracture.(8) Parental history of osteoporotic fractures predisposes females to low BMD and increases the risk of fracture based on results from the SOF. (10,12,85,123)

Physical Activity

During childhood, adolescence, and young adulthood, bone is greatly influence by exercise or mechanical loading. As mechanical loading increases, BMD also increases. Physical inactivity is associated with lower BMD across the entire lifespan. Physical inactivity inhibits osteoblast bone formation and accelerates osteoclast bone resorption leading to increased risk of OP. (124) Physical activity, three to five times per week, may contribute to preservation of BMD and reduction in fracture risk due to the effects skeletal loading.(93,119,125)

Smoking

Smoking alters estrogen metabolism, which has been shown to accelerate bone loss. A meta-analysis on the effects of smoking, BMD, and risk of hip fracture in females concluded that smoking was associated with lower BMD. (126) At age 50, the risk of hip fracture was the same for female smokers and non-smokers but increased thereafter for smokers. In postmenopausal females, current smokers lost 2% more BMD with each increasing decade of life compared to

non-smokers. At age 80, smokers had 6% less BMD than non-smokers. Smoking has an independent, direct effect on bone in both males and females and lower BMD among smokers increases the lifetime risk of hip fracture for males and females 40% and 31% respectively.(127)

Alcohol Consumption

Moderate consumption, less than seven drinks per week, of alcohol containing beverages has been reported to be positively associated with BMD.(8) Chronic alcohol consumption, however, may cause lower bone density because alcohol has a toxic effect on the mechanisms of bone formation.(128) Additionally, intoxication may increase the risk of falling.(128)

Caffeine Consumption

Research on the relationship between caffeine consumption and BMD is conflicting. In the Rancho Bernardo study, lower BMD was identified in females who drank two cups of coffee everyday and did not consume milk regularly.(129) Another study of 138 postmenopausal females did not show any relationship between caffeine consumption and BMD measured at the whole body and total hip.(130) Research has not shown an association between caffeine consumption and BMD among males.

Reproductive History

Older age at menarche and earlier age at menopause are both associated with lower BMD.(12,131) Even though pregnancy affects calcium homeostasis, at least one pregnancy was associated with higher spine BMD because of the weight gain during the pregnancy. Females may have experienced low BMD during pregnancy, but this condition typically resolved two to six months after giving birth. An international study of 580 early postmenopausal, Caucasian European females aged 45-61 years, investigated reproductive and menstrual factors that affect BMD.(131) Results from this study identified a positive association between BMD and number

of pregnancies, younger age at menarche, longer years of menstruation and/or reproductive years, and hormone therapy (HT) use while duration of breast feeding, oral contraceptive use, and premenopausal amenorrhea were not associated with BMD.(131) Hysterectomy was associated with rapid loss of bone if estrogen-containing HT was not prescribed shortly after surgical menopause. Based on a review of the literature, we expect that females who have a hysterectomy will have lower BMD compared to females who experience natural menopause. We also expect that parity and HT will be positively associated with BMD among postmenopausal Tobagonian females (Chapter 4).

If we rely solely on the limited data from studies in the US, postmenopausal AA females begin menopause with substantially higher BMD and lower risk of fracture compared to Caucasians, but this protection may vary with older age. (6,61,132,133)

Medical Conditions

Diabetes

Persons with impaired glucose tolerance or type 2 diabetes typically have higher mean BMD compared to those with normal hypoglycemic index levels.(134-136) Strotmeyer et al. found that older AA and Caucasian American males and females with type 2 diabetes had 4-5% higher total hip BMD, independent of body composition variables.(137) Further exploration of the relationship between diabetes and BMD suggests persons with diabetes have lower rates of bone turnover that may mediated by hypoparathyroidism and this condition reduces age-related bone loss.(135) Other studies have suggested that diabetes is associated with an elevated fracture risk, especially among older Caucasian females with diabetes.(108,134,138)

Hypertension & Stroke

Hypertension is a very common condition, especially among AAs, that manifests from elevated systolic (pressure when heart contracts to pump blood to the body) and/or diastolic (pressure when the heart relaxes between beats) blood pressure. A study of older hypertensive, Caucasian females who were not treated with thiazide diuretics found lower BMD and increased bone loss at the femoral neck. Abnormalities in calcium metabolism may have mediated the effect of hypertension on BMD.(139) Use of thiazide diuretics is associated with increased BMD in both males and postmenopausal females. The benefit of thiazide use is blunting of calcium excretion, a mechanism similar to estrogen use.(140) Thiazide diuretics are prescribed primarily for hypertension treatment.

Persons with hypertension are three times more likely to have a stroke. Data from NHANES I did not find an association between BMD and stroke for AAs and Caucasians between the ages of 45 and 74 years.(141) Persons with a history of stroke have up to a 4-fold increased risk of hip fracture due in part to their high incidence of falls and loss of bone mass following stroke-related paralysis.(142)

Rheumatoid Arthritis (RA)

Corticosteroids are a common treatment for RA patients. A study that examined BMD among people with RA showed that females who took corticosteroids had the significantly lower BMD compared to those who were not prescribed corticosteroids. (143) The negative association between corticosteroid use and lower BMD has been investigated for a number of years. (144,145) Researchers suggest that limited functional ability (i.e., lack of weight bearing movement and/or exercise) contributed to lower BMD in females not taking corticosteroids.

Osteoarthritis (OA)

OA is a chronic condition that affects articular joints and the prevalence of OA increases with age. Eighty percent of people aged 60 and older have radiologic evidence of OA. (146) OA is more severe among older females compared to males. (146) Hip OA is more common among older Caucasian females than AA females. Hip and spinal OA are associated with higher BMD, despite higher bone turnover. (146,147) People with severe OA develop osteophytes and the presence or severity of osteophytes may be associated with higher BMD. (146,147)

Breast Cancer

Breast cancer is common in females with elevated estrogen levels, particularly estradiol. On the other hand, females with a history of fracture typically have lower levels of estrogen; which is an independent risk factor for fracture. Based on this information, studies have shown that females with a previous history of fractures were at lower risk of developing breast cancer. Cauley et al. recently reported that during four years of follow-up, the risk of breast cancer was 2.0-2.5 times higher among females with BMD above the lowest quartile compared to females with BMD in the lowest quartile. (148) Similar results were obtained in the SOF study population where females with higher BMD had increased risk of breast cancer.(149) A study of 8,000 postmenopausal females identified a positive relationship between femoral neck BMD and breast cancer risk. After adjusting for covariates, there was a 1.5 to 2.0-fold increased risk of breast cancer with each increasing quartile of femoral neck BMD compared to the lowest quartile.(150) Estrogen is thought to be the link between breast cancer and higher BMD, which is supported by the influence of hormone therapy on BMD. It is hypothesized the BMD may indicate the cumulative effect of estrogen exposure. Recently, Nelson et al. examined BMD

among 221 AA females with newly diagnosed breast cancer and found an association between BMD and breast cancer risk. (151)

Thyroid Diseases

Both hypothyroidism and hyperthyroidism may impair bone formation. Hyperthyroidism may invoke long-lasting effects on bone metabolism including increased rates of bone turnover, which reduces bone strength, BMD, and accelerates bone loss. Increased rates of bone turnover are mediated by excess thyroid hormone and estrogen deficiency. (152)

Coronary Heart Disease

Both coronary heart disease (CHD) and OP are more common in postmenopausal females than younger females. (154) Postmenopausal estrogen deficiency increases the risk of developing both CHD and OP, which is characterized by accelerated bone loss and low BMD.(153) Risk factors for CHD overlap with lifestyle factors associated with OP.

Medication Use

Exogenous Hormones

Estrogen-containing HT reduces bone turnover and decreases bone loss by decreasing urinary calcium excretion soon after menopause.(29) Age-related bone loss is reduced by 0.5% per year by using HT as well as a 45% reduction in risk of fracture. Conjugated equine estrogen is the most commonly prescribed form of HT in the US. (155) Progestin added to estrogen HT may enhance bone-sparing properties found in estrogen. (155) HT was thought to most beneficial during early postmenopause. (155) Randomized, controlled clinical trial data have shown that HT is associated with reduced fracture risk and reduces femoral neck bone loss by 30%, but discontinuation of HT leads to immediate and rapid bone loss comparable to the menopause period.(155)

Studies have shown that AA and other minority females are less likely to have physicians prescribe and use HT compared to Caucasians, such that the benefits of HT on BMD preservation may not be available to all females.(155,156) Other therapies, bisphosphates and selective estrogen receptor modulators, have also been shown to preserve bone among postmenopausal women. (157,158)

Among males, androgen deprivation therapy (ADT) is commonly used to treat prostate cancer.(159) This therapy is administered either by bilateral orchiectomy or use of gonadotropin-releasing hormone agonist, which progressively decreases BMD and increases fracture risk.(159,160)

Corticosteroids

Corticosteroids may induce generalized OP at trabecular sites. Prolonged use of exogenous glucocorticoids can lead to hypercortisolism which results in reduced bone formation, higher rates of bone resorption, and low BMD.(144,145) Systemic lupus erythematosus is more common in AA females and glucocorticoids are the common treatment for this condition.(161)

Statins

Statins are prescribed commonly to lower plasma cholesterol levels. This medication contains enzymes that limit cholesterol synthesis. Some research has suggested that statins may increase BMD and reduce fracture risk in postmenopausal females.(162) Beta-blockers treat hypertension, abnormal heart rhythms, and angina and these drugs may also influence bone.(163) Daily nitrate use in 317 older females was positively associated with hip and heel BMD compared to non-users.(164) Heparin, anticonvulsants, aluminum-containing antacids, and thyroid hormone are all suspected to increase bone loss.(93)

2.5. Bone Loss

When the rate of bone resorption exceeds the rate of bone formation, an imbalance occurs and this imbalance in bone remodeling coupled with aging are two key components for bone loss and weakened bone structural integrity.(26) Age-related bone loss causes low BMD in males and females as well as Caucasians and minorities. Bone loss may be influenced by low BMI, smoking, chronic alcohol consumption, physical inactivity, and HPTH.(34) Bone loss is not homogeneous, meaning increased rates of bone loss may be observed at one site while other sites have normal BMD.

Trabecular bone has a higher rate of bone turnover (due to its structure and surface area) compared to cortical bone and trabecular bone loss is more severe than cortical bone loss.(14) Depending on the severity of bone loss, OP ensues and trabecular bone sites (hip and spine) are most affected by OP.(14,26) With OP, trabecular bone is thinner and shows evidence of osteoclastic resorption, which causes deterioration of structural integrity.(14) OP in cortical bone causes tunneling resorption that may cause stress fractures and gradual thinning of cortical bone.(14)

Gender Differences in Patterns of Bone Loss

Both males and females lose bone with increasing age and deterioration in bone architecture. Healthy males experience a slower rate of bone loss compared to females because bone stress decreases bone loss more in males, probably due to periosteal apposition. Cortical bone loss occurs mostly at the inner structure, but periosteal apposition occurs at the outer surface. Periosteal apposition is the increase in width of long bones (axial skeleton), such that the same quantity of bone that is distributed over a wider area is stronger. This widening of bone, or periosteal apposition, compensates for age-related bone loss in men since it is estimated to be 3-fold higher for men compared to women. Among older males and females, alteration in bone

strength is less in males compared to females. (165) Age-related bone loss is approximately 25-30% for cortical bone and 35-50% for trabecular bone in females and among males the rates are 5-15% and 15-45%, respectively.(166) For example, females lose approximately 58% of femoral neck BMD and males lose on 39% over a lifetime.(50)

Among females, aging is accompanied by menopause, increased rates of bone remodeling, and an imbalance between bone formation and resorption; all of which results in excess loss of bone in females.(26) Estrogen deficiency that is present after menopause, surgical or natural, resulting from cessation of ovarian function leads to higher rates of bone turnover (i.e., decreased bone formation/decreased osteoblast function) and subsequent accelerated bone loss in females compared to males of similar age.(14,26) In the immediate postmenopause period females typically experience an imbalance between osteoclasts and osteoblasts, which causes increased rates of bone remodeling and accelerated trabecular bone loss. During menopause, trabecular bone loss increases three-fold while rates of cortical bone loss are slower. (14) Up to 20% of BMD is lost within five to seven years of menopause. (14)

A review of the literature suggests that in the five years following menopause, females lose bone at a rate of 2-4% per year and 10 years after menopause this rate decreases to 1-1.5% per year compared to a steady 0.5-0.7 per year for older males, beginning around age 55.(93) A combination of factors contributes to lower rates of bone loss in males. These factors include skeletal size, greater cortical BMD in later years (over age 60), and higher bone turnover that replaces damaged bone. Approximately 10 years after menopause bone loss is similar in females compared to males of the same age. (14,35) There is an accelerated loss of cortical bone among older (aged 65+) males and females. (14,35)

A recent study of 811 Caucasian males, aged 45-92 years, reported and average of

-0.47% annual hip bone loss and -0.34% at the femoral neck. (87) Predictors of bone loss included older age (aged 75+), low BMI (<24 kg/m^2), weight loss, current smoking, and physical activity. (87)

Ethnic Differences in Patterns of Bone Loss

In females, bone loss accelerates with age, changes in sex steroid hormones, and changes in body composition. (34) Substantial reductions in BMD have been observed in middle-aged females, but AA females start menopause with considerably higher BMD compared to Caucasian American females. (34,63,65,167) Postmenopausal bone loss is heavily influenced by biochemical markers, even though ethnic differences in biochemical markers of bone turnover and subsequent rates of bone loss are not consistently reported.(26)

Luckey et al. measured rates of bone loss (forearm and spine) between 121 AA and 122 Caucasian pre- and postmenopausal females. (63) Among premenopausal females, rates of bone loss were similar between AA and Caucasian American females. In early menopause (5 years or less), they found that bone loss was 2-fold faster among Caucasian Americans compared to AAs. Ethnic differences in the rate of bone loss attenuated among AA and Caucasian American females who were more than 5 years postmenopause.

Cauley et al. recently examined bone loss in 482 AA and 6007 Caucasian females, aged 65+, who participated in SOF.(97) Adjusted annual percent change in hip BMD was significantly greater among Caucasian females compared to AAs (-0.57% per year vs. -0.33% per year). The magnitude of the annual rate of bone loss was stronger for femoral neck BMD, where AA females had significantly lower rates. (97) Another longitudinal study reported that AAs had lower rates of bone remodeling compared to Caucasians. (63) This study suggested that the lower rates of bone remodeling and higher BMD may protect AAs from age-related bone

loss.(63) Whether the rates of bone loss among postmenopausal females vary by ethnicity is not clear, but research supports the association between higher levels of bone turnover markers and greater risk of accelerated bone loss.(37)

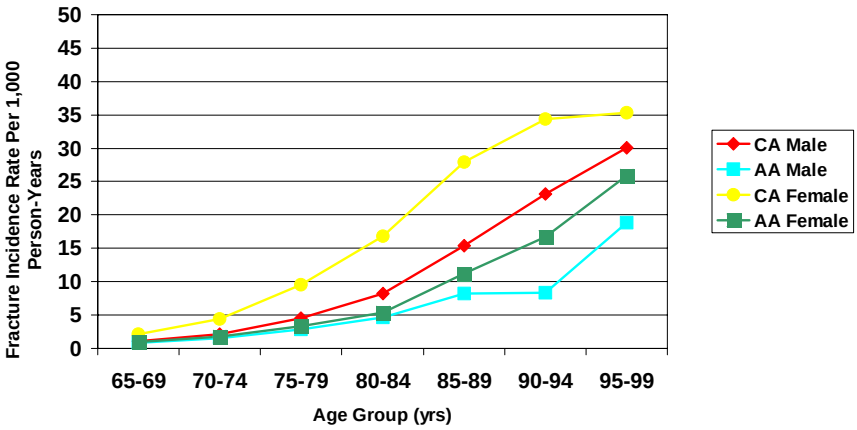
Bone loss has not been well studied in males because only a small number of longitudinal studies have male participants. (49,87,168,169) In the Rancho Bernardo study, bone loss was measured over 4 years for 507 Caucasian males aged 45-92 years.(87) Annual BMD loss averaged 0.47% and 0.34% at the hip and femoral neck, respectively. The annual percent change in hip BMD ranged from -0.2% (< 65 years) to -0.8% (≥ 75 years). Similar annual percent change in femoral neck BMD was observed, stratified by age group. Older age (75+), BMI <24 kg/m^2, weight loss, smoking, and physical inactivity were associated with greater bone loss. We were unable to find any published literature on bone loss in males of African ancestry.

In Chapter 5, we will examine longitudinal changes in trabecular bone in older AA and Caucasian males and females. This research should enhance the current body of literature on age-related changes in trabecular bone loss for older AAs and Caucasians since few longitudinal studies have studied rates of bone loss in AAs females.

2.6. Hip Fractures

Fracture incidence is bimodal, peaking in youth and older age.(1) In younger persons, fractures are attributed to traumatic accidents and at older ages, fractures of the spine, hip, and wrist are common manifestations of OP.(1,6) After age 50, fracture incidence increases for both males and females.(1,6,11,92) Since hip fractures are the most debilitating, costly, and extensively studied site compared to all other skeletal sites, this review of the literature will focus on gender and ethnic differences in hip fracture incidence.(1) Differences in hip fracture rates have been widely attributed to gender, ethnicity, BMD, behavioral, and lifestyle factors.(1,63,170) Figure 2-3

shows hip fracture incidence for African American (AA) and Caucasian American (CA) males and females in the US, between 1986 and 1989 based on a 5% sample of the Medicare population.(171)



Baron JA et al. Epidemiology 1994;5(1):42-47.

Figure 2-3. Hip fracture incidence rates (per 1,000 person-years) by gender and ethnicity, US 1986-89

As shown in Figure 2-3, hip fracture incidence increases exponentially with age for both males and females, despite ethnicity. (1,57) Dramatic increases in hip fracture incidence occurred approximately 15 years following menopause in females and after age 70 in males. (1,57)

Gender Differences in Hip Fracture

Thirty percent of all hip fractures occur in males and data suggests that U.S. males experience an estimated 150,000 hip fractures per year.(172) Caucasian females have a two-fold higher incidence of fracture compared to Caucasian males at any age. These gender differences

are attributed to higher BMD, slower rates of bone loss, and lower risk of falling among males compared to females.(1,16,170) Furthermore, U.S. Caucasian males and females aged 50 years and older have an estimated 13% and 40% lifetime risk of fracture, respectively. The increased risk of fracture among women is partly due to the longer life expectancy of females.(1,172) Even though Caucasian males have lower rates of fracture compared to Caucasian females, males have an increased mortality from these fractures.(38) Hip fracture incidence raters are similar for males and females of low risk ethnic groups, like Asians and AAs, suggesting that gender may not be a strong determinant of fracture risk among minorities.(1,170,173)

Ethnic Differences in Hip Fracture

Research has established that the risk of sustaining a fracture varies across ethnic groups.(7,8,117,170) Limited data are available for hip fracture incidence in minority males.(6,170,171,173) As shown in Figure 2-3, Baron et al. demonstrated that AA males and females had lower hip fracture incidence rates compared to Caucasians in the same age group using Medicare data.(171) Griffin et al. identified similar patterns of non-vertebral fracture incidence as Baron et al. among older Tennessee AAs compared to older Caucasians.(173) In this study, AA had 60% less fractures than Caucasians, after controlling for covariates.(173) A potential limitation of this study was that the study population was of lower socioeconomic status and the findings may not be generalizable to the entire US population. The higher rate of hip fracture among Caucasian males and females compared to AAs is consistent with other studies.(170,171,173)

In the US, risk of hip fracture is highest for Caucasian females with one out of every two females experiencing a hip fracture in her lifetime. Caucasian females have twice the incidence of hip fracture compared to AA females.(6,8,170,171,173) Postmenopausal Caucasian females

experience 75% of all hip fractures and the age-adjusted fracture incidence rates are substantially higher compared to non-Caucasian females.

The lifetime risk of hip fracture is only six percent for AA females, but the resulting morbidity and mortality is greater for AAs. (1,132) Although the incidence of osteoporotic fracture is lower among AA females through mid-life, hospital data suggested that hip fracture risk increases exponentially in older AA females. A longitudinal study to ascertain risk factors associated with nonvertebral fractures in community dwelling females consisting of 1,404 AAs and 1,186 Caucasians, aged 65 and older, confirmed the higher risk of fracture in Caucasian females. At baseline, less than one-fifth of AAs reported a previous fracture compared to one-third of Caucasians. (6) AAs were more likely to report a history of hip fracture and Caucasians reported a history of wrist fracture most often. (6) Caucasian females were twice as likely to sustain an incident hip fracture compared to AAs.(6) One explanation for the lower fracture risk in AA females compared to Caucasian females was higher bone mass, which may be a function of skeletal size.(35,170)

Rates of hip fracture also vary by geographical location and season. For example, the incidence of hip fracture is greater in the winter and age-adjusted hip fracture incidence rates are lower for Caucasian American females compared to Scandinavian females.(1) Within Europe, there is a seven-fold variation in fracture rates between the North and South, and this pattern is also observed in Asian females.(1) Similarly, in the US hip fracture rates are lower in the northeast and west compared to the southeast.(1) Geographical differences in hip fracture rates may be related to lifestyle factors. Lastly, worldwide hip fracture rates are higher in urban areas compared to rural areas, due in part to lower BMD among urban persons resulting from poorer nutrition, sedentary lifestyle, and higher prevalence of other risk factors for low BMD.(1)

Hip Fracture Risk Factors

Low BMD, previous history of fracture, and frequency of falls are all important risk factors for hip fracture.(1,50,93) The presence of multiple risk factors further increase the risk of fracture such that the presence of 5 or more hip fracture risk factors increases the risk of fracture 17-fold among Caucasian postmenopausal females.(93,121)

Gender Differences in Risk Factors for Hip Fracture

According to Campion and Maricic, major risk factors for fracture in Caucasian males include low BMD, hypogonadism, previous fracture history, and older age, although we know considerably less about risk factors in males.(172) A study by Grisso et al. observed higher risk of fracture in Caucasian males who reported physical inactivity and lower limb dysfunction.(7)

Well established risk factors for hip fracture in Caucasian females include age, low BMD, falls, low body weight and/or BMI, weight loss after age 50, gender, ethnicity, glucocorticoid use (greater than six months), caffeine consumption, sedentary lifestyle, cognitive impairment, personal and/or family history of fracture, smoking, excessive alcohol consumption, medical conditions, use of certain medications, and lifestyle factors.(6,13,14,116,117)

Ethnic Differences in Risk Factors for Hip Fracture

Risk factors for hip fracture in AA females are similar to Caucasian females based on very limited data and low BMD is an important predictor of fracture risk, for both ethnic groups.(3,6,8) In fact, the some of the protective factors against hip fracture, like current hormone replacement use and increased BMI, are also similar for AA and Caucasian females. BMI protection is related to increased adipose-based production of estrogen that influences BMD, greater gravitational forces on bone mass, and increased padding around hip to reduce the

impact of a fall. AA ethnicity has been reported to be protective for nonvertebral fractures, even in the presence of differences in lifestyle factors.(8)

Risk factors for hip fracture have been identified in cross-sectional, case-control, and longitudinal studies for Caucasian males and females. Ethnic differences in risk factors for hip fracture, specifically low BMD, are not well established because few studies have actually included ethnic minority males and females and even less is know about non-AA minorities. (170,171,173)

2.7. Synopsis

Correlates of BMD and risk factors for osteoporotic conditions have been studied for several decades. The volume of peer-reviewed literature on OP is enormous. This review of OP literature does not summarize the findings from available published articles, but focuses on gender and ethnic differences in the risk of developing OP. The determinants of OP in males and minorities are not well established and poorly understood since most studies that describe the determinants of BMD have been studied primarily in Caucasian females. Studies that examined the relationship between BMD and pathogenesis of osteoporotic conditions were reviewed, with an emphasis on gaps in the literature regarding gender and ethnic differences.

As mentioned previously, only a limited number of studies have included persons of African ancestry. Among these studies, most are cross-sectional in design. Cross-sectional studies are useful to generate hypotheses, but more longitudinal studies are warranted to comprehensively evaluate BMD and its determinants, as well as the subsequent risk of fracture among persons of African ancestry. The etiology of gender and/or ethnic differences in BMD is unknown and may be related to a combination of bone geometry, PBM, bone homeostasis, bone loss, lifestyle factors, and genetics factors. Since low BMD is an established predictor of fracture

risk, we will examine correlates of BMD among Tobagonian males (Chapter 3), postmenopausal Tobagonian females (Chapter 4), older Caucasians and AAs (Chapter 5). In Chapter 5, we also report ethnic differences in longitudinal rates of bone loss for U.S. AA and Caucasian males and females, age 65 and older and review the relevant literature.

This research will facilitate our understanding of the prevalence of low BMD, annual rates of bone loss, correlates of bone health, and risk factors for developing OP in persons of African ancestry residing in the United States and on the Caribbean Island of Tobago. This research will not address ethnic differences in bone turnover, hip geometry, PBM, or genetics.

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3. Correlates of Bone Mineral Density in Men of African Caribbean Ancestry: Tobago Bone Health Study

(Manuscript to be submitted)

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3.1. Abstract

Objective: To test the hypotheses that components of body weight (fat mass and lean mass), lifestyle factors, and health-related factors are correlated with bone mineral density (BMD), we conducted a cross-sectional, population-based study of African Caribbean males residing on the island of Tobago.

Materials and Methods: 1,784 ambulatory males, aged 40-84 years, were recruited from the Tobago Prostate Cancer Screening Study. Participants completed a questionnaire, physical examination, and dual-energy X-ray absorptiometry (DXA) examination that measured BMD for whole body, total hip, and femoral neck subregion. In this analysis we focused on BMD measured at the total hip and femoral neck subregion and utilized body composition data derived from whole body DXA scans.

Results: BMD was approximately 10% and 20% higher across age groups for Tobagonian males compared to NHANES III data for African and Caucasian American males of the same age. In multiple linear regression models, greater lean mass, history of working on a fishing boat and diabetes were significantly associated with higher BMD, while older age, taller height, and history of a fractured or broken bone were associated with lower BMD. Lean body mass explained 18% and 15% of the variance (R^2) in BMD measured at the total hip and femoral neck, respectively, after adjusting for covariates.

Conclusions: High BMD was observed in this population of middle-aged and older African Caribbean males and lean mass was the strongest correlate of BMD. Final models explained 25% of the variability in total hip and femoral neck BMD. (Word Count: < 250 words)

3.2. Introduction

Bone mineral density (BMD) is an important predictor of fracture risk and persons with lower BMD are at an increased risk of sustaining an osteoporotic fracture.(1-6) Several studies have identified the determinants of BMD for Caucasian males and females.(7-16) In Caucasian males, commonly reported determinants of BMD include weight, lifestyle factors, genetics, medical conditions, and medication use. Weight consists of several components, including fat mass and lean mass. The relative contribution of these components to BMD is not known, particularly for males and non-Caucasian populations.

The epidemiology of osteoporosis, risk of sustaining osteoporotic fractures, and determinants of bone mineral density (BMD) are poorly understood in persons of African ancestry, especially males. This is due in part to the paucity of literature on the etiology of BMD and related conditions such as osteoporosis and osteoporotic fracture for non-Caucasians.

Of the few studies that have included persons of African ancestry, BMD was 3-11% higher among persons of African ancestry compared to Caucasians, even after adjusting for important covariates.(17-23) Possible biological explanations for this ethnic difference in BMD include peak bone mass acquisition(24-27), bone geometry(28-32), and genetic factors(33-35). Lifestyle factors associated with BMD may further explain the ethnic differences in BMD, but research in this area is limited.(36) Studies of ethnic differences in BMD have been conducted primarily in Europe, US, and South Africa and the vast majority of these studies have included only females.(21,24,28,31,37)

To address this gap in knowledge, we conducted a population-based study to identify anthropometric, lifestyle and health-related correlates of hip BMD in middle-aged and older males of West African ancestry, residing on the Caribbean island of Tobago.

3.3. Methods

Trinidad & Tobago is a twin-island State situated at the southern end of the Caribbean chain of islands. The 1990 census for Trinidad & Tobago reported approximately 5,100 males aged 40 – 79 on the island of Tobago. The majority of the Tobagonian population (92%) was reported to be of West African ancestry.(38) The Institutional Review Boards of University of Pittsburgh and the Tobago Ministry of Health and Social Services approved this study.

A total of 1,841 males were recruited between 1998 and 2000 from a population-based prostate cancer screening study on the Island of Tobago, Trinidad & Tobago. A detailed summary of the Tobago Prostate Cancer Survey Study methods has been published elsewhere.(39) Briefly, the Tobago Prostate Cancer Survey Study is a longitudinal study of prostate cancer in males aged 40 years and older. To be eligible for the Tobago Bone Health Study, males had to be willing to participate, able to provide informed consent, and ambulatory. For this analysis, we excluded participants (n=57) with prostate specific antigen greater than 40 or Gleason score greater than 7 because these levels increase the likelihood of androgen deprivation therapy or orchiectomy to treat prostate cancer, which is inversely related to BMD.(40-42) A final sample of 1,784 males was included in the analysis.

Trained interviewers and nurses administered questionnaires to participants in the Tobago Health Studies Office. Questionnaires gathered information pertaining to demographic characteristics, medical history, fracture history, physical activity, and lifestyle variables. We focused on potential correlates of BMD based on the body of literature for males and females.

Ethnicity was self-reported. Physical activity was measured as a continuous variable by the number of hours walked per week. Occupational history was measured as a dichotomous variable and included several common occupations. Most lifestyle characteristics and health-related questions were measured as dichotomous variables. Nominal variables included marital status, occupational status, alcohol consumption, and smoking history. Smoking status was categorized as never, former, or current. Males who smoked cigarettes for less than six months were considered to have never smoked. We also quantified the number of alcohol-containing beverages consumed in the past 12 months.

Body weight was measured in kilograms using a calibrated balance beam scale and participants were allowed to wear indoor clothing with shoes removed. Standing height without shoes was measured in centimeters with a wall-mounted stadiometer. Body mass index (BMI) was calculated by dividing body weight (in kilograms) by height (in meters squared). Handgrip strength was measured in kilograms for both dominant and non-dominant hands using a dynamometer.

All participants received a DXA examination during the study period (QDR 4500W, Hologic, Inc: Bedford, MA). The DXA examination was performed by a trained, certified DXA technician. For all participants, the same scanner was used and DXA scans were completed using the array beam mode. Standardized positioning and utilization of QDR software was based on the manufacturer's recommended protocol. Scans were analyzed with QDR software version 8.26a. Total hip and the femoral neck subregion were assessed by scanning the left hip, unless the patient had hip replacement surgery, deformity or some other condition that did not allow for scanning of the left side (n=16). Body composition measures (bone mineral-free lean mass and fat mass), were assessed by whole body scans. To ensure consistency, the DXA

technician scanned a spine phantom daily and completed a weekly quality control whole body air scan, prior to completing any scans. Synarc, Inc. (Waltham, MA) monitored spine phantom data, reviewed DXA scans, and flagged scans if positioning errors occurred.

Data Analysis

We compared mean BMD measured at the hip and femoral neck subregion to a nationally representative sample of US African American (AA) and Caucasian males from the National Health and Nutrition Examination Survey (NHANES) III (1988-1994), stratified by 10-year age intervals (Figures 3-1 and 3-2). To identify variables that correlated with hip BMD, predictor variables were analyzed using age- and weight-adjusted models. The strength of the association is expressed as percent change in units of change chosen to approximate one standard deviation (SD) in the distribution for each continuous variable or null category for dichotomous variables. The formula used to calculate the percent difference in BMD per unit change (SD) of the independent variable (β) = (unstandardized β x unit change in independent variable) x 100. The corresponding 95% confidence intervals were calculated using: $\beta \pm 1.96$ x standard error of β.

To limit the number of predictors tested, only variables with p-value less than 0.10 in age-adjusted models were considered in multiple linear regression analyses. Multiple linear regression analyses were performed using the stepwise approach to identify correlates of hip and the femoral neck subregion in separate models. Age was forced into models for both total hip and the femoral neck subregion. The final model only included variables significantly associated with BMD at $p < 0.05$.

Multicollinearity was assessed with the variance inflation factor (VIF). It is suggested that a VIF greater than 10 for any one variable or the mean of VIFs substantially larger than 1 represents collinearity among the variables.(43,44) In those instances where the data captured

information from multiple variables that measured the same characteristic, we used the variable that was most correlated with BMD. For example, lean mass and fat mass, two major components of body weight, explained more of the variability in BMD than body weight or BMI. Therefore, the latter variables were not included in multiple regression analyses.

Potential interactions were derived from extant literature and initial review of the multiple linear regression models. We tested for possible interactions between alcohol consumption and smoking, lean mass and standing height, lean mass and history of working on a fishing boat, lean mass and alcohol consumption, as well as alcohol consumption and history of working on a fishing boat. None of the interactions tested were significant ($p < 0.05$) in models for the hip or femoral neck subregion. Data were analyzed using SAS software version 8.2 (SAS Institute, Cary, NC).(45)

3.4. Results

The distribution of age and mean BMD for 1,784 participants is shown in Table 2-1. The average age of participants in this study was 56.3 ± 10.4 (range 40 to 84 years), with males aged 40-69 years accounting for more than 85% of the study sample. Mean total hip BMD was considerably higher in this cohort of middle-aged and older males compared to NHANES III data for Caucasian (18-22%) and AA males (8-12%), with larger differences in the three older age groups (Figure 2-1).(46) Similar differences were observed at the femoral neck subregion when we compared mean BMD of Tobagonian males to data for US males (Figure 2-2).(46) Additional descriptive characteristics are shown in Tables 2 and 3 for the hip and femoral neck subregion, respectively, adjusted for age and age in conjunction with weight.

Physical and Anthropometric Variables

Bone mass was inversely related to age, decreasing approximately 3% at the hip and 4% at the femoral neck subregion for every additional 10 years in age (Tables 2-2 and 2-3). After adjusting for age, each standard deviation increase in lean mass was associated with a 6-7% increase in BMD at both sites. BMD increased 3-4% for each standard deviation increase in fat mass in age-adjusted models. Each 15 kg increase in body weight was associated with a 6% increase in BMD and 1 standard deviation increase in standing height and grip strength was also associated with nearly a 2% increase in BMD, after adjusting for age. Variables associated with BMD in age-adjusted models remained significant in age- and weight-adjusted models but to a smaller magnitude. In the age- and weight-adjusted model, more television watching was associated with significantly lower BMD at the femoral neck subregion.

Personal/Family History and Lifestyle Characteristics

Lifetime history of sustaining a fracture or broken bone was inversely related to BMD, after adjusting for age ($p = 0.0052$ total hip and $p = 0.0169$ femoral neck subregion). Current working status was not significantly associated with BMD, but history of working on a farm and history of working on a fishing boat were both positively associated with hip BMD after adjustment for age, with magnitudes of 2-4% higher BMD. Current physical activity and smoking did not have any significant effect on BMD in the age-adjusted analyses. Males who consumed at least one to five alcohol-containing beverages per week had 2% higher femoral neck BMD in age-adjusted models.

Medical History and Medication Use

Both hypertension and diabetes were associated with 3% higher BMD whereas diverticulitis was associated with 6-9% lower BMD. The proportion of males who had taken selected prescription and nonprescription medications in the last year was relatively low and

represented less than 20% of the study sample. None of the medications in this analysis was significantly associated with BMD.

Multiple Linear Regression Analyses

Complete data were available for 1,666 participants who were included in the multiple linear regression analyses for both the total hip and femoral neck subregion models. Models derived from stepwise regression analyses explained 25% of the total variance (R^2) in BMD measured at the hip and femoral neck subregion. Variables associated with total hip BMD are shown in Table 2-4. Each one unit increase in lean mass was associated with nearly an 8% increase in BMD, but a unit increase in standing height was associated with 2% lower BMD, after controlling for the effects of other variables in the model. In models considering lean mass or fat mass separately, each was independently related to hip total BMD ($p < 0.001$), but after adjustment for covariates, the effect of fat mass was negligible. Consistent associations were observed for the same independent variables at the femoral neck subregion BMD (Table 2-5). For example, each additional 10 years in age was associated with a 2.6% decrease in femoral neck BMD compared to a 1.3% decrease in BMD at the hip, when other variables were included in the model. At both sites, lean mass accounted for the greatest proportion (partial $R^2 = 15$-18%) of the variance in BMD.

3.5. Discussion

Mean BMD, measured at the total hip and femoral neck subregion, was 8-22% higher among Tobagonian males compared to US Caucasian and AA males of similar age as reported in the NHANES III.(46) One possible explanation for greater mean BMD in Tobagonian males compared to AA males is that admixture in the US for persons of African ancestry is approximately 25% (47) compared to only 6% on the island of Tobago. Another potential

explanation for higher BMD is lack of industrialization in Tobago. Residents encounter more weight bearing activities during work and leisure-time activities, possibly resulting in increased muscle strength and bone mass.

Older age, greater standing height, and history of a broken or fractured bone were inversely associated with BMD, whereas lean mass, history of working on a fishing boat, and history of diabetes were positively associated with BMD. BMD significantly decreased with each decade of life, consistent with the findings of published literature for Caucasian males.(7-11,15,21,46,48-56) Taller males had lower BMD in this study, which may be related to the overall lower body weight in this study population, resulting in less dense bone among taller persons (i.e., thinness). Similar to the finding by Orwoll for rural Caucasian males,(11) history of a broken bone or fracture was inversely associated with BMD. This association may be predictive of future fracture risk since history of fracture predisposes one to increased risk of fracture in the future.(3)

Some studies have suggested that both fat and lean mass were significant correlates of BMD among males and females of African ancestry (10,57,58) and other studies suggested that fat mass had a greater effect on bone mass in postmenopausal AA females (19,59-61). Our analysis demonstrated that lean mass was the variable most strongly associated with BMD at the total hip (partial R^2 = 18.4%) and femoral neck subregion (partial R^2 = 15.3%) rather than adiposity which confirms the findings of other studies. (17,19,59,62,63) For example, Dibba et al. suggested that lean mass, rather than body size, explained the higher femoral neck BMD among Gambian males compared to Caucasian males.(28)

We believe lean mass was influenced by lifetime muscle activity and mechanical loading on the skeleton. This proposed mechanism may have contributed to maintenance of BMD, as observed in this study. Ringsberg et al. have shown that physical activity and higher workload increased muscle strength, thereby preserving bone, among females who participated in long-term physical activity. (64) It has been postulated that aromatization of androgens into estrogen also occurs in lean mass, thereby positively influencing bone maintenance and integrity.(65,66) The positive association between BMD and history of working on a fishing boat may be a surrogate for lifetime vigorous physical activity, which better explains the role of skeletal loading on BMD compared to the current number of hours walked per week.

Diabetes was associated with higher BMD and this association has been reported in other studies with Caucasian males and females.(12,13) (67) One possible explanation for increased BMD among persons with type 2 diabetes is the anabolic effect that insulin has on bones, which preserves bone.(68,69) (70)

Predictors of BMD in this study extend results from previous studies of AA males and females.(37,71) George et al. examined correlates of BMD among older AA males and found that height, weight, and physical activity were positively associated with BMD measured at the femoral neck and smoking was inversely associated with BMD.(37) Significant correlates of BMD in this analysis were similar to those reported in the literature for females of African ancestry, where age was inversely associated with BMD and body weight was positively associated with BMD.(60,72-75) Broussard et al. reported that lower BMI, current smoking, and physical inactivity were associated with lower BMD among AA males who participated in NHANES III.(75)

In studies of Caucasian males, smoking, excessive alcohol consumption, physical inactivity, previous fractures, falling in the past 12 months, glucocorticoid use, rheumatoid arthritis, and gastrectomy were inversely associated with BMD.(7-11,52,54,76) We were unable to confirm that smoking, alcohol consumption, family history of hip fracture, and falling in the past 12 months were associated with lower BMD. The lack of an association between smoking, which has been noted in several studies,(7,77-79) may reflect the small proportion (13.5%) of smokers in this study population. Moderate alcohol consumption (1 to 5 drinks per week) was associated with higher BMD in age-adjusted models but this variable did not enter the multiple regression models. We also note that very few study participants had a family history of fracture (~3%) or reported falling in the previous year (~11.0%), which may explain the lack of association with BMD for these variables in our analysis.

Our analysis offers a unique opportunity to examine correlates of BMD in middle-aged and older males of West African ancestry; a sample of males that has not been well studied. BMD was measured with state-of-the art DXA technology. This population-based study characterized the correlates of BMD in a very stable population with low admixture. Persons of African ancestry comprise a segment of the worldwide population that is underrepresented in the vast majority of osteoporosis research. This analysis contributes to addressing gaps in the osteoporotic literature for males of African ancestry.

We should acknowledge the limitations of our analysis. First, data were collected using a cross-sectional study design, which only allows us to only evaluate associations not causality. Second, data on lifestyle and health-related factors were derived from patient self-report and are subject to recall bias. However, these data were collected prior to BMD measurements, so differential recall related to BMD is highly unlikely. Due to the lack of automated medical

history data, we were unable to verify medical history. Furthermore, our study was limited to males on the island of Tobago who were of West African ancestry and findings from this analysis may not be applicable to all males with similar ancestry residing on other Caribbean islands, in North America, or Europe.

In summary, among community-dwelling Caribbean males of West African ancestry residing on the island of Tobago, BMD was considerably higher than males in the US. Lean mass was the major predictor of BMD and explained most of the variability in BMD. Older age, history of a broken or fractured bone, and taller height were all risk factors that might identify African Caribbean males at risk for fracture. Some variables previously reported to influence BMD in US Caucasian males (e.g. smoking, excessive alcohol intake, and family history of fracture) were not important determinants of BMD in this population. Longitudinal analyses of changes in bone are needed to further evaluate correlates of BMD and confirm associations observed in this cross-sectional analysis.

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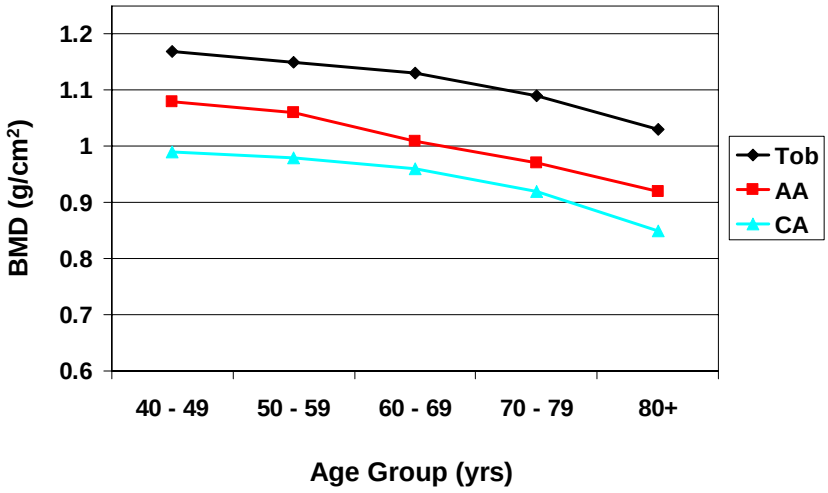
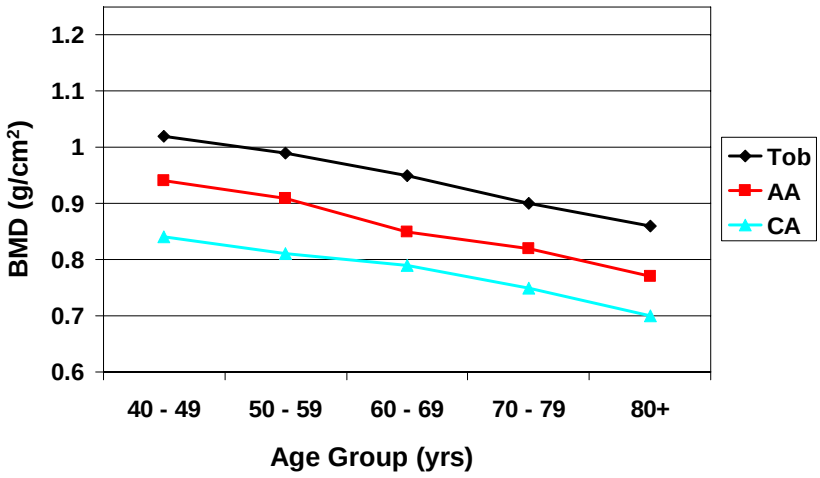


Looker et al. *Osteoporosis International* 1998; NHANES III

Figure 3-1. Mean total hip BMD (g/cm^2) for Tobago males compared to African American and Caucasian American males, NHANES III, US 1988-1994



Looker et al. *Osteoporosis International* 1998; NHANES III

Figure 3-2. Mean femoral neck BMD (g/cm^2) for Tobago males compared to African American and Caucasian American males, NHANES III, US 1988-1994

Table 3-1. Descriptive Characteristics (N=1,784)

Age Group *(y)*	***N(%)***
40-49	551 (30.9)
50-59	550 (30.8)
60-69	447 (25.1)
70-79	219 (12.3)
80+	17 (1.0)
BMD *(g/cm^2)*	***Mean ± SD***
Total hip	1.14 ± 0.15
Femoral neck subregion	0.98 ± 0.15

Table 3-2. Correlates of Total Hip Bone Mineral Density Expressed as the Percent Difference in BMD per Unit Change of the Variable

Characteristics	Mean ± SD or Prevalence (%)	Age-Adjusted Percent Difference in BMD per Unit Change (95% CI)[†]	Age- & Weight-Adjusted Percent Difference in BMD per Unit Change (95% CI)[†]
Physical & Anthropometric Characteristics			
Age *(years)*	56.3 ± 10.4	-2.76 (-3.44, -2.09)**	-1.81 (-2.44, -1.18)**
Weight *(kg)*	83.3 ± 14.8	5.98 (5.35, 6.61)§**	5.70 (5.06, 6.33)**
Standing height *(cm)*	174.8 ± 6.7	1.49 (0.79, 2.18)**	-0.84 (-1.54, -0.14)*
Body mass index (kg/m^2)	27.2 ± 4.4	5.36 (4.73, 5.98)**	----
Right grip strength *(kg)*	43.4 ± 11.0	1.92 (1.12, 2.73)**	0.61 (-0.16, 1.37)
Left grip strength *(kg)*	42.6 ± 10.6	2.00 (1.18, 2.82)**	0.64 (-0.14, 1.42)
Lean mass *(kg)*	61.0 ± 8.2	6.60 (5.96, 7.23)**	-----
Fat mass *(kg)*	16.6 ± 7.0	3.82 (3.16, 4.48)**	-----
Personal/Family History			
Fallen in past 12 months	194 (10.9)	1.52 (-0.64, 3.69)	1.63 (-0.38, 3.64)
Any back pain in past 12 months	929 (52.3)	1.21 (-0.14, 2.56)	0.84 (-0.41, 2.09)
Ever fractured or broken bone	347 (19.5)	-2.44 (-4.14, -0.73)*	-2.69 (-4.26, -1.12)*
Lifestyle characteristics			
Married or living as married	1241 (69.9)	0.31 (-1.17, 1.79)	0.00 (-1.37, 1.37)
Current smoker	240 (13.5)	-1.52 (-3.50, 0.47)	0.11 (-1.73, 1.96)
Alcohol drinks per week			
None	574 (32.2)	Reference	Reference
Up to 1 drink	505 (28.3)	1.35 (-0.40, 3.09)	0.54 (-1.08, 2.16)
More than 1 drink to 5 drinks	398 (22.3)	1.85 (-0.03, 3.74)	1.19 (-0.55, 2.94)
More than 5 drinks	307 (17.2)	-0.28 (-2.31, 1.76)	-0.26 (-2.14, 1.62)
Hours walked per week	29.8 ± 21.4	-0.10 (-0.78, 0.58)	0.48 (-0.16, 1.11)
Hours watched television per week	15.0 ± 11.5	-0.22 (-0.89, 0.45)	-0.45 (-1.08, 0.17)
Currently working	625 (35.0)	-1.10 (-3.19, 0.99)	-0.47 (-2.41, 1.46)
Ever worked on farm	908 (51.3)	1.48 (0.12, 2.83)*	1.40 (0.14, 2.65)*
Ever worked on fishing boat	314 (17.6)	3.81 (2.04, 5.57)**	3.63 (2.00, 5.26)**
Chemical pesticide use	326 (18.3)	-0.05 (-1.80, 1.69)	-0.31 (-1.92, 1.31)
Chemical fertilizer use	317 (17.8)	0.30 (-1.46, 2.06)	0.34 (-1.30, 1.97)
Medical History			
Family history of prostate cancer	128 (7.2)	-2.01 (-4.62, 0.60)	-0.82 (-3.24, 1.60)
Hypertension	571 (32.0)	3.76 (2.29, 5.23)**	1.02 (-0.39, 2.42)
Coronary heart disease	72 (4.0)	-0.24 (-3.70, 3.21)	-0.34 (-3.53, 2.85)
Stroke	45 (2.5)	0.32 (-4.02, 4.67)	-0.12 (-4.13, 3.90)
Diabetes	217 (12.2)	3.38 (1.29, 5.46)*	2.38 (0.45, 4.31)*
Arthritis	231 (13.0)	0.43 (-1.67, 2.54)	-1.02 (-2.98, 0.94)
Colorectal polyps	112 (6.3)	-1.92 (-4.69, 0.86)	-1.89 (-4.45, 0.67)
Osteoporosis	20 (1.1)	0.98 (-5.45, 7.40)	1.03 (-4.91, 6.96)
Diverticulitis	17 (1.0)	-7.43 (-14.35, -0.51)*	-5.55 (-11.94, 0.85)
Worse health compared to others same age	64 (3.6)	1.01 (-2.61, 4.64)	-0.92 (-4.27, 2.43)
Worse health compared to last year	246 (13.8)	1.87 (-0.08, 3.83)	1.64 (-0.17, 3.46)
Medication use in past 12 months			
Aspirin	216 (12.1)	0.33 (-1.75, 2.41)	-0.64 (-2.56, 1.29)
Nonsteroidal anti-inflammatory	302 (16.9)	0.60 (-1.20, 2.41)	-0.59 (-2.26, 1.08)
Ibuprofen	131 (7.3)	0.64 (-1.95, 3.22)	-0.78 (-3.18, 1.62)
Diuretics (anti-hypertensive)	17 (1.0)	3.54 (-3.39, 10.48)	4.20 (-2.40, 10.80)

[†] Indicates percent change in bone mass in g/cm^2 per indicated unit or 1 standard deviation

* p <0.05, ** p<0.0001;§ Effect of weight alone

Table 3-3. Correlates of Femoral Neck Bone Mineral Density Expressed as the Percent Difference in BMD per Unit Change of the Variable

Characteristics	Mean ± SD or Prevalence (%)	Age-Adjusted Percent Difference in BMD per Unit Change (95% CI)[†]	Age- & Weight-Adjusted Percent Difference in BMD per Unit Change (95% CI)[†]
Physical & Anthropometric Characteristics			
Age *(years)*	56.3 ± 10.4	-4.04 (-4.70, -3.39)**	-3.21 (-3.84, -2.59)**
Weight *(kg)*	83.3 ± 14.8	5.61 (4.98, 6.24)§**	5.06 (4.44, 5.69)**
Standing height *(cm)*	174.8 ± 6.7	2.05 (1.38, 2.73)**	0.11 (-0.58, 0.80)
Body mass index (kg/m^2)	27.2 ± 4.4	4.44 (3.82, 5.05)**	------
Right grip strength *(kg)*	43.4 ± 11.0	1.81 (1.03, 2.59)**	0.64 (-0.11, 1.39)
Left grip strength *(kg)*	42.6 ± 10.6	1.94 (1.15, 2.74)**	0.75 (-0.01, 1.51)
Lean mass *(kg)*	61.0 ± 8.2	6.00 (5.37, 6.62)**	------
Fat mass *(kg)*	16.6 ± 7.0	3.25 (2.61, 3.89)**	------
Personal/Family History			
Fallen in past 12 months	194 (10.9)	1.32 (-0.78, 3.42)	1.47 (-0.50, 3.45)
Any back pain in past 12 months	929 (52.1)	0.86 (-0.45, 2.17)	0.56 (-0.67, 1.78)
Ever fractured or broken bone	347 (19.5)	-2.02 (-3.67, -0.36)*	-2.22 (-3.77, -0.67)*
Lifestyle characteristics			
Married or living as married	1241 (69.6)	0.06 (-1.38, 1.49)	-0.26 (-1.60, 1.09)
Current smoker	240 (13.5)	-0.34 (-2.27, 1.58)	1.14 (-0.67, 2.95)
Alcohol drinks per week			
None	574 (32.2)	Reference	Reference
Up to 1 drink	505 (28.3)	1.54 (-0.16, 3.23)	0.79 (-0.80, 2.39)
More than 1 drink to 5 drinks	398 (22.3)	2.15 (0.32, 3.97)*	1.57 (-0.15, 3.28)
More than 5 drinks	307 (17.2)	0.23 (-1.74, 2.20)	0.25 (-1.60, 2.10)
Hours walked per week	29.8 ± 21.4	-0.11 (-0.77, 0.55)	0.40 (-0.23, 1.02)
Hours watched television per week	15.0 ± 11.5	-0.52 (-1.18, 0.13)	-0.73 (-1.34, -0.12)*
Currently working	1151 (64.5)	-1.05 (-3.08, 0.98)	-0.50 (-2.40, 1.40)
Ever worked on farm	908 (50.9)	1.56 (0.24, 2.88)*	1.50 (0.26, 2.73)*
Ever worked on fishing boat	314 (17.6)	3.42 (1.71, 5.13)**	3.28 (1.68, 4.89)**
Chemical pesticide use	326 (18.3)	-0.27 (-1.96, 1.42)	-0.49 (-2.08, 1.10)
Chemical fertilizer use	317 (17.8)	-0.26 (-1.97, 1.45)	-0.22 (-1.83, 1.39)
Medical History			
Family history of prostate cancer	128 (7.2)	-2.18 (-4.71, 0.35)	-1.13 (-3.51, 1.25)
Hypertension	571 (32.0)	2.89 (1.46, 4.32)**	0.42 (-0.97, 1.80)
Coronary heart disease	72 (4.0)	-0.62 (-3.97, 2.73)	-0.66 (-3.80, 2.47)
Stroke	45 (2.5)	0.08 (-4.14, 4.30)	-0.27 (-4.21, 3.68)
Diabetes	217 (12.2)	3.50 (1.48, 5.52)*	2.66 (0.76, 4.56)*
Arthritis	231 (12.9)	0.32 (-1.72, 2.37)	-0.93 (-2.86, 0.99)
Colorectal polyps	112 (6.3)	-1.87 (-4.56, 0.82)	-1.82 (-4.34, 0.70)
Osteoporosis	20 (1.1)	-0.88 (-7.12, 5.35)	-0.80 (-6.63, 5.04)
Diverticulitis	17 (1.0)	-8.78 (-15.49, -2.07)*	-7.08 (-13.37, -0.80)*
Worse health compared to others same age	64 (3.6)	-0.70 (-4.22, 2.81)	-2.40 (-5.69, 0.90)
Worse health compared to last year	246 (13.8)	1.16 (-0.74, 3.06)	0.98 (-0.80, 2.76)
Medication use in past 12 months			
Aspirin	216 (12.1)	-0.16 (-2.18, 1.85)	-0.99 (-2.88, 0.90)
Nonsteroidal anti-inflammatory	302 (16.9)	0.18 (-1.57, 1.94)	-0.85 (-2.50, 0.79)
Ibuprofen	131 (7.3)	0.12 (-2.38, 2.62)	-1.14 (-3.49, 1.22)
Diuretics (anti-hypertensive)	32 (1.8)	1.40 (-5.33, 8.13)	1.46 (-5.03, 7.94)

[†] Indicates percent change in bone mass in g/cm^2 per indicated unit or 1 standard deviation

* p <0.05, ** p<0.0001;[§] Effect of weight alone

Table 3-4. Statistically Significant Correlates of Hip BMD in Multiple Linear Regression Analyses, Expressed as Percent Difference in BMD per Unit/Standard Deviation of the Predictor Variables (n=1,666)

Variable	Percent Difference (95% CI)
	Total Hip BMD[a]
Age *(years)*	-1.3 (-1.9, -0.6)*
Lean mass *(kg)*	7.5 (6.8, 8.3)**
Standing height *(cm)*	-2.1 (-2.9, -1.4)*
Ever worked on a fishing boat *(yes)*	2.6 (1.0, 4.2)*
Diabetes *(yes)*	2.9 (1.0, 4.9)*
Ever fractured or broken a bone *(yes)*	-2.4 (-3.9, -0.8)*
Model $R^2 = 0.25$	

[a] Other possible predictors tested to explain variability in total hip BMD using $p<0.05$ as the criterion for entry in the model include: fat mass, grip strength, diverticulitis, current smoking, back pain in past 12 months, hypertension, history of farming, and worse health compared to 12 months ago. These variables were not significant at $p<0.05$.
* $p<0.05$, ** $p<0.0001$

Table 3-5. Statistically Significant Correlates of Femoral Neck BMD in Multiple Linear Regression Analyses, Expressed as Percent Difference in BMD per Unit/Standard Deviation of the Predictor Variables (n=1,666)

Variable	Percent Difference (95% CI)
	Femoral Neck BMD[a]
Age *(years)*	-2.6 (-3.3, -2.0)*
Lean mass *(kg)*	6.3 (5.6, 7.1)*
Diabetes *(yes)*	3.3 (1.4, 5.2)*
Ever worked on a fishing boat *(yes)*	2.5 (0.9, 4.1)*
Standing height *(cm)*	-1.0 (-1.7, -0.3)*
Ever fractured or broken a bone *(yes)*	-2.0 (-3.6, -0.5)*
Model $R^2 = 0.25$	

[a] Other possible predictors tested to explain variability in femoral neck BMD using $p<0.05$ as the criterion for entry in the model include: fat mass, grip strength, diverticulitis, hypertension, history of farming, and family history of prostate cancer.
* $p<0.05$, ** $p<0.0001$

4. Correlates of Bone Mineral Density among Postmenopausal Women of African Caribbean Ancestry: Tobago Women's Health Study

(Manuscript to be submitted)

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4.1. Abstract

Objective: To identify correlates of BMD among postmenopausal females of West African ancestry residing on the Caribbean island of Tobago.

Materials and Methods: 340 ambulatory females are included in this cross-sectional analysis. Participants completed an administered questionnaire and had anthropometric measures taken. Total hip and the femoral neck subregion BMD was measured using dual energy x-ray absorptiometry.

Results: In multiple linear regression models, 37-38% of the variability in femoral neck and total hip BMD was predicted, respectively. Each 16 kilogram increase in weight was associated with 5% higher BMD, and explained over 10% of the variability of BMD, after considering the effects of other covariates. Each 8 year increase in age was associated with 5% lower BMD. Current use of both thiazide diuretics and oral hypoglycemic medication were associated with 4-5% higher BMD, whereas history of thyroid hormone use was associated with 10-15% lower BMD.

Conclusion: Correlates of BMD identified in this analysis are similar to those reported for African American and Caucasian females. Body weight was a strong predictor of BMD and accounted for 12-14% of the variability in BMD, after adjustment for covariates.

(ABSTRACT < 250 WORDS)

4.2. Introduction

Bone mineral density (BMD) is one of the strongest predictors of future fracture risk. (1,2) It is well-established that African Americans (AA) have greater BMD across the entire life span compared to Caucasian Americans (3-5), which is due in part to higher peak bone mass.(6,7) Although AA females have considerably higher BMD than Caucasian females, this is not the case for all females of African ancestry. Aspray and colleagues established that among older West African females, BMD was considerably lower than Caucasian British females. (8) Similarly, Dibba et al. did not observe any ethnic differences in BMD among Gambians compared to British males and females.(9) These studies suggested that among West Africans, BMD was comparable to, or even lower than, Caucasians.(8-10) Although African females have similar and sometimes lower BMD than Caucasians, the risk of fracture is not increased among African females.(10)

Lifestyle and health-related factors influence BMD and subsequent fracture risk. Numerous studies have examined risk factors associated with lower BMD among postmenopausal Caucasian American females. (11-15) Fewer studies, however, have examined risk factors associated with lower BMD among AA females.(16-18) Risk factors correlated with BMD in AA females appear to be similar to those observed for Caucasian females and include sedentary lifestyle, low BMI, and family history of osteoporotic fractures.(19,20) Whether these risk factors are applicable to females of African ancestry in other countries is not known. We do know, however, that osteoporosis is a serious public health issue for postmenopausal females, regardless of ethnicity. Population dynamics predict a drastic increase in older persons of African ancestry and steep increases in fracture incidence rates are also expected. More studies are

needed to evaluate the role of race and ethnicity in conjunction with lifestyle and health-related factors to better understand ethnic differences in BMD and subsequent fracture risk.

To better understand the interrelationships between bone health and demographic, lifestyle, anthropometric, and health-related factors, we conducted a cross-sectional analysis of data from postmenopausal females on the Caribbean island of Tobago to identify correlates of BMD. Our objectives were: (1) to compare BMD measured at the total hip and femoral neck subregion among postmenopausal Tobagonian females to measurements from US non-Hispanic black and non-Hispanic white females of the same age (NHANES III); (2) to identify the demographic, anthropometric, health-related, lifestyle, and reproductive factors that were correlated with BMD, and (3) to identify the best subset of predictors of BMD in a sample of postmenopausal females of West African ancestry residing in Tobago.

4.3. Methods

Trinidad & Tobago is a twin-island State situated at the southern end of the Caribbean chain of islands. The majority of the Tobagonian population (92%) was reported to be of West African ancestry. (35) The Institutional Review Boards of University of Pittsburgh and the Tobago Ministry of Health and Social Services approved this study.

To increase awareness about the Women's Health Study, recruitment flyers were posted near the Tobago Health Studies Office in downtown Scarborough, Tobago. Recruitment efforts also included word-of-mouth referral by research staff and male participants in the Tobago Prostate Cancer Survey Study. Potential study participants were females aged 50 years and older, postmenopausal, ambulatory, willing to provide informed consent, and residents on the Caribbean island of Tobago. Postmenopausal status was defined as self-reported cessation of menses at least 12 months prior to study enrollment. Ethnicity was self-reported and participants

provided detailed information on the ethnic origin of their parents and grandparents. A total of 350 females were recruited to participate in the Women's Health Study between October 2002 and December 2002. For the purpose of this cross-sectional analysis, we excluded 10 women who were not of African ancestry (all four grandparents), resulting in a sample of 340 women.

Trained interviewers and nurses administered questionnaires to participants in the Tobago Health Studies Office. Questionnaires gathered information pertaining to demographic characteristics, medical history, medication use, reproductive history, fracture history, physical activity, and lifestyle variables. We focused on potential correlates of BMD based on the body of literature for postmenopausal women. Physical activity was measured as a continuous variable by the number of hours walked per week. Television watching was dichotomized at the 75^{th} percentile of total hours per week. Other lifestyle characteristics and health-related questions were measured as dichotomous variables. Medical history was based on self-report. Any mention of joint pain, regardless of site or type of arthritis, was considered arthritis. Nominal variables included marital status, alcohol consumption, and smoking history. Smoking status was categorized as never, former, or current. Women who reported that they had smoked cigarettes for less than six months were considered to have never smoked.

Participants were asked to bring prescription and nonprescription medication to the interview for verification by trained study personnel. Medication names were cross-referenced with a drug handbook to identify drug class. Selected over-the-counter medication that was used at least three-times per week was considered regular use.

Fasting blood glucose, blood pressure, and pulse were measured after 5 minutes of rest by nursing staff using standard techniques with research quality glucometers (Accu-Chek: Roche Diagnostics, Indianapolis, IN or Prestige: Home Diagnostics, Cincinnati, Ohio) and blood

pressure machines (Omron: Omron Healthcare Corp, Vernon Hills, IL). Body weight was measured in kilograms using a calibrated balance beam scale and participants were allowed to wear indoor clothing with shoes removed. Standing height without shoes was measured in centimeters with a wall-mounted stadiometer; sitting height was also measured in centimeters. We calculated average sitting and standing height based on 2 repeated measurements of each height. If the values differed by more than 2 centimeters, an additional measurement was taken and the average was based on the 2 values that were within 2 centimeters. Body mass index (BMI) was calculated by dividing weight (in kilograms) by standing height (in meters squared). Handgrip strength was measured in kilograms for both dominant and non-dominant hands using an adjustable hydraulic dynamometer (Preston Grip Dynamometer, JA Preston Corp., Jackson, MS). We calculated average grip strength based on 2 repeated measurements and if the values differed by more than 2 kilograms, participants completed another measure of grip strength and the average was based on the 2 values within 2 kilograms. An inelastic tape measure was used for hip and waist measurements that were taken just prior to the dual energy x-ray absorptiometry (DXA) examination. Hip circumference was measured at the greatest protuberance of the buttock and the waist circumference measurement was obtained at the level of the umbilicus, both in centimeters.

All participants received a DXA examination during the study period (QDR 4500W, Hologic, Inc: Bedford, MA). For all participants, the same scanner was used and DXA scans were completed using the array beam mode. Standardized positioning and utilization of QDR software was based on the manufacturer's recommended protocol. Scans were analyzed with QDR software version 8.26a. The left hip was scanned to obtain areal BMD measures at the total hip and the femoral neck subregion. Body composition measures (bone mineral-free lean

mass and fat mass), were assessed by whole body scans. To ensure consistency a spine phantom was scanned daily and quality control whole body air scan was completed weekly, prior to completing any scans. Synarc, Inc. (Waltham, MA) monitored spine phantom data, reviewed DXA scans, and flagged scans if positioning errors occurred.

Data Analysis

We compared mean BMD measured at the hip and femoral neck subregion to a nationally representative sample of US non-Hispanic black and non-Hispanic white women from the National Health and Nutrition Examination Survey (NHANES) III (1988-1994), stratified by 10-year age intervals. To identify variables that correlated with hip BMD, predictor variables were analyzed using age- and weight-adjusted models, since age and weight have been shown to correlate with BMD. The strength of the association is expressed as percent change in units of change chosen to approximate one standard deviation (SD) in the distribution for each continuous variable and yes (1) or no (0) for dichotomous variables. The formula used to calculate the percent difference in BMD per unit change (SD) of the independent variable (β) = (unstandardized β x unit change in independent variable) x 100. The corresponding 95% confidence intervals were calculated using: $\beta \pm 1.96$ x standard error of β.

To limit the number of predictors tested, only variables with a p-value less than 0.10 in age-and weight-adjusted models were considered in multiple linear regression analyses. Multiple linear regression analyses were performed using the stepwise approach to identify correlates of hip and the femoral neck subregion in separate models. Age was forced into models for both the total hip and femoral neck subregion. The final model only included variables significantly associated with BMD at $p < 0.05$.

Multicollinearity was assessed with the variance inflation factor (VIF), which suggests that a VIF greater than 10 for any one variable or the mean of VIFs substantially larger than 1 represents collinearity among the variables. In some instances, our data captured information from multiple variables that measured the same characteristic and we selected the variable that was most correlated with BMD. BMI and components of body weight (lean and fat mass) were significantly associated with higher BMD in age-adjusted models, but to a lesser extent than body weight, so we did not consider BMI or lean and fat mass in multiple linear regression models. Similarly, diabetes mellitus was identified using three variables: (1) self-report of physician diagnosed diabetes; (2) fasting blood glucose; and (3) oral hypoglycemic medication. Oral hypoglycemic medication was most strongly correlated with BMD and this variable was used as a potential predictor in the multiple regression models.

Potential interactions were derived from extant literature and initial review of the multiple linear regression models. We tested for interactions including age and weight, and weight and history of using thyroid hormone medication. None of the interactions tested were significant ($p < 0.05$) in models for the hip or femoral neck subregion (data not shown). Data were analyzed using SAS software version 8.2 (SAS Institute, Cary, NC).

4.4. Results

Demographic Characteristics

Age distribution and mean BMD for 340 participants are shown Table 3-1. The average age was 63.9 ± 8.0 years and ranged from 50 to 94 years. Compared to NHANES III estimates, age-specific total hip BMD among Tobagonian females was 10-18% higher than AA females and 29-30% higher than Caucasian females (Figure 4-1). The direction and magnitude of ethnic group comparisons in BMD was similar at the femoral neck subregion (Figure 3-2).

Correlates of total hip and femoral neck BMD, adjusted for age and age + body weight, are shown in tables 3-2 and 3-3, respectively. BMD was inversely associated with age and educational attainment. BMD decreased 6% for every 8 additional years in age. Females who completed high school had 3% lower BMD compared to females who did not graduate after adjusting for age, but it was not significant.

Physical and Anthropometric Measures

Each standard deviation increase in body weight was associated with a 7% increase in BMD measured at the hip and femoral neck subregion. After adjusting for age, each 16 kg increase in body weight accounted for 5-6% higher BMD at the femoral neck subregion and hip, respectively. Each 5.8 kg/m^2 increase in BMI was associated with 6% higher hip and 5% higher femoral neck BMD in age-adjusted models. Each standard deviation increase in lean mass and fat mass were each associated with 5% higher BMD, after adjustment for age. Height measurements, both sitting and standing, elevated blood pressure (>120/80), and average right grip strength were not significantly associated with BMD at the sites examined after adjusting for age or age in conjunction with weight. A 1% increase in hip BMD was associated with every 7 kg increase in left grip strength after adjusting for age, but this association attenuated when we also adjusted for weight. A fasting blood glucose measure greater than 100 mg/dl was associated with 3-5% higher hip and femoral neck BMD after age adjustment and remained significant for hip BMD in the age- and weight-adjusted model.

Personal and Family History

Females who reported a fall in the past 12 months had 3% higher hip BMD compared to those who did not fall in the age-adjusted model, but the association was no longer statistically significant in the age- and weight-adjusted model. Report of falling was not significantly

associated with BMD at the femoral neck subregion. Among females who reported recent back pain, hip BMD was 4-6% higher after adjustment for age and age along with weight. A similar increase in femoral neck BMD was observed for females with recent back pain, but this association did not remain significant in the age- and weight-adjusted model. Personal history of a broken or fractured bone was not significantly associated with BMD for either site. Family history of hip fracture was associated with lower hip and femoral neck BMD, but this variable did not reach statistical significance in femoral neck adjusted models.

Lifestyle Characteristics

Females who reported watching at least 16 hours of TV per week had 3% lower femoral neck BMD after adjustment for age and weight. No other lifestyle characteristics examined were significantly related to BMD.

Medical History

A history of diabetes was associated with 5 - 6% higher hip and femoral neck BMD, respectively, after age adjustment. The association between higher BMD and diabetes remained significant after adjusting for the effects of age in combination with weight at both sites. Five percent higher hip BMD and 3% higher femoral neck BMD was associated with any report of arthritis pain in age-adjusted models. After adjusting for age and weight, a history of coronary heart disease was associated with 5-6% higher BMD at both sites. Graves' disease was associated with a 7% decrease in hip BMD after adjustment for age and weight.

Medication Use

Females who reported ever taking thyroid medication had 13-14% lower hip BMD and 10-11% lower decrease in femoral neck BMD, after adjustment for the effects of age and age in addition to weight. Regular use of aspirin was associated with 6% lower hip and femoral neck

BMD in age-adjusted models and this association remained significant after weight adjustment. Current use of thiazide diuretics was associated with 5-6% higher BMD at both sites, after adjustment for the effects of age and weight. Similarly, diabetes prescription medication was associated with a 5-7% increase in BMD at both sites. A 21% increase in hip BMD and 19% increase in femoral neck BMD were observed for the few females who were currently using statins in age-adjusted models. This association, however, was no longer significant after additional adjustment for weight. Current use of prescription and over-the-counter nonsteroidal anti-inflammatory drugs was associated with 6% higher hip BMD and 5% higher femoral neck BMD in age-adjusted models only. Females who were taking beta-blockers had 7% lower hip BMD and 6 % lower femoral neck BMD even after adjustment for the effects of age and weight.

Reproductive History

The vast majority of females (93.2%) reported ever becoming pregnant. Among those who gave birth to at least one child, parity and breast-feeding were each associated with a 5% increase in BMD in age-adjusted models but these associations were no longer significant after additional adjustment for weight. Age- and weight-adjusted femoral neck BMD was 3% lower among females who had a hysterectomy.

Multiple linear regression models

Complete data were available for 339 participants. Models derived from stepwise regression analyses explained 38% of the total variance (R^2) in total hip BMD and 37% of the variability in femoral neck BMD. Variables associated with total hip BMD are shown in Table 3-4. Each unit increase in body weight was associated with a 6% increase in hip BMD; and every additional 8 years in age was associated with 5% lower BMD, after controlling for the

effects of ever thyroid medication use (-), current diabetes medication use (+), recent back pain (+), thiazide diuretic use (+), current use of beta-blockers (-), and family history of fracture (-).

Body weight was the highest predictor of femoral neck BMD (Table 5) with each unit increase in body weight and age resulting in 5% higher BMD, taking into consideration the effects of ever thyroid medication use (-), current diabetes medication use (+), regular aspirin use (+), current use of beta-blockers (-), and thiazide diuretic use (+).

4.5. Discussion

To our knowledge, this analysis is one of few studies that identified correlates of BMD among postmenopausal females of African ancestry residing outside the US. One interesting finding was that Tobagonian females had 10-18% and 29% higher BMD compared to AA and Caucasian American females, respectively.

It is well established that BMD is significantly higher among AAs compared to Caucasian Americans, but the fact that BMD was highest among Tobagonian females was unexpected. Greater skeletal size and bone size (depth) may partially explain the higher BMD that was observed among postmenopausal Tobagonian females compared to US females of similar age. Areal BMD accounts for only bone length and width, not bone depth. Reference data did not allow for direct comparison of volumetric BMD, which takes bone depth into consideration, between Tobagonian and US females. Research suggests that people of African ancestry have genetic potential for high BMD, but this potential is typically not realized among native Africans because of nutritional and lifestyle factors. It is reasonable to consider the lower levels of genetic admixture among Tobagonian females as a possible reason for higher BMD that we observed in this analysis compared to AAs, where genetic admixture is more prevalent.(21)

Correlates explained 37% and 38% of the variability in BMD measured at the femoral neck subregion and total hip, respectively. The amount of variability accounted for in this analysis is considerably higher than other studies where only 20-30% of the variability in hip BMD is explained by risk factors.(17,20)

A recent study by Robbins et al. investigated the association between BMD and demographic, health-related, and functional status variables for AA males and females, aged 67-96, in the Cardiovascular Health Study. (17) BMD, measured at the hip, was significantly higher for AA males compared to females. The model that best predicted BMD in AA females included weight, age, and income group, which accounted for 28% of the variability in hip BMD. Weight was a dominant predictor of BMD, explaining 21% of the variability in BMD. (17) Our results extend the findings of a slightly older study population of AAs.

Among the best subset of predictors for BMD in this analysis, body weight explained 12-14% of the variability in BMD. The positive association between body weight and BMD is consistent with other studies of both AA and Caucasian females. (16,17,20,22,23) Since we observed higher BMD among Tobagonian females compared to AA females, it is reasonable to suspect that these differences in BMD were accounted for by differences in body weight, but Tobagonian females were not heavier than AA females. Because the average weight and BMI of Tobagonian females were comparable to AA females (24), the perception that higher BMD among Tobagonian females can be attributed to higher weight does not seem to be applicable. (25,26)

Low BMI and current cigarette smoking were identified as risk factors for low BMD among AA females based on data from NHANES III. (16) In other studies of AA females, BMD was inversely associated with age, cigarette smoking, and steroid use and positively associated

with body weight and moderate alcohol consumption. (19) In this analysis, we unable to demonstrate an association between BMD and smoking, which is probably due to the low prevalence of smoking (0.9%), but we were able to confirm the strong association between body weight and BMD.

In a large sample of postmenopausal females, we confirmed that use of thiazide diuretics (27, 28), aspirin (29, 30), and history of diabetes (31, 32) were significant predictors of higher BMD. Lower BMD was associated with increasing age (16, 17), use of thyroid medication (33), family history of fracture (14, 18, 34), and use of beta-blockers. We also observed a positive association between BMD and report of recent back, a possible surrogate for osteoarthritis, which has been shown to be associated with higher BMD. A major strength of this study was the inclusion of females over the age of 70 years, who represented 23% of the study population. Taking into account age-related changes in BMD, it does not appear that the higher BMD among Tobagonian women is only associated with younger age.

We should acknowledge potential limitations in this analysis. Self-reported data are subject to inaccurate recall, resulting in biased estimates of measures of association. We cannot be certain about the accuracy of self-reported health conditions or lifetime medication use. These observations should be confirmed in longitudinal analyses to evaluate possible cohort effects. Prospective studies will allow us to monitor changes in correlates of BMD over time since some factors may influence BMD at certain phases of the lifecycle while other factors have an impact on BMD throughout the entire lifecycle. Due to the lack of automated medical history data, we were unable to verify medical history. This study focused on a rural, community-based sample of postmenopausal females and these correlates of BMD may not be generalizable to other postmenopausal females of African ancestry.

Our findings provide support for heterogeneity in BMD among persons of African ancestry. We observed ethnic gradations in BMD such that persons of African ancestry with lower genetic admixture had higher BMD. We explored the association between selected risk factors and BMD to identify the best predictors of BMD among African Caribbean postmenopausal females. Our findings demonstrated that body weight was a strong predictor of BMD. The amount of variability in BMD explained by these correlates, however, was substantially greater than other studies of Caucasian and AA females.

Most studies that examined correlates of BMD did not include Caribbean females of African ancestry. While our analysis focused only on Tobagonian females, longitudinal investigations will all for a comprehensive evaluation of BMD and its determinants, as well as the subsequent risk of fracture in this population. These investigations should include biochemical, physical, and dietary factors that are known to be associated with BMD. We believe our findings will contribute to the limited research that has been done on etiology of fracture risk among females of West African ancestry.

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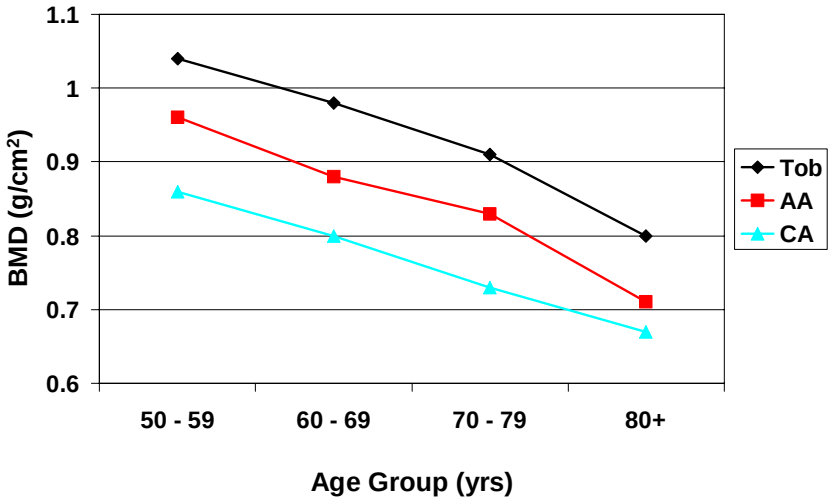
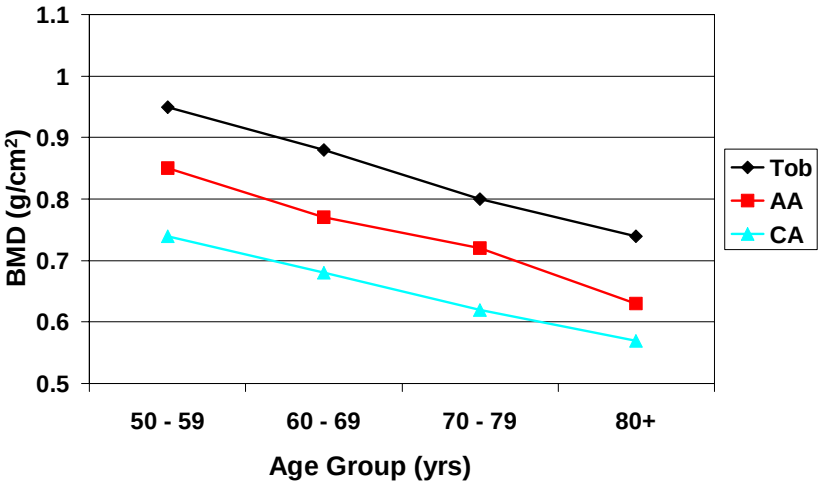


Looker et al. *Osteoporosis International* 1998; NHANES III

Figure 4-1. Mean total hip BMD (g/cm^2) for Tobago females compared to African American and Caucasian American females, NHANES III, US 1988-1994



Looker et al. *Osteoporosis International* 1998; NHANES III

Figure 4-2. Mean femoral neck BMD (g/cm^2) for Tobago females compared to Tobago females compared to African American and Caucasian American females, NHANES III, US 1988-1994

Table 4-1. Descriptive characteristics (N=340)

Age Group ***(y)***	***N (%)***
50-59	113 (33.2)
60-69	150 (44.1)
70-79	66 (19.4)
80+	11 (3.2)
BMD ***(g/cm^2)***	***Mean ± SD***
Total hip	0.98 ± 0.16
Femoral neck subregion	0.88 ± 0.15

Table 4-2. Correlates of Total Hip Bone Mineral Density Expressed as the Percent Difference in BMD per Unit Change of the Variable

Characteristics	Mean ± SD or Prevalence (%)	Age-Adjusted Percent Difference in BMD per Unit Change (95% CI)[†]	Age- & Weight-Adjusted Percent Difference in BMD per Unit Change (95% CI)[†]
Demographics			
Age *(years)*	63.9 ± 8.0	-5.97 (-7.54, -4.40)[**]	-4.24 (-5.75, -2.73)[**]
High school graduate	116 (34.1)	-2.48 (-5.88, 0.91)	-0.82 (-3.98, 2.34)
Physical & Anthropometric Measures			
Weight *(kg)*	80.6 ± 16.1	7.26 (5.76, 8.77)[§**]	6.04 (4.53, 7.54)[**]
Standing height *(cm)*	162.9 ± 6.2	0.07 (-1.59, 1.74)	-1.50 (-3.07, 0.07)
Sitting height *(cm)*	152.8 ± 3.8	0.82 (-0.90, 2.55)	-0.48 (-2.09, 1.14)
Body mass index (kg/m^2)	30.4 ± 5.8	5.99 (4.52, 7.45)[**]	--
Right grip strength *(kg)*	27.6 ± 6.8	1.31 (-0.46, 3.09)	0.65 (-0.96, 2.27)
Left grip strength *(kg)*	25.9 ± 6.7	1.39 (0.17, 3.69)[*]	3.60 (-3.04, 10.24)
Lean mass *(kg)*	46.7 ± 7.2	5.49 (3.93, 7.04)[**]	--
Fat mass *(kg)*	29.8 ± 9.4	5.31 (3.80, 6.82)[**]	--
Elevated blood pressure *(>120/80)*	270 (79.4)	-0.67 (-4.61, 3.27)	-2.21 (-5.85, 1.42)
Elevated fasting blood glucose *(>100 mg/dl)*	137 (40.3)	4.93 (1.76, 8.10)[*]	3.31 (0.34, 6.28)[*]
Personal/Family History			
Fallen in past 12 months	115 (33.8)	3.40 (0.10, 6.69)[*]	2.31 (-0.75, 5.36)
Recent back pain	112 (33.0)	5.59 (2.29, 8.88)[*]	3.73 (0.64, 6.83)[*]
Ever fractured or broken bone	47 (14.0)	-0.46 (-5.04, 4.12)	-0.38 (-4.58, 3.82)
Family history of fracture	8 (2.4)	-5.03 (-15.37, 5.31)	-8.77 (-18.30, 0.77)
First degree relative with breast cancer	32 (9.4)	-0.88 (-6.27, 4.50)	0.06 (-4.90, 5.02)
Lifestyle characteristics			
Married or living as married	176 (51.8)	2.67 (-0.49, 5.83)	1.28 (-1.67, 4.22)
Current smoker	1 (0.9)	14.64 (-14.31, 43.59)	16.23 (-10.41, 42.86)
Past smoker	8 (2.4)	0.17 (-10.19, 10.53)	-1.17 (-10.71, 8.38)
Hours walked per week	18.3 ± 16.8	0.25 (-1.33, 1.83)	0.18 (-1.27, 1.64)
Watch TV $\geq$ 16 hours per week	91 (26.8)	-0.58 (-4.12, 2.97)	-1.85 (-5.12, 1.43)
Coffee drinker	111 (32.7)	1.25 (-2.09, 4.60)	1.82 (-1.26, 4.89)
Tea drinker	199 (58.9)	0.72 (-2.48, 3.92)	-0.04 (-2.99 2.92)
Caffeinated soda drinker	172 (51.2)	1.05 (-2.13, 4.23)	-0.18 (-3.13, 2.77)
Ever alcohol consumption	221 (65.0)	1.07 (-2.25, 4.38)	2.53 (-0.60, 5.65)
Alcohol consumption in past 12 months	112 (33.0)	0.22 (-3.21, 3.65)	1.32 (-1.85, 4.49)
Medical History			
Breast Cancer	4 (1.2)	-0.74 (-15.30, 13.83)	1.58 (-11.83, 15.00)
Hypertension	191 (56.2)	3.08 (-0.11, 6.27)	1.24 (-1.75, 4.23)
Coronary heart disease	26 (7.7)	5.73 (-0.15, 11.61)	5.68 (0.27, 11.09)[*]
Stroke	8 (2.4)	1.67 (-8.72, 12.05)	4.83 (-4.75, 14.40)
Diabetes	69 (20.3)	5.51 (1.62, 9.40)[*]	4.60 (1.01, 8.20)[*]
Arthritis	147 (43.2)	5.32 (2.19, 8.44)[*]	2.52 (-0.49, 5.53)
Colorectal polyps	19 (5.6)	0.63 (-6.22, 7.48)	-0.86 (-7.16, 5.45)
Osteoporosis	8 (2.4)	-2.93 (-13.28, 7.42)	-0.50 (-10.05, 9.06)
Diverticulitis	6 (1.8)	1.86 (-10.08, 13.81)	5.66 (-5.37, 16.68)
Ulcer	20 (5.9)	-1.86 (-8.55, 4.83)	-0.16 (-6.34, 6.02)
Cancer	7 (2.1)	-3.08 (-14.09, 7.93)	-1.01 (-11.17, 9.16)
High cholesterol	100 (29.4)	2.94 (-0.50, 6.37)	2.52 (-0.65, 5.68)
Bronchitis	17 (5.0)	3.50 (-3.70, 10.70)	3.11 (-3.52, 9.74)
Number of teeth loss	18 ± 11.2	-0.01 (-0.16, 0.14)	-0.04 (-0.18, 0.10)

Excellent self-rated health	181 (53.2)	-2.46 (-5.64, 0.72)	-1.16 (-4.11, 1.80)
Hyperthyroid	21 (6.2)	-4.86 (-11.37, 1.64)	-6.56 (-12.54, -0.58)*
Hypothyroid	10 (2.9)	-4.77 (-14.05, 4.51)	-3.99 (-12.54, 4.56)
Reproductive History			
Age at menarche *(years)*	13.7 ± 1.7	-0.26 (-1.86, 1.35)	-0.07 (-0.94, 0.80)
Age at last menstrual period *(years)*	48.2 ± 5.7	0.48 (-1.14, 2.10)	0.10 (-0.16, 0.36)
Reproductive window *(years)*	34.5 ± 6.1	0.08 (-0.19, 0.35)	0.90 (0.66, 1.15)
Ever pregnant	317 (93.2)	8.91 (2.73, 15.09)*	7.11 (1.38, 12.83)*
Had live birth	296 (87.1)	5.48 (0.84, 10.12)*	3.78 (-0.53, 8.08)
Ever had still birth	57 (16.8)	0.20 (-2.60, 2.99)	-1.67 (-4.27, 0.94)
Ever had miscarriage	129 (37.9)	-0.62 (-2.18, 0.95)	-0.76 (-3.21, 1.69)
Ever breast fed child	283 (83.2)	4.90 (0.72, 9.07)*	3.08 (-0.81, 6.96)
Missed period for more than 12 months, excluding pregnancy	13 (3.8)	4.21 (-3.98, 12.41)	1.46 (-6.13, 9.05)
Hysterectomy	100 (29.4)	-2.90 (-6.34, 0.53)	-3.23 (-6.39, -0.08)
Oophorectomy	53 (15.6)	-2.47 (-6.84, 1.89)	-2.12 (-6.14, 1.90)
Ever Medication Use			
Hormone therapy *(estrogen or progestin)*	52 (15.3)	-3.37 (-7.76, 1.02)	-2.55 (-6.61, 1.50)
Oral contraceptives	121 (35.6)	1.52 (-1.87, 4.92)	2.53 (-0.60, 5.66)
Thyroid medication	15 (4.4)	-13.68 (-21.20, -6.17)*	-14.78 (-21.64, -7.91)**
Regular medication use (3 or more times per week)			
Aspirin	62 (18.2)	6.09 (2.07, 10.11)*	4.32 (0.56, 8.07)*
Acetaminophen	34 (10.0)	0.53 (-4.70, 5.76)	2.32 (-2.52, 7.15)
Ibuprofen	33 (9.7)	3.52 (-1.79, 8.83)	-0.12 (-5.10, 4.87)
Current Medications			
Hormone therapy *(estrogen or progestin)*	7 (2.1)	-3.55 (-14.60, 7.50)	-1.21 (-11.40, 8.99)
Thiazide diuretics	52 (15.3)	6.73 (2.40, 11.05)*	5.39 (1.38, 9.40)*
Diabetes medication	60 (17.7)	7.43 (3.36, 11.50)*	6.14 (2.36, 9.92)*
Ace inhibitors	61 (17.9)	3.43 (-0.66, 7.52)	2.71 (-1.07, 6.48)
Beta blockers	27 (7.9)	-7.30 (-13.05, -1.54)*	-7.00 (-12.29, -1.70)*
Nonsteroidal anti-inflammatory drugs	51 (15.0)	5.60 (1.23, 9.97)*	2.10 (-2.05, 6.26)

† Indicates percent change in bone mass in g/cm^2 per indicated unit or 1 standard deviation

*p <0.05, **p<0.0001

§ Adjusted for weight alone

Table 4-3. Correlates of Femoral Neck Bone Mineral Density Expressed as the Percent Difference in BMD per Unit Change of the Variable

Characteristics	Mean ± SD or Prevalence (%)	Age-Adjusted Percent Difference in BMD per Unit Change (95% CI)[†]	Age- & Weight-Adjusted Percent Difference in BMD per Unit Change (95% CI)[†]
Demographics			
Age *(years)*	63.9 ± 8.0	-6.25 (-7.67, -4.82)[§**]	-4.75 (-6.13, -3.37)[**]
High school graduate	116 (34.1)	-2.92 (-6.00, 0.16)	-1.50 (-4.39, 1.40)
Physical & Anthropometric Measures			
Weight *(kg)*	80.6 ± 16.1	6.58 (5.18, 7.99)[§**]	5.23 (3.85, 6.61)[**]
Standing height *(cm)*	162.9 ± 6.2	0.74 (-0.77, 2.24)	-0.58 (-2.02, 0.87)
Sitting height *(cm)*	152.8 ± 3.8	1.32 (-0.24, 2.88)	0.22 (-1.26, 1.70)
Body mass index (kg/m^2)	30.4 ± 5.8	4.93 (3.58, 6.28)[**]	--
Right grip strength *(kg)*	27.6 ± 6.8	0.89 (-0.71, 2.49)	0.33 (-1.16, 1.82)
Left grip strength *(kg)*	25.9 ± 6.7	1.11 (-0.50, 2.71)	2.02 (0.51, 3.53)
Lean mass *(kg)*	46.7 ± 7.2	4.52 (3.10, 5.95)[**]	--
Fat mass *(kg)*	29.8 ± 9.4	4.66 (3.29, 6.04)[**]	--
Elevated blood pressure *(>120/80)*	270 (79.4)	0.20 (-3.39, 3.78)	-1.13 (-4.47, 2.22)
Elevated fasting blood glucose *(>100 mg/dl)*	137 (40.3)	3.45 (0.55, 6.35)[*]	2.04 (-0.70, 4.77)
Personal/Family History			
Fallen in past 12 months	115 (33.8)	1.89 (-1.12, 4.90)	0.94 (-1.87, 3.75)
Recent back pain	112 (33.0)	4.36 (1.35, 7.36)[*]	2.75 (-0.10, 5.59)
Ever fractured or broken bone	47 (14.0)	-1.28 (-5.43, 2.87)	-1.21 (-5.05, 2.63)
Family history of hip fracture	8 (2.4)	-2.98 (-12.40, 6.43)	-6.20 (-14.96, 2.56)
First degree relative with breast cancer	32 (9.4)	-1.12 (-6.02, 3.77)	-0.31 (-4.68, 4.25)
Lifestyle characteristics			
Married or living as married	176 (51.8)	0.53 (-2.36, 3.41)	-0.71 (-3.41, 1.99)
Current smoker	1 (0.9)	21.65 (-4.62, 47.92)	23.02 (-1.35, 47.39)
Past smoker	8 (2.4)	1.65 (-7.77, 11.08)	0.50 (-8.26, 9.26)
Hours walked per week	18.3 ± 16.8	0.55 (-0.89, 1.99)	0.49 (-0.85, 1.83)
Watch TV $\geq$ 16 hours per week	91 (26.8)	-2.01 (-5.23, 1.21)	-3.12 (-6.11, -0.13)[*]
Coffee drinker	111 (32.7)	0.09 (-2.96, 3.13)	0.57 (-2.26, 3.40)
Tea drinker	199 (58.9)	-1.36 (-4.26, 1.54)	-2.02 (-4.72, 0.68)
Caffeinated soda drinker	172 (51.2)	1.65 (-1.24, 4.53)	0.59 (-2.11, 3.30)
Ever alcohol consumption	221 (65.0)	-0.73 (-3.75, 2.28)	0.30 (-2.51, 3.11)
Alcohol consumption in past 12 months	112 (33.0)	-1.42 (-4.53, 1.69)	-0.49 (-3.39, 2.42)
Medical History			
Breast Cancer	4 (1.2)	-5.02 (-18.25, 8.21)	-3.02 (-15.33, 9.28)
Hypertension	191 (56.2)	2.31 (-0.60, 5.22)	0.70 (-2.04, 3.45)
Coronary heart disease	26 (7.7)	5.29 (-0.06, 10.64)	5.24 (0.28, 10.21)[*]
Stroke	8 (2.4)	-0.64 (-10.08, 8.81)	2.08 (-6.72, 10.88)
Diabetes	69 (20.3)	4.58 (1.03, 8.12)[*]	3.79 (0.48, 7.09)[*]
Arthritis	147 (43.2)	3.35 (0.48, 6.22)[*]	0.85 (-1.92, 3.62)
Colorectal polyps	19 (5.6)	1.50 (-4.73, 7.73)	0.22 (-5.58, 6.01)
Osteoporosis	8 (2.4)	-0.53 (-9.95, 8.89)	1.58 (-7.19, 10.34)
Diverticulitis	6 (1.8)	2.16 (-8.71, 13.03)	5.45 (-4.67, 15.56)
Ulcer	20 (5.9)	-2.58 (-8.66, 3.50)	-1.12 (-6.79, 4.55)
Cancer	7 (2.1)	-6.07 (-16.06, 3.91)	-4.29 (-13.60, 5.02)
High cholesterol	100 (29.4)	0.99 (-2.14, 4.13)	0.63 (-2.29, 3.54)
Bronchitis	17 (5.0)	0.24 (-6.32, 6.80)	-0.10 (-6.19, 6.00)
Number of missing teeth	18 ± 11.2	0.04 (-0.10, 0.18)	0.01 (-0.11, 0.14)

Excellent self-rated health	181 (53.2)	-2.53 (-5.42, 0.36)	-1.41 (-4.11, 1.30)
Hyperthyroid	21 (6.2)	-1.80 (-7.73, 4.14)	-3.25 (-8.76, 2.26)
Hypothyroid	10 (2.9)	-0.83 (-9.29, 7.62)	-0.16 (-8.01, 7.69)
Reproductive History			
Age at menarche *(years)*	13.7 ± 1.7	0.12 (-1.33, 1.58)	0.23 (-1.12, 1.59)
Age at last menstrual period *(years)*	48.2 ± 5.7	1.04 (-0.43, 2.52)	1.12 (-0.25, 2.50)
Reproductive window *(years)*	34.5 ± 6.1	0.15 (-0.09, 0.40)	0.16 (-0.07, 0.39)
Ever pregnant	317 (93.2)	6.49 (0.84, 12.13)*	4.92 (-0.36, 10.19)
Had live birth	296 (87.1)	5.03 (0.81, 9.25)*	3.56 (-0.40, 7.51)
Ever had still birth	58 (17.1)	-0.55 (-3.09, 1.98)	-2.18 (-4.57, 0.20)
Ever had miscarriage	129 (37.9)	-1.16 (-2.58, 0.26)	-1.02 (-2.34, 0.30)
Ever breast fed child	283 (83.2)	4.66 (0.86, 8.45)*	3.09 (-0.47, 6.66)
Missed period for more than 12 months, excluding pregnancy	13 (3.8)	3.11 (-4.35, 10.57)	0.73 (-6.24, 7.69)
Hysterectomy	100 (29.4)	-2.80 (-5.92, 0.33)	-3.08 (-5.98, -0.19)*
Oophorectomy	53 (15.6)	-3.14 (-7.10, 0.83)	-2.83 (-6.52, 0.85)
Ever Medication Use			
Hormone therapy *(estrogen or progestin)*	52 (15.3)	-2.96 (-6.95, 1.04)	-2.25 (-5.97, 1.47)
Oral contraceptives	121 (35.6)	0.40 (-2.69, 3.50)	1.27 (-1.61, 4.14)
Thyroid medication	15 (4.4)	-10.00 (-16.88, -3.12)*	-10.94 (-17.31, -4.58)*
Regular medication use (3 or more times per week)			
Aspirin	62 (18.2)	6.02 (2.37, 9.67)*	4.50 (1.06, 7.93)*
Acetaminophen	34 (10.0)	0.31 (-4.45, 5.07)	1.85 (-2.59, 6.29)
Ibuprofen	33 (9.7)	2.10 (-2.74, 6.94)	-1.08 (-5.65, 3.50)
Current Medications			
Hormone therapy *(estrogen or progestin)*	7 (2.1)	-0.18 (-10.24, 9.88)	1.86 (-7.50, 11.21)
Thiazide diuretics	52 (15.3)	5.98 (2.05, 9.92)*	4.83 (1.15, 8.51)*
Non-thiazide diuretics	6 (1.8)	-0.73 (-8.19, 6.72)	-0.69 (-7.62, 6.24)
Diabetes medication	60 (17.7)	6.01 (2.29, 9.73)*	4.89 (1.41, 8.37)*
Beta blockers	27 (7.9)	-6.22 (-11.46, -0.98)*	-5.96 (-10.83, -1.10)*
Nonsteroidal anti-inflammatory drugs	51 (15.0)	4.81 (0.83, 8.78)*	1.78 (-2.03, 5.59)

† Indicates percent change in bone mass in g/cm^2 per indicated unit or 1 standard deviation

*p <0.05, **p<0.0001

§ Adjusted for weight alone

Table 4-4. Statistically Significant Correlates of Hip BMD in Multiple Linear Regression Analyses, Expressed as Percent Difference in BMD per Unit/Standard Deviation of the Predictor Variables (n=339)

			Percent Difference (95% CI)
Variable	**Partial R^2**	**Model R^2**	**Total Hip BMD[a]**
Age *(years)*	Forced	0.141	-4.74 (-6.18, -3.31)**
Weight *(kg)*	0.135	0.276	5.70 (4.25, 7.15)**
Ever thyroid medication *(%yes)*	0.037	0.313	-14.62 (-21.30, -7.94)*
Current diabetes medication (*%yes)*	0.022	0.335	5.22 (1.85, 8.85)*
Recent back pain *(%yes)*	0.012	0.347	3.78 (0.86, 6.71)*
Current thiazide diuretic use *(%yes)*	0.011	0.358	5.03 (1.18, 8.89)*
Current use of beta-blockers *(%yes)*	0.010	0.368	-6.09 (-11.22, -0.97)*
Family history of fracture *(%yes)*	0.008	0.376	-9.38 (-18.38, -0.38)*

Other possible predictors tested to explain variability in total hip BMD using $p<0.05$ as the criterion for entry in the model include: average handgrip strength, fall in past 12 months, any type of arthritis, hyperthyroid, parity, breast fed child, aspirin use, statin use, and nonsteroidal anti-inflammatory drugs.
*$p < 0.05$, **$p<0.0001$

Table 4-5. Statistically Significant Correlates of Femoral Neck BMD in Multiple Linear Regression Analyses, Expressed as Percent Difference in BMD per Unit/Standard Deviation of the Predictor Variables (n=339)

			Percent Difference (95% CI)
Variable	**Partial R^2**	**Model R^2**	**Total Hip BMD[a]**
Age *(years)*	Forced	0.179	-5.34 (-6.69, -3.99)**
Weight *(kg)*	0.115	0.294	4.81 (3.47, 6.16)**
Ever thyroid medication	0.023	0.317	-10.06 (-16.31, -3.81)*
Current diabetes medication	0.016	0.333	3.90 (0.49, 7.70)*
Aspirin use 3 or more times per week	0.012	0.345	4.32 (0.93, 7.70)*
Current use of beta-blockers	0.009	0.354	-6.00 (-10.84, -1.15)*
Current thiazide diuretic use	0.011	0.365	4.42 (0.79, 8.05)*

[a]Other possible predictors tested to explain variability in femoral neck BMD using $p<0.05$ as the criterion for entry in the model include: recent back pain, any arthritis, parity, breast fed child, hysterectomy, garlic, statins, watching 16+ hours of TV per week, and nonsteroidal anti-inflammatory drugs.
*$p<0.05$, **$p<0.0001$

5. Bone Mineral Density and Body Composition Changes in Older African American and Caucasian Men and Women

(Manuscript to be submitted)

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5.1. Abstract

Objective: Age-related bone loss has been well documented for Caucasian females, considerably less information is known about Caucasian males and ethnic minorities. We studied ethnic differences in rates of bone loss within gender and we also examined the relationship between components of body weight and bone loss.

Materials and Methods: Longitudinal analysis of ambulatory Caucasian (270 females, 187 males) and African American (74 females, 47 males) participants aged 65-87 years, from the CHS. Whole body, total hip and femoral neck subregion BMD was measured an average of 4.0 years apart.

Results: At baseline African American females had 12% higher body weight and 10% greater BMI than Caucasian females. Baseline BMD was 16-20% higher and lean and fat mass were 7-12% greater in African American females compared to Caucasian females. Among males, African Americans had 5-6% higher baseline body weight and BMI, 5-12% greater baseline BMD, and 5% higher lean mass compared to Caucasians. BMD, lean, and fat mass decreased over time in all four groups. After adjusting for covariates, African American males lost significantly less total hip BMD compared to Caucasian males, -0.04% per year vs. -0.45% per year respectively. Otherwise, we did not find ethnic differences in rates of bone loss.

Conclusion: This analysis demonstrated that older African American and Caucasian females experience similar rates of bone loss at the total hip and femoral neck with advancing age. African American males lost significantly less total hip BMD than Caucasian males, but femoral neck rates of bone loss were similar. (ABSTRACT LESS THAN 250 WORDS)

5.2. Introduction

Bone mineral density (BMD) is a major determinant of bone strength and a significant predictor of fracture risk.(1,2) BMD varies widely by gender and ethnicity.(3-6) With advancing age, males and females experience bone loss that contributes to a curvilinear decline in BMD, decline in neuromuscular function, skeletal fragility, and increased risk of fracture.(3,4,6-10) Postmenopausal females (i.e., cessation of ovarian function) experience higher rates of bone loss up to 15 years after menopause compared to males of the same age.(6,10-13) Females in the eighth and ninth decade of life experience accelerated rates of bone loss greater than the immediate postmenopausal period, which also contributes to an increased fracture risk.(14) Hip fracture rates increase rapidly with age for both males and females, even though females sustain the vast majority (75-80%) of all incident hip fractures.(15) Age-related incidence of osteoporotic fractures vary by ethnic groups and fracture rates are approximately 50 percent lower in African American (AA) males and females compared to Caucasian males and females.(10,16) Ethnic differences in BMD is one possible explanation for ethnic differences in fracture incidence rates.

Body composition is an important determinant of BMD and body composition is comprised of four major components: lean mass, fat mass, bone mineral, and water.(11,17-21) It is established that lean and fat mass are positively related to BMD, even among older persons.(20,22) The proposed mechanism for the positive association between fat and lean mass with BMD may be from increased mechanical loading on bone.(3,20,22) Research has shown that age-related changes in anthropometric measures are associated with bone loss in postmenopausal Caucasian females, specifically body weight and body composition.(1,7,21,23-26) These changes include an increase in fat mass and a progressive decline in both lean mass

and BMD with increasing age.(3,27,28) Among males, body composition changes are usually observed at ages older than 70 years; among females, these changes are observed in the early postmenopausal period and continue as females age.(28) Age-related changes in body composition may contribute to higher rates of bone loss. A recent study reported that among Caucasian males, aged 45-92 years, the annual percent change in BMD was -0.47% at the hip and -0.34% at the femoral neck.(29) Several predictors of bone loss were identified in this study, including older age (> 75 years) and BMI < 24 kg/m^2. Otherwise, considerably less information is known about the determinants of bone loss among older males and ethnic differences in rates of bone loss.(3,30-33)

In this analysis, we examined baseline and annualized percentage change in BMD and body composition by ethnicity within gender. We tested the hypotheses that (a) Caucasian males and females will experience higher rates of bone loss compared to AA males and females, and (b) greater changes in body weight and/or components of body weight will be related to higher rates of bone loss. We report the association between change in BMD and body composition for AA and Caucasian males and females.

5.3. Methods

Participants

The Cardiovascular Health Study (CHS) is a prospective, observational cohort study that examined risk factors for and health consequences of cardiovascular disease in older adults, aged 65 years and older.(34) Detailed methods for the CHS have been described elsewhere.(34) Briefly, four US Field Centers participated in the CHS. During 1992-93, a concerted effort was made to increase AA recruitment in the CHS and the majority of AA participants in this analysis were part of the enhanced recruitment cohort. The study sample was recruited from a subset of

participants enrolled in the CHS. (34) Eligibility criteria for the CHS study included random sampling from the Healthcare Financing Administration Medicare database of community-dwelling persons, aged 65 and older.(34) In addition, participants were required to provide written, informed consent and expected to remain in their current geographical area for three years following recruitment into the CHS. Any potential participant who was wheelchair-bound or receiving radiation treatment, chemotherapy or hospice care for cancer was excluded from the study.

This longitudinal analysis measured changes in BMD (whole body, total hip, and the femoral neck) subregion, body weight, and body composition variables (fat mass and lean mass) for Caucasian and AA males and females, aged 65 and older. For our investigation of changes in BMD, lean mass, and fat mass, longitudinal data were available for 587 participants (348 females, 21% AA; and 239 males, 20% AA). All participants were enrolled in the Allegheny County, Pennsylvania CHS cohort.

BMD and Body Composition

Participants completed the baseline BMD examination in year 7 (1994-95) and a subsequent follow-up BMD examination in year 11 (1998-99), an average of 3.98 ± 0.11 years between examinations. BMD for whole body, total hip, and the femoral neck subregion was measured by dual-energy X-ray absorptiometry (DXA; QDR 2000 or 2000+, Hologic, Inc: Bedford, MA). For each participant, the same scanner was used at each visit and all scans were completed using the array beam mode. Standardized positioning and utilization of QDR software was based on the manufacturer's recommended protocol. Scans were analyzed with software version 7.10. In addition, lean mass and fat mass measurements were calculated by the QDR software using whole body DXA data and calculated lean mass values exclude bone

mineral content. To ensure consistency, trained staff scanned a spine phantom daily, prior to completing any scans, on the two DXA scanners in Pittsburgh. The coefficient of variation for total hip was less than 0.75%. Data from the DXA measurements were monitored for quality control by the University of California, San Francisco.

Body weight was measured in kilograms with a calibrated balance beam scale. Height was measured in centimeters with a wall-mounted stadiometer. Body mass index (BMI) was calculated by dividing body weight (in kilograms) by height (in meters squared). Waist circumference was measured in centimeters at the umbilicus. Hip circumference was also measured in centimeters at the widest part of the hips. Handgrip strength (in kilograms) was measured for both dominant and non-dominant hands using a dynamometer.

Other Measures

Participants completed a self-administered questionnaire that gathered information about demographic characteristics, medical history, reproductive history, fracture history, physical activity, self-rated health status, and lifestyle variables. Ethnicity was self-reported. Education, marital status, lifestyle factors, medical history, medication use, history of fall and/or fracture variables were measured as categorical variables. Continuous variables included age and anthropometric measures.

Potential covariates were chosen based on previous research that suggested certain variables were correlated with BMD and annualized percent change in BMD.(1-4,11,13,15,19,23,31) Potential covariates included: demographic (age, gender, and ethnicity) anthropometric (baseline weight or baseline lean and fat mass, change in weight or change in lean or fat mass, baseline BMD, height, and dominant handgrip strength), lifestyle (current smoking status, change in level of physical activity in the past 12 months, fair/poor self-reported

health, and consumption of four more alcohol-containing beverages per week), health-related (history of a broken bone, hypertension, arthritis, diabetes, previous cancer diagnosis, and previous diagnosis of osteoporosis), and medication use (postmenopausal hormone therapy (PHT), statin use, calcium supplementation use, and thiazide diuretic use) variables.

Data Analysis

We measured ethnic differences in rates of bone loss, changes in body weight and changes in body composition, stratified by age and gender. Annualized percentage change in areal BMD, body weight, and body composition variables were calculated by the following formula: [(Follow-up BMD, body weight or body composition - baseline BMD, body weight, or body composition)/ duration of follow-up] x 100 and expressed as percent change per year. (35) Since areal BMD may be confounded by bone size, we calculated an estimate of annualized percentage change in volumetric bone mineral apparent density (BMAD). Femoral neck BMAD was estimated from the equation: $BMC_{\text{femoral neck}}/(\text{area}^2_{\text{femoral neck}})$. (36) Data analysis for this paper was generated using SAS ® software, Version 8.1 of the SAS System for Windows.(37) Unadjusted ethnic differences for the descriptive variables were examined using Student's t-test for continuous variables and the chi-square test for categorical variables.

Age-adjusted analysis of covariance (ANCOVA) techniques were used to estimate mean differences in annual rates of bone loss, adjusted for age, baseline BMD, dominant handgrip strength, diabetes, postmenopausal hormone therapy (PHT; females only), self-rated fair/poor health, alcohol consumption, current smoking status, and annualized percentage change in lean and fat mass.. Variables correlated ($p < 0.05$) with BMD and others known to be associated with BMD were used as potential predictors to build multiple regression models. Stepwise multiple linear regression (MLR) modeling techniques were used to derive a parsimonious model to

account for the variance in the change in BMD at all skeletal sites measured in gender-specific subgroups. To identify whether body weight or components of body weight (lean and fat mass) accounted for more variability in changes in BMD, we examined two different variable sets: (1) baseline weight, change in weight, and covariates; and (2) baseline lean and fat mass, change in lean and fat mass, and covariates.

5.4. Results

Descriptive Characteristics

Baseline descriptive characteristics of the study are shown in Table 5-1. Body weight, body mass index (BMI), and handgrip strength were all significantly higher for AA females compared to Caucasian females. AA females were more likely to report diabetes and heart disease compared to Caucasian females. A higher percentage of Caucasian females reported use of PHT and calcium supplements than AA females. Fewer ethnic differences were observed among males. AA males had higher body weight and BMI than Caucasian males. AA males were more likely to report being a current smoker compared to Caucasian males. For both genders, AAs were more likely to report a history of hypertension and fair/poor health status compared to Caucasians. There were no ethnic differences in age, height, or history of osteoporosis, fractures, cancer, change in physical activity, or use of statins or thiazide diuretics.

BMD

Baseline BMD measured at the total hip and femoral neck subregion was 16.0% and 19.7% greater in AA females compared to Caucasians females at baseline. Comparable baseline measures were observed for males at 10.8% and 11.8%, respectively (Table 5-1). Age-adjusted annual rates of bone loss rates are shown in Table 5-2 by gender and ethnicity. Age-adjusted BMD decreased over time in all four groups and no significant ethnic differences were observed

at any skeletal site for both males and females (Table 5-2). Using ANCOVA, AA males experienced significantly less total hip bone loss compared to Caucasian males (-0.04% per year vs. -0.45% per year), after adjustment for covariates (Table 5-3). Among females, there were no ethnic differences in rates of bone loss after adjustment for covariates (Table 4-3). Similar results were observed for absolute change in BMD/BMAD at any skeletal site for both males and females (data not shown).

Body Composition

Baseline fat and lean mass were 7-12% greater for AA females compared to Caucasian females (Table 5-1). AA males had 5% greater baseline lean mass compared to Caucasian males. There were no significant ethnic differences for annualized percentage change in lean or fat mass among males or females, even after adjustment for age (Table 5-2) and other covariates (Table 5-3). We did not find any ethnic differences for absolute change in body composition variables among men and women (data not shown). We tested for interaction between ethnicity and fat mass or lean mass and they were not significant interactions.

MLR Analysis

Final multiple regression models are listed in Tables 5-4 and 5-5. Models that included baseline weight and change in weight plus other covariates did not explain as much variability (R^2 = 0.035 to 0.169; data not shown) for annual change in BMD as models with body composition variables: baseline lean and fat mass, changes in lean and fat mass (R^2 = 0.077 to 0.243) along with other covariates. Based on this information, data are shown only for models containing body composition variables (Tables 5-4 and 5-5).

Gender-Specific Stepwise MLR Analyses

Among females, change in fat mass was a significant predictor in all three models for total hip, femoral neck BMD, and femoral neck BMAD (Table 5-4). Females who lost fat mass over time had higher rates bone loss at all three sites measured. A longitudinal decrease in lean mass was also a significant predictor of bone loss at the total hip. Age, diabetes, and current cigarette smoking were negatively associated with changes in total hip BMD and PHT use was positively related to changes in total hip BMD. Twenty-two percent of the variability in annualized percent change in total hip BMD was explained by this model. Among females, current smokers lost considerably more femoral neck BMD compared to non-smokers. Self-rated poor or fair health and moderate consumption alcohol containing beverages were also related to changes in femoral neck BMD only. Ethnicity did not enter any of the models. Age, PHT use, and lean mass did not remain in models for femoral neck BMD/BMAD.

Among males, loss of lean mass over time was associated with higher rates of bone loss at the total hip and femoral neck (Table 5-5). For the model that predicted change in total hip BMD, higher rates of change in lean mass were also associated with greater rates of bone loss at the total hip. Age and thiazide diuretic use were negatively related to changes in total hip BMD. Age and self-rated fair or poor health were negatively related to changes in femoral neck BMD. Ethnicity did not enter any of the models. Calcium supplement use was positively related to changes in femoral neck BMD/BMAD.

5.5. Discussion

In this analysis, AA participants had greater baseline body weight, lean, fat, and bone mass compared to Caucasians, but rates of bone loss were not significantly different for AAs compared to Caucasians as other studies had suggested (3,38). Interestingly, in unadjusted analyses AA males had significantly higher rates of bone loss at the femoral neck compared to

Caucasian males. Otherwise, no ethnic differences were observed for rates of bone loss. We did, however, observe gender differences in rates of bone loss. Among females, age-adjusted bone loss was greater at the total hip than at the femoral neck while males experienced more bone loss at the femoral neck, especially AA males, suggesting that physical and endocrine factors influence age-related bone loss differently for males and females. (32,39) Estimated volumetric BMAD did not attenuate ethnic differences within gender that we observed for changes in BMD and/or body composition. It is important to note that BMAD may correct for body size but does not consider skeletal size. In the gender-specific stepwise multiple linear regression models, ethnicity did not enter the model, suggesting that differences in annualized percentage change in BMD were explained by covariates other than ethnicity.

Although AA females had slower rates of bone loss at all skeletal sites compared to Caucasian females in the CHS, these findings did not reach statistical significance. In another longitudinal study, slower rates of total hip bone loss were also observed among premenopausal AA females compared to Caucasian females, but they did not find any ethnic differences in the rate of bone loss among postmenopausal females. (38)

Caucasian females in this study lost considerably less total hip BMD per year (0.37%) compared to Caucasian females in the Study of Osteoporotic Fractures (SOF) (0.57 % per year).(40) Similar differences were observed for Caucasian females in CHS and SOF for femoral neck bone loss rates. Among AA females, however, rates of bone loss at the total hip were comparable to AA females in SOF (-0.34% per year vs. -0.33% per year). AA females in CHS had a slightly higher rate of bone loss at the femoral neck compared to AA females in SOF (-0.27% per year vs. -0.20% per year), this difference may be a related to the shorter duration of follow-up (2 years) for AA females in SOF compared to 4 years in the CHS.

Total hip BMD is a stronger predictor fracture risk in older, Caucasian females.(41) The healthy nature of our study cohort may explain the lack of significant ethnic differences in rates of bone loss observed in this study. Furthermore, the parent study that originally recruited participants for this ancillary analysis did not initially measure BMD and therefore, our study sample may have a select group of subjects.

We observed significantly slower rates of total hip bone loss and higher rates of femoral neck bone loss in AA males compared to Caucasian males, although the findings for femoral neck were not statistically significant. This information is valuable because to our knowledge, only one other study has compared rates of bone loss in AA males to Caucasian males and similar to our findings, Caucasian males lost significantly more total hip BMD over time.(38) Caucasian males in this study lost an average of -0.41% hip BMD per year compared to -0.47% per year for Caucasian males in the Rancho Bernardo study.(29) Rates of femoral neck bone loss were higher in the CHS compared to the other study (-0.49% per year vs. -0.34% per year). We should note that the CHS study population was older than the Rancho Bernardo study, which may explain the higher rates of femoral neck bone loss in the CHS.

The relative contribution of changes in body composition (lean and fat mass) were stronger determinants of bone loss compared to changes in body weight for both males and females in this study, before and after controlling for the effects of covariates. Additionally, lean and fat mass explained more variability in rates of bone loss compared to age and lifestyle factors. Specifically, decreases in fat mass over time were positively associated with higher rates of bone loss in females whereas declines in lean mass over time contributed to higher rates of bone loss in males, suggesting body composition variables influence BMD differently by gender. The contribution of lean and fat mass in relation to BMD has been examined in a cross-sectional

study and the contribution of lean and fat mass did differ by gender among younger males and females. (42) Similar to our findings, BMD was significantly related to fat mass in females and lean mass in males. In the Rancho Bernardo study, BMI and weight loss at least 5% or more of baseline bodyweight were significant predictors of BMD among middle-aged males.(29)

Some previously published studies have also shown that fat mass is protective against bone loss in postmenopausal females. (19,21,23,33) Most of these studies, however, analyzed body composition variables at one time point and tested whether these variables predicted bone loss. Our study is unique because we examined longitudinal changes in fat and lean mass. We found that change in fat mass over time is an important predictor of change in BMD in older postmenopausal females of both Caucasian and AA ethnicity. Specifically, females who lost more fat mass also experienced greater rates of bone loss. Our finding is supported by the idea that females with less fat mass have lower levels of estradiol, which may contribute to lower BMD.(20) Similar to Baumgartner et al., in our study fat mass was more significantly related to longitudinal changes in BMD for females than lean mass.(11) Wu et al. suggested that the protective effect of fat mass on bone loss in postmenopausal females may be hormonal since heavier body weight is associated with increased concentrations of sex hormones.(23) Among postmenopausal females, fat mass may facilitate the conversion of androgen to estrogen, which increases BMD.(3,22,43) In contrast, change in lean mass appeared to be a more important predictor in males suggesting that muscle plays a significant role on bone mass, which may be related higher levels of testosterone in males, which are positively associated with BMD and negatively associated with fat mass.(43)

There are a number of strengths to our study including BMD was measured by trained and certified DXA technicians. Our analysis used a longitudinal design to examine changes in

lean mass, fat mass, and bone in a population-based cohort of older males and females of Caucasian and AA ethnicity. We included a number of covariates in our analysis. There are however, a few limitations for this analysis including the relatively small sample of AAs, especially males.

Osteoporosis is an important public health issue in aging epidemiology. Our analysis is one of only few published studies that examined baseline and longitudinal changes in bone, lean, and fat mass in a sample of community-dwelling persons, aged 65 and over, by ethnic group within gender. Body composition variables were significant determinants of bone loss in all groups. After adjusting for covariates, AA males had slower rates of bone loss at the total hip compared to Caucasian males. This finding may be protective against future hip fracture risk. Conversely, our findings did not confirm ethnic differences in rates of bone loss among AA and Caucasian females. Furthermore, higher BMD may not protect AA females against accelerated rates of age-related bone loss.

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Table 5-1. Baseline Descriptive Characteristics

	Females		Males	
	Caucasian	**African American**	**Caucasian**	**African American**
N	270	74	187	47
Variables Mean (±) SD				
Age (y)	70.7 ± 3.8	71.1 ± 4.4	71.2 ± 4.1	71.1 ± 4.4
Weight (kg)	65.1 ± 11.5**	72.6 ± 13.4**	78.2 ± 9.7*	82.5 ± 13.4*
Height (cm)	158.2 ± 6.0	159.6 ± 6.1	172.5 ± 6.8	172.7 ± 6.9
BMI (kg/m^2)	26.2 ± 4.5**	28.8 ± 4.7**	26.2 ± 3.3*	27.4 ± 4.6*
Grip Strength (kg)	22.3 ± 5.2**	26.7 ± 6.2**	37.8 ± 7.5	39.4 ± 9.4
Total Hip BMD (g/cm^2)	0.72 ± 0.12**	0.84 ± 0.15**	0.92 ± 0.15*	1.02 ± 0.17*
Femoral Neck BMD (g/cm^2)	0.61 ± 0.11**	0.73 ± 0.13**	0.76 ± 0.13**	0.85 ± 0.15**
Femoral Neck BMAD (g/cm^3)	0.13 ±0.03**	0.15 ± 0.03**	0.14 ± 0.03**	0.16 ± 0.03**
Fat Mass (kg)	28.1 ± 9.5*	31.1 ± 9.6*	22.2 ± 7.1	22.3 ± 8.8
Lean Mass (kg)	34.8 ± 4.3**	38.9 ± 4.9**	51.8 ± 5.7*	54.5 ± 6.9*
Selected Covariates (% yes)				
Current Smoker	26 (9.7%)	10 (13.5%)	8 (4.3%)*	8 (17.0%)*
Diabetes	19 (7.0%)**	17 (23.0%)**	22 (11.8%)	10 (21.3%)
Osteoporosis	40 (15.3%)	6 (8.3%)	4 (2.2%)	0 (0.0%)
Cancer	39 (14.4%)	7 (9.5%)	24 (12.8%)	2 (4.3%)
Hypertension	75 (28.4%)**	42 (58.3%)**	43 (23.2%)*	19 (41.3%)*
Heart Disease	38 (14.5%)*	18 (24.3%)*	31 (16.9%)	7 (14.9%)
Arthritis	126 (47.0%)	42 (56.7%)	69 (37.1%)	20 (43.5%)
Calcium Supplements	73 (27.1%)*	8 (11.0%)*	15 (8.1%)	2 (4.3%)
Alcohol Consumption $\geq$ 4 per week	38 (14.1%)*	4 (5.4%)*	52 (27.8%)	11 (23.4%)
Reported Fair/ Poor Health	20 (7.4%)*	14 (18.9%)*	19 (10.2%)*	11 (23.4%)*
Ever Broken Bone	10 (3.7%)	3 (4.0%)	5 (2.6%)	0 (0.0%)
Statin Use	32 (11.9%)	5 (6.8%)	11 (5.9%)	2 (4.3%)
Thiazide Diuretics	48 (17.8%)	15 (20.3%)	21 (11.2%)	7 (14.9%)
Current PHT Use	47 (17.4%)*	5 (6.8%%)*	--	--
Change in physical activity in last 12 months				
Less	88 (32.6%)	28 (37.8%)	41 (22.2%)	10 (21.3%)
More	159 (58.9%)	38 (51.4%)	128 (61.2%)	33 (70.2%)
Same	23 (8.5%)	8 (10.8%)	16 (8.7%)	4 (8.5%)

N, number of subjects
Ethnic differences within gender: * p <0.05; ** p <0.0001

Table 5-2. Age-Adjusted Annualized Percent Changes in BMD and Body Composition[a]

	Females		Males	
	Caucasian	**African American**	**Caucasian**	**African American**
N	270	74	187	47
	Mean ± SE			
Bone Density				
Total Hip BMD (g/cm^2)	-0.37 ± 0.07	-0.34 ± 0.14	-0.41 ± 0.08	-0.22 ± 0.16
Femoral Neck BMD (g/cm^2)	-0.29 ± 0.08	-0.27 ± 0.16	-0.49 ± 0.09	-0.87 ± 0.18
Femoral Neck BMAD (g/cm^3)	-0.47 ± 0.11	-0.27 ± 0.22	-0.58 ± 0.12	-0.55 ± 0.24
Body Composition (kg)				
Lean Mass	-0.11 ± 0.07	-0.26 ± 0.13	-0.43 ± 0.08	-0.54 ± 0.15
Fat Mass	-0.61 ± 0.10	-0.57 ± 0.20	-0.51 ± 0.11	0.40 ± 0.22

[a] negative values imply loss in BMD and/or body composition over the follow-up period
N, number of subjects

Table 5-3. Adjusted[*] Annualized Percent Changes in BMD[a]

	Females		Males	
	Caucasian	**African American**	**Caucasian**	**African American**
N	270	74	187	47
	Mean ± SE			
Total Hip BMD (g/cm^2)	-0.38 ± 0.08	-0.26 ± 0.16	-0.45 ± 0.08[§]	-0.04± 0.16[§]
Femoral Neck BMD (g/cm^2)	-0.31 ± 0.08	-0.22 ± 0.17	-0.52 ± 0.09	-0.74 ± 0.18
Femoral Neck BMAD (g/cm^3)	-0.48 ± 0.11	-0.20 ± 0.24	-0.61 ± 0.12	-0.37 ± 0.25

[*]Adjusted for age, baseline BMD, baseline weight, dominant handgrip strength, diabetes, PHT (females only), height, and current smoker

[a] Negative values imply loss in BMD and/or body composition over the follow-up period

N, number of subjects

Ethnic differences within gender: [§]$p < 0.05$

Table 5-4. Final Multiple Regression Models for Annualized Percentage Change in BMD/BMAD Among Females

	Total Hip Areal BMD Model R^2 = 0.216**		**Femoral Neck Areal BMD** Model R^2 =0 .135**		**Femoral Neck Volumetric BMAD** Model R^2 = 0.078**	
	Std β	p-value	Std β	p-value	Std β	p-value
Change in Fat Mass	0.338	<0.0001	0.230	<0.0001	0.209	0.0001
Change in Lean Mass	0.135	0.0003	--	--	--	--
Age	-0.189	0.0018	--	--	--	--
Diabetes	-0.108	0.0325	-0.119	0.0257	-0.128	0.0192
Current Smoker	-0.101	0.0452	-0.126	0.0251	--	--
Dominant Handgrip Strength	--	--	0.122	0.0214	0.128	0.0291
Self-rated Fair/Poor Health	--	--	-0.140	0.0022	--	--
Consumption of less than 4 alcohol containing beverages per week	--	--	0.105	0.0487	--	--

[a] Stepwise regression modeling was utilized to identify the best prediction model. Variables met $p < 0.10$ for entry into the model and $p < 0.05$ to remain in the model. Potential covariates that were tested but did not remain in any model include: ethnic group, baseline fat mass, hypertension, arthritis, physical activity, height, and ever diagnosed with cancer.
Model p-value: * $p < 0.05$; ** $p < 0.0001$

Table 5-5. Final Multiple Regression Models for Annualized Percentage Change in BMD/BMAD Among Males

	Total Hip Areal BMD Model $R^2 = 0.243$**		**Femoral Neck Areal BMD** Model $R^2 = 0.133$**		**Femoral Neck Volumetric BMAD** Model $R^2 = 0.081$*	
	Std β	p-value	Std β	p-value	Std β	p-value
Change in Lean Mass	0.262	<0.0001	0.159	0.0023	0.235	0.0004
Change in Fat Mass	0.266	<0.0001	--	--	--	--
Age	-0.214	0.0005	-0.184	0.0089	--	--
Thiazide Diuretic Use	-0.124	0.0396	--	--	--	--
Baseline Lean Mass	--	--	-0.134	0.0499	--	--
Calcium Supplement Use	--	--	0.151	0.0151	0.156	0.0176
Self-rate Fair/Poor Health	--	--	-0.142	0.0324	--	--

[a] Stepwise regression modeling was utilized to identify the best prediction model. Variables met $p < 0.10$ for entry into the model and $p < 0.05$ to remain in the model. Potential covariates that were tested but did not remain in any model include: ethnic group, baseline fat mass, hypertension, arthritis, physical activity, height, and ever diagnosed with cancer.
Model p-value: * $p < 0.05$; ** $p < 0.0001$

6. Discussion

This dissertation research focused on the interrelationships between bone health and demographic, lifestyle, anthropometric, and health-related factors in males and females of African ancestry residing on the Caribbean Island of Tobago and in the US. Three complementary analyses were undertaken to identify:

1. Correlates of BMD among Tobagonian males, aged 40+ years
2. Correlates of BMD among postmenopausal Tobagonian females, aged 50+ years
3. Rates of bone loss among older (aged 65+ years) AA males and females compared to Caucasians. Predictors of bone loss were also identified in this analysis.

A. Correlates of BMD among Tobagonian Males

Tobagonian males had ~8-12% higher hip BMD compared to NHANES data for AA males and ~20-23% higher hip BMD compared to NHANES data for Caucasian males. (1) The differences in BMD between Tobagonian and US males did not increase substantially with advancing age. (1) Tobagonian males aged 70-79 years had hip BMD that was higher than AA and Caucasian males aged 40-49 years. Differences in BMD between Tobagonian and US males were slightly attenuated at the femoral neck. Tobagonian males had ~8-12% higher femoral neck BMD compared to AA males and ~18-22% higher than Caucasian males. This finding was unexpected because other published studies of persons of African ancestry, residing in Africa or the UK, reported lower BMD among Africans compared to the reference Caucasian group. (2-5) The higher BMD among males of African ancestry, despite country of residence, compared to Caucasians suggest that similar biological mechanisms may exist.

Significant correlates of BMD among Tobagonian males were the same for total hip and femoral neck BMD. Age (-), lean mass (-), history of diabetes (+), history of working on a

fishing boat (+), and history of a broken or fracture bone (-) explained 25% of the variability in BMD. Lean mass was a significant predictor of BMD ($p<0.0001$). Taaffe et al. also found that among a large sample of older AA males, lean mass was a significant determinant of BMD.(6) Based on this finding, maintenance of lean mass, possibly through physical activity, is definitely a modifiable risk factor that may reduce the risk of developing low BMD and increased fracture risk among males. The higher hip BMD among Tobagonian males compared to US males could be attributed to the influence of lean mass on BMD.

B. Correlates of BMD among Tobagonian females

When we compared BMD for Tobagonian females to NHANES III data (1), postmenopausal Tobagonian females had 10-18% higher hip BMD compared to AA females and the largest difference in BMD was observed for females aged 80+ years. Hip BMD was drastically different between Tobagonian females and Caucasian females. Tobagonian females had 29-30% higher hip BMD compared to Caucasians.(1) Tobagonian females aged 80+ years (n=11) had mean hip BMD comparable to AA females aged 60-69 years and Caucasian females aged 50-59 years. Compared to AA females, femoral neck BMD was also 10-17% higher for Tobagonian females. Tobagonian females had 20-25% higher femoral neck BMD compared to Caucasian females. (1) The higher BMD among females of African ancestry, despite country of residence, compared to Caucasian suggests that similar biological mechanisms may exist.

Significant correlates of BMD among Tobagonian females included age (-), body weight (+), history of diabetes (+), family history of fracture [(-); hip only], and use of certain medications. Surprisingly these correlates explained 37-38% of the variability in BMD, which is higher than our findings for Tobagonian males (R^2=25%). Most studies only report that 20-30% of the variability in BMD is explained by the best subset of predictors for US females. (7-12)

Unlike Tobagonian males, body weight was a significant predictor of BMD among Tobagonian females, rather than components of body weight like lean mass and/or fat mass. Our observed gender differences in body weight and components of body weight were not totally unexpected. The effect of reproductive hormones, quantity of lean mass, and PBM attainment all contribute to the explanation of the strong correlation between lean mass and BMD in males but moderate correlation in females. (6, 13) Body weight positively influences adipose-based estrogen, which protects bone. (13, 14) Greater body weight imposes more gravitational force on bone, similar to weight-bearing exercise, which increases BMD. (13)

We compared population-based data from NHANES (1999-2002) that was stratified by age group (40-59 and 60+ years) to the average weight and BMI of Tobagonian females. (15) We suspected that mean body weight or BMI would be different between AA females (80.3 kg, 31.1 kg/m^2, respectively) and Tobagonian females (78.2 kg, 29.9 kg/m^2, respectively) aged 60 years and older, but this was not the case. Tobagonian females aged 60+ years had somewhat lower body weight and BMI compared to AA females of the same age. When we compared the reported body weight and BMI for AA females aged 40-59 years to Tobagonian females aged 50+, we still did not observe any differences in body weight or BMI that could possibly explain the differences in BMD.

A recent study by Robbins et al. also found that body weight was a significant correlate of BMD among AA males and females in the CHS.(12) Other studies have suggested that fat mass was a significant determinant of BMD among postmenopausal females (6,16-19), but body weight was more strongly correlated with BMD in our analysis of Tobagonian females. One possible explanation for the contribution of body weight, not its components, to BMD is that in our sample of Tobagonian women, the correlations between lean and fat mass with BMD were

almost equal, suggesting the combined effect of lean mass and fat mass positively influenced BMD.

When we compared the correlates of BMD among Tobagonian males and females, we observed some similarities in the predictors of BMD. They include age, history of diabetes, and anthropometric variables. We did not, however, ask Tobagonian males to bring medication to the research office at the time the interview was conducted.

C. Ethnic Differences in Rates of Bone Loss

The third analysis measured rates of bone loss at the hip and femoral neck subregion among older AA and Caucasian male and female participants in the CHS, aged 65+ years. At baseline, AA males had 5-12% higher BMD and AA females had 10-20% higher BMD compared to Caucasians. AAs were also heavier, as measured by body weight and BMI, than Caucasians. Four years after the initial baseline DXA exam, all four groups experienced bone loss. Among females, Caucasian and AA females had similar rates of bone loss, 0.37% per year and 0.34% per year, at the total hip and comparable changes at the femoral neck. Among males, Caucasians had a 50% greater bone loss at the hip compared to AAs. At the femoral neck, however, AA males had 50% greater bone loss compared to Caucasian males. Greater bone loss at the femoral neck among AA males was quite surprising since research among AA females showed lower or comparable rates of bone loss to Caucasians at the femoral neck. (20,21) After adjustment for covariates, Caucasian males had significantly higher rates of hip bone loss compared to AA males. We did not find any significant differences in rates of bone loss, despite higher BMD and anthropometric measures for AA females. Partial adjustment for bone size, BMAD, did not attenuate the ethnic differences in rates of bone loss. (22)

We then examined correlates that were related to rates of bone loss. Among females, loss of fat mass was a significant determinant of hip and femoral neck bone loss. Age (-) and loss of lean mass (-) were significant determinants of bone loss at the total hip BMD, but not the femoral neck. In males, age (-) and loss of lean mass (-) were significant determinants of rates of bone loss at the hip and femoral neck subregion. Overall, the rates of bone loss for females in this analysis were comparable to other longitudinal analyses for AA females and Caucasian males and females. (20,23)

D. Overall Strengths of the Three Complementary Analyses

This research examined correlates of BMD in persons of African Ancestry in cross-sectional and longitudinal analyses. Our study participants were males and females of African ancestry who were living in the US and on Caribbean Island of Tobago, and they share West African heritage. The overall sample sizes of all three studies were relatively large. To our knowledge, no other studies have examined correlates of BMD in a large sample of African Caribbean males and females. Furthermore, we are not aware of any other published data that reported changes in BMD over time among males of African ancestry.

E. Overall Limitations of the Three Complementary Analyses

By the nature of our recruitment, we may have preferentially selected participants who were healthier than other people in their respective communities. So our research may not be generalizable to all persons of African ancestry. Second, we cannot be certain about the accuracy of self-reported medical history or lifetime medication use because of the possibility of misclassification bias. Third, the number of AA males (n=47) in females (n=74) included in the bone loss analysis was small. Fourth, only one of our analyses examined changes in BMD over time, which is the best way to evaluate risk factors associated with lower BMD and subsequent

fracture risk, or temporal trend. Lastly, DXA only measures two-dimensional bone, length and width, not thickness. Thicker bones are denser and DXA does not address differences in skeletal size (i.e. bone thickness), which influences BMD.

6.1. Public Health Impact

The public health burden of osteoporosis (OP) threatens longevity and quality of life. Societal burdens of OP include higher economic costs associated with treating fractures and overall costs to health care systems. The public health burden associated with OP is expected to increase drastically with the anticipated longer life expectancy worldwide, especially among minorities. Whether the increased burdens of OP will be related to aging (i.e., frailty) and/or increases in prevalent risk factors is not known.

Research has shown that while AA have had lower hip fracture rates in the past (24-26), a recent National Hospital Discharge Survey study by Orces et al. showed that population-based trends for hip fracture-related hospitalizations increased 121% for AA males and 27% for AA females between 1990-2000. (27) This research supports the need for understanding risk factors associated with low BMD among persons of African ancestry.

In the few studies with AA, higher BMD has been consistently reported in the literature for AA compared to Caucasians, but the underlying mechanisms for these ethnic differences are poorly understood. The paucity of research that examined correlates of BMD among males and females of African ancestry does not address gaps in the literature. It appears that persons of African ancestry do not have an increased risk of sustaining osteoporotic fractures, but to know for certain we must first understand the underlying mechanisms that are associated with lower BMD, which is a significant predictor of fracture risk.

In this body of research, we explored the ethnic and gender differences in the correlates of BMD and rates of bone loss among middle-aged and older males and females of African ancestry. To our knowledge, we have undertaken one of the first analyses to evaluate bone loss in males of African ancestry. Bone loss and increased risk of hip fracture are both sequelae of aging, despite gender or ethnicity.

Ethnicity plays an important role in disease prevalence since it encompasses cultural, geographical, dietary, and lifestyle characteristics. Once we are able to better identify persons of African ancestry who may be at risk for osteoporotic fractures, prevention and intervention strategies can be developed. Understanding risk factors for low BMD among persons of African ancestry may influence preventive strategies and early diagnosis of OP and its related conditions.

The primary goal of this research was to identify modifiable risk factors that were associated with lower BMD and higher rates of bone loss in persons of African ancestry. Since non-industrialized countries are adapting to a more 'Western' lifestyle, we believe that the risk factors associated with increased bone loss among AAs may be applicable to Tobagonians.

This research delineates the demographic, lifestyle, and health-related risk factors for low BMD among persons of African ancestry. Furthermore, this research may provide insight into the contribution of ethnicity in association with modifiable risk factors for lower BMD. With this knowledge, our research may enhance efforts focused on reducing the burden of osteoporotic morbidity and mortality among persons of African ancestry, and possibly lessen the public health threat associated with OP. The public health significance of this research may facilitate intervention and prevention strategies to identify persons of African ancestry who may be at risk of developing osteoporosis.

6.2. Final Summary and Conclusions

OP is typically asymptomatic until fracture, so it is very important to identify factors associated with BMD. OP is also more prevalent among postmenopausal Caucasian females, but postmenopausal females of African ancestry also may be at increased risk of developing OP, despite higher BMD.

Research has shown that BMD is a significant determinant of osteoporotic fractures. (7,8,28-32) Risk of sustaining an osteoporotic fracture is substantially lower among persons of African ancestry compared to Caucasians. A potential explanation for the ethnic differences in fracture risk has been attributed to ethnic differences in BMD, PBM, and genetics, but most of this research has been conducted in the US or UK. In the US, for example, it was reported that AAs had 10-15% higher BMD compared to Caucasians, even after adjusting for important covariates.(6) Lifestyle factors typically account for some of the variability in BMD and we suspect these factors may partially explain ethnic differences in BMD.

Few studies have compared BMD among Africans to AAs and the findings failed to show higher BMD among Africans compared to AAs. (1,2) More studies, however, have compared BMD among West Africans to Caucasians and although BMD was not significantly higher among West Africans (1,3,4), the risk of fracture was considerably lower for West Africans compared to Caucasians. (1,3) The lower risk of fracture among West Africans, despite lower BMD, has been attributed to bone geometry, lifestyle and genetic factors.

In conclusion, we demonstrated that Tobagonians had higher BMD (i.e., denser bones) than NHANES data for AAs and Caucasians. (1) We also confirmed that commonly reported risk factors for low BMD in Caucasians are similar for persons of African ancestry. Weight and components of weight were significant determinants BMD among males and females of African ancestry, residing in the US and on the Caribbean Island of Tobago.

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APPENDIX

Sample Questionnaire from Tobago Women's Health Study

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