PREDICTORS OF BONE HEALTH IN POST-MENOPAUSAL WOMEN

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ABSTRACT

Osteoporosis, a skeletal disorder characterized by compromised bone-strength and an increased risk of bone fracture, is becoming increasingly prevalent, and the health and economic burden of osteoporosis is only expected to increase as the population ages. Osteoporosis disproportionately effects women, and past studies looking at exercise as a preventative factor have primarily focused on white women. Through the FIERCE study, total body bone mineral density (BMD) measurements of 213 post-menopausal African- American women living in the Washington D.C. area were collected via dual-energy x-ray absorptiometry (DXA), the gold standard in the field. Additionally, medical histories and anthropometric measurements were recorded. Participants were assigned to one of three exercise groups after the baseline visit- supervised exercise, home based exercise, or control. We hypothesized that participants assigned to an exercise group would experience improvements or preservation in BMD levels among postmenopausal Black women at increased risk for breast cancer, as prior studies have showed exercise affecting hip BMD and resistance training preventing spine bone loss. After six months of maintaining their exercise assignments, BMD measurements were taken via DXA once again. Age at baseline had a significant effect on BMD level ($p=0.0049$) as did total percent body fat at baseline ($p<0.0001$). The average change in BMD levels in supervised, home-based, and control assignments were -0.001, 0.008, and -0.003 g/cm^2 respectively ($p=0.24$). There was no significant difference in these change of BMD levels among exercise assignments ($p= 0.93$), after controlling for repeated measures, age and total percent body fat ($p= 0.71$). Further studies are needed to see

if a longer time in an exercise intervention is needed to see improvements in BMD levels, as exercise represents a low cost and noninvasive possible intervention for osteoporosis.

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Many thanks,
Lauren Carlson

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CHAPTER 1

INTRODUCTION

Osteoporosis, a skeletal disorder characterized by compromised bone-strength and an increased risk of bone fracture, is becoming increasingly prevalent.[1] It has been estimated that osteoporosis causes more than 8.9 million fractures a year. In the United States alone, over 1.5 million fractures per year were due to osteoporosis, resulting in healthcare costs of between 12 and 18 billion dollars per year. The health and economic burden of osteoporosis is only expected to increase as the population ages.[2]

1.1 Diagnostic Strategies

There are two main diseases of poor bone health, osteopenia and osteoporosis. Both osteopenia and osteoporosis are characterized by bone loss. Osteoporosis is the more severe disease of the two. These diseases are typically diagnosed with a DXA scan. The DXA scan gives a measure of bone mineral density (BMD), defined as grams of mineral per square centimeter or cubic centimeter.[1] From the BMD measurement, a T-score is calculated. The T-score compares the BMD measurements of a participant to the BMD levels of a young (30 years old) adult. A T score of less than -1 means a patient's BMD is more than one standard deviation lower than the average BMD of young adults. This would be indicative of osteopenia. A T score of -2.5 or lower means that a patient's BMD is more than 2.5 standard deviations lower than the average BMD of young adults. This is indicative of osteoporosis. The areas of screening for these bone disorders are usually the hip and the spine, although some trials have proposed total body BMD level measurements as an alternative.[3] Studies comparing the two methods have had mixed results, with some reporting good correlations between the two measures, while others report that whole-body

BMD levels tend to underestimate abnormal BMD levels, leading to cases of osteopenia and osteoporosis that are missed.[3–5]

1.2 Biological Mechanisms

Bone is formed and removed by two bone cell types: osteoblasts, and osteoclasts. Osteoblasts are primarily responsible for deposition of new bone matrix and its mineralization, whereas osteoclasts resorb the mineralized matrix. Both osteoblasts and osteoclasts are short-lived cells, with osteoclasts living between 1 and 25 days and osteoblasts living 1-200 days. They are typically removed via apoptosis, but some osteoblasts remain and cover bone surfaces, thus called "lining cells". Estrogen and androgens act to increase the lifespan and generation of these cells. Estrogen also seems to inhibit apoptosis to some degree, as increases in osteocyte apoptosis has been observed in those with estrogen deficiency.[6]

1.3 Risk Factors of Osteoporosis and Poor Bone Health

1.3.1 Age

Age is among the strongest risk factors for osteoporosis and decreased bone health. The prevalence of osteoporotic fractures increases from 4% in women aged 50-59 years to 52% of women older than 80 years. The type of osteoporotic fracture experienced also varies with age, as the typical sequence of fractures in those with osteoporosis goes from a fracture in the lower end of radius starting at age 50 years, followed by vertebral fractures at ages 60-75 years and hip fractures starting in the late 70's. This decrease in bone health is directly correlated to increased bone resorption, accumulation of micro damage, numerous areas of demineralization throughout bone, and loss of horizontal structs in trabecular bone architecture. Additionally, by the age of seventy years, bone mass typically decreases by 30-40%.[7]

1.3.2 Gender

While osteoporosis does impact both males and females, osteoporosis is a primary concern in women's health, with women twice as likely to experience fractures when compared to men.[8] Women are particularly susceptible to osteoporosis and poor bone health after menopause, characterized by a cessation of ovulatory function. Estrogen (the primary sex hormone in women) and androgens (the primary sex hormones in males) are both imperative for bone health, as they have an influence on the generation and lifespan of osteoclasts and osteoblasts. Estrogen in women is primarily synthesized in the granulosa and theca cells of the ovarian follicles. In men, however, only approximately 15% of estrogen is secreted directly from the testes, most of the estrogen is instead derived from peripheral aromatization, the conversion of androgens to estrogen in fat cells via an enzyme called aromatase. These differences in sources of estrogen are likely the root cause of gender disparities in bone health. When women go through menopause and experience cessation of ovarian function, estrogen is produced at lower amounts. Thus, bone turnover decreases substantially. Men, however, do not experience a similar sensation to menopause; their androgens remain relatively stable. Additionally, estrogen levels in men remain at a level sufficient to maintain skeletal homeostasis, even as they age.[6]

1.3.3 Race

BMD scores and osteoporosis vary by race and location. From a worldwide standpoint, fractures are most prevalent in Scandinavian countries, with Sweden reporting a 13.1% lifetime risk of hip fracture at 50 years in men, and a lifetime risk of 28.5% of hip fracture at 50 years in women, compared to 6% and 15.8% in men and women in the United States, respectfully. While worldwide data can be hard to obtain, as some countries do not have data available, it is clear that sun exposure and latitude has an impact on bone health.[9] In the United States, Black women have

reported the highest mean BMD values and lowest hip fracture rates. Rates of hip fractures are roughly 50% lower in African American women and Asian women compared to white women.[9]

There are likely many interacting factors leading to lower rates of fractures in Black women compared to white women. Body weight is thought to influence BMD, but BMD remains higher in Black women compared to white women across all weights. These high BMD scores likely are protective against fractures. Additionally, differences in hip geometry could be a key reason for these disparities in hip fractures, as longer hip axis lengths have been linked to an increased risk of hip fracture, and hip axis lengths are shorter among Black women compared to whites, even after adjusting for height. It is also possible that these disparities are to disparities in the healthcare system, as 33% of white women enrolled in Medicare have screenings for BMD, compared to only 5% of Black women enrolled in Medicare.[9]

Despite higher BMD scores among Black women, some troubling trends support a need to study this population extensively. Compared to white women, Black women experience a longer period of hospitalization after hip fracture compared to white women. Furthermore, Black women have been reported to have a higher mortality rate during hospitalization for hip fracture when compared to white women.[1] As the life expectancy among African Americans and Hispanic Americans is increasing, this will likely correspond with increases in the prevalence of fractures in these minority populations. As of 2005, 12% of all fractures occurred in nonwhites, but it is estimated that this will rise to 21% by 2025.[9] Thus, preventative factors in minority women and Black women specifically need to be studied extensively.

1.4 Lifestyle Factors or Dietary Factors

1.4.1 Physical Activity

Typically, physical activity is associated with a higher BMD, with athletes exhibiting higher levels of BMD than non-athletes.[10] However, this relationship may be U-shaped in certain scenarios, given that distance runners, often with low BMIs, tend to have low BMD levels. Higher BMI is associated with higher BMD likely due to increased aromatase activity and greater mechanical stimulus. However, obesity does not seem to be protective to osteoporosis in post-menopausal women, and can actually be a risk factor for falls.[11]

There is some evidence that exercise preserves BMD levels in post-menopausal women, which represents a possible public health intervention.[12,13] It does not appear that all exercise is created equal, however, as prior studies have found resistance training to be effective in preventing spine loss, and impact exercise tends to affect hip BMD. Data on aerobic exercise, however, seems to be less consistent. It is thought that a combined exercise intervention, combining two different types of exercise, may have the best overall impact on bone health.[12] However, previous studies have been limited by small sample sizes, and the exercise interventions proposed were predominately on-site and supervised, which may not be representative as a public health intervention outside of a clinical trial. Additionally, many of these studies focused primarily on white women.

1.4.2 Diet

Dietary factors have been studied with inconsistent results. Calcium and Vitamin D are thought to improve bone health, as Vitamin D regulates homeostasis of calcium and phosphorus, and it is also known to play a role in mineralization, growth, and remodeling of bone.[14] However, clinical studies examining Vitamin D_3 and calcium have been inconsistent. Calcium increases

BMD and decreases the risk for osteoporosis in lean men and women.[1] Likewise, a retrospective study found that lower vitamin D levels were associated with developing complex regional pain syndrome type I (CRPS) in post-menopausal Korean women who had a history of a distal radius fracture. CRPS is characterized by unexplained severe pain that is constant and is also accompanied by swelling, autonomic dysfunction, and joint stiffness. Thus, these studies imply some sort of imperative role of Vitamin D in bone health.[14] However, the largest clinical trial of women, Women's Health Initiative (n=36,282), found no significant reduction of the incidence of hip fractures when participants were given supplements of 1,000 mg elemental calcium carbonate plus 400 IU of vitamin D_3.[15]

1.4.3 Inflammation and Diet

Inflammation is also associated with bone loss. In older adults, biomarkers of inflammation are correlated with bone loss and increased bone resorption.[16] The Women's Health Initiative also investigated the link the link between an anti-inflammatory diet and BMD in post-menopausal women. Postmenopausal women with a lower inflammatory diet had lower hip BMD at initial measurement, but lost less of said BMD over a 6 year follow up compared to women who consumed a more inflammatory diet. However, a significant relationship between an inflammatory diet and hip fracture incidence was only present in younger white women. Thus, dietary factors seem to have different levels of influence depending on body type, age, and race of women. More studies are needed to evaluate diet in bone health among minority populations, particularly Black women.

1.5 At Risk Populations

Breast cancer survivors are at particular risk for osteoporosis, as women with breast cancer are often prescribed estrogen deprivation therapies and cytotoxic chemotherapies that result in

higher bone turnover and bone loss. Women with breast cancer also tend to experience premature cessation of ovarian function. It is estimated that osteoporosis effects 20-30% of breast cancer survivors, however there is some preliminary evidence that this prevalence varies based on race, and Black women are less susceptible to osteoporosis post breast cancer treatments.[17] In the present study we are focused on women at increased risk of breast cancer, which may provide insight into preventative measures that can be taken to preserve bone health in this at-risk population.

1.6 Additional Protective Factors

Some factors thought to be preventative to osteoporosis and osteopathic fracture have been extensively studied. Estrogen plus progesterone therapy, for instance, increases BMD and decreases the risk for osteoporosis and fracture in women.[18]

1.7 Windows of Estrogen

While osteoporosis is thought to be in conjunction with the post-menopausal stage in women, it is important to consider earlier windows of estrogen that could perhaps be an indicator of long-term bone health, whether that be during child-baring years or even in childhood. Age at menarche and bone health have been linked in prior studies, with epidemiological studies linking later ages of menarche with elevated risk of lower BMD scores and later osteoporosis diagnoses. [19] This is particularly important when we consider the role of race in bone health, as some studies have reported earlier ages of menarche among African American girls when compared to white girls.[20]

1.8 Aims of Study

The predictors of bone health in 213 African- American postmenopausal women living in the Washington D.C. area were examined in a randomized clinical trial among women who were

randomized into one of three groups- supervised, home-based, and a control group. The aims of the study are: 1) to understand how body composition and relevant medical history (age at menarche, age at first childbirth) influence BMD levels; and 2) to determine the effect of exercise on BMD levels. By looking at Black post-menopausal women, we will be focusing on an understudied group at a time where preserving bone health is crucial.

CHAPTER 2

METHODS

2.1 Study Design

This is a 6-month, three-arm, randomized controlled trial comparing a supervised facility-based exercise and a home-based exercise intervention to a control group.

2.2 Subjects

Subjects (n=213) were 45-65 year-old African- American postmenopausal (last menstrual cycle ≥ 12 months) women living in the Washington D.C. area. All subjects had metabolic syndrome (MetS). MetS is defined here as at least two of the following: elevated fasting glucose (≥ 100 mg/dL), reduced HDL cholesterol (< 50 mg/dL), or elevated triglycerides (≥ 150 mg/dL), and elevated blood pressure (≥ 130/85 mmHg). Further eligibility criteria included (1) waist circumference > 35 inches (88 cm); (2) 5-year individual invasive breast cancer risk ≥ 66% using the "CARE" model; (3) have a cell phone with text messaging capabilities; (4) able to read and speak English; (5) reside in close proximity to or have access to Georgetown-Lombardi Cancer Center's Office of Minority Health and Health Disparities Research (OMH). Subjects had no physical limitations that prevented exercising and were able to commit to a regular exercise regimen. Exclusion criteria included history of breast cancer, except for non-melanoma skin cancer, diabetes or taking anti-diabetic medications (including insulin), current regular exercise regimen ("regular" defined as at least two times per week of at least 20 minutes of moderate or vigorous activity), and current enrollment in another physical activity and/or dietary clinical trial or diet/ weight loss program. After confirming eligibility, participants were randomly assigned, in a 1:1:1 ratio, to supervised facility-based exercise, home-based exercise, or control group

using a block randomization scheme. All participants had comprehensive measurements taken at baseline, and then at 3 and 6 months post randomization. The study was approved by the Georgetown University Institutional Review Board (IRB Number:2012-012). Signed informed consent was obtained from each subject.

2.3 Care Model

The Breast Cancer Risk Assessment Tool, otherwise known as the Gail model, has been typically used for counseling and to determine the eligibility for breast cancer prevention trials. However, it was found that a different, newer model, called the CARE model better predicted breast cancer risk in minority women, particularly in African- American women. The CARE model uses the risk factors age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, and number of previous benign breast biopsies. The mean 5- year breast cancer risk was 1.29% (Range: 0.20- 4.50%) for the CARE model, and 1.67% was considered to be the cutoff-point for elevated risk. However, in this study, women were included if their risk according to the CARE model was $\geq$ 1.40%.[21]

2.4 Study Variables

The following variables were collected for every participant.

2.4.1 Demographics

Demographic parameters included age, race, and education (did not attend school/ grades 1-4/ grades 5-8/ some high school/ high school diploma/ vocational or training school after high school/ some college/ college/ some graduate school Master's degree/ Doctoral degree). Self-reported age at menarche and age of first childbirth were collected.

2.4.2 Anthropometric Measurements

Three assessments, one at baseline and two follow-up assessments at 3 and 6-months, were conducted. Assessments included the following:

Height and weight measurements were recorded with light clothes and no shoes via a stadiometer and beam balance, respectively. Weight was recorded to the nearest ½ pound, and height was read to the nearest ¼ inch.

Body mass index (BMI). BMI was calculated by weight in kilograms, divided by height in meters squared (kg/m^2).A BMI ranging from 25- 30 30 kg/m^2 was classified as "overweight," while a BMI greater than or equal to 30 kg/m^2 was classified as "obese".

*Dual-Energy X-ray Absorptiometry (DXA)***.** Subjects underwent a DXA scan at visits 1 and 6 (6 months apart) to determine objective measures of whole body bone mineral density, T-scores, total fat percentage, percent gynoid fat (i.e., percent of hip and upper thigh tissue made up of fat), and percent android fat (i.e., percent of tissue between the ribs and pelvis made up of fat). During the DXA scan, the patient laid in the supine position on the DXA table while a scanner arm located above the patient, scanned across the body from head to toe.

2.4.3 Bone Health Measurements

Bone Mineral Density (BMD), defined as grams of mineral per square centimeter or cubic centimeter, serves as a measure of bone health.[1] To assess bone health, a BMD age and gender matched z-score is calculated. A T-score of less than -2.5 means that the BMD is 2.5 standard deviations or more lower than young adults. A T-score this low would be indicative of osteoporosis. Likewise, a T-score between -1 and -2.5 is indicative of osteopenia In addition to diagnosing osteoporosis, BMD scores can be used to estimate the risk of osteoporotic fracture- a

higher BMD indicates a lower risk of osteoporotic fracture.[22] There are a variety of ways to measure BMD, but the gold standard is by dual-energy x-ray absorptiometry (DXA).

2.4.4 Physiological Measurements

VO2 Max. VO_2 max is a measurement of the maximum rate of oxygen one can use during exercise. VO_2 max is measured in milliliters of oxygen used in one minute per kilogram of body. A critical factor for endurance exercise performance because it sets the upper limit for aerobic metabolism.[23] To measure VO_2 max, participants exercise on a bike or treadmill at increasing intensity, until exhaustion. This exercise is done while wearing a face mask to measure the amount of oxygen the participant is inhaling and the amount of air the participant is exhaling.

*Heart Rate***.** Heart rate is the number of times a participant's heart beats in one minute. It is measured in beats per minute. A Polar heart rate monitor around the wrist is one method of collecting heart rate.

*Rate of Perceived Exertion (RPE)***.** Rate of perceived exertion is visual aid with a scale. In this study, it ranged from 1-20. Participants can point to how difficult they find a particular exercise, with "1" being a fairly easy exercise that takes minimal effort to complete, to "20", which would be an exercise that takes maximum effort.

2.5 Exercise Interventions

2.5.1 Supervised Facility-Based

Participants in the facility-based exercise intervention arm were required to meet and maintain a goal of 150 minutes/ week of moderate intensity exercise for 6 months. This exercise took place 3 times a week at the OMH, under the supervision of an exercise physiologist. Exercise duration gradually increased from 75 minutes per week at week 1 to 150 minutes per week by

week 4, using American College of Sports Medicine guidelines for progression in obese/overweight, low-risk individuals.[24] Heart rate, measured via Polar heart rate monitors, and rating of perceived exertion (RPE) were monitored during exercise. Prior to the start of the supervised exercise intervention, participants met with the study exercise physiologist to determine their VO_2 max and set exercise goals. Moderate intensity exercise was defined as a heart rate in the range of 45-65% of their VO_2 max, as determined during baseline testing, and with an RPE in the rand of 11-14 on the 20-point scale. Moderate intensity exercises primarily utilized treadmills and exercise bikes.

2.5.2 Home-Based Exercise Intervention

The participants randomized to this intervention arm were required to exercise 150 minutes/week, Participants were taught to exercise at an intensity equal to 50% of their heart rate reserve and were instructed to progress to a goal of 30-45 minutes of aerobic exercise at least 4 times per day. The ultimate goal for this group was to achieve a total of 10,000 steps per day, as measured by pedometers. Exercises for this intervention were completed at home, but each participant did meet with the study exercise physiologist prior to the start of this intervention to determine individual goals. All exercises in this arm were customized to each participant's baseline fitness level, activity tolerance and personal preferences. Exercise adherence was encouraged via weekly text messages.

2.5.3 Control Group

Participants in the control group were asked to maintain their current daily activities and exercise habits for the duration of the study and record the type of physical activity (mode), total minutes of physical activity (duration), heart rate and RPE (intensity), and any comments/questions. Participants in the control group received healthy lifestyle information to the

group, via text messages.

2.6 Data Abstraction

BMD and T-scores were taken from DXA scans that were measured for the prior FIERCE study during the baseline visit and the 6-month follow up. This was merged with the baseline measurements of age, BMI, education level, age at menarche, age at first childbirth, and history of breast cancer in immediate family, and exercise assignment to create a new dataset with our variables of interests.

2.7 Statistical Analysis

Means and standard deviations were generated for all continuous variables in the dataset both overall and stratified by exercise assignment. All continuous variables were relatively normally distributed, as shown by histograms via formal tests (Shapiro-Wilks). Frequency distributions were generated for categorical variables both overall and stratified by exercise assignment. Baseline characteristics were compared across the 3 study arms using analysis of variance (ANOVA) or chi-square tests, as appropriate.

A regression model with BMD as the dependent variable and BMI and total percent body fat and their interaction as independent variables was used to investigate a potential interaction between BMI and total percent body fat. A multiple linear regression was then selected via backwards selection analysis from the variables age, total percent body fat, age at menarche, age at childbirth, and BMI. A backwards selection analysis was used to avoid issues with multicollinearity. The same methods were repeated to look at influences on participant's T-scores.

Changes in BMD levels at baseline and at six month follow up across exercise groups were compared via ANOVA. Changes in BMD levels were analyzed again via a multivariate repeated measures ANCOVA, controlling for age and total percent body fat. Assumptions for every

statistical analysis were checked. All analyses were performed using SAS 9.4 (Cary, North Carolina, USA).

CHAPTER 3

RESULTS

3.1 Study Population

The average age of participants was 58.3 years, and more than 90% of participants had a high school or higher education. All participants in the study had children, and roughly 40% of participants reported having a first degree relative diagnosed with breast cancer. A first degree relative includes a mother, full-blooded sisters, or daughters. Study population characteristics were similar across groups. Full population characteristics can be seen in Table 3.1.

Table 3.1 Baseline Characteristics of Study Population

	Supervised Facility Based Exercise Intervention	Home-Based Exercise Intervention	Control Group	P-value
n (%)	73	69	71	
Age, mean (sd):	58.1 (5.1)	58.3 (4.7)	58.4 (5.3)	0.93
Education level, n (%)				0.54
< High school	7 (9.6%)	4 (5.8%)	6 (8.5%)	
High school/ some college	33 (45.2%)	41 (59.4%)	36 (50.7%)	
≥College	33 (45.2%)	24 (34.8%)	29 (40.8%)	
Age at menarche, n (%)				0.98
7-11 years	20 (27.4%)	20 (29.0%)	20 (28.2%)	
12-13 years	43 (58.95)	42 (60.9%)	43 (60.6%)	
>=14 years	10 (13.7%)	7 (10.1%)	8 (11.3%)	
Unknown	0	0	0	
Age at first live birth, n (%)				0.56
<20 years	27 (37%)	25 (36.2%)	19 (26.8%)	
20-24 years	13 (17.8%)	8 (11.6%)	17 (23.9%)	
25- 29 years	10 (13.7%)	9 (13.0%)	7 (9.9%)	
>= 30 years	6 (8.2%)	11 (15.9%)	10 (14.1%)	
Unknown	0	0	0	
No live births	17 (23.3%)	16 (23.2%)	18 (25.4%)	
Known family history of breast cancer in first degree relatives, n (%)				0.18
Yes	29 (39.7%)	32 (46.4%)	24 (33.8%)	
No	44 (60.3%)	35 (50.7%)	47 (66.2%)	
Unknown	0	2 (2.9%)	0	

3.2 Subject Anthropometrics at Baseline

Overall, anthropometric measurements taken at baseline were similar across exercise assignments (see Table 3.2). The average BMI of participants was 35.7 kg/m^2. Almost all participants had BMI levels that categorized them as overweight or obese. The majority, 80%

(n=170) had a BMI greater than 30 kg/m^2, classifying them as obese. Overweight participants with BMI in the range of 25-30 kg/m^2 made up 18% of the cohort. Only 2% (n=4) participants had BMI levels in the range of 18-25 kg/m^2, classifying them as normal weight. The overall average BMD measurement of the cohort was 1.23 g/cm^2, and the average T-score was 1.31. This T-score means that the BMD levels in our study population were in the "normal" range compared to a population of young (30 years old) adults.

Table 3.2 Baseline Anthropometric Variables of Study Population

	Supervised Facility-Based Exercise Intervention Arm	Home-Based Exercise Intervention	Control Group	P-value
n (%)	73	69	71	
BMI, in kg/m^2, mean(sd)	35.2 (6.1)	36.1 (7.2)	35.9 (7.6)	0.71
BMD, in g/cm^2, mean (sd)	1.23 (0.1)	1.24 (0.09)	1.22 (0.09)	0.83
T-Score, mean (sd)	1.32 (1.3)	1.37 (1.16)	1.24 (1.15)	0.83
Bone Health				0.35
Healthy n(%)	66 (99.0%)	61 (96.8%)	61 (93.8%)	
Osteopenia n(%)	1 (1.0%)	2 (3.2%)	4 (6.2%)	
Osteoporosis n(%)	0	0	0	
Total percent body fat (sd)	48.6 (5.0)	48.8 (5.8)	57.8 (8.6)	0.88

3.3 Testing for Interactions

To determine which of these variables best predicts BMD, interactions between variables must be examined. The clearest example of a possible interaction within these factors is BMI and total percent body fat. Thus, a model that included BMD as the dependent variable and total percent body fat, BMI, and their interaction as the independent variables was tested. This model was highly statistically significant (p-value= 0.0003 but there did not appear to be a significant interaction

between BMI and total percent body fat (p-value= 0.5601). The interaction term was removed from the model and the model remained statistically significant (p-value= 0.0001). Full results of these models can be seen in Table 3.3.

Table 3.3 Testing for Interaction between BMI and Total Percent Body Fat

Variable	Parameter Estimate	Standard Error	P-Value
Intercept	1.11	0.27	<0.0001*
BMI (baseline)	-0.004	0.007	0.60
Total Percent Body Fat (Baseline)	0.002	0.006	0.70
BMI*Total Percent body Interaction	0.000	0.000	0.56
****With Interaction term removed*****			
Intercept	0.96	0.072	<0.0001*
BMI (baseline)	0.000	0.000	0.64
Total Percent Body Fat (Baseline)	0.005	0.000	<0.0001*

3.4 Model Selection BMD Score

Using a backward selection analysis, as to avoid issues with multicollinearity, a final model consisting of only total percent body fat and age was selected from the predictors age, family history of breast cancer, BMI at baseline, total percent body fat at baseline, age at first live birth, and age at menarche (see Table 3.4). The model identified using backward selection was significant (p value <.0001) and the adjusted R-squared value was 0.12, meaning these variables explain only 12% of the variance in weight. For every one year increase in age, BMD levels dropped by approximately 0.004 g/cm^2 (p=0.0049). For everyone unit increase in total percent body fat, BMD levels increased by approximately 0.005 g/cm^2 (p<.0001). These same methods were reported when looking at predictors of T- Scores.

Table 3.4 Results of Regression Model with all Predictors

Predictor of BMD	Type III Sums of Squares	Mean Square	P-Value
Age (Baseline)	0.041	0.041	0.0254*
Family History of Breast Cancer	0.020	0.007	0.4672
BMI (Baseline)	0.001	0.001	0.7722
Menarche	0.035	0.018	0.1143
Total Percent Body Fat (Baseline)	0.124	0.124	0.0001*
Age at First Live Birth	0.019	0.005	0.6765

3.5 Testing for Interaction

A model that included T-score as the dependent variable and total percent body fat, BMI, and their interaction as the independent variables was highly statistically significant (p-value= 0.0003 but once again there did not appear to be a significant interaction between BMI and total percent body fat (p-value= 0.5507). The interaction term was removed from the model and the model remained statistically significant (p-value <.0001). The results of the model can be seen in Table 3.5.

Table 3.5 Testing for Interaction between BMI and Total Percent Body

Variable	Parameter Estimate	Standard Error	P-Value
Intercept	-0.19	3.37	0.9539
BMI (baseline)	-0.05	0.09	0.5967
Total Percent Body Fat (Baseline)	0.03	0.07	0.7026
BMI*Total Percent Body Fat Interaction	0.001	0.002	0.5507
****With Interaction term removed*****			
Intercept	-2.14	0.90	0.0183
BMI (baseline)	0.006	0.01	0.6214
Total Percent Body Fat (Baseline)	0.07	0.02	<0.0001*

3.6 Model Selection T-Score

Using a backward selection analysis to avoid issues with multicollinearity, a final model with predictors predicting T-scores was selected. The chosen model consisted of only total percent body fat and age was selected. The model identified using backward selection was significant (p value <.0001) and the adjusted R-squared value was 0.12, meaning these variables explain only 12% of the variance in weight. For every one year increase in age, T-scores levels dropped by approximately .046 g/cm^2 (p= 0.0043). For every one unit increase in total percent body fat, BMD levels increased by approximately 0.06 g/cm^2 (p<.0001). The results of all predictors can be seen in Table 3.6.

Table 3.6 Results of Regression Model with all predictors

Predictor of BMD	Type II Sums of Squares	Mean Square	P-Value
Age (Baseline)	6.52	6.52	0.0236
Family History of Breast Cancer	3.22	1.07	0.4644
BMI (Baseline)	0.10	0.10	0.7785
Age at Menarche	5.45	2.73	0.1162
Total Percent Body Fat (Baseline)	19.71	19.7	0.0001
Age at First Live Birth	3.00	0.75	0.6638

3.7 Repeated Measures ANCOVA- BMD Scores

To analyze if BMD scores changed from baseline to 6-months post exercise regimen, we used a repeated measures ANCOVA analysis. Age and total percent body fat were controlled for in this model. Changes in BMD scores did not differ by exercise assignments (see Figure 1).

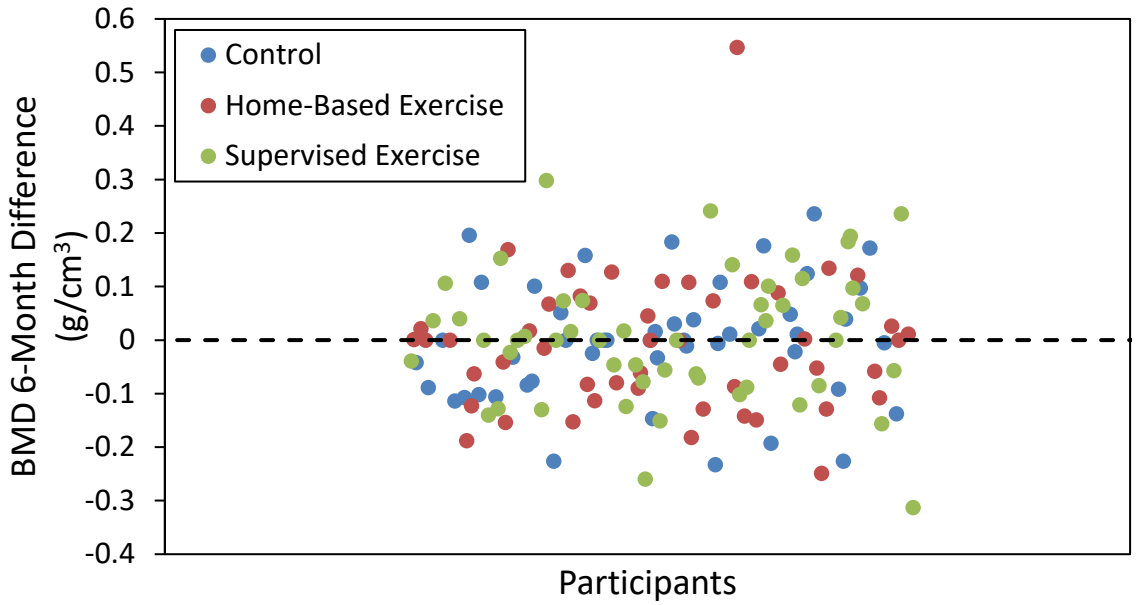

Figure 3.1 Difference in BMD Levels after Six Months

Figure 3.1 displays the difference in BMD levels (BMD levels measured at V2- BMD levels measured at V1). The average change in BMD in the supervised group was -0.001, the average change in the home-based intervention was 0.008, and the average change in the control group was -0.003. Full results can be seen in Table 3.7. There was no significance in change in BMD levels among exercise assignments, even after controlling for age and total percent body fat ($p= 0.71$).

Table 3.7 BMD (g/cm^2) Level Changes at Baseline and Follow Up

	Supervised Facility-Based Exercise Intervention Arm	Home-Based Exercise Intervention	Control Group	P-Value
BMD at Baseline Mean (SD)	1.23 (0.1)	1.24 (0.09)	1.22 (0.09)	0.83
BMD at 6 Months Mean (SD)	1.23 (0.08)	1.21 (0.08)	1.25 (0.09)	0.10
Change in BMD Mean (SD)	-0.001 (0.03)	0.008 (0.03)	-0.003 (0.04)	0.24

CHAPTER 4

DISCUSSION

4.1 Primary Findings

The average BMD level of this cohort was 1.23 g/cm^2, with an average T score of 1.31. The study population average, then, had healthy/ normal bones, as a T score of -1 or above is indicative of normal bone density. 4.0% of the study cohort (n=7) had a T score of lower than –1 but greater than -2.5, indicative of osteopenia. This is less than the prevalence of the greater population, as 28% of Black women are reported to have osteopenia according to NHANES. Also according to NHANES, 8% of Black women have osteoporosis, but this study had no participants with T-scores indicative of osteoporosis (<-2.5).[25]

The primary findings in this study were total percent body fat and age were the two key indicators of total body BMD levels in post-menopausal Black women (p values <0.001 and 0.0049, respectively). These same two factors were also the two key indicators of T- scores in post-menopausal Black women (p values <0.001 and 0.0043, respectively). Additionally, it was found that 6 months of exercise did not seem to change BMD scores in post-menopausal women, regardless of type and design of exercise trial (p= 0.71).

The finding that total percent body fat and age had an influence on BMD and T scores was relatively consistent with prior literature, as total percent body fat is likely an indicator of aromatase activity and provides greater mechanical stimulus. Likewise, bone health is known to decline with age. However, the fact that BMI was not associated with BMD or T scores shows that BMI not an indicator of aromatase activity or a measure of mechanical stimulus. BMI is thus likely a faulty measurement for body composition. Prior studies using BMI as a measurement should be interpreted with caution.

4.2 Limitations

This study had several limitations. There are a few methods to measure BMD, but the DXA, used in this study, is considered to be the gold standard.[1] However, DXA can be administered differently- it can be performed locally or for the whole body. It is thought that the some of the best areas for BMD assessment are the hip, lumbar spine, and forearm. Additionally, certain areas are best for certain patients. For instance, forearm BMD measurements are taken in patients with hyperparathyroidism or morbid mobesity.[4] However, such localized measurements can sometimes be faulty. Spine BMD, among one of the more common and studied areas for BMD measurements can be misleading, particularly patients who experience spondylosis. Spondylosis is general wear and tear damage in the spinal disks that come with aging. Patients with spondylosis can grow osteophytes, or growth spurts. These osteophytes can drive up BMD scores in parts of the spine, while areas of the spine without osteophytes that are not measured have lower BMD scores, and a misdiagnosis could occur. [4] Whole- body measurements, used by the current study, offer an alternative. These measurements should give an assessment of BMD that is not hindered by local inconsistencies. However, it must be certain that these whole-body measurements correlate with the local measurements.

Some studies have reported high correlations with whole-body measurements and local measurements, particularly with hip or spine BMD measurements.[3] Many studies, however, seem to confirm the contrary, particularly in vulnerable populations. One study found that whole body measurements tend to underestimate cases when there is abnormal BMD or osteoporosis in patients over 50 years.[4] This is crucial, as this is an age where women are particularly susceptible to osteoporosis or osteopenia. Therefore, the authors suggest changing the T score cut off points for osteoporosis or osteopenia (<-2.5 and <-1, respectively) when using whole-body BMD scores.[4]

Likewise, a study looking at subjects with chronic obstructive pulmonary disease (COPD), a disease which makes patients particularly susceptible to osteoporosis found that whole-body BMD measurements underestimates BMD and osteoporosis cases compared to local DXA measurements in the hip and hip and lumbar spine.[5]

In this analysis, whole-body BMD measurements were examined closely. BMD levels were examined longitudinally to see if whole-body BMD measurements changed with exercise interventions. Significant changes in BMD levels across different groups of exercise interventions were not seen, but it is possible that exercise tends to target certain regions of BMD. For instance, prior literature states that resistance training is particularly effective in preventing spine loss, whereas impact exercise tends to affect hip BMD.[12] Thus, it is possible that participants in the current study did gain BMD scores, it just was not counted for with whole-body BMD measurements.

Furthermore, some evidence suggests that BMD may not be the best indicator of bone health, as it does not measure bone strength. Some literature has proposed the use of "bone quality," which integrates both BMD and bone strength.[1]

4.3 Future Directions

The finding that BMD levels did not change with exercise interventions is inconsistent with prior studies, albeit the literature is sparse. Some studies show that exercise trials are an effective way of improving or maintaining BMD levels.[12] Given that this is the first exercise trial of our knowledge in Black women, more studies are needed to see what types of interventions can improve or maintain BMD levels in this population. Care should be taken to see not only what interventions are needed to improve or maintain BMD levels, but also how long participants need

to stay in the interventions to see results. Most prior studies range from 8 months to one year, whereas the current study had six month interventions.[12]

This study focused on an understudied population and more studies are needed to validate the findings in Black women, particularly Black women that are representative of the entire United States population, rather than only the D.C. area. Further studies should focus on geographical diversity of participants as Vitamin D exposure is thought to influence bone health, as vitamin D. Vitamin D regulates homeostasis of calcium and phosphorus, and it is also known to play a role in mineralization, growth, and remodeling of bone.[14] However, it is thought that the dominant source of vitamin D for most women is sunlight exposure, as dietary sources are derived from foods with limited consumption. Thus, a Black woman from the southern most parts of the United States may have differences in bone health and bone health predictors compared to Black women living in the D.C. area.

Finally, as studies compare local and whole-body BMD measurements, it is essential that a study population like the current one is considered and included. With both the incidence of osteoporosis in minority populations and breast cancer survivorship expected to increase, it is expected that more postmenopausal Black women will be at risk for osteoporosis or osteopenia. Thus, it is imperative the scientific community is committed to finding the best way to measure bone health and wellness in older Black women.

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