# SIX MONTHS OF RESISTANCE TRAINING OR PLYOMETRICS EXERCISE POSITIVELY AFFECTS BONE MINERAL DENSITY AND BONE TURNOVER MARKER RATIOS IN MEN WITH OSTEOPENIA

---

A Thesis Presented to the Faculty of the Graduate School
University of Missouri

---

In Partial Fulfillment
Of the Requirements for the Degree

Master of Science

---

By

ANDREW W. DAWSON

Dr. Pamela Hinton, Thesis Supervisor

July 2011

The undersigned, appointed by the Dean of the Graduate School, have examined the thesis entitled

SIX MONTHS OF RESISTANCE TRAINING OR PLYOMETRICS EXERCISE POSITIVELY AFFECTS BONE MINERAL DENSITY AND BONE TURNOVER MARKER RATIOS IN MEN WITH OSTEOPENIA

Presented by Andrew W. Dawson

A candidate for the degree of Master of Science

And hereby certify that in their opinion is worthy of acceptance

---

Pamela Hinton, PhD

---

John Thyfault, PhD

---

Scott Rector, PhD

ACKNOWLEDGEMENTS

I have no doubt that these last two years have been the most challenging of my life thus far. However, regardless of the long days, early mornings, and late nights (that sometimes resulted in sleep-overs) in the lab, I am glad I did it. Fighting through the challenges of graduate school have made me a better person, and when I look back at all of the knowledge I have gained, skills I have acquired, and lessons I have learned, I will always appreciate graduating from this program.

There are so many people that need to be recognized for helping and supporting me through my pursuit of this master's degree that I could probably add another 10 pages onto this thing. First and foremost, I would like to thank God for blessing me with the strength and determination to succeed in earning my master's degree. Without His help, I would not be where I am today. I would also like to thank my advisor, Dr. Pamela Hinton, for all of her help, advice, and guidance in completing my thesis project and teaching me valuable skills in the lab. With her help, I was able to think critically and improve my writing ability – two skills that were exceptionally critical when working on my thesis project, which will also benefit me for the rest of my life. In addition, I would like to thank Drs. John Thyfault and Scott Rector for serving on my thesis committee and providing their expert advice to improve my thesis project. Thanks to Drs. Chris Hardin and Tom Thomas for their guidance throughout my graduate school journey, as well as helping me establish my assistantships. Thanks to the many other professors that provided their knowledge and expertise in the field to make me a better student: Drs.Tom LaFontaine, Steve Ball, Kevin Fritsche, and many others. I also have to thank all of the graduate students for their help and support, including my lab team: Bob Rogers, Lynn Eaton, Melissa Carter, Peggy Nigh, and Tim Sinak – without their help, collecting all of my data and training our subjects would have been impossible. Of course I can't forget to thank Ryan Puck for providing a friendly competition to see who could finish their thesis first.

I would like to thank my family and friends for their endless support during the past two years. Thanks to my dad, mom, and Dave for always being there to provide encouragement and support of everything I've done. Thanks to my brother, Ben, for always providing comic relief during stressful times, and to my grandparents, Maw Maw and Paw Paw, for always supporting me, as well as reminding me to "never, never, never give up." Last, but certainly not least, I would like to thank my fiancée, Kristen, for her never-ending love, care, encouragement, and patience through this journey. She has been right by my side through all of the ups and downs over the past two years, and I don't think I will ever be able to thank her enough.

TABLE OF CONTENTS

LIST OF FIGURES

**LIST OF TABLES**

ABSTRACT

It is well known that certain types of weight-bearing physical activity and exercise that result in bone loading have positive effects on bone mineral density (BMD). However, there are limited data on the long-term effects of high-impact, weight-bearing exercise interventions on BMD in adult males, particularly in men with osteopenia. **PURPOSE:** To 1) determine the effects of six months of resistance training (RT) or plyometrics (PLYO) exercise on changes in BMD in healthy, recreationally active, males with osteopenia; and 2) determine the effects of six months of RT or PLYO exercise on changes in bone turnover in healthy, recreationally active males with osteopenia. **METHODS**: Twenty-one recreationally active (>4 h/wk of activity) healthy males (25-55 y) with a hip or lumbar spine (L1-L4) T-score between -1.0 to -2.5 standard deviations below the standard mean of a young, healthy adult were randomized into a 6-mo RT (N = 9) or PLYO (N = 8) exercise program. Subjects who qualified, but chose not to participate in the intervention served as controls (CON, N = 4). Dual energy X-ray absorptiometry was used to measure bone area, BMC, and BMD of the lumbar spine (LS) (L1-L4), total left hip (HIP) and whole body (WB). The intensity of the regular weekly RT and PLYO interventions was progressive, consisting of light, moderate, and heavy cycles. RT subjects completed two training sessions/wk on non-consecutive days for 6 mo, consisting of three sets/exercise, which varied in intensity based on their one-repetition maximum. PLYO subjects completed three training sessions/wk on non-consecutive days for 6 mo, accumulating up to 100 jumps. RT and PLYO participants completed 7-d diet and PA logs at baseline and 6 mo to monitor changes in diet or PA during the duration of the study. CON subjects completed a 3-day diet record and 7 day physical activity log at baseline and 6 mo. RT and PLYO subjects consumed a daily

dietary supplement of 1200 mg of calcium and 400 IU of vitamin D. Blood samples were collected between the hours of 6-9 am or biochemical analysis at baseline and 6 mo of the study, after a 10-hr overnight fast and 24 hr prior to any Physical activity . Serum concentrations of osteocalcin (OC), bone-alkaline phosphatase (BAP), tartrate-resistant acid phosphatase isoform 5b (Trap5b) and carboxyterminal telopeptide of type I collagen (CTX) were measured via ELISA to determine bone turnover activity. Two-way ANOVA with repeated measures was used to determine 1) training group (RT, PLYO, CON) and time (baseline, 6 mo) effects on BMD, as well as group by time interactions; and 2) training group (RT, PYLO) and time (baseline, 6 mo) on markers of bone turnover. All statistical analyses were completed using SPSS. **RESULTS**: There was a significant increase in WB BMD from baseline to 6 mo in both the RT and PLYO groups (+1.32 and 0.52 %; $p = 0.070$, respectively). There were no significant changes in any marker of bone turnover. However, a significant increase in the BAP/CTX and OC/CTX ratios from baseline to 6 mo in the RT and PLYO was observed (+29.9 and 35.2%, $p = 0.036$ and 0.077, respectively). **CONCLUSION**: The results of this study are the first to show that participation in 6 mo of RT or PLYO can improve WB BMD and bone turnover ratios in osteopenic men. Since the mineralization of bone is a lengthy process, continued research on the effects of RT and PLYO on bone health is encouraged.

## INTRODUCTION

Osteoporosis and its consequential fractures are a nationally recognized health problem in the United States. Osteoporosis is defined by the World Health Organization as “a systematic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, or a bone mineral density (BMD) of the lumbar spine or femoral neck that is -2.5 standard deviations below the mean for a young adult woman, with a resulting increase in bone fragility and susceptibility to fracture." The precursor to osteoporosis, osteopenia, is characterized by a BMD in the range of -1.0 and -2.5 standard deviations below the young adult mean (49).

In the past, the treatment and prevention of osteoporosis has been focused on females, because of the high rate of bone loss post-menopause, often resulting in debilitating osteoporotic fractures. However, there are currently 2 million males with osteoporosis in the United States, and almost 12 million more with osteopenia (1). Men who endure an osteoporotic fracture have an increased mortality risk (54, 55), with the 12-month mortality rate following a hip fracture being 32% compared to 17% in women (57). Furthermore, it is estimated that the number of men with hip fracture worldwide will reach 1.8 million by 2050 (54, 55), causing osteoporosis in men to become a major concern in the United States.

Costs resulting from osteoporotic fracture are massive, direct health care expenditures ranging from 12-18 billion dollars, with indirect costs from loss of productivity adding to the total cost of care (34). With the prevalence of osteoporosis and osteopenia on the rise coupled with large costs associated with the disease, the economic

burden of osteoporosis and osteopenia is enormous. Thus, with such high costs associated with osteoporotic fracture, prevention is more cost effective than treatment.

**Factors that affect bone health.** After the second decade of life, bone content begins to decline by about 4% per decade (2), and one in five men over the age of 50 years old will suffer an osteoporotic fracture during their lifetime (48, 54). Inadequate attainment of BMD during growth and failure to maintain bone mass during aging are the two primary causes researchers have cited for low BMD in adulthood (12). Therefore, the primary goal during adulthood should be to minimize age−related bone loss.

There are several factors that influence the maintenance of bone health in adulthood including genetics, age-related changes, nutrition, environmental factors, and weight-bearing activity. Although genetics cannot be changed, factors such as nutrition, environment/life-style, and weight-bearing physical activity can be modified to reduce the risk of developing osteopenia or osteoporosis and improve overall bone health. For example, obtaining adequate calcium has been shown to attenuate age-related bone loss, i.e., men who consume amounts of calcium closer to the RDA have greater BMD (17). Likewise, blood levels of serum 25-hydroxyvitamin D (25(OH)D), or vitamin D, has been shown to be significantly related to hip fracture risk. As a result, elderly adults are recommended to obtain serum levels of 60 nmol 25(OH)D to lower hip fracture risk (65). In addition to nutritional factors, lifestyle and behavioral factors play a role in bone health during adulthood. For example, smoking and excessive alcohol consumption have been shown to negatively affect bone health (17, 20, 79, 84). Thus, maintaining a diet which supports bone health (i.e. calcium, vitamin D, etc.) and avoiding environmental

risk factors such as smoking, may provide a valuable method to positively affect bone mass later in life.

In conjunction with these nutritional and lifestyle behavior modifications, participation in weight-bearing exercise may be an important factor in preventing the loss of bone mass during aging in adult males. Although weight – bearing exercise during adulthood may not be as effective at promoting bone formation as compared to periods of growth, small gains in BMD may be possible to achieve in adult men (74, 98, 121). Of equal importance, the bone mass gained during growth may be maintained with weight-bearing exercise, attenuating the age-related bone loss commonly seen during progressive aging (58). However, there are very limited data on the long-term effects of high-impact, weight-bearing exercise interventions on BMD in adult males. In fact, there are only a few studies that exceed six months of resistance training (RT), and virtually no studies examining the effects of a plyometrics (PLYO) exercise on BMD in men, particularly men with osteopenia. Therefore, research is needed that determines if long-term, high-impact, weight-bearing exercise, i.e. RT and PLYO, can induce positive changes in the bone remodeling cycle, which in turn may promote positive changes in BMD in adult men with osteopenia.

**The remodeling cycle.** The remodeling cycle is the tightly coupled process of activation, resorption, reversal, and formation within bone cells of the skeleton which determines the structural integrity of bone. Bone remodeling is a continuous process throughout life, through which pockets of old bone are replaced by new bone to maintain bone structure and mineral homeostasis (23). Groups of osteoclasts and osteoblasts, or a bone remodeling units (BRUs), carry out these processes of activation, resorption,

reversal, and formation phases of bone remodeling (13) – a systematic cycle takes approximately 3-6 months to complete (29). For instance, the resorption phase lasts approximately 2-4 weeks, and the completion of the formation phase can take up to six months to complete (23).

Bone remodeling does not negatively affect bone unless it becomes excessive, or a negative balance occurs. After the completion of skeletal growth during young adulthood, the capacity of BRUs to rapidly and effectively model and remodel bone is diminished, resulting in a negative balance of bone turnover (102, 103). In men, this negative balance is primarily due to reduced bone formation from the BRUs (63), but can also be attributed to an increase in the volume of bone resorption by the BRU (70), resulting in a negative balance favoring resorption over formation (70). This negative balance promotes structural decay during progressive aging (128), leading to increased risk of bone fragility. Thus, effective strategies are needed to prevent the compromise in bone‟s material properties as a result of aging, thus minimizing bone loss and preventing osteoporosis later in life.

**Characteristics of mechanical loading to induce an osteogenic response.** It is well known that certain types of physical activity and exercise that involve bone-loading have positive effects on BMD. However, certain exercises seem to be more effective at inducing osteogenesis and improving bone strength than others. For instance, it is necessary for an exercise regimen to include the appropriate activity type, intensity, frequency, and duration to obtain the most beneficial osteogenic gains. For example, previous animal research has shown that mechanical forces have osteogenic effects only if the stress to bone is dynamic in nature (43, 64), i.e. intermittent strain versus

continuous strain on bone. In addition, the intensity of loading, which includes the magnitude and rate of strain, also affect the osteogenic effect of certain bone-loading exercises. In order to be osteogenic, the magnitude of strain must surpass a "minimum effective strain (MES)" threshold, which causes bone modeling to increase bone mass (31). Furthermore, the rate of loading also plays a crucial role in the skeleton"s adaptive response to loading. Previous research has shown that increasing the frequency of loading while maintaining a constant strain magnitude can cause a significant increase in bone formation (112), suggesting that both strain magnitude and frequency play pivotal roles in the osteogenic response of bone to exercise. Lastly, the frequency and duration of bone-loading activities are crucial for the best osteogenic bone response, as bone can become "deaf" to the mechanical signaling of bone if the exercise is not broken up into shorter, more frequent bouts (50). For example, response to applied loads saturates quickly, and that a small exposure ($\leq$ 100) to dynamic strain appears to be equally as sufficient to produce an osteogenic stimulus compared to additional applied strains. Of equal importance, an adequate amount of rest time is needed to restore mechanosensitivity to desensitized bone cells and elicit the greatest osteogenic response to loading. For instance, approximately 10-14 seconds between repetitions, eight hours between loading sessions, and one week of rest for every six weeks of exercise is needed to restore mechanosensitivity to bone cells (88). Thus, if extrapolated to humans, these principles should be incorporated as the foundation exercise interventions to promote bone formation, as they should confer the greatest osteogenic response.

**Mechanism of how exercise affects bone.** The human skeleton contains an intrinsic biological control system that directs bone formation to areas that experience

high mechanical stress, or strains, thus strengthening the skeleton in highly stressed regions (31, 115). Julius Wolff first recognized that bone‟s architecture can be affected by mechanical loads, and as a result, he developed “Wolff‟s law” in 1892 (125). Wolff‟s law states that bone adapts its form and function to the stimuli applied to the skeleton (125). This system responds to strains detected by bone is also called the bone‟s “mechanostat” (31). The mechanostat involves cells within the bone tissue detecting and responding to mechanical loads in regions of high mechanical strain (31). It is necessary for the applied mechanical load to exceed a “MES” threshold to provide the necessary stimulus to activate bone remodeling (31).

At the cellular level, this mechanosensory function operates by a network of bone lining cells, osteoblasts, and osteocytes that transduce stress signals to activate resorption and/or formation (15, 22, 61). Specifically, osteocytes within the mineralized matrix are in direct communication with one another and surface osteoblasts (including bone lining cells) through gap junctions due to an extracellular fluid shift when mechanical stimulus is applied (15, 31, 61, 115). This fluid shift associated with mechanical strain produces a rapid flux of intracellular calcium across these junctions, which is thought to facilitate the transmission of information regulating modeling and remodeling between osteoblasts and osteocytes (22, 61). The mechanosensory response in areas of high strain that surpass this threshold causes bone formation to increase and reduced bone resorption, resulting in increased cross-sectional area and reduced porosity, both of which strengthen the bone (31, 61, 115). Therefore, in order to have an effective exercise intervention, mechanical loading must past the threshold that causes stimuli to regulate bone remodeling, such as resistance training or plyometrics. Passing this threshold is crucial to preserve, or even

improve, bone integrity and strength by positively regulating the balance between formation and resorption. Thus, the type of exercise participated in during adulthood is a crucial factor in promoting positive, osteogenic response in bone.

**Physical activity and bone health during adulthood.** It is well known that certain types of physical activity and exercise that result in bone loading have positive effects on BMD. As previously mentioned, weight-bearing physical activities have been shown to have beneficial effects on bone health across the age spectrum. Likewise, physical inactivity and/or participation in non-weight bearing activities may be detrimental to skeletal health in adulthood, due to the lack of high-impact, weight bearing activity that could stimulate an osteogenic response. This is best seen in cases of skeletal unloading, or removal of weight-bearing loading on the skeleton, i.e., bed rest, spinal cord injury, or space-flight. Once high-impact physical activity is absent, detrimental effects on skeletal health occur. Thus, physical inactivity and participation in activities that do not surpass the minimum threshold to promote an osteogenic response remain a risk factor for low BMD, as BMD will continue to decline throughout the aging process. Consequently, a regular high-impact, weight-bearing exercise regimen should be followed. The studies that have been completed provide promising results describing the positive effect of physical activity on bone health, and leave many valuable questions to be answered by future research.

**Resistance training and adult BMD.** There is evidence that resistance training intervention positively affects regional BMD in both younger (7, 98), middle- (74), and older-aged men (14, 67, 72, 74, 98). For example, Ryan et al (98) found a significant increase in BMD at the hip including the femoral neck, Ward's triangle and greater

trochanter, as well as total body BMC and leg BMC after a six month whole-body RT exercise intervention in a cohort of younger adult men (n = 10) and women (n=7) ($P<0.05$). However, total body and lumbar spine BMD did not change with RT.

Unlike young adulthood, middle- and late-adulthood is a time when BMD begins to decline with age. However, exercise interventions have shown that it is still possible to maintain, and potentially gain BMD in middle-and late adulthood (60, 74, 121). For example, Menkes et al (74) found that BMD increased in the femoral neck BMD by 3.8 % and by 2% in the lumbar spine BMD in previously inactive middle-aged men, ages 54-61, after four months of RT. Similarly, Vincent et al (121) investigated the effects of 6 mo of high- or low-intensity resistance exercise on BMD in older adults, ages 60-83 y, and found a significant increase in femoral neck BMD compared to baseline. Furthermore, Kukuljan et al (60) revealed that a 12 multi-component exercise program (RT and impact exercise) resulted in a 1.8% gain in femoral neck BMD relative to no-exercise ($p < 0.001$) in older men, ages 50-79 y.

**Plyometrics and adult BMD.** While there is some evidence that plyometrics, or jump training, positively affects BMD in women, there are no studies examining the effects of a plyometrics intervention on BMD in men. However, Welsh et al (123), found that 12 months of high-impact step-aerobics significantly increased (+2.21%) greater trochanter BMD in men and women between the ages of 50 and 73 years old. In addition, femoral neck BMD increased non-significantly. However, femoral neck BMD decreased by -1.9% in the control group, which was significantly different from the change in the exercise group (123). Furthermore, total body BMD did not change in the exercise group, but decreased by 0.79% in the controls (123). The results provided from Welsh et al

(123) supports that high-impact aerobic exercise in men over 50 years old is reasonable and effective at increasing proximal femur BMD and maintaining whole body BMD (123).

The previous results suggest that RT and PLYO not only can maintain BMD in men, but also may increase BMD throughout adulthood. Regular participation in RT exercise may improve bone health in adult men, and consequently reduce the risk of developing osteopenia and osteoporosis. Furthermore, participation in high-impact step-aerobics positively affected bone health in adult men, providing optimistic results for a future study to examine the long term effects of structured plyometrics exercise on BMD in men. Unfortunately, studies examining the effects of RT or PLYO on BMD in adult men with osteopenia are nonexistent. Thus, there is a critical need for more research to determine if these results can be extrapolated to men with osteopenia, suggesting an effective treatment for osteopenia and prevention of osteoporosis.

**Bone turnover markers, physical activity, and BMD.** In clinical and research settings, BMD measurement is used primarily as an indicator for risk of osteoporotic fracture (73). However, a BMD measurement, such as by dual X-ray absorptiometry (DXA), only provides a static representation of bone structure and metabolism – a slow process that may take several months to see noticeable change in BMD, thus limiting its usefulness (68). Fortunately, BMD measurements are not the only method to assess changes in bone activity, as bone biochemical markers that reflect bone turnover can also be utilized as a valuable method to track cellular changes in bone. Bone turnover markers can be used to monitor the acute effects of exercise on bone remodeling, and to investigate the mechanisms behind exercise-induced changes in bone mass (68). In

particular, the measurement of biochemical markers of bone turnover may reveal the direction of balance between bone formation and resorption, potentially elucidating the mechanism behind increased BMD prior to noticeable changes occurring. For example, Bone-alkaline phosphatase (BAP) and osteocalcin (OC) are both products of active osteoblasts which are expressed during different phases of osteoblast development, and are considered to reflect different aspects of osteoblast function and of bone formation (13, 104). In contrast, tartrate-resistant acid phosphatase (TRAP5b) and carboxyterminal telopeptide of type I collagen (CTX) are considered markers of bone resorption. TRAP5b is an osteoclast-specific enzyme that is released into blood during bone resorption, which reflects the number and activity of osteoclasts (37). In addition, CTX is released into circulation during the degradation of type I collagen, with the highest contribution coming from bone (109).

**Long-term effects of physical activity on markers of bone turnover.** There have been several studies examining the effects of short-term physical activity on bone turnover markers in men. However, there are far fewer data on the long – term effects of physical activity and bone turnover in adult men. Of the available studies, there is a trend for longitudinal weight-bearing exercise interventions to result in an increase (32, 74, 100, 121), or no change (99), in bone formation markers in adult men. In addition, a reduction in biomarkers of bone resorption has also been reported as a result of a long-term weight-bearing exercise intervention (123).

These changes are likely due to the type of exercise utilized within the study, as use of weight-bearing or high-impact activity seems to promote a positive balance in bone turnover. For example, Fujimura et al (32) examined the effects of four months of high

intensity RT on bone turnover in 17 Oriental males, 23-31 y of age. In the RT group, serum osteocalcin (OC) concentration and bone-specific alkaline phosphatase (BAP) activity were significantly increased within the first month after the beginning of resistance exercise training, and they remained elevated throughout the training period. However, Fujimura et al (32) found that there was no significant change in plasma pro-collagen type-I C-terminal concentration, suggesting that the RT enhanced bone formation without prior bone resorption. Likewise, studies from both Menkes et al (74) and Sartorio et al (100) revealed an increase in BAP in elderly men (mean age = 59 and 72 y, respectively) who strength trained three times per week for 16 weeks compared to non-exercise controls. Moreover, Menkes et al (74) also detected a rise in serum OC in the exercise group, as well as an increase in lumbar spine and femoral neck BMD (2% and 3.8%, respectively $p < 0.05$). Furthermore, both research groups observed either a decrease (100), or no change (74) in markers of bone resorption, further suggesting the positive influence of RT on bone turnover. Instead of measuring biomarkers of bone formation, Welsh et al (123) revealed that pyridinoline (PYD) and deoxypyridinoline (DPD) crosslinks, urinary markers of bone resorption, were significantly reduced compared to baseline (-19.0%, $P = 0.0019$ and -20.0%, $P = 0.021$, respectively) in men and women (ages 50-73 y) after 6 months of tri-weekly, high-impact step-aerobics classes.

In addition to the importance of the type of activity, the intensity of training also appears to act as an influential factor in the response of bone turnover markers to exercise interventions. For example, Vincent and Braith (121) investigated the effects of 6 mo of high- or low-intensity RT on BMD and biochemical markers of bone turnover in adult

men and women aged 60-83 y. Subjects were either assigned to high-intensity RT (80% of 1RM), low-intensity RT (50% of 1RM), or a non-exercise control group. Vincent and Braith (121) found that both high- and low-intensity RT interventions significantly increased serum concentrations of OC compared to the non-exercise control group. Moreover, the high-intensity RT group: 1) had a greater increase in OC than the low-intensity group (+39.0% vs. +25.1%, respectively, $P < 0.05$); 2) had a significant increase in BAP (+7.1%, $P < 0.05$); and 3) femoral neck BMD increased significantly by 1.96% ($P < 0.05$) (121). The results presented by Vincent and Braith (121) suggest that exercise magnitude of bone loading may play a critical role in the response of bone turnover to exercise interventions.

The above studies suggest that weight-bearing exercise can induce changes in the bone turnover process that have the potential to positively affect BMD. Further studies are needed to determine if alterations in concentrations of both markers of bone formation and resorption are associated with beneficial changes in BMD in adult men. In addition, there are no data on the effects of a structured plyometrics exercise intervention on markers of bone resorption or formation in men. Thus, additional studies are needed to assess serum markers of bone formation and resorption after a longitudinal plyometrics exercise intervention to help elucidate the value of an alternate – type of exercise program to improve BMD in adult males. Moreover, due to the absence of data on exercise interventions in men with known osteopenia, a study is needed which describes the long-term effects resistance training or plyometrics exercise intervention on serum markers of bone turnover in osteopenic men. This may help demonstrate the relationship between long-term bone turnover markers and changes in BMD due to weight-bearing

and high-impact exercise in osteopenic men, helping to construct an effective treatment to improve BMD for this at risk population.

**Limitations of previous studies.** There is an overall lack of data on the effects of exercise interventions on BMD in adult men. However, of the studies that do examine exercise and BMD, there are several limitations that leave many questions unanswered regarding the effectiveness of exercise interventions role in improving bone mass in adult men.

Beside the limitation that relatively few studies have examined the effects of RT in adult men, it is likely that the study design of these previous interventions prevented changes in BMD from reaching their full potential. Specifically, all of the previous studies used exercises that did not optimally load, e.g. directly strain, the hip or spine – two of the most significant areas to improve bone density. For example, Ryan et al (98) had their subjects perform leg press, chest press, leg curl, latissimus pull-down, leg extension, military press, seated row, triceps pushdown, abdominal crunch, biceps curl, and sit-ups, but only observed changes in hip BMD. This may be due to minimal, if not absent, compression of the spine to produce an osteogenic response. Likewise, the use of resistance machines for exercise intervention likely provided minimal, if no, strain on the hip and/or lumbar spine (74). Therefore, a study was needed that used exercises that directly loaded the skeleton.

Comparable to RT, there are no studies examining the effects of structured plyometrics exercise on BMD in adult men. Although Welsh et al (123) documented the effects step aerobics, there are no studies examining a structured plyometrics program designed with the appropriate type, intensity, frequency, and duration of exercise to cause a maximal

osteogenic response, as suggested by the influential work of Hurt and Liskova (43, 45, 46, 64), Rubin and Lanyon (62, 95, 96), and Turner and Robling (89, 91, 115). Due to osteogenic potential of plyometrics exercise, a study was needed that incorporated these fundamental principles into their exercise intervention to truly determine the effects of high-impact exercise on bone mineral density in adult men.

Most importantly, there are no studies examining the effects of high-impact, weight bearing exercise interventions on BMD and markers of bone turnover in otherwise healthy adult men with osteopenia – a group with elevated risk of developing osteoporosis. Thus, a study was needed to elucidate the effects of an exercise intervention to develop an effective, low-cost approach to maintain, or even improve, bone density for these at risk men.

**Specific Aims.** The specific aims of this study were to 1) determine the effects of chronic resistance training or plyometrics exercise intervention on changes in BMD in healthy, recreationally active, males with osteopenia; and 2) determine the effects of chronic resistance training or plyometrics exercise on changes in bone turnover in healthy, recreationally active males with osteopenia.

**Hypotheses.** Our hypotheses were four-fold: 1) six months of RT or PLYO exercise intervention will maintain, or improve, BMD in osteopenic men; 2) six months of PLYO will cause a greater increase in BMD compared to RT in osteopenic men due to the osteogenic potential of PLYO exercise; 3) six months of RT or PLYO exercise intervention will result in an elevation of serum markers of bone formation and a reduction of serum markers of bone resorption compared to baseline in osteopenic men; and 4) six months of PLYO will result in a greater increase of bone formation markers,

and decrease in resorption markers, compared to RT in osteopenic men due to the osteogenic potential of PLYO exercise.

## MATERIALS AND METHODS

The effects of six-months of RT or PLYO exercise intervention on changes in BMD and markers of bone turnover in males with osteopenia were examined using a longitudinal intervention study design (**Figure 1**).

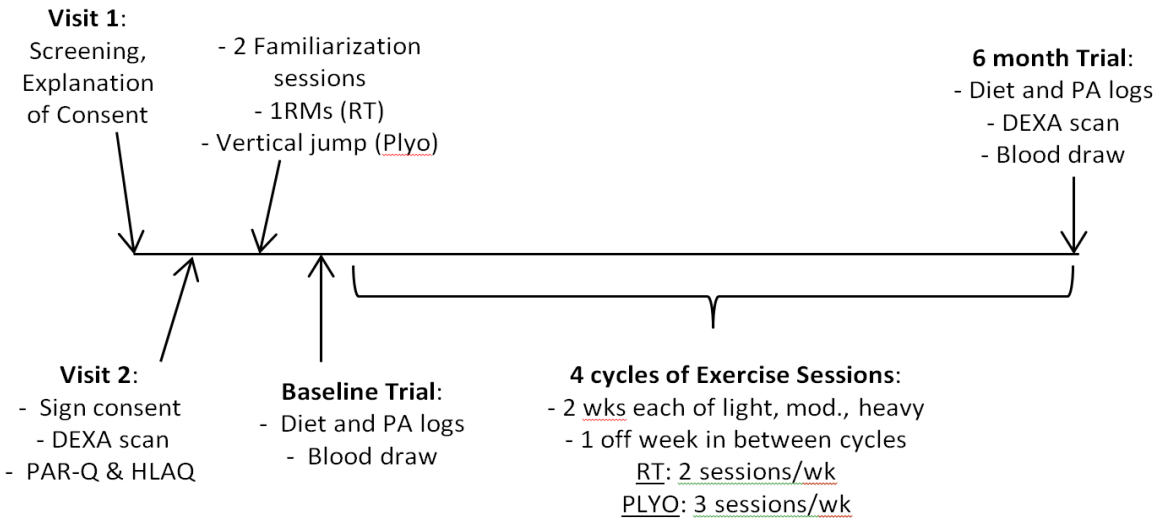



**FIGURE 1. Timeline of experimental design describing milestones within the six-month exercise intervention.**

**Experimental subjects.** Twenty-one recreationally active (>4 h/wk of activity) healthy males, ages ranging from 25-55 years, with a hip or lumbar spine (L1-L4) T-score between -1.0 to -2.5 standard deviations below the standard mean of a young, healthy adult participated in this study. Subjects who qualified for the study, but chose not to participate, served as a control group (n = 4) to examine the efficacy of the exercise intervention to increase BMD six months post qualification. Subjects were recruited from the Columbia, MO region through the University of Missouri Info email, bulletin board advertisements, local track and athletic clubs, flyers, and local sporting goods stores. To

be eligible for the study, participants had to be male aged 25-65 y, with a BMD T-score between 1.0 – 2.5 standard deviations below the average. In addition, participants also needed to be active, participating in at least four hours of structured, moderate – intensity, physical activity per week. Exclusion criteria included a current or previous medical condition affecting bone health (including osteoporosis, or a T-score of < -2.5), currently taking any medications that affect bone metabolism or prevent exercise, a joint disorder, cigarette smoking, excess alcohol consumption (> 3 drinks/d, or 21 drinks/wk), and/or currently taking anti-inflammatory steroids. Prior to initial screening, all participants were informed of any risks associated with this study and give written consent to participate. After consent, subjects completed anthropometric measures, medical and Historical Leisure Activity questionnaires, and dual energy X-ray absorptiometry (DXA) scans of the whole body, lumbar spine, and total hip to determine bone area ($cm^2$), bone mineral content (BMC, g), and bone mineral density (BMD, $g/cm^2$). Study participants who completed the screening process, but chose not to participate in the exercise intervention were asked to undergo an additional DXA scan approximately six months after screening to be used as non-intervention controls. These non-intervention controls were used to assess the changes in BMD associated with participation in the exercise intervention group vs. a non-participating group after six months‟ time. In addition, control subjects provided data on previous participation in physical activity since their original screening, as well as a 7 day diet log describing nutrient intakes during an average week. Approval for the study was obtained from the University of Missouri-Columbia Health Sciences Institutional Research Board.

**Interventions.** All training sessions were performed at the McKee Gymnasium Exercise Center located on the University of Missouri campus. Participants were randomized into resistance training (RT) or plyometrics (PLYO) exercise interventions. Each study participant completed two familiarization sessions instructed by qualified study personnel to ensure safe and proper technique of all exercises performed. Prior to exercise sessions, subjects in both groups completed 10 minutes of a cardiovascular warm-up, and 5 minutes of stretching and cool-down post exercise training.

The exercise interventions developed for this study were based upon the principle that certain exercises are more effective at inducing osteogenesis and improving bone strength than others. Particularly, previous research has shown that it is necessary for an exercise regimen to include exercise that is dynamic in nature, with the magnitude of loading surpassing the minimum effective strain (MES) threshold to result in the greatest osteogenic response (31, 43-46, 64, 115). In addition, shorter, more frequent bouts of loading ,with adequate amounts of rest time within a loading cycle, is needed to restore mechanosensitivity to desensitized bone cells and elicit the greatest osteogenic response to loading.

**Resistance training.** Subjects randomized into the RT intervention completed two training sessions per week on non-consecutive days for six months. The RT exercises included: squats, military press, deadlifts, bent over row, lunges, and calf raises. To account for strength adaptations as a result of strength training improvements, prior to and every six weeks during the six month intervention subjects performed a maximal strength test, or one-repetition max (1RM). This test involved a warm-up set of 5-10 repetitions, equal to 40-60% of the perceived maximal repetition for each exercise. After

a brief rest period, a second set of 3-5 repetitions at an intensity between 60-80% of the subject‟s perceived maximal repetition was performed. Subsequent attempts to reach a 1RM were performed by increasing weight prior to each set performed until failure was achieved between 3-5 attempts. One-repetition maximums were performed for the squat, military press, and deadlift; while modified maximums (10 repetitions) were calculated for the bent over row, lunge, and calf raise exercises in which 1RMs are not safe or commonly performed.

During the regular weekly RT sessions, exercise training consisted of light, moderate, and heavy workloads during the six week training cycle. The first two weeks of each cycle, or light cycle, consisted of one warm-up set (10 repetitions at 20% of 1RM) and three moderate intensity sets (10 repetitions at 50% 1RM). Weeks 3-4 incorporated one warm-up set (10 repetitions at 20% 1RM), two moderate sets (10 repetitions of 60% 1RM), and one high intensity set (6-8 repetitions of 70-75% 1RM). During weeks 5-6, subjects completed one warm-up set (10 repetitions at 20% 1RM), two moderate intensity sets (10 repetitions of 60% 1RM), and one heavy set (3-5 repetitions at 80-90% 1RM). Week seven was used as a rest week.

**Plyometrics.** Subjects randomized to the plyometrics exercise intervention completed three training sessions per week on non-consecutive days for six months. The plyometrics jumps included: squat jumps, forward hops, split squat jumps, lateral box push offs, bounding, lateral bounding, lateral hurdle, zig-zag hops, box-drill, single leg lateral hurdle, and progressive depth jumps (10-100cm).

The intensity of the regular weekly plyometrics intervention was progressive, consisting of light, moderate, and heavy cycles. The first two weeks were the light cycle,

consisting of four sets of jumps incorporating 10 repetitions each (squat jump, forward hop, split squats, and lateral box push off). Moderate intensity weeks 3-4 consisted of eight sets of jumping exercise, including 10 repetitions each (squat jumps, forward hops, split squat jumps, lateral box push offs, bounding, lateral bounding, lateral hurdle, zig-zag hops). Weeks 5-6 were the heavy cycle, with 10 sets of jumps, incorporating 10 repetitions each (includes progressive depth jumps). A rest period of 10 s was incorporated in between each repetition.

**Anthropometric data.** The anthropometric data collected from study participants included: age, body weight, height, and percent body fat. The participant"s height was measured to the nearest 0.5 cm and body mass was measured to the nearest 0.05 kg. These measures were used to determine BMI ($kg/m^2$) for each subject. Percent body fat was measured by using DXA.

**Questionnaires.** Study participants completed a medical history questionnaire, physical activity readiness questionnaire (PAR-Q), and a modified Historical Leisure Activity Questionnaire (HLAQ) (59). The medical history questionnaire and PAR-Q were used as a screening tool to determine the safety or possible risk of exercising for each subject based upon their answers to specific health history questions. The HLAQ was used to collect data on historical leisure time physical activity across the lifespan, and consists of: type of activity, ages of participation in that activity, hours per week, weeks per year, and level of competition. All subjects were required to provide accurate information about their medical and sports/activity history and meet all of the inclusion/exclusion criteria to participate.

**Bone mineral content, density, and body composition.** Bone density scans were performed to determine eligibility and baseline measurements, as well as to determine changes related to participation, or no participation, in exercise interventions after six months. Dual energy X-ray absorptiometry (DXA) (Hologic QDR 4500, Waltham, MA) was used to measure bone area, BMC, and BMD of the lumbar spine (L1-L4), total left hip and whole body. Definitions for osteoporosis and osteopenia from the World Health Organization (WHO) were used to categorize participants as having normal BMD (> -1.0 standard deviations (SD)), osteopenia (< -1.0 SD, > -2.5 SD), or osteoporosis (≤ -2.5 SD) of the spine or hip as established for a young, adult population (49). Areal BMD ($g \bullet cm^{-2}$) was calculated from bone area ($cm^2$) and BMC in grams (g) by the software supplied with the DXA scanner. The measurement of bone area was used to determine if changes are due to density or content.

**Diet and physical activity monitoring.** Exercise intervention participants completed 7-day diet and physical activity logs at baseline and six months to monitor changes in diet or physical activity during the duration of the study. In addition, control subjects completed a 3-day diet record and 7 day physical activity log. Diet logs were analyzed using the analysis program Food Processor 8.0 (ESHA Research, Salem, OR). Daily energy expenditure from reported physical activity was calculated from each participant‟s activity log using The Compendium of Physical Activities (5). Subjects chose a standardized meal to consume the evening prior to the baseline acute exercise training session. This meal was repeated prior to the six month acute exercise session to control for the same dietary nutrient intake prior to acute exercise testing. On the day of the exercise session, subjects consumed a liquid meal replacement (16 fluid ounces)

(Wal-Mart Stores, Bentonville, AR) four hours prior to exercise testing. This provided a universal control meal for all subjects prior to exercise testing, thus assuring results from the exercise-intervention were not influenced by an uncontrolled meal prior to treatment.

**Calcium and vitamin D supplementation.** All intervention subjects consumed a daily dietary supplement of 1200 mg of calcium and 400 IU of vitamin D (Nature Made Nutritional Products, Mission Hills, CA) to ensure that each subject received 100% of the daily recommended intake of each nutrient. In addition, the amount of calcium and vitamin D consumed by control subjects was examined from the 3-d diet record to determine the amount of each nutrient was consumed by each subject.

**Blood samples.** Blood samples were collected for biochemical analysis at baseline and six months of the study. The samples were collected at the Exercise Physiology laboratory at the University of Missouri after a 10 – hour overnight fast and 24 hours prior to any exercise between the hours of 6-9 am to control for diurnal variation. Trained study personnel used a butterfly needle (Angel Wing 23G x 3/4 in. /12 in., Kendall, Mansfield, MA) to collect a 15-ml blood sample from the antecubital vein. Collected samples were put into SST tubes and centrifuged at 4$^{o}$C for 15 minutes at 2000 g (Marathon 21000R centrifuge, Fisher Scientific, Pittsburgh, PA). The plasma and serum samples were immediately transferred to 1.5-ml cryogenic vials (Fisher Scientific, Pittsburgh, PA) and stored at -80 $^{o}$C for later analysis.

**Bone turnover analysis.** Bone turnover markers were only examined in intervention subjects. Markers of bone formation are products of active osteoblasts expressed during different phases of osteoblast development, and are considered to reflect different aspects of osteoblast function and of bone formation (13, 104). Osteocalcin

(OC) and bone-alkaline phosphatase (BAP) were the two markers of bone formation measured in this study. OC is a bone matrix protein synthesized by mature osteoblasts, and constitutes roughly 15% of the non-collagenous bone matrix, whereas bone-alkaline phosphatase (BAP) is a membrane-bound enzyme byproduct of osteoblast activity (13, 21).

Tartrate-resistant acid phosphatase isoform 5b (Trap5b) and carboxyterminal telopeptide of type I collagen (CTX) were used to assess bone resorption in this study. Trap-5b is an osteoclast-specific enzyme that is released into blood during bone resorption. This biomarker reflects the number and activity of osteoclasts. CTX is released into circulation during the degradation of type I collagen, with the highest contribution from bone (13, 21).

The concentrations of bone turnover markers previously mentioned were measured in serum via commercially available ELISA kits. The BAP, OC, and Trap5b kits were obtained from Quidel Corporation (San Diego, CA) and had intra-assay CVs of 3.9, 4.8, and 2.2%, respectively. The ELISA kit for CTX was obtained from Immunodiagnostic systems (Fountain Hills, AZ) and had an intra-assay CV of 1.7%. Bone turnover marker assays were evaluated in duplicate and all samples for a study participant were performed in a single run to eliminate inter-assay variability. In addition, the ratios of formation to resorption markers were examined.

**Statistical analysis**. Descriptive statistics (means ± standard deviation) were performed on demographic and anthropometric variables. Pearson correlation matrices were used to investigate potential covariates. In addition, the assumptions of ANOVA

were tested to determine if the collected data was independent, normally distributed, and maintained homogeneity of variance. The assumption of independence was satisfied since the sample populations in this study were independent of one another, or in other words, their outcomes did not affect each other. To check for normality of the collected data, histograms, P-P plots, and Q-Q plots were visually inspected for normal distribution. In addition, the Kolomogrov-Smirnov test was used to further determine normality. After inspection, CTX and Trap5b concentrations, as well as BAP/TRAP5b , OC/TRAP5b, and OC/CTX ratios, were not normally distributed. Thus, the aforementioned variables were $\log_{10}$ transformed, which resulted in normal distributions. The homogeneity of variance, or homoscedasticity, was evaluated by Mauchly's test. All data were determined to meet the assumption of homoscedasticity.

Once the assumptions of ANOVA were met, one-way analysis of variance (ANOVA) was performed on BMD, diet, and physical activity to determine the difference among group means at baseline. Two-way ANOVA with repeated measures was used to determine training group (RT, PLYO, CON) and time (baseline, 6 mo) effects on BMD, as well as group by time interactions. An additional two-way ANOVA was performed to determine the effects of training group (RT, PYLO) and time (baseline, 6 mo) on markers of bone turnover. All statistical analysis was performed on SPSS (SPSS/11.0, Chicago, IL). P Values $\leq 0.10$ were considered statistically significant.

## RESULTS

The characteristics of the study participants, including anthropometrics, and physical activity from baseline to six months are listed in **Table 1**; data are expressed as means ± standard error. Twenty-one of the 22 subjects completed either RT (n = 9), PLYO (n = 8), or CON (n = 4) in this study. One control subject was excluded due to the addition of bone-loading physical activity during the period prior to follow-up testing. In addition, only two CON subjects received a baseline DXA scan.

Groups were not significantly different in age, height, body weight, BMI, or percent body fat at baseline (**Table 1**). In addition, physical activity (hr/wk) accumulated in addition to the intervention was not different between PLYO, RT, and CON at baseline and six months.

TABLE 1. Baseline characteristics

| Characteristics | Resistance Training (n = 9) | Plyometrics (n = 8) | Control (n = 4)† |
|---|---|---|---|
| **Age (y)** | | | |
| Baseline | 38 ± 3 | 44 ± 3 | 40 ± 5 |
| Post- 6 mo | - | - | - |
| **Height (m)** | | | |
| Baseline | 1.82 ± 0.03 | 1.76 ± 0.02 | 1.77 ± 0.01 |
| Post- 6 mo | - | - | - |
| **Weight (kg)** | | | |
| Baseline | 79.31 ± 4.27 | 70.01 ± 3.78 | 72.40 ± 1.43 |
| Post- 6 mo | 79.32 ± 4.01 | 71.23 ± 3.53 | 72.16 ± 1.48 |
| **BMI ($kg/m^2$)** | | | |
| Baseline | 23.8 ± 1.2 | 22.5 ± 1.1 | 23.2 ± 0.6 |
| Post- 6 mo | 23.8 ± 1.0 | 23.0 ± 1.1 | 23.1 ± 0.5 |
| **Body Fat (%)** | | | |
| Baseline | 18.5 ± 1.7 | 17.5 ± 1.7 | 16.6 ± 1.1 |
| Post- 6 mo | 17.7 ± 1.5 | 17.6 ± 1.4 | 20.0 ± 1.0 |
| **LBM (kg)** | | | |
| Baseline | 61.00 ± 2.91 | 57.63 ± 2.23 | 55.17 ± 0.05 |
| Post- 6 mo | 61.33 ± 3.12 | 57.31 ± 2.46 | 54.83 ± 0.68 |
| **PA hrs/wk** | | | |
| Baseline | 1 ± 1 | 2 ± 1 | 1 ± 0 |
| Post- 6 mo | 1 ± 0 | 2 ± 2 | 1 ± 0 |
| **PA kcal/wk** | | | |
| Baseline | 572 ± 115 | 740 ± 355 | 50 ± 11 |
| Post- 6 mo | 358 ± 76 | 658 ± 335 | 198 ± 0 |

Values displayed as mean ± S.E. BMI: body mass index; LBM: whole body lean body mass; PA: physical activity; S.E.: standard error of measurement

***Dietary intake***

RT and PLYO groups did not differ significantly in total energy, protein, carbohydrate, fat, and vitamin D intakes at baseline or post-six months of intervention as assessed by one-way ANOVA (**Table 2**). In addition, there were no differences among groups (RT, PLYO, and CON) in intakes of the aforementioned nutrients after six months of treatment (**Table 2**), meaning that each participants in each group consumed similar quantities of each nutrient. However, calcium intake differed significantly between the RT and PLYO groups at baseline, as the RT group consumed greater amounts of calcium compared to the PLYO group (1171 mg vs. 750 mg, respectively; $p = 0.042$). In contrast, there was no significant difference found in calcium intake post-six months of intervention due to supplemental calcium (1200 mg/d); however, there was a significant difference between the exercise groups (RT and PLYO) and control group, with the exercise groups consuming more calcium compared to the CON group (1779 mg and 1956 mg vs. 560 mg, respectively; $p = 0.002$).

TABLE 2. Total energy, macronutrient nutrient, calcium†, and vitamin D† intakes.

| | RT (n = 9) | PLYO (n = 8) | CON (n = 4) |
|---|---|---|---|
| **Total Energy** | | | |
| Baseline | 2579 ± 267 | 1985 ± 301 | - |
| Post -6 mo | 2565 ± 154 | 2083 ± 249 | 2265 ± 612 |
| **Protein (g)** | | | |
| Baseline | 108 ± 11 | 81 ± 13 | - |
| Post -6 mo | 121 ± 14 | 88 ± 9 | 95 ± 22 |
| **Carbohydrate (g)** | | | |
| Baseline | 329 ± 26 | 259 ± 58 | - |
| Post -6 mo | 307 ± 14 | 258 ± 34 | 239 ± 66 |
| **Fat (g)** | | | |
| Baseline | 90 ± 15 | 68 ± 8 | - |
| Post -6 mo | 100 ± 10 | 77 ± 8 | 93 ± 31 |
| **Calcium (mg)** | | | |
| Baseline | 1171 ± 96 [a] | 654 ± 141 | - |
| Post -6 mo | 1779 ± 85 [b] | 1933 ± 40 [b] | 559 ± 134 |
| **Vitamin D (IU)** | | | |
| Baseline | 150 ± 34 | 125 ± 48 | - |
| Post-6 mo | 473 ± 84 | 525 ± 56 | 29 ± 16 |

Values displayed as mean ± S.E. S.E.: standard error of measurement; %Δ: percent change. † Post-6 mo treatment group averages include 1200 mg of calcium and 400 IU of vitamin D supplementation. [a]: Significantly different from PLYO at baseline, one-way ANOVA, $p < 0.05$. [b]: significantly different from CON, one-way anova, $p < 0.05$.

***Bone mineral density***

Individuals randomized to RT or PLY did not differ in whole body, total left hip, or lumbar spine BMD at baseline (**Table 3**). Mean percent change in WB BMD was 1.32 ± 1.14 and 0.52 ± 2.00 percent in the RT and PLYO groups, respectively. A significant main effect for time for whole body BMD was found (**Table 3**; **Figure 2**, $p = 0.070$), suggesting that the exercise interventions increased BMD from baseline to six months; however, there were no group by time interactions, meaning that both exercises increased WB BMD from baseline to six months of intervention. Hip and LS BMD did not change significantly after the 6-mo interventions (Tables 5 and 6).

In addition to comparing the effects of RT and PLYO on BMD, we also examined changes in BMD following the exercise intervention relative to the non-exercise-intervention control group. A repeated measures two-way ANOVA that included both exercise interventions (RT, PLYO) and the control group (CON) was used to test for differences in changes in BMD (**Tables 7-9)**. Unexpectedly, a main effect for time for WB (**Figure 3**, $p = 0.059$) and LS BMD (**Figure 4**, $p = 0.051$) was found, while there was no group by time interaction found – suggesting that the non-exercise control group also had gains in BMD from baseline to six months of treatment.

TABLE 3. Changes in bone mineral density of the whole body, hip, and lumbar spine after six months of resistance training or plyometrics in men with osteopenia

| **Regional BMD ($g/cm^2$)** | **RT (n = 9)‡** | **PLYO (n = 8)** | **CON (n = 4)†** |
|---|---|---|---|
| **Whole Body** | | | |
| Baseline | 1.160 ± 0.018 | 1.126 ± 0.023 | 1.122 ± 0.026 |
| Post -6 mo treatment***** | 1.172 ± 0.018 | 1.132 ± 0.025 | 1.143 ±0.012 |
| %Δ | 1.32 ± 0.40 | 0.52 ± 0.07 | 1.71 ± 2.58 |
| **Left Hip** | | | |
| Baseline | 0.902 ± 0.018 | 0.905 ± 0.038 | 0.984 ± 0.051 |
| Post -6 mo treatment | 0.906 ± 0.020 | 0.902 ± 0.037 | 0.969 ± 0.044 |
| %Δ | 0.40 ± 0.44 | -0.30 ± 0.85 | -1.33 ± 1.31 |
| **Lumbar Spine ($L_1$-$L_4$)** | | | |
| Baseline | 0.950 ± 0.020 | 0.901 ± 0.023 | 0.943 ± 0.007 |
| Post -6 mo treatment***** | 0.962 ± 0.020 | 0.905 ± 0.023 | 0.956 ± 0.005 |
| %Δ | 1.24 ± 0.79 | 0.49 ± 0.65 | 1.33 ± 0.35 |

Values displayed as mean ± S.E. BMD: bone mineral density; S.E.: standard error of measurement; %Δ: percent change. ‡ Whole body (n = 8) † Whole body (n = 2).
***** Significant main effect for time. $P < 0.100$

TABLE 4. Whole body bone mineral density (g/cm$^2$) for RT and PLY – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 1.143 ± 0.015 | 0.981 – 1.239 | 0.070 |
| | Post – Six months | 1.152 ± 0.015 * | 0.972 – 1.274 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 8) | 1.166 ± 0.021 | 1.095 – 1.274 | 0.225 |
| | PLYO (n = 8) | 1.129 ± 0.021 | 0.972 – 1.201 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 1.160 ± 0.021 | 1.172 ± 0.022 | 0.513 |
| | PLYO | 1.126 ± 0.021 | 1.132 ± 0.022 | |

Values displayed as mean ± SE. N = 16.
* Significant main effect for time, repeated measures two-way ANOVA, $p \leq 0.10$

TABLE 5. Total left hip bone mineral density (g/cm$^2$) for RT and PLY– Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 0.913 ± 0.020 | 0.690 – 1.048 | 0.938 |
| | Post – Six months | 0.913 ± 0.020 | 0.0674 – 1.013 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 0.923 ± 0.028 | 0.845 – 0.999 | 0.649 |
| | PLYO (n = 8) | 0.904 ± 0.030 | 0.674 – 1.048 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 0.921 ± 0.028 | 0.924 ± 0.028 | 0.444 |
| | PLYO | 0.905 ± 0.030 | 0.902 ± 0.030 | |

Values displayed as mean ± SE. N = 17.
No significant main effects or group by time interaction

TABLE 6. Lumbar spine ($L_1$-$L_4$) bone mineral density ($g/cm^2$) for RT and PLY – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 0.923 ± 0.015 | 0.800 – 1.048 | 0.166 |
| | Post – Six months | 0.930 ± 0.015 | 0.814 – 1.055 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 0.950 ± 0.022 | 0.835 – 1.055 | 0.136 |
| | PLYO (n = 8) | 0.904 ± 0.021 | 0.800 – 0.999 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 0.945 ± 0.021 | 0.954 ± 0.021 | 0.579 |
| | PLYO | 0.901 ± 0.022 | 0.905 ± 0.022 | |

Values displayed as mean ± SE. N = 17.
No significant main effects or group by time interaction

TABLE 7. Whole body bone mineral density ($g/cm^2$) for RT, PLY, and CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 1.136 ± 0.016 | 0.981 -1.147 | 0.059 |
| | Post – 6 mo | 1.148 ± 0.017 * | 0.972 – 1.274 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 8) | 1.166 ± 0.021 | 1.095 – 1.274 | 0.414 |
| | PLYO (n = 8) | 1.129 ± 0.021 | 0.972 – 1.201 | |
| | CON (n = 2) | 1.131 ± 0.040 | 1.096 – 1.147 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 1.160 ± 0.021 | 1.172 ± 0.022 | 0.702 |
| | PLYO | 1.126 ± 0.021 | 1.132 ± 0.022 | |
| | CON | 1.121 ± 0.039 | 1.140 ± 0.041 | |

Values displayed as mean ± SE.
* Significant main effect for time, repeated measures two-way ANOVA, $p \leq 0.10$

TABLE 8. Total left hip bone mineral density ($g/cm^2$) for RT, PLY, and CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 0.937 ± 0.020 | 0.690 – 1.048 | 0.317 |
| | Post – 6 mo | 0.932 ± 0.020 | 0.674 – 1.030 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 0.904 ± 0.030 | 0.845 – 0.999 | |
| | PLYO (n = 8) | 0.923 ± 0.028 | 0.674 – 1.048 | 0.397 |
| | CON (n = 4) | 0.976 ± 0.043 | 0.830 – 1.045 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 0.921 ± 0.029 | 0.924 ± 0.028 | |
| | PLYO | 0.905 ± 0.031 | 0.902 ± 0.030 | 0.313 |
| | CON | 0.983 ± 0.044 | 0.996 ± 0.042 | |

Values displayed as mean ± SE. RT (N = 9), PLYO (N = 8), CON (N = 4)
No significant main effects or group by time interaction

TABLE 9. Lumbar spine ($L_1$-$L_4$) bone mineral density ($g/cm^2$) for RT, PLY, and CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 0.937 ± 0.020 | 0.800 – 1.048 | 0.051 |
| | Post – 6 mo | 0.932 ± 0.020 * | 0.814 – 1.055 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 0.950 ± 0.022 | 0.835 – 1.055 | 0.207 |
| | PLYO (n = 8) | 0.904 ± 0.021 | 0.800 – 0.999 | |
| | CON (n = 4) | 0.949 ± 0.028 | 0.924 – 0.963 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 0.945 ± 0.021 | 0.954 ± 0.021 | |
| | PLYO | 0.901 ± 0.022 | 0.905 ± 0.022 | 0.723 |
| | CON | 0.943 ± 0.028 | 0.955 ± 0.029 | |

Values displayed as mean ± SE. RT (N = 9), PLYO (N = 8), CON (N = 4)
* Significant main effect for time, repeated measures two-way ANOVA, $p \leq 0.10$

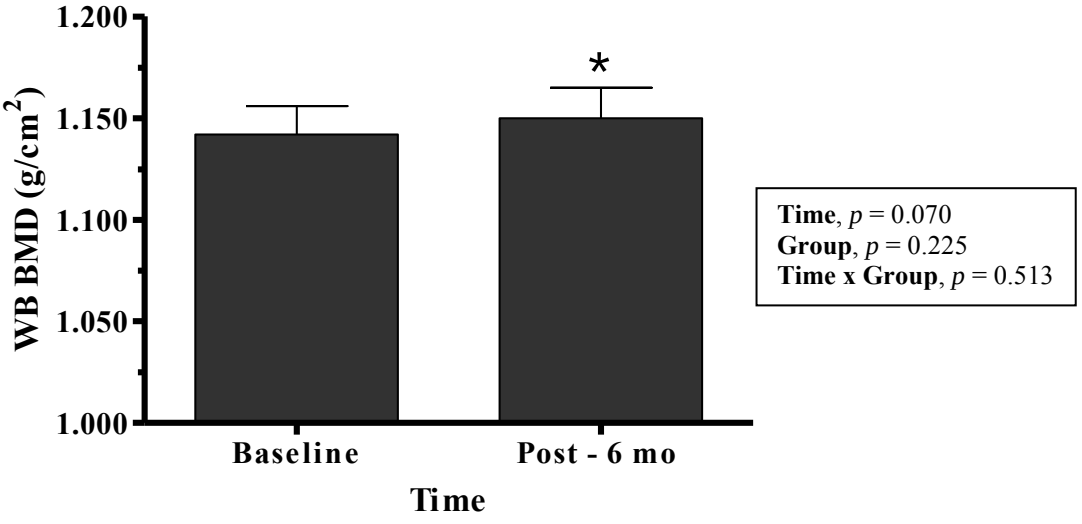



**FIGURE 2. Two-way repeated measures ANOVA – main effect for time for whole body bone mineral density (WB BMD) and intervention groups (RT and PLYO); *P* = 0.070**

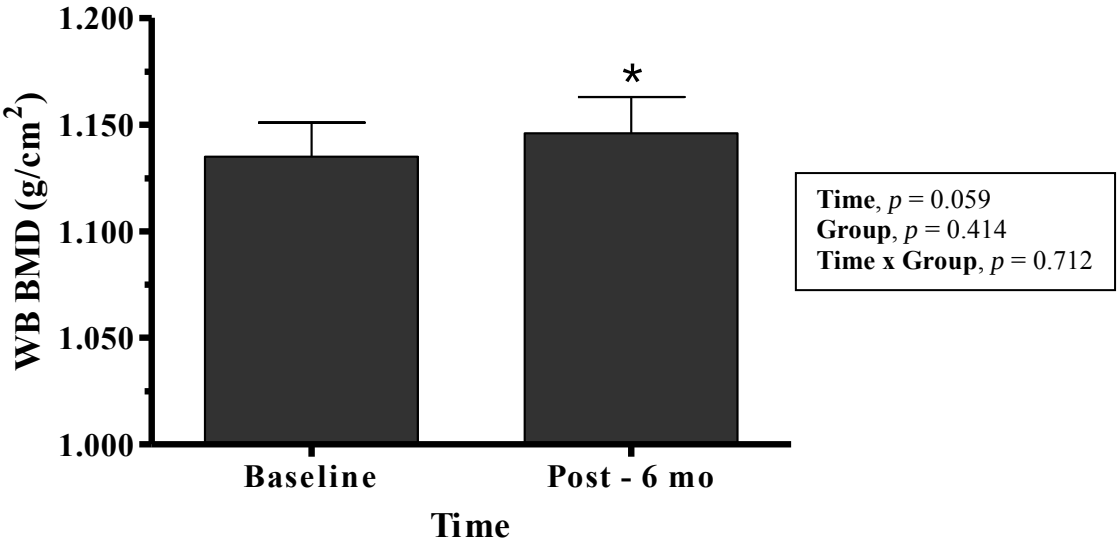



**FIGURE 3. Two-way repeated measures ANOVA – main effect for time for whole body bone mineral density (WB BMD) and all groups (RT, PLYO, and CON); *P* = 0.059**

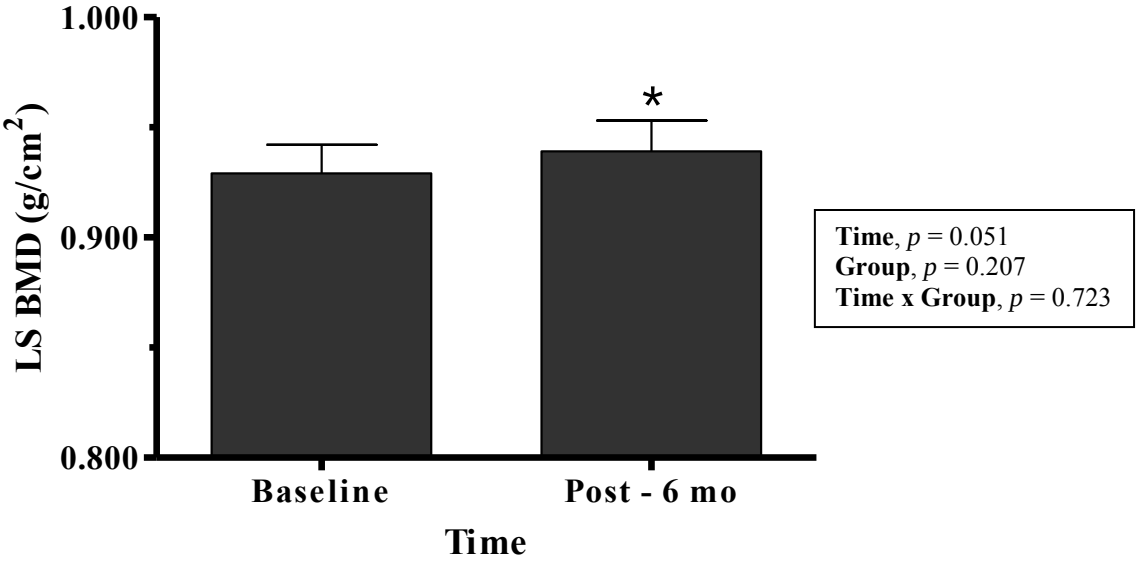



**FIGURE 4. Two-way repeated measures ANOVA – main effect for time for lumbar spine ($L_1$-$L_4$) bone mineral density (LS BMD) and all groups (RT, PLYO, and CON); *P* = 0.051**

***Bone mineral content***

There were no group differences in whole body, total left hip, or lumbar spine BMC at baseline (**Table 10**). Two-way repeated measures ANOVA for BMC and can be found in **Appendix A.** A significant main effect for time for whole body BMC was found in RT and PLYO groups (**Table A4**), suggesting the exercise increased BMC from baseline to six months. In addition, a significant main effect for time for WB and LS BMC was found for all groups (**Tables A10** and **A12**, respectively), meaning WB and LS BMC increased significantly from baseline to post-six months after the interventions – including the CON group.

TABLE 10. Changes in bone mineral content of the whole body, hip, and lumbar spine after six months of resistance training or plyometrics in men with osteopenia

| **Regional BMC (g)** | **RT (n = 9) ‡** | **PLYO (n = 8)** | **CON (n = 4)†** |
|---|---|---|---|
| **Whole Body** | | | |
| Baseline | 2670.48 ± 126.14 | 2477.20 ± 70.42 | 2367.21 ± 138.48 |
| Post -6 mo treatment* | 2733.07 ± 127.08 | 2479.70 ± 77.92 | 2468.37 ± 55.63 |
| %Δ | 1.32 ± 0.47 | 0.53 ± 0.78 | 2.23 ± 1.98 |
| **Left Hip** | | | |
| Baseline | 35.52 ± 2.01 | 36.46 ± 1.67 | 36.05 ± 0.64 |
| Post -6 mo treatment | 36.09 ± 2.10 | 36.70 ± 1.84 | 36.03 ± 0.61 |
| %Δ | 1.47 ± 0.53 | 0.58 ± 1.41 | 0.0429 ± 2.32 |
| **Lumbar Spine ($L_1$-$L_4$)** | | | |
| Baseline | 67.00 ± 3.23 | 62.19 ± 2.38 | 61.91 ± 2.14 |
| Post -6 mo treatment* | 67.61 ± 3.18 | 62.19 ± 2.02 | 63.06 ± 2.21 |
| %Δ | 0.92 ± 0.64 | 0.16 ± 0.72 | 1.89 ± 1.40 |

Values displayed as mean ± S.E. BMC: bone mineral content; S.E.: standard error of measurement; %Δ: percent change. ‡ Whole body (n = 8) † Whole body (n = 2).
* Significant main effect for time. $P < 0.100$

***Bone area***

Individuals randomized to RT or PLY did not differ in whole body, total left hip, or lumbar spine bone area at baseline (**Table 11**). Two-way repeated measures ANOVA for bone area can be found in **Appendix A.** Average change in bone area of the whole body, hip, and lumbar spine was less than 1% (**Table 11**), confirming that the changes in bone density were not artifacts of errors in the DXA scans, i.e., if the follow-up DXA scan measures a larger, or smaller, area of bone examined than what was measured at baseline, it may produce false changes in BMD, as bone area is not expected to change during adulthood.

TABLE 11. Changes in bone mineral area of the whole body, hip, and lumbar spine after six months of resistance training or plyometrics in men with osteopenia.

| **Regional Area ($cm^2$)** | **RT (n = 9) ‡** | **PLYO (n = 8)** | **CON (n = 4)†** |
|---|---|---|---|
| **Whole Body** | | | |
| Baseline | 2306.60 ± 84.81 | 2201.85 ± 50.06 | 2109.27 ± 75.42 |
| Post -6 mo treatment | 2329.61 ± 81.09 | 2191.84 ± 49.06 | 2161.08 ± 62.62 |
| %Δ | 1.07 ± 0.61 | -0.44 ± 0.36 | 0.53 ± 0.0.59 |
| **Left Hip** | | | |
| Baseline | 39.27 ± 1.81 | 40.36 ± 1.09 | 36.96 ± 2.12 |
| Post -6 mo treatment | 39.69 ± 1.78 | 40.73 ± 1.34 | 37.52 ± 2.45 |
| %Δ | 1.06 ± 0.37 | 0.84 ± 1.03 | 1.38 ± 1.07 |
| **Lumbar Spine** | | | |
| Baseline | 70.58 ± 2.96 | 68.84 ± 1.52 | 65.61 ± 1.83 |
| Post -6 mo treatment | 70.40 ± 3.14 | 68.60 ± 1.45 | 65.96 ± 2.06 |
| %Δ | -0.30 ± 0.47 | -0.32 ± 0.60 | 0.54 ± 1.48 |

Values displayed as mean ± S.E. S.E.: standard error of measurement; %Δ: percent change ‡ Whole body (n = 8) † Whole body (n = 2).

***Bone turnover markers***

Groups were not significantly different in OC, BAP, TRAP5b, or CTX concentrations, as assessed by one-way ANOVA (**Table 12**).There were no significant main effects for time for any marker of bone turnover (**Tables 13-16**), suggesting that neither RT or PLYO exercise caused a statistically significant change in markers of bone turnover from baseline to six months of intervention.

TABLE 12. Changes in markers of bone turnover after six months of resistance training or plyometrics in men with osteopenia

| **Bone Turnover Markers** | **Resistance Training (n = 9)** | **Plyometrics (n = 7)** |
|---|---|---|
| **Osteocalcin (ng/mL)** | | |
| Baseline | 6.9 ± 1.2 | 6.5 ± 0.7 |
| Post -6 mo treatment | 7.1 ± 0.9 | 6.4 ± 0.5 |
| %Δ | 23.7 ± 19.9 | 1.5 ± 9.1 |
| **Bone Alkaline Phosphatase (U/L)** | | |
| Baseline | 25.3 ± 2.7 | 22.2 ± 1.8 |
| Post -6 mo treatment | 27.7 ± 2.8 | 23.1 ± 2.0 |
| %Δ | 14.9 ± 12.6 | 4.0 ± 4.2 |
| **Carboxy-terminal collagen crosslinks (ng/mL)** | | |
| Baseline | 0.379 ± 0.10 | 0.223 ± 0.02 |
| Post -6 mo treatment | 0.315 ± 0.05 | 0.187 ± 0.02 |
| %Δ | -1.97 ± 13.42 | -13.80 ± 8.14 |
| **Tartrate-Resistance Acid Phosphatase 5b (U/L)** | | |
| Baseline | 3.6 ± 1.3 | 2.4 ± 0.5 |
| Post-6 mo treatment | 2.9 ± 0.8 | 2.4 ± 0.4 |
| %Δ | 15.8 ± 26.5 | 16.1 ± 25.5 |

Values displayed as mean ± S.E. S.E.: standard error of measurement; %Δ: percent change

TABLE 13. Osteocalcin (ng/L) – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 6.5 ± 0.8 | 3.2 – 14.6 | 0.926 |
| | Post – Six months | 6.6 ± 0.6 | 4.5 – 11.4 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n= 9) | 7.0 ± 0.6 | 3.2 – 14.6 | 0.399 |
| | PLYO (n = 7) | 6.2 ± 0.7 | 4.1 – 9.0 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 6.9 ± 1.0 | 7.0 ± 0.7 | 0.959 |
| | PLYO | 6.2 ± 1.1 | 6.2 ± 0.8 | |

Values displayed as mean ± SE. N = 16.
No significant main effects or group by time interaction

TABLE 14. Bone-alkaline phosphatase (U/L) – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 23.7 ± 1.7 | 14.6 – 42.5 | 0.369 |
| | Post – 6 mo | 25.4 ± 1.8 | 15.15 – 45.3 | |
| **Group** | | | **Range** | ***p* – value** |
| | RT (n = 9) | 26.5 ± 1.8 | 15.5 – 42.5 | 0.237 |
| | PLYO (n = 7) | 22.6 ± 1.7 | 14.6 – 30.8 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 25.3 ± 2.2 | 27.7 ± 2.4 | 0.668 |
| | PLYO | 22.2 ± 2.6 | 23.1 ± 2.7 | |

Values displayed as mean ± SE. N = 16.
No significant main effects or group by time interaction

TABLE 15. Tartrate-resistant acid phosphatase isoform-5b (ng/mL) – Repeated measures two-way ANOVA †

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 3.0 ± 0.8 | 1.1 – 12.2 | 0.774 |
| | Post – 6 mo | 2.6 ± 0.5 | 0.9 – 8.5 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 5.0 ± 0.1 | 0.2 – 12.2 | 0.760 |
| | PLYO (n= 7) | 2.4 ± 0.5 | 0.9 – 4.9 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 3.6 ± 1.3 | 2.9 ± 0.8 | 0.755 |
| | PLYO | 2.4 ± 0.5 | 2.4 ± 0.4 | |

Values displayed as mean ± SE. N = 16.
† Data Log10 transformed
No significant main effects or group by time interaction

TABLE 16. Carboxy-terminal collagen crosslinks (ng/mL) – Repeated measures two-way ANOVA †

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 0.291 ± 0.050 | 0.134 – 0.964 | 0.145 |
| | Post – 6 mo | 0.657 ± 0.044 | 0.104 – 0.482 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 0.325 ± 0.065 | 0.104– 0.964 | 0.093 |
| | PLYO (n = 7) | 0.206 ± 0.017 | 0.133 – 0.321 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 0.350 ± 0.086 | 0.301 ± 0.044 | 0.638 |
| | PLYO | 0.222 ± 0.018 | 0.190 ± 0.015 | |

Values displayed as mean ± SE. N = 16.
† Data Log10 transformed
No significant main effects or group by time interaction

***Bone turnover ratios***

The RT and PLYO groups were not significantly different in any bone turnover marker ratio at baseline, as assessed by one-way ANOVA. There was a significant main effect for time for the BAP/CTX ratio (**Table 19**; **Figure 5**, $p = 0.036$) and OC/CTX ratio (**Table 21**; **Figure 6**, $p = 0.059$), as the BAP/CTX and OC/CTX ratios increased significantly from baseline to six months – suggesting that the exercise interventions increased serum levels of BAP and OC, in combination with reductions serum levels of CTX.

TABLE 17. Changes in bone turnover ratios after six months of resistance training or plyometrics in men with osteopenia

| **Bone Turnover Markers** | **Resistance Training (n = 9)** | **Plyometrics (n = 7)** |
|---|---|---|
| **BAP/Trap5b** | | |
| Baseline | 12.1 ± 2.0 | 12.7 ± 2.2 |
| Post -6 mo treatment | 19.7 ± 8.7 | 12.5 ± 2.2 |
| %Δ | 54.9 ± 40.2 | 14.0 ± 18.2 |
| **BAP/CTX** | | |
| Baseline | 85.0 ± 12.7 | 103.2 ± 10.7 |
| Post -6 mo treatment* | 108.4 ± 22.4 | 128.0 ± 15.0 |
| %Δ | 29.9 ± 18.2 | 26.5 ± 11.4 |
| **OC/Trap5b** | | |
| Baseline | 3.0 ± 0.5 | 3.6 ± 2.8 |
| Post -6 mo treatment | 4.9 ± 1.93 | 3.8 ± 2.8 |
| %Δ | 60.2 ± 87.6 | 3.9 ± 17.4 |
| **OC/CTX** | | |
| Baseline | 20.7 ± 1.7 | 28.3 ± 3.2 |
| Post-6 mo treatment* | 26.6 ± 4.3 | 34.1 ± 3.1 |
| %Δ | 35.2 ± 25.2 | 28.0 ± 16.3 |

Values displayed as mean ± S.E. S.E.: standard error of measurement; %Δ: percent change

* Significant main effect for time. $P < 0.100$

TABLE 18. BAP/TRAP5b ratio – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 12.4 ± 1.5 | 3.0 – 20.3 | 0.427 |
| | Post – Six months | 16.6 ± 5.0 | 3.7 – 88.2 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 15.9 ± 3.9 | 3.5 – 20.3 | 0.592 |
| | PLYO (n = 7) | 12.6 ± 4.5 | 3.0 – 19.9 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 12.1 ± 2.0 | 19.7 ± 6.7 | 0.399 |
| | PLYO | 12.7 ± 2.3 | 12.5 ± 7.6 | |

Values displayed as mean ± SE. N = 16.
No significant main effects or group by time interaction

TABLE 19. BAP/CTX ratio – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 94.1 ± 8.6 | 39.3 – 156.4 | 0.036 |
| | Post – 6 mo | 118.2 ± 14.4** | 49.2 – 254.5 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 96.7 ± 14.1 | 39.3 – 254.5 | 0.390 |
| | PLYO (n = 7) | 115.6 ± 16.0 | 66.3 – 189.4 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 85.0 ± 11.4 | 108.4 ± 19.0 | 0.947 |
| | PLYO | 103.2 ± 12.9 | 128.0 ± 21.6 | |

Values displayed as mean ± SE. N = 16.
** Significant main effect for time, repeated measures two-way ANOVA $p < 0.05$

TABLE 20. OC/TRAP5b ratio – Repeated measures two-way ANOVA †

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 3.2 ± 0.4 | 1.2 – 5.3 | 0.588 |
| | Post – 6 mo | 4.4 ± 1.2 | 0.7 – 19.7 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 3.9 ± 1.2 | 0.7 – 19.7 | 0.891 |
| | PLYO (n = 7) | 3.7 ± 0.9 | 1.1 – 9.3 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 3.0 ± 0.5 | 4.8 ± 1.9 | 0.654 |
| | PLYO | 3.6 ± 0.7 | 3.8 ± 1.1 | |

Values displayed as mean ± SE. N = 16.
† Data Log10 transformed
No significant main effects or group by time interaction

TABLE 21. OC/CTX ratio – Repeated measures two-way ANOVA

| **Time*** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 24.0 ± 1.9 | 13.4 – 40.9 | 0.077 |
| | Post – 6 mo* | 29.9 ± 2.9 | 9.7 – 47.2 | |
| **Group *** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 20.7 ± 1.7 | 9.7 – 47.2 | 0.047 |
| | PLYO (n = 7) | 28.3 ± 3.2 | 19.4 – 44.3 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 20.7 ± 2.3 | 26.6 ± 3.7 | 0.991 |
| | PLYO | 28.3 ± 2.6 | 34.1 ± 4.2 | |

Values displayed as mean ± SE. N = 16.
* Significant main effect for time, repeated measures two-way ANOVA, $p \leq 0.10$
* Significant main effect for group, repeated measures two-way ANOVA, $p \leq 0.05$

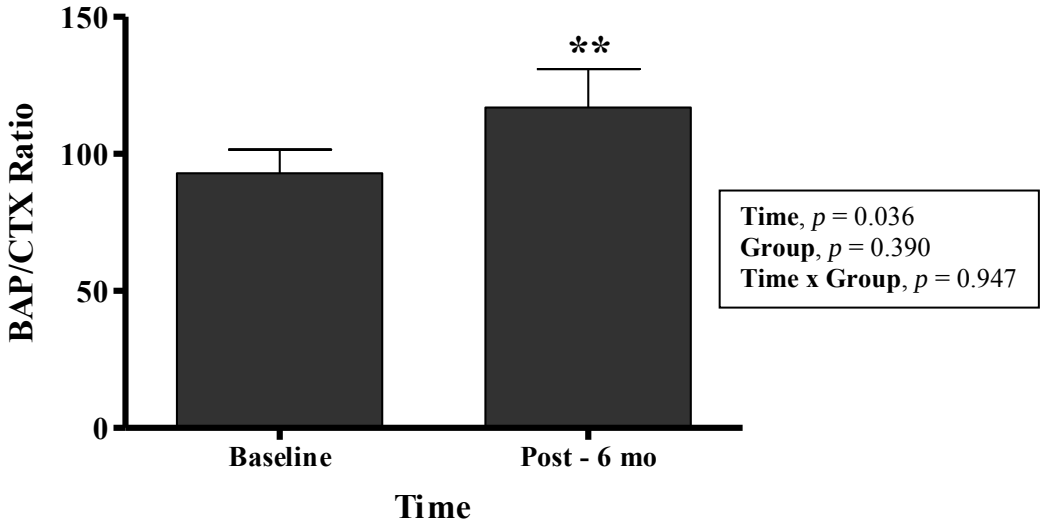



**FIGURE 5. Two-way repeated measures ANOVA – main effect for time for bone-alkalkine phosphatase to carboxy-terminal collagen crosslinks ratio and exercise intervention groups. *P* = 0.036**

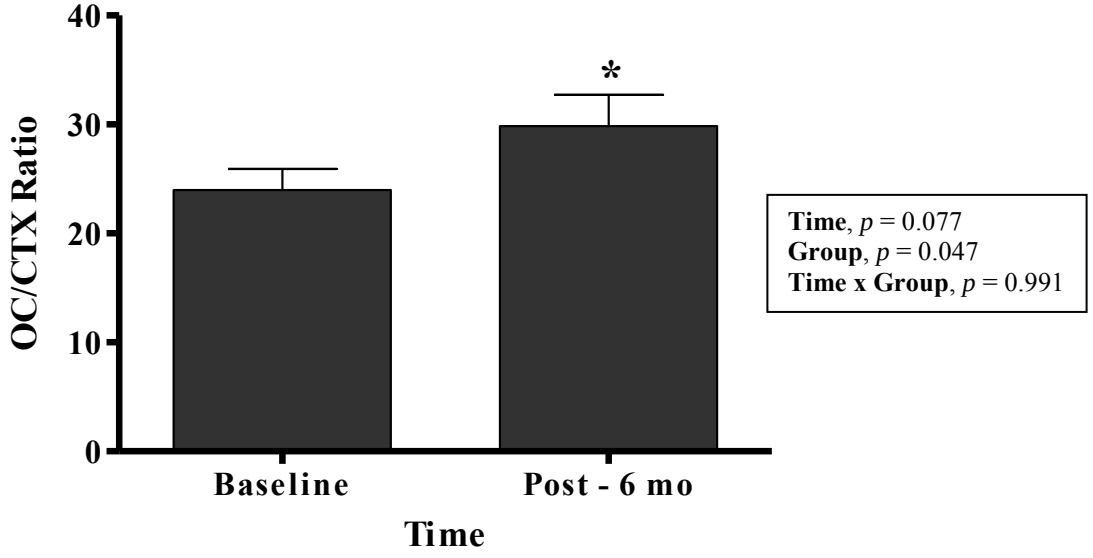



**FIGURE 6. Two-way repeated measures ANOVA – main effect for time osteocalcin to carboxy-terminal collagen crosslinks ratio and exercise intervention groups. *P* = 0.077**

## DISCUSSION

The purpose of this six-month longitudinal intervention study was to 1) determine the effects of resistance training (RT) or plyometrics (PLYO) exercise intervention on changes in bone mineral density (BMD) in healthy, recreationally active, males with osteopenia; and 2) determine the effects of resistance training or plyometrics exercise on changes in bone turnover in healthy, recreationally active males with osteopenia. The results of this study are novel, as there is no available data on the chronic effects of exercise and bone health in men with osteopenia.

Our results revealed a significant increase in whole body BMD from baseline to six months in the resistance training and plyometrics intervention groups when combined. In addition, an increase over time with no differences between groups for whole body (WB) and lumbar spine (LS) BMD was found when comparing the RT and PLYO groups to a non-intervention control group. Furthermore, we found an increase over time with no differences between groups for the bone-alkaline phosphatase to carboxy-terminal collagen crosslinks ratio (BAP/CTX) and osteocalcin to carboxy-terminal collagen crosslinks ratio (OC/CTX) from baseline to six months in the RT and PLYO exercise intervention groups, meaning the exercise interventions improved the BAP/CTX and OC/CTX ratios. However, no single serum marker of bone formation or resorption was significantly elevated in RT or PLYO.

**Effects of six months of resistance training or plyometrics exercise intervention on bone mineral density in males with osteopenia.** Our first hypothesis was that six months of RT or PLYO exercise intervention would maintain, or improve, BMD in osteopenic men compared to a non-exercise control group. We first examined

the effects of RT or PLYO on BMD via repeated measures two-way ANOVA. Our results revealed a significant increase in WB BMD from baseline to six months of exercise intervention in both groups (**Figure 2**; $p = 0.070$). Specifically, the average WB BMD increased 1.32 (± 1.14) and 0.52 (± 2.00) percent in the RT and PLYO groups, respectively (**Table 3**). In comparison to our results, several previous research studies found differing results on the effects of exercise intervention on WB BMD (14, 98, 123). For example, Ryan et al (98) found that WB BMD did not change after six months of RT, consisting of exercise three times per week (12-15 RMs) on 11 pneumatic exercise machines. Likewise, in a study by Welsh et al (123), high-impact aerobics (including stepping and jumping), completed 2-3 d/wk, did not significantly change WB BMD exercise group. However, the control group had a 0.79% reduction in WB BMD in the CON. Furthermore, previous studies have shown that several months (4-12 mo) of resistance training exercise has positive effects on LS and hip BMD (74, 98, 121). However, we did not see any significant changes in left hip (HIP) or LS BMD for either group. This is may be due to the lengthy process of the bone turnover cycle and bone mineralization. The process of bone turnover has been suggested to take approximately three to six months to complete one cycle (29). For example, the sequential stages of activation, resorption, and reversal can take up to one, four, and two weeks, respectively (23, 29). Moreover, the process of bone mineralization by osteoblasts, also known as the bone formation phase, can take up to six months to complete (23, 29). Furthermore, it has also been suggested that it may take up to a year in order to be able to detect a gain in BMD due to increase in bone mineralization via dual X-ray absorptiometry (DXA). Thus, examining RT or PLYO for a longer duration may produce greater changes in BMD that

would be detectable via DXA scan. In addition, the low sample size in our study may have caused it to be under-powered, thus resulting in a lack of significance in our statistical analysis. However, our results are encouraging, as WB BMD increased over the six month intervention time period when groups were combined in the RMANOVA . Furthermore, the repeated measures two-way ANOVA revealed a minor trend for LS BMD in both groups (**Table 6**; $p = 0.166$). Although not currently significant, continuation of the RT and PLYO intervention may result in a significant gain in LS BMD at a later time.

After six months of exercise, WB BMD increased 1.32 (± 1.14) and 0.52 (± 2.00) percent in the RT and PLYO, respectively, and LS BMD increased 1.24 ± 0.79 and 0.49 ± 0.65, respectively (**Table 3)**. Robling et al (91) previously found that mechanically loading the ulna of adult rats for 16 weeks produced a 5% gain in BMD, which resulted in a 64% increase in ulnar bone strength and 94% increase in energy absorbed before fracture. Thus, small gains in BMD can confer great gains in bone strength. Piper et al (83) completed a review of bisphosphonate therapy on improvements in BMD. In the studies that examined only men, bisphosphonate therapies showed improvements in BMD ranging from 0.9 – 4.8, 1.4 – 3.5, and 3.7 – 8% increases in hip, femoral neck, and LS, respectively, after 1-3 years of drug therapy. However, bisphosphonate therapy has been associated with serious side-effects, including osteonecrosis of the jaw, gastrointestinal problems, joint and bone pain, and an over-impaired remodeling cycle (53, 97). Although our exercise interventions did not produce significant changes in the LS or hip after six months of treatment, they may produce similar positive effects in BMD after a year of treatment. In addition, exercise is generally associated with positive,

rather than negative, "side-effects", such as lean muscle mass hypertrophy and increased strength. Thus, examining RT and PLYO for a longer duration may result in positive changes in BMD – without the negative side effects as seen with drug therapy.

Most importantly, these data are the first to show resistance training and plyometrics as effective interventions to improve WB BMD in osteopenic men. Thus, these promising results suggest that further investigation on the effectiveness of RT and PLYO on improving BMD in osteopenic men is warranted.

**Exercise intervention vs. control subjects.** In addition to comparing the effects of RT and PLYO on BMD, we also compared the changes in BMD following the exercise intervention to subjects who chose not to participate in the exercise intervention. Our results from the repeated measures two-way ANOVA showed a significant increase over time with no differences between any group for WB (**Figure 3**; $p = 0.059$) and LS BMD (**Figure 4**; $p = 0.051$) in the RT, PLYO, and CON groups. However, recruiting subjects that had previously qualified, but chose not to participate in the intervention six months prior, to participate in a follow-up study was challenging, which resulted in a small sample size (n = 4). In addition, two of the four CON subjects did not receive a baseline whole body DXA scan, which resulted in the CON WB BMD data to have a sample size of two. Therefore, although our results suggest that the non-intervention control group also gained BMD, the small sample size is likely providing inaccurate results, i.e. concluding that CON WB and LS BMD increased based on two subjects data is likely to be erroneous. Due to these limitations, ongoing recruitment of this small, limited population is encouraged in order to obtain a larger sample size.

In addition to the positive effects of weight-bearing exercise on BMD, we hypothesized that six months of PLYO would cause a greater increase in BMD compared to RT in osteopenic men. It has been known for many years that bone cells are sensitive to mechanical forces. Previous research has shown that fluid shear forces are the stimulus behind strain-induced osteogenesis in the skeleton (115).

Our hypothesis was based on the previous research performed in animal models that indicated that the type, intensity, frequency, and duration of exercise dictate the osteogenic response of bone. For example, the magnitude and frequency of loading have been shown to play pivotal roles in osteogenic response to weight-bearing exercise in animal models. Specifically, the magnitude of loading must surpass a "minimum effective strain" (MES) (30), and loading has been shown to be more osteogenic when broken up into shorter, more frequent bouts, with rest periods inserted between strains (91, 114, 115, 117). Since our PLYO exercise intervention was designed based upon these principles, i.e. plyometrics have greater ground reaction forces (GRFs) and adequate rest was included between each jump repetition and loading cycle, we anticipated to see greater changes in the PLYO group compared to the RT intervention. Nevertheless, these results are the first to show plyometrics may be an effective, alternative exercise to resistance training to improve bone health in men, particularly in men with osteopenia.

**Effects of resistance training or plyometrics on changes in markers of bone turnover in males with osteopenia**. We predicted that six months of RT or PLYO exercise intervention would result in an elevation of serum markers of bone formation and a reduction of serum markers of bone resorption compared to baseline in osteopenic

men. Interestingly, we found no statistically significant changes in any single marker of bone formation (BAP, OC) or resorption (CTX, TRAP5b) concentration for both RT and PLYO. However, we did observe a significant increase in the BAP/CTX and OC/CTX ratios (**Figures 5-6**, respectively) from baseline to six months in the RT and PLYO exercise intervention groups. The increase over time with no differences between groups for the BAP/CTX and OC/CTX ratios in both RT and PLYO groups suggests that the weight-bearing exercise caused an elevation in the bone formation markers, BAP and OC, while suppressing CTX after six months of intervention in men with osteopenia.

Similar to our findings, previous research has shown that several months of resistance training positively affects BAP and OC in men. For example, Menkes et al.(74) and Fujimura et al.(32) found that four months RT resulted in a 26% and 30% increase in serum BAP concentrations, respectively, as well as significant increases in OC. Additionally, Menkes et al. (74) observed a 3.8% increase in femoral neck BMD ($P < 0.05$). Likewise, Vincent and Braith (121) found that six months of high-intensity resistance training (eight repetitions at 80% of 1RM for one set) significantly increased BAP 7.1% and OC 39% ($P < 0.05$), in combination with an increase in femoral neck BMD in elderly men and women. Although we did not see any significant change in a single serum marker of bone turnover or femoral neck BMD, we did see positive changes in BAP/CTX and OC/CTX ratios, as well as a significant increase in whole body BMD in both exercise groups.

BAP and OC are both products of active osteoblasts which are expressed during different phases of osteoblast development, and are considered to reflect different aspects of osteoblast function and of bone formation (13, 104). Specifically, OC is a bone matrix

protein synthesized by mature osteoblasts, whereas BAP is a membrane-bound enzyme by-product of osteoblast activity (13, 21). In addition during the degradation of type I collagen, CTX is released into circulation, thus providing a serum biomarker for bone resorption by osteoclasts (109). Although there were few significant changes in BMD from the exercise interventions, this increase in the BAP/CTX and OC/CTX ratios suggests that the six months of RT or PLYO exercise intervention causes a positive balance in the bone remodeling cycle, i.e. formation became predominant and/or resorption was attenuated, which may result in a net gain in BMD in the future.

**Effectiveness of resistance training vs. plyometrics to promote osteogenesis.** In conjunction with the positive effects on markers of bone turnover, we hypothesized that six months of PLYO would result in a greater increase of bone formation markers, and decrease in resorption markers, compared to RT in osteopenic men. After the six month intervention, we did not see any significant changes in any serum marker of bone turnover measured. However, both RT and PLYO interventions caused a positive balance in the remodeling cycle via bone turnover ratios. As previously mentioned, our hypothesis was based on the principles of type, intensity, frequency, and duration of loading explored in animal models. Thus, the mechanism behind the present results may suggest that humans, specifically osteopenic men, may respond differently to skeletal loading than the classic animal models. For example, the GRFs obtained from plyometrics and resistance training may both be sufficient enough to cause a positive balance in bone turnover. Therefore, in addition to the novel finding that six months of RT or PLYO both influence bone turnover in osteopenic men, these results also suggest that PLYO is a similarly effective mode of exercise to produce a positive balance in the

bone turnover cycle as compared to RT. This is new, valuable information, as it allows osteopenic men who cannot, or do not enjoy, RT to partake in an alternative exercise program that positively affects the remodeling cycle. Investigating the current methods of training for a longer duration and larger sample size will produce greater insight to the long term effects of RT and PLYO in this population of osteopenic men.

**Limitations and strengths.** There are several limitations and strengths to the current study, with the most limiting likely being the sample population. For example, the population we recruited for this study was very small, i.e. active, otherwise healthy osteopenic men, aged 25-60 y. This constraint is the reason for the relatively small sample sizes. Specifically, recruitment of the control subjects was particularly difficult, as the qualifications to participate were even more specific, which led to a very small sample size. Although the study was a longitudinal exercise intervention, we could only control each subject"s diet and additional physical activity via questionnaire. For example, providing each subject with six months of pre-determined "control" meals was not feasible, and we could not follow each subject to ensure they were not participating in additional weight-bearing physical activity. In addition, we could not control for the amount of effort each subject put into each exercise repetition on a daily basis, e.g. effort may have been less than maximal at times. In addition, the measurement of bone turnover markers represents average turnover of all skeletal sites, i.e. it is not site specific. Additionally, there is evidence that hormonal status also plays a role in bone turnover; however, we did not measure serum hormones in this study. Lastly, six months of exercise was likely not long enough to elicit a significant osteogenic response in hip or lumbar spine BMD adult males. Thus, a longer duration study would be beneficial.

**Strengths**. There are many strengths to the current study. First, there is an overall lack of data on the effects of exercise interventions on BMD in adult men. Thus, the primary strength of the current study is that it is the first to examine the long-term effects of RT or PLYO on BMD and bone turnover markers in men, specifically men with osteopenia. Additionally, the present exercise interventions were designed based on the fundamental principles of type, intensity, frequency, and duration of exercise to cause a maximal osteogenic response. In addition, all of the previous studies used exercises that did not optimally load, e.g. directly strain, the hip or spine – two of the most significant areas to improve bone density. For example, previous studies implemented exercises that loaded the axial skeleton, e.g. bicep curls, in addition to the use of resistance machines for their exercise intervention, which likely provided minimal, if no, strain on the hip and/or lumbar spine (74).

In conjunction with the ideal principles of loading to cause an osteogenic response applied in this study, there are many strengths the execution of the study as well. For example, we measured the effects of two different modes of exercise on bone health in men – one being a novel form of exercise in bone metabolism research in men, i.e. plyometrics. This revealed that there are two available types of exercise to potentially positively affect BMD in osteopenic men. Although six months of exercise may not be long enough to see significant results in the hip or spine BMD, the longitudinal design of this study is superior to cross-sectional studies. For example, each one of our exercise sessions was supervised by qualified personnel to ensure the completion of all reps and sets per exercise session, as well as proper technique were performed. Furthermore, we provided calcium and vitamin D supplements to our participants to ensure everyone was

consuming at least the RDA. This allowed us to show changes in BMD and bone turnover markers was due to exercise intervention, rather than calcium and vitamin D intake flux. Additionally, we measured multiple markers of bone turnover. Some studies only measure one aspect of bone turnover, e.g. only resorption, or measure one marker of resorption and formation. By measuring two markers for each aspect of bone turnover, i.e. two resorption and two formation, we were able to measure and observe multiple aspects of the bone turnover cycle, e.g. osteoclast activity (Trap5b) vs. collagen breakdown (CTX). Moreover, the timing of samples we collected was very precise to avoid diurnal variation. Lastly, we carefully inspected each DXA scan to ensure that the bone area did not change, which allowed us to assume that changes in BMD in exercise groups was not artifact from the DXA scanner.

## CONCLUSION

It has become well know that osteoporosis and its consequential fractures are a serious health problem in the United States, resulting in loss of productivity and billions of dollars of health care costs. Cost-effective intervention strategies are needed to improve BMD in people at increased risk of developing osteoporosis, for example, men with osteopenia. The results of this study are the first to show that plyometrics or resistance training are two viable exercises to potentially improve BMD and bone turnover ratios in osteopenic men. These findings should be followed up by further research to further improve exercise interventions to effectively combat osteoporosis in men.

## REFERENCES


**1.** NOF 2002 America's bone health: the state of osteoporosis and low bone mass in our nation. *National Osteoporosis Foundation*. 2002.

**2.** Prevention and management of osteoporosis. *World Health Organ Tech Rep Ser*. 2003;921:1-164, back cover.

**3.** Adler RA. Management of osteoporosis in men on androgen deprivation therapy. *Maturitas*. 2011;68(2):143-7.

**4.** Aghaloo TL, Felsenfeld AL, and Tetradis S. Osteonecrosis of the jaw in a patient on Denosumab. *J Oral Maxillofac Surg*. 2010;68(5):959-63.

**5.** Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Jr., Schmitz KH, Emplaincourt PO, Jacobs DR, Jr., and Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 Suppl):S498-504.

**6.** Allen MR, and Burr DB. Mandible matrix necrosis in beagle dogs after 3 years of daily oral bisphosphonate treatment. *J Oral Maxillofac Surg*. 2008;66(5):987-94.

**7.** Almstedt HC, Canepa JA, Ramirez DA, and Shoepe TC. Changes in Bone Mineral Density in Response to 24 Weeks of Resistance Training in College-Age Men and Women. *J Strength Cond Res*. 2010.

**8.** Anderson FH, Francis RM, Peaston RT, and Wastell HJ. Androgen supplementation in eugonadal men with osteoporosis: effects of six months' treatment on markers of bone formation and resorption. *J Bone Miner Res*. 1997;12(3):472-8.

**9.** Anderson HC. Matrix vesicles and calcification. *Curr Rheumatol Rep*. 2003;5(3):222-6.

**10.** Armas LAG, Lappe JM, and Heaney RP. Calcium, Bone Strength and Fractures. In: ES Orwoll, JP Bilezikian and D Vanderschueren editors. *Osteoporosis in men: The effects of gender on skeletal health*. San Diego, CA: Academic Press; 2010, pp. 235-41.

**11.** Bachrach LK. Acquisition of optimal bone mass in childhood and adolescence. *Trends Endocrinol Metab*. 2001;12(1):22-8.

**12.** Bailey DA, Faulkner RA, and McKay HA. Growth, physical activity, and bone mineral acquisition. *Exerc Sport Sci Rev*. 1996;24:233-66.

**13.** Banfi G, Lombardi G, Colombini A, and Lippi G. Bone metabolism markers in sports medicine. *Sports Med*. 2010;40(8):697-714.

**14.** Bemben DA, and Bemben MG. Dose-response effect of 40 weeks of resistance training on bone mineral density in older adults. *Osteoporos Int*. 2010.

**15.** Bonewald LF, and Johnson ML. Osteocytes, mechanosensing and Wnt signaling. *Bone*. 2008;42(4):606-15.

**16.** Burger EH, Klein-Nulend J, and Smit TH. Strain-derived canalicular fluid flow regulates osteoclast activity in a remodelling osteon--a proposal. *J Biomech*. 2003;36(10):1453-9.

**17.** Burger H, de Laet CE, van Daele PL, Weel AE, Witteman JC, Hofman A, and Pols HA. Risk factors for increased bone loss in an elderly population: the Rotterdam Study. *Am J Epidemiol*. 1998;147(9):871-9.

**18.** Burr DB, Robling AG, and Turner CH. Effects of biomechanical stress on bones in animals. *Bone*. 2002;30(5):781-6.

**19.** Casez JP, Fischer S, Stussi E, Stalder H, Gerber A, Delmas PD, Colombo JP, and Jaeger P. Bone mass at lumbar spine and tibia in young males--impact of physical fitness, exercise, and anthropometric parameters: a prospective study in a cohort of military recruits. *Bone*. 1995;17(3):211-9.

**20.** Cauley JA, Fullman RL, Stone KL, Zmuda JM, Bauer DC, Barrett-Connor E, Ensrud K, Lau EM, and Orwoll ES. Factors associated with the lumbar spine and proximal femur bone mineral density in older men. *Osteoporos Int*. 2005;16(12):1525-37.

**21.** Civitelli R, Armamento-Villareal R, and Napoli N. Bone turnover markers: understanding their value in clinical trials and clinical practice. *Osteoporos Int*. 2009;20(6):843-51.

**22.** Civitelli R, Beyer EC, Warlow PM, Robertson AJ, Geist ST, and Steinberg TH. Connexin43 mediates direct intercellular communication in human osteoblastic cell networks. *J Clin Invest*. 1993;91(5):1888-96.

**23.** Clarke B. Normal bone anatomy and physiology. *Clin J Am Soc Nephrol*. 2008;3 Suppl 3:S131-9.

**24.** Cohen-Solal ME, Baudoin C, Omouri M, Kuntz D, and De Vernejoul MC. Bone mass in middle-aged osteoporotic men and their relatives: familial effect. *J Bone Miner Res*. 1998;13(12):1909-14.

**25.** Cohen B, Millett PJ, Mist B, Laskey MA, and Rushton N. Effect of exercise training programme on bone mineral density in novice college rowers. *Br J Sports Med*. 1995;29(2):85-8.

**26.** Dawson-Hughes B, Harris SS, Krall EA, and Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*. 1997;337(10):670-6.

**27.** Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, Ebetino FH, and Rogers MJ. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther*. 2001;296(2):235-42.

**28.** Ebeling PR, Sandgren ME, DiMagno EP, Lane AW, DeLuca HF, and Riggs BL. Evidence of an age-related decrease in intestinal responsiveness to vitamin D: relationship between serum 1,25-dihydroxyvitamin D3 and intestinal vitamin D receptor concentrations in normal women. *J Clin Endocrinol Metab*. 1992;75(1):176-82.

**29.** Favus MJ. Primer on the metabolic bone diseases and disorders of mineral metabolism. Washington D.C.: American Society for Bone and Mineral Research; 2003.

**30.** Frost HM. Bone "mass" and the "mechanostat": a proposal. *Anat Rec*. 1987;219(1):1-9.

**31.** Frost HM. Bone's mechanostat: a 2003 update. *Anat Rec A Discov Mol Cell Evol Biol*. 2003;275(2):1081-101.

**32.** Fujimura R, Ashizawa N, Watanabe M, Mukai N, Amagai H, Fukubayashi T, Hayashi K, Tokuyama K, and Suzuki M. Effect of resistance exercise training on bone formation and resorption in young male subjects assessed by biomarkers of bone metabolism. *J Bone Miner Res*. 1997;12(4):656-62.

**33.** Gallagher JC. The pathogenesis of osteoporosis. *Bone Miner*. 1990;9(3):215-27.

**34.** Gass M, and Dawson-Hughes B. Preventing osteoporosis-related fractures: an overview. *Am J Med*. 2006;119(4 Suppl 1):S3-S11.

**35.** Gennari L, Khosla S, and Bilezikian JP. Estrogen and fracture risk in men. *J Bone Miner Res*. 2008;23(10):1548-51.

**36.** Gunter K, Baxter-Jones AD, Mirwald RL, Almstedt H, Fuller A, Durski S, and Snow C. Jump starting skeletal health: a 4-year longitudinal study assessing the effects of jumping on skeletal development in pre and circum pubertal children. *Bone*. 2008;42(4):710-8.

**37.** Halleen JM, Alatalo SL, Suominen H, Cheng S, Janckila AJ, and Vaananen HK. Tartrate-resistant acid phosphatase 5b: a novel serum marker of bone resorption. *J Bone Miner Res*. 2000;15(7):1337-45.

**38.** Halloran BP, Portale AA, Lonergan ET, and Morris RC, Jr. Production and metabolic clearance of 1,25-dihydroxyvitamin D in men: effect of advancing age. *J Clin Endocrinol Metab*. 1990;70(2):318-23.

**39.** Hannan MT, Felson DT, Dawson-Hughes B, Tucker KL, Cupples LA, Wilson PW, and Kiel DP. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. *J Bone Miner Res*. 2000;15(4):710-20.

**40.** Harris SS, Dawson-Hughes B, and Perrone GA. Plasma 25-hydroxyvitamin D responses of younger and older men to three weeks of supplementation with 1800 IU/day of vitamin D. *J Am Coll Nutr*. 1999;18(5):470-4.

**41.** Heaney RP. Dairy and bone health. *J Am Coll Nutr*. 2009;28 Suppl 1:82S-90S.

**42.** Heaney RP, and Weaver CM. Newer perspectives on calcium nutrition and bone quality. *J Am Coll Nutr*. 2005;24(6 Suppl):574S-81S.

**43.** Hert J, Liskova M, and Landa J. Reaction of bone to mechanical stimuli. 1. Continuous and intermittent loading of tibia in rabbit. *Folia Morphol (Praha)*. 1971;19(3):290-300.

**44.** Hert J, Liskova M, and Landrgot B. Influence of the long-term, continuous bending on the bone. An experimental study on the tibia of the rabbit. *Folia Morphol (Praha)*. 1969;17(4):389-99.

**45.** Hert J, Pribylova E, and Liskova M. Reaction of bone to mechanical stimuli. 3. Microstructure of compact bone of rabbit tibia after intermittent loading. *Acta Anat (Basel)*. 1972;82(2):218-30.

**46.** Hert J, Sklenska A, and Liskova M. Reaction of bone to mechanical stimuli. 5. Effect of intermittent stress on the rabbit tibia after resection of the peripheral nerves. *Folia Morphol (Praha)*. 1971;19(4):378-87.

**47.** Huuskonen J, Vaisanen SB, Kroger H, Jurvelin JS, Alhava E, and Rauramaa R. Regular physical exercise and bone mineral density: a four-year controlled randomized trial in middle-aged men. The DNASCO study. *Osteoporos Int*. 2001;12(5):349-55.

**48.** Johnell O, and Kanis J. Epidemiology of osteoporotic fractures. *Osteoporos Int*. 2005;16 Suppl 2:S3-7.

**49.** Kanis JA, Melton LJ, 3rd, Christiansen C, Johnston CC, and Khaltaev N. The diagnosis of osteoporosis. *J Bone Miner Res*. 1994;9(8):1137-41.

**50.** Karlsson MK, Magnusson H, Karlsson C, and Seeman E. The duration of exercise as a regulator of bone mass. *Bone*. 2001;28(1):128-32.

**51.** Karlsson MK, Nordqvist A, and Karlsson C. Physical activity increases bone mass during growth. *Food Nutr Res*. 2008;52.

**52.** Karsdal MA, Henriksen K, Arnold M, and Christiansen C. Calcitonin: a drug of the past or for the future? Physiologic inhibition of bone resorption while sustaining osteoclast numbers improves bone quality. *BioDrugs*. 2008;22(3):137-44.

**53.** Kennel KA, and Drake MT. Adverse effects of bisphosphonates: implications for osteoporosis management. *Mayo Clin Proc*. 2009;84(7):632-7; quiz 8.

**54.** Khosla S. Update in male osteoporosis. *J Clin Endocrinol Metab*. 2010;95(1):3-10.

**55.** Khosla S, Amin S, and Orwoll E. Osteoporosis in men. *Endocr Rev*. 2008;29(4):441-64.

**56.** Khosla S, Atkinson EJ, Melton LJ, 3rd, and Riggs BL. Effects of age and estrogen status on serum parathyroid hormone levels and biochemical markers of bone turnover in women: a population-based study. *J Clin Endocrinol Metab*. 1997;82(5):1522-7.

**57.** Kiebzak GM, Beinart GA, Perser K, Ambrose CG, Siff SJ, and Heggeness MH. Undertreatment of osteoporosis in men with hip fracture. *Arch Intern Med*. 2002;162(19):2217-22.

**58.** Kohrt WM, Bloomfield SA, Little KD, Nelson ME, and Yingling VR. American College of Sports Medicine Position Stand: physical activity and bone health. *Med Sci Sports Exerc*. 2004;36(11):1985-96.

**59.** Kriska AM, Sandler RB, Cauley JA, LaPorte RE, Hom DL, and Pambianco G. The assessment of historical physical activity and its relation to adult bone parameters. *Am J Epidemiol*. 1988;127(5):1053-63.

**60.** Kukuljan S, Nowson CA, Bass SL, Sanders K, Nicholson GC, Seibel MJ, Salmon J, and Daly RM. Effects of a multi-component exercise program and calcium-vitamin-D3-fortified milk on bone mineral density in older men: a randomised controlled trial. *Osteoporos Int*. 2009;20(7):1241-51.

**61.** Lanyon LE. Osteocytes, strain detection, bone modeling and remodeling. *Calcif Tissue Int*. 1993;53 Suppl 1:S102-6; discussion S6-7.

**62.** Lanyon LE, and Rubin CT. Static vs dynamic loads as an influence on bone remodelling. *J Biomech*. 1984;17(12):897-905.

**63.** Lips P, Courpron P, and Meunier PJ. Mean wall thickness of trabecular bone packets in the human iliac crest: changes with age. *Calcif Tissue Res*. 1978;26(1):13-7.

**64.** Liskova M, and Hert J. Reaction of bone to mechanical stimuli. 2. Periosteal and endosteal reaction of tibial diaphysis in rabbit to intermittent loading. *Folia Morphol (Praha)*. 1971;19(3):301-17.

**65.** Looker AC, and Mussolino ME. Serum 25-hydroxyvitamin D and hip fracture risk in older U.S. white adults. *J Bone Miner Res*. 2008;23(1):143-50.

**66.** MacLaughlin J, and Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest*. 1985;76(4):1536-8.

**67.** Maddalozzo GF, and Snow CM. High intensity resistance training: effects on bone in older men and women. *Calcif Tissue Int*. 2000;66(6):399-404.

**68.** Maimoun L, and Sultan C. Effects of physical activity on bone remodeling. *Metabolism*. 2010.

**69.** Malik P, Gasser RW, Kemmler G, Moncayo R, Finkenstedt G, Kurz M, and Fleischhacker WW. Low bone mineral density and impaired bone metabolism in young alcoholic patients without liver cirrhosis: a cross-sectional study. *Alcohol Clin Exp Res*. 2009;33(2):375-81.

**70.** Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev*. 2000;21(2):115-37.

**71.** Marcus R. Osteoporosis. San Diego: Academic Press; 2001.

**72.** McCartney N, Hicks AL, Martin J, and Webber CE. Long-term resistance training in the elderly: effects on dynamic strength, exercise capacity, muscle, and bone. *J Gerontol A Biol Sci Med Sci*. 1995;50(2):B97-104.

**73.** Melton LJ, 3rd, Atkinson EJ, O'Fallon WM, Wahner HW, and Riggs BL. Long-term fracture prediction by bone mineral assessed at different skeletal sites. *J Bone Miner Res*. 1993;8(10):1227-33.

**74.** Menkes A, Mazel S, Redmond RA, Koffler K, Libanati CR, Gundberg CM, Zizic TM, Hagberg JM, Pratley RE, and Hurley BF. Strength training increases regional bone mineral density and bone remodeling in middle-aged and older men. *J Appl Physiol*. 1993;74(5):2478-84.

**75.** Miller PD. Anti-resorptives in the management of osteoporosis. *Best Pract Res Clin Endocrinol Metab*. 2008;22(5):849-68.

**76.** Mirsa B, and Silverberg SJ. Alterations in Mineral Metabolism in the Aging Male. In: E Orwoll, JP Bilezikian and D Vanderschueren editors. *Osteoporosis in men: The effects of gender on skeletal health*. San Diego: Academic Press; 2010.

**77.** Mosley JR, March BM, Lynch J, and Lanyon LE. Strain magnitude related changes in whole bone architecture in growing rats. *Bone*. 1997;20(3):191-8.

**78.** NOF. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation; 2009.

**79.** Papaioannou A, Kennedy CC, Cranney A, Hawker G, Brown JP, Kaiser SM, Leslie WD, O'Brien CJ, Sawka AM, Khan A, Siminoski K, Tarulli G, Webster D, McGowan J, and Adachi JD. Risk factors for low BMD in healthy men age 50 years or older: a systematic review. *Osteoporos Int*. 2009;20(4):507-18.

**80.** Parfitt AM. The coupling of bone formation to bone resorption: a critical analysis of the concept and of its relevance to the pathogenesis of osteoporosis. *Metab Bone Dis Relat Res*. 1982;4(1):1-6.

**81.** Parfitt AM. Targeted and nontargeted bone remodeling: relationship to basic multicellular unit origination and progression. *Bone*. 2002;30(1):5-7.

**82.** Peris P, Pares A, Guanabens N, Del Rio L, Pons F, Martinez de Osaba MJ, Monegal A, Caballeria J, Rodes J, and Munoz-Gomez J. Bone mass improves in alcoholics after 2 years of abstinence. *J Bone Miner Res*. 1994;9(10):1607-12.

**83.** Piper PK, Jr., and Gruntmanis U. Management of osteoporosis in the aging male: focus on zoledronic acid. *Clin Interv Aging*. 2009;4:289-303.

**84.** Pye SR, Devakumar V, Boonen S, Borghs H, Vanderschueren D, Adams JE, Ward KA, Bartfai G, Casanueva FF, Finn JD, Forti G, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean ME, Pendleton N, Punab M, Silman AJ, Wu FC, and O'Neill TW. Influence of Lifestyle Factors on Quantitative Heel Ultrasound Measurements in Middle-Aged and Elderly Men. *Calcif Tissue Int*. 2010.

**85.** Ralston SH. Genetic determinants of bone mass and osteoporotic fracture. In: JP Bilezikian, LG Riggs and TJ Martin editors. *Principles of Bone Biology*. San Diego: Elselvier; 2008, pp. 1611-34.

**86.** Reid IR. Bisphosphonates: new indications and methods of administration. *Curr Opin Rheumatol*. 2003;15(4):458-63.

**87.** Remes T, Vaisanen SB, Mahonen A, Huuskonen J, Kroger H, Jurvelin JS, Penttila IM, and Rauramaa R. The association of bone metabolism with bone mineral density, serum sex hormone concentrations, and regular exercise in middle-aged men. *Bone*. 2004;35(2):439-47.

**88.** Robling AG, Burr DB, and Turner CH. Partitioning a daily mechanical stimulus into discrete loading bouts improves the osteogenic response to loading. *J Bone Miner Res*. 2000;15(8):1596-602.

**89.** Robling AG, Burr DB, and Turner CH. Recovery periods restore mechanosensitivity to dynamically loaded bone. *J Exp Biol*. 2001;204(Pt 19):3389-99.

**90.** Robling AG, Duijvelaar KM, Geevers JV, Ohashi N, and Turner CH. Modulation of appositional and longitudinal bone growth in the rat ulna by applied static and dynamic force. *Bone*. 2001;29(2):105-13.

**91.** Robling AG, Hinant FM, Burr DB, and Turner CH. Improved bone structure and strength after long-term mechanical loading is greatest if loading is separated into short bouts. *J Bone Miner Res*. 2002;17(8):1545-54.

**92.** Robling AG, Hinant FM, Burr DB, and Turner CH. Shorter, more frequent mechanical loading sessions enhance bone mass. *Med Sci Sports Exerc*. 2002;34(2):196-202.

**93.** Rogers RS, and Hinton PS. Bone loading during young adulthood predicts bone mineral density in physically active, middle-aged men. *Phys Sportsmed*. 2010;38(2):146-55.

**94.** Roodman GD. Cell biology of the osteoclast. *Exp Hematol*. 1999;27(8):1229-41.

**95.** Rubin CT, and Lanyon LE. Dynamic strain similarity in vertebrates; an alternative to allometric limb bone scaling. *J Theor Biol*. 1984;107(2):321-7.

**96.** Rubin CT, and Lanyon LE. Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg Am*. 1984;66(3):397-402.

**97.** Ruggiero SL. Bisphosphonate-related osteonecrosis of the jaw: an overview. *Ann N Y Acad Sci*. 2011;1218:38-46.

**98.** Ryan AS, Ivey FM, Hurlbut DE, Martel GF, Lemmer JT, Sorkin JD, Metter EJ, Fleg JL, and Hurley BF. Regional bone mineral density after resistive training in young and older men and women. *Scand J Med Sci Sports*. 2004;14(1):16-23.

**99.** Ryan AS, Treuth MS, Rubin MA, Miller JP, Nicklas BJ, Landis DM, Pratley RE, Libanati CR, Gundberg CM, and Hurley BF. Effects of strength training on bone mineral density: hormonal and bone turnover relationships. *J Appl Physiol*. 1994;77(4):1678-84.

**100.** Sartorio A, Lafortuna C, Capodaglio P, Vangeli V, Narici MV, and Faglia G. Effects of a 16-week progressive high-intensity strength training (HIST) on indexes of bone turnover in men over 65 years: a randomized controlled study. *J Endocrinol Invest*. 2001;24(11):882-6.

**101.** Schoenau E, and Fricke O. Mechanical influences on bone development in children. *Eur J Endocrinol*. 2008;159 Suppl 1:S27-31.

**102.** Seeman E. Bone modeling and remodeling. *Crit Rev Eukaryot Gene Expr*. 2009;19(3):219-33.

**103.** Seeman E, and Delmas PD. Bone quality--the material and structural basis of bone strength and fragility. *N Engl J Med*. 2006;354(21):2250-61.

**104.** Seibel MJ. Biochemical markers of bone turnover: part I: biochemistry and variability. *Clin Biochem Rev*. 2005;26(4):97-122.

**105.** Smith MR. Bisphosphonates to prevent osteoporosis in men receiving androgen deprivation therapy for prostate cancer. *Drugs Aging*. 2003;20(3):175-83.

**106.** Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, Santanna J, Loh L, Lenrow DA, Holmes JH, Kapoor SC, Atkinson LE, and Strom BL. Effects of testosterone replacement in hypogonadal men. *J Clin Endocrinol Metab*. 2000;85(8):2670-7.

**107.** Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG, Jr., and Strom BL. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab*. 1999;84(6):1966-72.

**108.** Szulc P, Joly-Pharaboz MO, Marchand F, and Delmas PD. Insulin-like growth factor I is a determinant of hip bone mineral density in men less than 60 years of age: MINOS study. *Calcif Tissue Int*. 2004;74(4):322-9.

**109.** Szulc P, Montella A, and Delmas PD. High bone turnover is associated with accelerated bone loss but not with increased fracture risk in men aged 50 and over: the prospective MINOS study. *Ann Rheum Dis*. 2008;67(9):1249-55.

**110.** Toth E, Csupor E, Meszaros S, Ferencz V, Nemeth L, McCloskey EV, and Horvath C. The effect of intranasal salmon calcitonin therapy on bone mineral density in idiopathic male osteoporosis without vertebral fractures--an open label study. *Bone*. 2005;36(1):47-51.

**111.** Trovas GP, Lyritis GP, Galanos A, Raptou P, and Constantelou E. A randomized trial of nasal spray salmon calcitonin in men with idiopathic osteoporosis: effects on bone mineral density and bone markers. *J Bone Miner Res*. 2002;17(3):521-7.

**112.** Turner CH, Forwood MR, and Otter MW. Mechanotransduction in bone: do bone cells act as sensors of fluid flow? *FASEB J*. 1994;8(11):875-8.

**113.** Turner CH, Owan I, and Takano Y. Mechanotransduction in bone: role of strain rate. *Am J Physiol*. 1995;269(3 Pt 1):E438-42.

**114.** Turner CH, and Robling AG. Exercises for improving bone strength. *Br J Sports Med*. 2005;39(4):188-9.

**115.** Turner CH, and Robling AG. Mechanisms by which exercise improves bone strength. *J Bone Miner Metab*. 2005;23 Suppl:16-22.

**116.** Turner RT. Skeletal response to alcohol. *Alcohol Clin Exp Res*. 2000;24(11):1693-701.

**117.** Umemura Y, Ishiko T, Yamauchi T, Kurono M, and Mashiko S. Five jumps per day increase bone mass and breaking force in rats. *J Bone Miner Res*. 1997;12(9):1480-5.

**118.** Umemura Y, Nagasawa S, Honda A, and Singh R. High-impact exercise frequency per week or day for osteogenic response in rats. *J Bone Miner Metab*. 2008;26(5):456-60.

**119.** USFDA. Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa). US Food and Drug Administration; 2008.

**120.** Van Pottelbergh I, Goemaere S, Zmierczak H, De Bacquer D, and Kaufman JM. Deficient acquisition of bone during maturation underlies idiopathic osteoporosis in men: evidence from a three-generation family study. *J Bone Miner Res*. 2003;18(2):303-11.

**121.** Vincent KR, and Braith RW. Resistance exercise and bone turnover in elderly men and women. *Med Sci Sports Exerc*. 2002;34(1):17-23.

**122.** Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, and Swerdloff RS. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab*. 2004;89(5):2085-98.

**123.** Welsh L, and Rutherford OM. Hip bone mineral density is improved by high-impact aerobic exercise in postmenopausal women and men over 50 years. *Eur J Appl Physiol Occup Physiol*. 1996;74(6):511-7.

**124.** Woitge HW, Friedmann B, Suttner S, Farahmand I, Muller M, Schmidt-Gayk H, Baertsch P, Ziegler R, and Seibel MJ. Changes in bone turnover induced by aerobic and anaerobic exercise in young males. *J Bone Miner Res*. 1998;13(12):1797-804.

**125.** Wolff J. Das gesetz der transformation der knochen. *Berlin: A Hirschwald*. 1892.

**126.** Wood J, Bonjean K, Ruetz S, Bellahcene A, Devy L, Foidart JM, Castronovo V, and Green JR. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther*. 2002;302(3):1055-61.

**127.** Wright VJ. Osteoporosis in men. *J Am Acad Orthop Surg*. 2006;14(6):347-53.

**128.** Zebaze R, and Seeman E. Age-related Changes in Bone Remodeling and Microarchitecture. In: E Orwoll editor. *Osteoporosis in Men: The effects of gender on skeletal health*. San Diego, CA: Academic Press; 2010, pp. 167-78.

# APPENDIX A: ADDITIONAL TABLES

TABLE A1. Whole body bone area ($cm^2$) for RT and PLY – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 2267.67 ± 49.24 | 2162.05 – 2373.29 | 0.682 |
| | Post – Six months | 2271.09 ± 47.61 | 2168.98 – 2373.21 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 8) | 2342.71 ± 68.25 | 2196.33 – 2489.10 | 0.151 |
| | PLYO (n = 8) | 2196.05 ± 68.25 | 2049.66 – 2342.43 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 2333.48 ± 69.64 | 2351.95 ± 67.33 | 0.087 |
| | PLYO | 2201.85 ± 69.64 | 2190.24 ± 67.33 | |

Values displayed as mean ± SE. N = 16.

TABLE A2. Total left hip bone area ($cm^2$) for RT and PLY – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 40.28 ± 1.09 | 37.96 – 42.60 | 0.171 |
| | Post – Six months | 40.60 ± 1.14 | 38.18 – 43.03 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 40.33 ± 1.52 | 37.09 – 43.57 | 0.924 |
| | PLYO (n = 8) | 40.55 ± 1.61 | 37.11 – 43.98 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 40.19 ± 1.49 | 40.47 ± 1.56 | 0.843 |
| | PLYO | 40.36 ± 1.58 | 40.73 ± 1.66 | |

Values displayed as mean ± SE. N = 17.

TABLE A3. Lumbar spine ($L_1$-$L_4$) bone area ($cm^2$) for RT and PLY – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 69.65 ± 1.70 | 65.80 – 73.27 | 0.576 |
| | Post – Six months | 69.54 ± 1.75 | 66.01 – 73.30 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 70.59 ± 2.37 | 65.54 – 75.64 | 0.574 |
| | PLYO (n = 8) | 68.60 ± 2.51 | 63.24 – 73.96 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 70.71 ± 2.34 | 70.47 ± 2.40 | 0.560 |
| | PLYO | 68.60 ± 2.49 | 68.60 ± 2.55 | |

Values displayed as mean ± SE. N = 17.

TABLE A4. Whole body bone mineral content (g) for RT and PLY – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 2595.47 ± 72.23 | 2440.55 – 2750.40 | 0.035 |
| | Post – Six months | 2621.56 ± 74.63 | 2461.48 – 2781.64 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 8) | 2739.21 ± 103.57 | 2517.08 – 2961.34 | 0.096 |
| | PLYO (n = 8) | 2477.82 ± 103.57 | 2255.69 – 2699.95 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 2713.75 ± 102.15 | 2764.68 ± 105.56 | 0.043 |
| | PLYO | 2477.20 ± 102.15 | 2478.43 ± 105.56 | |

Values displayed as mean ± SE. N = 17.

TABLE A5. Total left hip bone mineral content (g) for RT and PLY – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 36.74 ± 1.33 | 33.92 – 39.57 | 0.159 |
| | Post – Six months | 37.13 ± 1.41 | 34.13 – 40.14 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 37.29 ± 1.71 | 33.70 – 40.89 | 0.798 |
| | PLYO (n = 8) | 36.58 ± 1.81 | 32.77 – 40.39 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 37.02 ± 1.68 | 37.56 ± 1.77 | 0.580 |
| | PLYO | 36.70 ± 1.77 | 36.70 ± 1.88 | |

Values displayed as mean ± SE. N = 17.

TABLE A6. Lumbar spine ($L_1$-$L_4$) bone mineral content (g) for RT and PLY – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 64.33 ± 2.01 | 60.05 – 68.62 | 0.174 |
| | Post – Six months | 64.80 ± 1.94 | 60.67 – 68.933 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 67.13 ± 2.53 | 61.81 – 72.44 | 0.213 |
| | PLYO (n = 8) | 62.01 ± 2.69 | 56.37 – 67.65 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 66.83 ±2.58 | 67.42 ± 2.50 | 0.719 |
| | PLYO | 61.84 ± 2.74 | 62.19 ± 2.65 | |

Values displayed as mean ± SE. N = 17.

TABLE A7. Whole body bone area ($cm^2$) for RT, PLY, CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 2214.87 ± 55.51 | 2096.56 -2333.18 | 0.515 |
| | Post – 6 mo | 2221.02 ± 53.92 | 2106.09 – 2335.95 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 8) | 2342.71 ± 68.25 | 2196.33 – 2489.10 | 0.199 |
| | PLYO (n = 8) | 2196.05 ± 68.25 | 2049.66 – 2342.43 | |
| | CON (n = 2) | 2115.07 ± 133.57 | 1830.40 – 2399.74 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 2333.48 ± 69.64 | 2351.95 ± 67.33 | 0.195 |
| | PLYO | 2201.85 ± 69.64 | 2190.24 ± 67.33 | |
| | CON | 2109.27 ± 135.96 | 2120.87 ± 132.08 | |

Values displayed as mean ± SE.

TABLE A8. Total left hip bone area ($cm^2$) for RT, PLY, CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 39.17 ± 1.03 | 0.690 – 1.048 | 0.077 |
| | Post – 6 mo | 39.57 ± 1.10 | 0.674 – 1.030 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 40.33 ± 1.52 | 37.09 – 43.57 | |
| | PLYO (n = 8) | 40.55 ± 1.61 | 37.11 – 43.98 | 0.465 |
| | CON (n = 4) | 37.24 ± 2.28 | 32.45 – 42.03 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 40.19 ± 1.49 | 40.47 ± 1.56 | |
| | PLYO | 40.36 ± 1.58 | 40.73 ± 1.66 | 0.885 |
| | CON | 36.96 ± 2.22 | 37.52 ± 2.36 | |

Values displayed as mean ± SE.

TABLE A9. Lumbar spine ($L_1$-$L_4$ bone area ($cm^2$) for RT, PLY, CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 68.31 ±1.53 | 65.09 – 71.53 | 0.886 |
| | Post – 6 mo | 68.34 ± 1.58 | 65.03 – 71.66 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 70.59 ± 2.37 | 65.54 – 75.64 | 0.495 |
| | PLYO (n = 8) | 68.60 ± 2.51 | 63.24 – 73.96 | |
| | CON (n = 4) | 65.77 ± 3.34 | 58.78 – 72.79 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 70.71 ± 2.34 | 70.47 ± 2.40 | |
| | PLYO | 68.60 ± 2.49 | 68.60 ± 2.55 | 0.667 |
| | CON | 65.61 ± 3.30 | 65.96 ± 3.40 | |

Values displayed as mean ± SE.

TABLE A10. Whole body bone mineral content (g) for RT, PLY, CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 2519.39 ± 81.89 | 2344.84 -2693.93 | 0.021 |
| | Post – 6 mo | 2553.49 ± 83.86 | 2374.75 – 2372.23 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 8) | 2739.21 ± 103.57 | 2517.08 – 2961.34 | 0.148 |
| | PLYO (n = 8) | 2477.82 ± 103.57 | 2255.69 – 2699.95 | |
| | CON (n = 2) | 2392.28 ± 202.36 | 1960.96 – 2823.61 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 2713.75 ± 102.15 | 2764.68 ± 105.56 | 0.109 |
| | PLYO | 2477.20 ± 102.15 | 2478.43 ± 105.56 | |
| | CON | 2367.21 ± 200.59 | 2417.35 ± 205.41 | |

Values displayed as mean ± SE.

TABLE A11. Total left hip bone mineral content (g) for RT, PLY, CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 36.51 ± 1.16 | 34.07 – 38.95 | 0.375 |
| | Post – 6 mo | 36.76 ± 1.24 | 34.17 – 39.37 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 37.29 ± 1.71 | 33.70 – 40.89 | |
| | PLYO (n = 8) | 36.58 ± 1.81 | 32.77 – 40.39 | 0.912 |
| | CON (n = 4) | 36.04 ± 2.57 | 30.65 – 41.43 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 37.02 ± 1.68 | 37.56 ± 1.77 | |
| | PLYO | 36.70 ± 1.77 | 36.70 ± 1.88 | 0.731 |
| | CON | 36.05 ± 2.50 | 36.03 ± 2.66 | |

Values displayed as mean ± SE.

TABLE A12. Lumbar spine ($L_1$-$L_4$) content (g) for RT, PLY, CON – Repeated measures two-way ANOVA

| **Time** | | **Mean ± S.E.** | **Range** | ***p* – value** |
|---|---|---|---|---|
| | Baseline | 63.52 ± 1.80 | 59.74 – 67.31 | 0.050 |
| | Post – 6 mo | 64.22 ± 1.74 | 60.56 – 67.88 | |
| **Group** | | **Mean ± S.E.** | **Range** | ***p* – value** |
| | RT (n = 9) | 67.13 ± 2.53 | 61.81 – 72.44 | 0.354 |
| | PLYO (n = 8) | 62.01 ± 2.69 | 56.37 – 67.65 | |
| | CON (n = 4) | 62.48 ± 3.80 | 54.50 – 70.46 | |
| **Time x Group** | | **Baseline** | **Post-Six Months** | ***p* – value** |
| | RT | 66.83 ±2.58 | 67.42 ± 2.50 | |
| | PLYO | 61.84 ± 2.74 | 62.19 ± 2.65 | 0.663 |
| | CON | 61.91 ± 3.88 | 63.06 ± 3.75 | |

Values displayed as mean ± SE.

TABLE A13. Changes in strength after six months of resistance training

| Characteristics | Resistance Training (n = 9) |
|---|---|
| **1RM (lbs)** | |
| Squat Baseline | 186 ± 12 |
| Squat Post- 6 mo | 279 ± 16 |
| Δ% | 94 ± 6 |
| MP Baseline | 98 ± 8 |
| MP Post- 6 mo | 122 ± 9 |
| Δ% | 25 ± 5 |
| Deadlift Baseline | 184 ± 22 |
| Deadlift Post 6- mo | 260 ± 24 |
| Δ% | 41 ± 6 |

Values displayed as mean ± SE. 1RM: one repetition maximum; MP: military press.

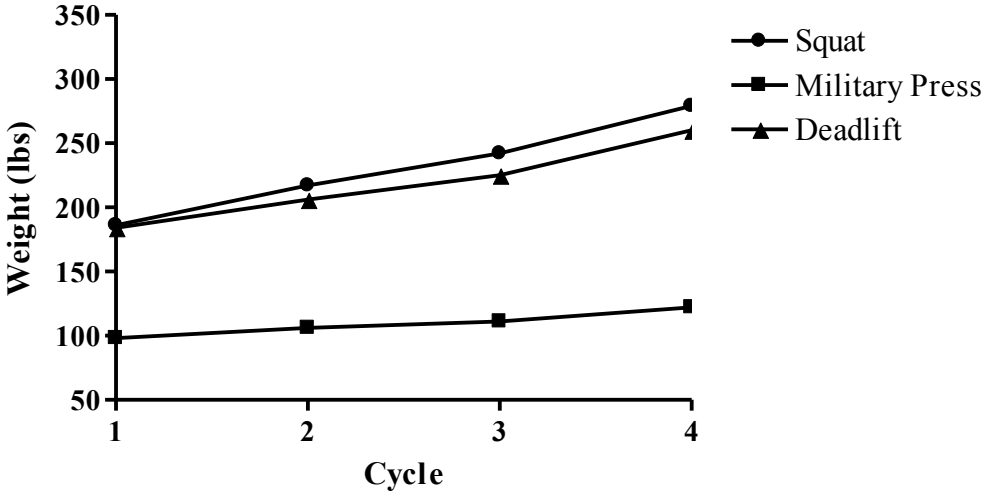



**FIGURE A1. Progressive improvements in squat, military press, and deadlift weight during six months of resistance training. N = 9.**

TABLE A14. Follow-up paired t-tests within group showing group influence on main effect for time.

| | RT (n = 9) | *p*-value | PLYO (n = 8) | *p*-value |
|---|---|---|---|---|
| **WB BMD** | | | | |
| Baseline | 1.162 ± 0.018 | 0.074 | 1.126 ± 0.023 | 0.485 |
| Post -6 mo | 1.172 ± 0.018 | | 1.132 ± 0.024 | |
| **LS BMD** | | | | |
| Baseline | 0.945 ± 0.020 | 0.228 | 0.901 ± 0.023 | 0.370 |
| Post -6 mo | 0.954 ± 0.020 | | 0.907 ± 0.024 | |
| **BAP/CTX** | | | | |
| Baseline | 160.53 ± 26.99 | 0.075 | 231.38 ± 28.99 | 0.340 |
| Post -6 mo | 237.78 ± 46.63 | | 264.54 ± 30.74 | |
| **OC/CTX** | | | | |
| Baseline | 22.48 ± 2.30 | 0.345 | 29.14 ± 3.32 | 0.189 |
| Post -6 mo | 27.51 ± 4.35 | | 35.00 ± 3.15 | |

Values displayed as mean ± S.E. S.E.: standard error of measurement; WB: whole body; LS: lumbar spine; BAP: bone-alkaline phosphatase; CTX: carboxy-terminal telopeptide of type I collagen; OC: osteocalcin.

# APPENDIX B: EXTENDED LITERATURE REVIEW

Osteoporosis and its consequential fractures are a nationally recognized health problem in the United States. In the past, the treatment and prevention of osteoporosis has been focused on females, because of the high rate of bone loss post-menopause, often resulting in debilitating osteoporotic fractures. In addition, men have a greater mortality risk after fracture compared to women (54, 55). Billions of dollars are spent every year as a result of direct and indirect heath care expenses from osteopenic fracture (34). With such a large economic burden associated with osteoporosis, in addition to the reduced quality of living, prevention is more cost effective than treatment.

Researchers have cited two central causes of low bone mineral density: inadequate attainment of bone mineral density during growth; and failure to maintain bone mass during aging (12). Therefore, after the acquisition of peak bone mass, the primary goal during adulthood should be to minimize age−related bone loss. For example, one in five men over the age of 50 years old will suffer an osteoporotic fracture during their lifetime (48, 54). This loss may be attributed to a variety of factors including a reduction in bone formation, negative balance between bone resorption and bone formation, diet/vitamin intake, older age, smoking, and physical inactivity.

**Factors affecting bone health.** The acquisition of peak bone mass in childhood and adolescence has been shown to be important in the prevention of osteoporosis (11, 36, 51). Peak bone mass (PBM) is the amount of bone present in the skeleton at the end of its maturation process, which is typically attained in the second decade of life (101). Rogers and Hinton (93) previously revealed that bone loading during young adulthood positively predicts adult BMD, suggesting that participation in high-impact, weight-bearing physical activity to promote PBM during that time period may provide important residual benefits into adulthood. However, after

the second decade of life, bone content begins to decline by about 4% per decade (2), and one in five men over the age of 50 years old will suffer an osteoporotic fracture during their lifetime (48, 54). Inadequate attainment of BMD during growth and failure to maintain bone mass during aging are the two primary causes researchers have cited for low bone mineral density in adulthood (12). Therefore, the primary goal during adulthood should be to minimize age−related bone loss.

There are several factors that influence the maintenance of bone health in adulthood including genetics, age-related changes, nutrition, environmental factors, and weight-bearing activity. Although genetics cannot be changed, factors such as nutrition, environment, and weight-bearing physical activity can be modified to reduce the risk of developing osteopenia or osteoporosis and improve overall bone health. Thus, interventions which include adequate nutrition affecting bone mineralization (i.e. calcium, vitamin D, etc.), avoiding environmental risk factors such as smoking, and weight – bearing physical activity, may provide a valuable method to positively affect bone mass later in life.

**Non-modifiable risk factors.** Genetic factors and hormonal balance are key players in non-modifiable risk factors in the pathogenesis of skeletal fragility and osteoporosis in men. Several studies using twin pairs or parent-offspring models have shown high levels of heritability of BMD (85). For example, studies examining monozygotic, or identical, twins have shown that genetics account for up to 50-80% of the variance in BMD (85). Genetic factors likely influence skeletal growth by determining the amount of bone mass attained in early adulthood (peak bone mass), leaving some males more susceptible to developing osteoporosis with advanced aging. For example, Cohen-Solal et al (24) found that male offspring of subjects with osteoporosis have reduced bone mass prior to age-related bone loss, suggesting the expression genetic influence for

increased osteoporotic risk from an early age. Furthermore, a three-generation study in males by Van Pottelbergh et al (120) revealed that sons of men with osteoporosis have reduced bone size and reduced volumetric BMD, despite normal markers of bone remodeling. These results further support the notion that genetics has a strong influence on skeletal growth and development.

In addition to genetic predisposition to osteoporosis, age-related changes in hormonal status are an additional non-modifiable risk factor in adult men. The age-related decrease in serum 25(OH) D levels and declining renal function can cause secondary hyperparathyroidism, which is excessive parathyroid hormone (PTH) production (76). Parathyroid hormone increases with advanced aging (38). PTH is released from the parathyroid gland when blood calcium levels are decreased, which directly stimulates osteoclastic bone resorption and causes an increased flux of calcium from bone to the blood (41). Furthermore, a decrease in growth hormone (GH) and insulin-like growth factor (IGF-I) , sometimes called the growth hormone insulin-like growth factor system, can be seen with advanced aging in men. These decreases in GH and IGF-I may contribute to impaired bone formation with aging (108). In addition to PTH and GH/IGF-I, sex steroids also play a part in age-related bone loss. There is an increased risk for bone loss and fracture in males who have a lower than normal level of testosterone, also called hypogonadism (127). Testosterone therapy in men with hypogonadism has been shown to positively affect bone mass in most patient groups (127). In addition to testosterone, estradiol levels in males also contribute to skeletal health, as shown when estrogen deficiency resulted in increased bone loss in men (35). The reduction in these sex hormones with aging is likely due to an increase in sex-hormone binding globulin (SHBG), which binds free testosterone and estradiol in the blood. For example, Khosla et al (56) found a two-fold increase in SHBG during advanced aging, which was associated with a reduction in levels of free sex-hormones.

**Modifiable risk factors.** Adequate nutrition, responsible lifestyle behaviors, and continued participation in weight-bearing physical activity are essential to minimize bone loss during adulthood. Adequate dietary calcium is essential to maintain bone health. Dawson-Hughes et al (26) showed that the incorporation or supplementation of calcium in the daily diet has been shown to reduce the rate of bone loss from the spine, hip, and total body in adult males. However, it is important to note that the men the intervention group receiving supplemental calcium started the study consuming less than (748mg/d) the recommended daily allowance (1,200 mg/d). Since calcium is a threshold nutrient, once the adequate intake is met, additional intake doesn‟t confer greater benefits. Thus, this result may reflect that these men were affected by calcium supplements because they were below the RDA, suggesting the importance of meeting the calcium RDA. For example, in a cross-sectional study by Cauley et al (20), a positive relationship was found between dietary calcium intake and BMD in adult men, i.e., men who had consumed amounts of calcium closer to the RDA had greater BMD. Similarly, Burger et al (17) observed that the rate of age-related bone loss was attenuated with higher dietary calcium intake in a group of 1856 elderly men.

Reduced calcium intake also affects the parathyroid gland. Parathyroid glands quickly respond to very small changes in blood calcium levels, which secrete parathyroid hormone (PTH) in response to low blood calcium concentrations. With low dietary calcium intake, PTH stimulates skeletal resorption by increasing the activity and number of osteoclasts in order to maintain serum concentrations of calcium (10). While remodeling improves bone strength by repairing acquired defects, excess remodeling contributes to structural weakness in bone (42). In addition, alterations in vitamin D play a key role in the development of age-related bone loss (76). Most studies report a fall in the circulating concentration of vitamin D with advancing age

(76). In addition, blood levels of serum 25-hydroxyvitamin D (25(OH)D) -have been reported to be significantly higher in males than females, but both sexes experience a decline with increasing age (65). Looker et al (65) reported serum 25(OH)D to be significantly related to hip fracture risk, and that elderly adults are recommended to obtain serum levels of 60 nmol 25(OH)D to lower hip fracture risk. A reduced availability of vitamin D from the diet and sunlight are associated with aging (76), and vitamin D absorption from the gastrointestinal tract also seems to decrease in the elderly (28). This decrease may be due to an age-related reduction in intestinal vitamin D receptor concentration (28), as reported by Harris et al (40), when younger men had a 90% greater increase in 25(OH)D levels compared to older men in response to the same supplementation dosage. Furthermore, aging is also associated with the decreased cutaneous production 7-dehydrocholesterol in the skin, which allows vitamin D to be converted to pre-vitamin D, a precursor to the much needed vitamin $D_3$ (66). Moreover, a decline in the ability of the kidney to form $1,25(OH)_2D$ also occurs with aging, and has been implicated as a possible mechanism for age-related osteoporosis (33).

Besides nutritional factors, lifestyle and behavioral factors play a role in the maintenance of BMD during adulthood in men. For example, several studies reported a negative association between smoking or excessive alcohol consumption and bone mass (17, 20, 79, 84). For example, Papaioannou et al (79) performed a systematic review on risk factors for low BMD in healthy men aged 50 years or older. They found that current, and former, smokers were at greater risk of developing low BMD compared to non-smokers (79). Moreover, two longitudinal studies included in the review revealed that current smoking was predictive of bone loss at the hip (17, 39), which occurred at almost double the rate compared with subjects who had never smoked, (17, 39) and even former smokers (39). As for excess alcohol consumption, Malik et al (69)

conducted a cross-sectional study on low bone density and impaired bone metabolism in young men and women (27-50 y). In the males only, BMD of the lumbar spine and proximal femur were significantly reduced (69). It has been suggested that osteoblastic dysfunction, which results in diminished bone formation and reduced bone mineralization, may be the reason for reduced BMD in alcoholic patients (116). However, Peris et al (82) found that BMD improved significantly after two years of alcohol abstinence, suggesting that alcohol has damaging effects on bone formation, but can improve after a period of abstinence.

In addition to these nutritional and lifestyle behavior modifications, participation in weight-bearing exercise is also a valuable factor in preventing the loss of bone mass during aging in adult males. Although weight – bearing exercise during adulthood may not be as effective at promoting bone formation as compared to periods of growth, small gains in BMD may be possible to achieve in adult men (74, 98, 121). Of equal importance, the bone mass gained during growth may be maintained with weight-bearing exercise, attenuating the age-related bone loss commonly seen during progressive aging (58).Thus, there is a critical importance for adult men to ensure they are consuming a balanced diet, including adequate amounts of calcium and vitamin D, refrain from smoking and consuming excess alcohol, and partake in high-impact, weight-bearing physical activity. Addressing these modifiable risk factors may positively influence the remodeling cycle within the human skeleton.

**The process of bone turnover – the remodeling cycle.** The remodeling cycle is the sequential process of activation, resorption, reversal, and formation within bone cells of the skeleton. It is helpful to understand the differences between bone turnover coupling, balance, and rate. Coupling is the sequence of phases in remodeling, in which activation precedes resorption, which precedes reversal, which precedes formation, as seen in Figure 1. Balance refers to the

equilibrium between bone removed and bone replaced by the processes of resorption and formation. When in balance, these two processes result in the maintenance of bone mineralization (29). If there is an imbalance in the process, either formation or resorption will become predominant, and there will either be a resulting net gain or loss of bone. Rate is the speed of remodeling, or turnover, which is occurring. If turnover rate is high, then the sequence (or coupling) of activation, resorption, reversal, and formation is rapid (80, 81).

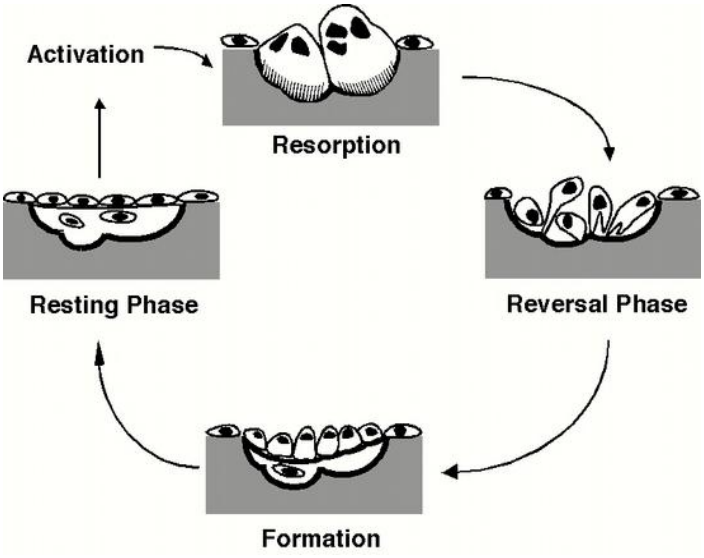



**FIGURE 1**. **The bone remodeling sequence (shown here on trabecular bone surface). In the remodeling sequence, activation precedes resorption, which precedes reversal, which precedes formation. (From Favus MJ, (ed) Primer on the metabolic bone diseases and disorders of mineral metabolism. 5th edn, pp 5-6, 2003. American Society for Bone and Mineral Research, Washington)(29)**

Bone remodeling is a continuous process throughout life, through which pockets of old bone are replaced by new bone to maintain bone structure and mineral homeostasis (23). Remodeling takes place on trabecular (also called cancellous) bone surfaces and in cortical bone (also called compact) by a coupled process carried out by the bone remodeling unit (BRU) (Figure 2) (23).

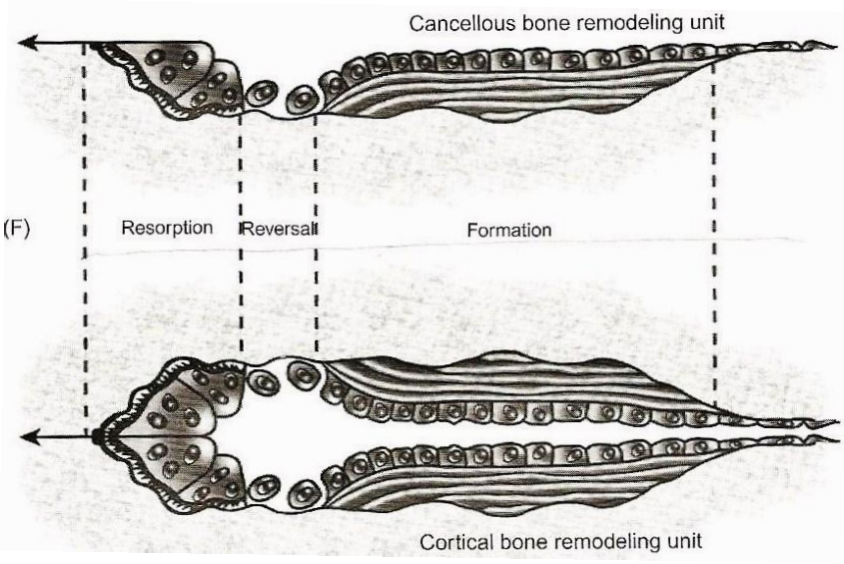



**FIGURE 2. Cross-sectional diagrams of BRUs in cancellous bone (A) and cortical bone (B) during the remodeling sequence. The arrows indicate the direction of remodeling. (From Seibel MJ, Robins SP, Bilezikian JP. (eds) Dynamics of bone and cartilage metabolism . 2nd edn, pp 377-389, 2006. Academic Press, New York).**

The BRU is composed of a tightly coupled group of osteoclasts and osteoblasts that carry out the sequential processes of activation, resorption, reversal, and formation phases of bone

remodeling, resulting in removal of old bone and formation of new bone (23). This systematic cycle takes about 3-6 months to complete (29).

The activation phase, which is approximately one week long (29), involves recruitment and activation of osteoclast precursors, lifting of the endosteum that contains the lining of cells off the bone surface, and fusion of multiple osteoclasts precursors to form „preosteoclasts" (23, 29, 94). The preosteoclasts bind to the bone matrix to create a „sealing zone" ready for resorption (29, 94).

Bone resorption is the next phase, which is carried out by multinucleated cells called osteoclasts (29, 102). Resorption lasts approximately 2-4 wks (29), during which osteoclasts acidify the resorption area by pumping hydrogen ions and other proteins resulting in the digestion of the old bone matrix and a hollowed cavity ready for new bone formation (102, 103)

The transition from bone resorption to formation is called the reversal phase, which lasts approximately 1-2 wks (71). During reversal, preosteoblasts are recruited to begin new bone formation in the cavity left by osteoclasts (29, 102, 103). The signals that link the end of bone resorption to the beginning of bone formation are yet to be determined (29).

During the bone formation phase, the osteoblast is the bone lining cell responsible for laying down new bone matrix, called osteoid, in the resorptive cavity (23, 29). Osteoblasts regulate mineralization of bone matrix by releasing small vesicles that contain calcium and phosphate (9). At the completion of bone formation, which takes approximately 4-6 months, osteoblasts are buried in the bone matrix where they become osteocytes or bone lining cells (29, 102). Osteocytes maintain intimate contact with each other through gap junctions, which act as a network of sensor cells (or syncytium) that detect changes in mechanical strain in bone and send

signals to the bone surface to initiate a new bone remodeling cycle (15). Bone lining cells may serve as a blood-bone barrier by regulating the influx and efflux of mineral ions into and out of bone extracellular fluid (16). In addition, bone lining cells have the ability to re-differentiate into osteoblasts upon sensing mechanical loading (16, 29). The end result of a completed remodeling cycle by a bone remodeling unit is the production of a new osteon, or a new functional unit in bone.

Once adulthood has been reached, changes in bone mass and geometry may affect skeletal health and maintenance through the rest of adulthood. Unlike the growth period when remodeling rate is rapid, adulthood is characterized by a reduction in remodeling rate (102, 103). The compromise in bone‟s material properties and geometry can be attributed to (103) a reduction in bone formation (63), an increase in the volume of bone resorption by the BRU (70), and structural decay due to the increased rate of bone remodeling, resulting in a negative balance favoring resorption over formation (70). Thus, utilizing factors to minimize bone loss and prevent osteoporosis and its consequential fractures later in life.

Bone remodeling is not harmful to bone unless it becomes excessive. Bone turnover during adulthood maintains bone strength by removing damaged bone and replacing it with new bone, restoring the skeletal macro- and micro-architecture (81, 128). However, after the completion of skeletal growth, the capacity of BRUs to rapidly and effectively model and remodel bone is diminished, resulting in a negative balance of bone turnover (102, 103). In men, this negative balance is primarily due to reduced bone formation from the BRUs (63), but can also be attributed to an increase in the volume of bone resorption by the BRU (70), resulting in a negative balance favoring resorption over formation (70). This negative balance in the amount of bone resorbed and formed by the BRUs is found on the endocortical, intracortical, and trabecular

areas of bone‟s endosteal surface, promoting structural decay during progressive aging (128). Therefore, effective strategies are necessary to prevent the compromise in bone‟s material properties and geometry as a result from advanced aging, thus minimizing bone loss and prevent osteoporosis and its consequential fractures later in life.

**Pharmacological therapies to modify bone turnover**. The most thoroughly studied pharmacological agents for the management of osteoporosis in a variety of populations, including males, are the bone-active agents, or anti-resorptive agents, that reduce bone turnover. These drugs for the treatment of osteoporosis in men can be classified in to anti-resorptive or anabolic agents (83). Anti-resorptive agents, or drugs that inhibit osteoclast function, include most of the commonly used therapies in men (83). For example, some of these drugs include calcitonin, testosterone, selective estrogen receptor modulators (SERMs), and bisphosphonates (83). However, bisphosphonates are the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of osteoporosis in men (3). The National Osteoporosis Foundation (NOF) recommends drug treatment for men aged 50 and older with prior hip or vertebral fracture, with osteoporosis (T-score $\leq$ -2.5 at the femoral neck or spine) or with osteopenia (T-score between -1.0 and -2.5 at the femoral neck or spine), and an absolute 10-year risk of hip fracture based on the FRAX fracture risk assessment tool (78). Thus, the option of taking these medications to people with, or at risk of developing, osteoporosis is quite attractive.

**Mechanisms of drug therapy**. The mechanisms of action of individual anti-resorptive medications as whole differ; however, their effect on increasing bone strength and reducing the risk of fragility fractures share common pathways. For example, they all aim to increase BMC and reduce bone turnover (75). For example, calcitonin is a peptide derived from the

parafollicular cells of the thyroid, and is an inhibitor of osteoclast activity (52). In 2002, Trovas et al (111) administered daily 200 IU intranasal calcitonin to 28 osteoporotic men for 12 months. They found that after 12 months of therapy, the treated group had significantly suppressed markers of bone resorption (DPD, NTX, and CTX), and to a lesser extent in markers of bone formation (BAP, OC, PICP, PINP) (111). In addition, subjects had increased lumbar spine BMD, but not at the hip (111). Similarly, Toth et al (110) found that 18 months of intranasal calcitonin significantly increase LS and hip BMD, as well as reduced vertebral fractures. However, calcitonin is not approved in the US for the treatment of male osteoporosis (83).

Testosterone also has been shown to increase BMD in hypogonadal men (106, 122). Anderson et al (8) treated 21 men, aged 34-73, with osteoporosis and prior vertebral fracture every two weeks for six months. They found that LS BMD increased, and all serum markers of bone turnover decreased, but markers of bone resorption were the most reduced (DPD, NTX) (8). In contrast, Snyder et al (107) randomized 108 men, aged 65 year and older, without osteoporosis to a daily testosterone patch or placebo. They found no treatment effect in the men without osteoporosis (107). Thus, the effect of testosterone on improving BMD may be limited to men with osteoporosis. Regardless, there is a lack of data assessing the effect of testosterone replacement on fracture risk, and testosterone is not approved in the US for the treatment of osteoporosis (83).

In addition to calcitonin and testosterone treatment, bisphosphonates (BP) are a common prescription to people with osteoporosis. BPs are chemically stable derivatives of inorganic pyrophosphate. They can be classified based on the presence or absence of a nitrogen atom in the R2 side chain of the structure (83), with the nitrogen containing BPs being the more potent inhibitors of osteoclast action (27). BPs have a high affinity for the major constituent of bone –

hydroxyapatite. They are incorporated into the cavity sites of active osteoclast-mediated bone resorption on the bone surface, or the resorption lacunae, allowing them to accumulate at local resorption sites where they can affect osteoclast activity (53, 83). It is here that they reduce the depth of the resorption cavity, which in turn reduces the surface area for osteoclast remodeling (53, 75, 83). This is suggested to be one of the mechanisms by which BPs increase bone mineral content and bone strength. The other mechanism of which bisphosphonates promote bone health is through cellular effects on osteoclasts. During resorption, osteoclasts internalize and accumulate BPs, as they were bound to hydroxyapatite. Within the osteoclast, the non-nitrogen containing BPs (etidronate, tiludronate) are incorporated into ATP, creating nonhydrolyzable ATP equivalents (75, 83). These ATP analogs are toxic to osteoclasts, leading to mitochondrial inhibition and osteoclastic apoptosis (86). The nitrogen-containing BPs negatively affect the osteoclast cytoskeleton, inhibit osteoclast precursor differentiation, and inhibit osteoblast-mediated osteoclast activation (83, 105). By this mechanism, BP therapy has been shown to be an effective method to slow bone remodeling and increase BMD in men and women, even after three months of treatment.

**Adverse health risks and concerns**. The aforementioned therapies appear to be near-flawless to protect or improve bone health in men. However, each of these treatments is subject to unpleasant, or even harmful, side-effects, which has led some physicians to suggest a "drug holiday" from the treatments. For example, the use of calcitonin may result in nausea or allergic reaction after injection. Moreover, this drug has not been approved for use in males with osteoporosis in the United States. Likewise, testosterone therapy has been shown to improve BMD in men with low testosterone, or are hypogonadal, but has not has not been approved to treat osteoporosis in men in the U.S, which may be due to the universal anabolic properties of the

hormone, e.g. it is also anabolic to tumor cells. In addition to calcitonin and testosterone, BPs have also had short-term and long-term adverse health effects associated with them. As for short term adverse effects of BP therapy, the most commonly cited reason for patient intolerance to oral bisphosphonate therapy is upper GI adverse effects, i.e. nausea, abdominal pain, and gastritis. Furthermore, patients who have received IV BP therapy have had a transient acute phase reaction, which usually lasts 24 to 48 hours, and is characterized by fever, myalgia, and arthralgia (53). In fact, 1 in 3 patients experiences such a reaction with the first infusion of IV zoledronic acid (53), the only IV BP approved by the FDA for treatment of osteoporosis in men (83), which is followed by less frequent reactions on subsequent injections, e.g. 1 in 15 the second time, and 1 in 35 the third (53). Furthermore, the FDA recently issued an alert highlighting the possibility of severe and sometimes incapacitating bone, joint, and/or musculoskeletal pain at any point after patients begin taking a bisphosphonate (119). Moreover, although discontinuation of BP therapy improves symptoms in some of these patients, others appear to have slow or incomplete resolution (53). Lastly, and although rare, ocular inflammation, ocular pain, ad photophobia have been shown to occur with both oral and IV BP therapy weeks, months, or years after initial BP treatment (53).

In conjunction with the short-term risks of BP therapy, long-term effects also may occur. For example, osteonecrosis of the jaw (ONJ) is the most widely reported adverse effect of long-term BP therapy. Based on a growing number of case reports and institutional review, BP therapy is suggested to possibly cause exposed and necrotic bone that is isolated to the jaw (97). One hypothesis to this extreme adverse effect is tied to the mandible‟s ability to remodel and would heal. That is, the inhibition of osteoclast function prevents normal bone turnover to an extent that local micro-damage from normal mechanical loading or injury, e.g. removal of teeth,

cannot heal, or be repaired (remodeled) correctly (6). This was also demonstrated in the drug Denosumab®, which is a monoclonal antibody that targets osteoclasts through a separate mechanism than BPs (4, 97). Thus, this inhibition of normal bone turnover results in a "lack of healing," which eventually results in bone necrosis. Another theory is that certain bisphosphonates, i.e. zolendronic acid, also have anti-angiogenic properties, which could have an inhibitory effect on circulating levels of vascular endothelial growth factor, thus limiting the local bone blood supply to promote healing (126). Furthermore, the combination of these theories may exacerbate the likelihood of developing ONJ. However, the theory of severe suppression of bone turnover can be extrapolated to the rest of the skeleton. For example, long-term BP therapy may lead to the over-suppression of bone remodeling, an impaired ability to repair skeletal micro-fractures, and increased skeletal fragility.

With the potential adverse side-effects of pharmacological treatment, physicians should use caution in prescribing anti-resorptive medications to patients who are not in immediate need of therapy. For instance, for people who are not quite osteoporotic yet, i.e. osteopenic, additional modalities to improve bone health should be used. For example, weight-bearing physical activity, e.g. resistance training, has been shown to have positive effects on bone health in adult men (74, 98, 121). In addition to improvements in bone health, resistance training is associated with additional positive, rather than negative, side-effects, such as lean muscle mass hypertrophy, increased strength, and improved balance – a factor also shown to reduce the risk osteoporotic fracture as a result from falling. As for men at risk for developing osteopenia, research is needed in order to determine if weight-bearing, high-impact exercise can positively affect bone health. Luckily, our lab group is attempting to fill that gap. Beside the physiological implications, choosing to participate in exercise, rather than pharmacological therapy, has the

potential to save a significant amount of money, as individuals and health insurance companies would be relieved of the price of medication.

**Characteristics of exercise to produce an osteogenic response.** Certain exercises are more effective at inducing osteogenesis and improving bone strength than others. To be the most effective, it is necessary for the exercise regimen to include the appropriate type, intensity, frequency, and duration to obtain the most beneficial osteogenic gains. For example, mechanical forces have osteogenic effects only if the stress to bone is dynamic in nature. In addition, the intensity of loading, including the magnitude and rate of strain on the skeleton, also play important roles in the osteogenic effect of mechanical loading. Finally, the frequency and duration of loading regimens are also essential for optimal osteogenic bone response, as bone can become "deaf" to the mechanical signaling of bone if the exercise is not broken up into shorter, more frequent bouts. The following will give examples of fundamental research conducted to evidence these principles of bone loading.

**Type.** Since the early experiments of Hert & Liskova and Rubin & Lanyon, it has been clear that bone adapts only in response to dynamic loads and not to static loads. For example, Hert and Liskova conducted a series of experiments on the tibia of sixty-five three month old-mature rabbits using either continuous or intermittent loading (43, 64). For the intermittent loading, the rabbits were subjected to 0.2-0.4 s intervals, with 1-2 s between each stimulus, for 1-3 h/day, totaling up to 30 days (64). The bone was rhythmically stressed by transverse bending, which corresponded in range to physiological values. The tibiae were X-rayed and the thickness of the cortical bone was estimated. The structure of the bone tissue and surface were studied on histological cross-sections of the tibial diaphysis, which was divided into several tissue samples which were used for examination of bone apposition or resorption, or histological examination of

bone structure (64). They found that in all intermittently stressed bones, new bone tissue was deposited on the lateral and medial wall of the tibia on both the periosteal and endosteal surface (64). The deposits of new bone were thickest in the spots that received the most stress, i.e. cortical bone layer of the stressed sides (medial or lateral) was thicker than in the control limb (64). Specifically, the cortical bone thickness was found to be higher by an average of 80.4% in the lateral and 38.1% in the medial wall of the experimental rabbits compared to the control limb (64). They concluded that these results were evidence that intermittent (dynamic) stress is an osteogenic stimulus to functional adaptation of bone.

Rubin and Lanyon also demonstrated that dynamic loads are what are needed to see bone adaptation (62). They used mature male turkeys to assess the effects of disuse, static, and dynamic loading (525 N) on remodeling by observing total bone area, periosteal enclosed area, endosteal enclosed area, and percentage intracortical porosity (62). Turkey ulnas were either: unloaded, loaded continuously in compression (static), or loaded intermittently in compression (dynamic) for a single 100 s period per day for eight weeks. Rubin and Lanyon found that the unloaded ulnas showed no remodeling activation the periosteal surface and consequently no difference in the periosteal enclosed area between left and right sides (62). Additionally, the endosteal closed area increased by 11 (±2.4) %, while intracortical remodeling increased 4.82%, and the percentage porosity increased between 0.61 and 4.82% in the unloaded turkeys. Overall, the combined changed resulted in a 13.5 (±3.2) % reduction of total bone area for the unloaded group (62). Interestingly, the static loading group had similar results, in that total bone area was reduced by 8.0 (±4.0) % (62). Conversely, the dynamic loading group increased their total bone area by 25.0 (± 9.5) %, with the primary gains coming from gains in the periosteal surface (62). Rubin and Lanyon concluded that it appears that a static loading with the same strain as dynamic

loading has no effect on bone remodeling, whereas the same load applied intermittently (dynamically) for a short daily period is associated with a substantial increase in bone mass, primarily on the periosteal surface (62).

However, recent observations not only reveal that static loads not only fail to elicit an osteogenic response, but may suppress normal appositional growth. For instance, Robling et al (90) applied a compressive end-load to the ulnae of growing male rats for 10 min/day for two weeks. The rats received one of three loading treatments: static loading at 8.5 N; static loading at 17 N; or dynamic loading (2 Hz) at 17 N (90). The dynamic loading increased osteogenesis significantly on both periosteal and endocortical surfaces, as expected from Hert, Lanyon, and Rubin"s previous studies (90). The static loading at either load magnitude had no effect on endocortical bone formation rate, but actually suppressed periosteal bone formation instead (90). Robling"s results suggest that dynamic loading is required not only to stimulate appositional bone growth, but also to prevent suppression caused by static loading (90).

**Intensity.** The primary mechanical variables associated with load intensity include the magnitude of strain and rate of strain on bone. Both of these factors play a critical role in the osteogenic response of exercise on bone.

**Magnitude.** The skeleton has the intrinsic ability to direct bone formation in response to high mechanical stresses (or strains), thus strengthening the skeleton at highly stressed regions (115). This system, sometimes called the "mechanostat," involves cells within the bone tissue to detect and respond to mechanical loads (30). As a part of Harold Frost"s mechanostat hypothesis in 1987, it is suggested that bone strains in or above the 1500-3000 microstrain range surpass a "minimum effective strain (MES)" threshold, which causes bone modeling to increase cortical

bone mass (30). However, strains below the 100-300 MES microstrain range release bone multicellular unit (BMU) remodeling, which then removes existing cortical, endosteal, and trabecular bone (30). Mosley et al conducted a study on 240 growing male Sprague-Dawely rats (77). They administered short daily periods of controlled dynamic loading in vivo through the flexed carpus and olecranon to the intact ulna of the rats. Unlike the methodology of other studies, this technique involved neither surgical preparation, nor direct loading of the periosteum, allowing them to examine bone formation in vivo, without overstressing the rats. The rodents used their limbs normally between loading cycles, attempting to mimic normal activity, in which short periods of exercise are generally superimposed on longer periods of less strenuous activity. In vivo strain gauges were used to assess strain patterns associated with normal activities for the rat ulna, which typical peak strain magnitudes during unrestricted movement varied between 0.0007 and 0.0012, with peak strain rates between 0.023 and 0.038 sec (77). Mosely et al (77) found that the response to a single 10 minute period of loading/day with peak strains of 0.002 (1200 cycles at 2 Hz, and a loading/unloading rate of +/-0.03 sec-1), resulted in the modification of the normal growth related medial to lateral modeling drift, which simultaneously reduced the rate of lateral periosteal bone deposition and medial bone resorption. This reduced the total amount of new bone formation as well as the mid-shaft curvature of the ulna in the normal modeling pattern. Mosely et al (77) also found that at higher peak strain amplitudes (-0.004), adaptive straightening was accompanied by an increase in bone mass. This was due to an increase in the mineral apposition rate on the previously forming lateral face, and cessation of resorption on the medial ulna surface, with reversal to formation. Mosely et al (77) concluded that at moderate peak strain magnitude (-0.002), modification of drift produced a straighter bone, associated with a reduced periosteal bone formation. Furthermore, at higher strain magnitude (-

0.004), adaptive modeling produced a straighter bone associated with increased periosteal bone formation (77). Moreover, Mosely et al (77) suggest that their experiments show that the growing rat ulna underwent adaptive changes in both bone mass and architecture when short daily periods of axial loading that produced strains within a physiological range, were superimposed on the loading associated with normal activity. Thus, these studies show that the magnitude of loading during exercise is an important factor in an osteogenic response.

**Rate of strain.** The observation that dynamic, cyclic loads are required to initiate an adaptive response implies that bone must be responsive to more than strain magnitude. It is now clear that rate-related phenomena are also critical to bone"s adaptive response (18). For example, Turner et al. (112, 113) demonstrated the relationship between strain rate and bone adaptation with two experiments in 1994 and 1995. They hypothesized that interstitial fluid flow affects bone formation, and tested their hypothesis by indirectly by measuring the effects of different loading frequencies on bone formation rate in vivo on adult female rats (112). Using the four point tibial bending model, the right tibiae of the rats were subjected to bending at frequencies of 0.05, 0.1, 0.2, 0.5, 1.0, and 2.0 Hz for a 2-wk period (112). The rats were then sacrificed and histomorphometric measurements of bone formation were made of the mid-shaft of the tibia. The histomorphometry revealed that increasing the frequency of loading while maintaining a constant strain magnitude caused a significant increase in bone formation rate at frequencies of 0.5–2.0 Hz, but not for rates lower than 0.5 Hz (112). However, due to all animals received 36 cycles/day of loading, the duration of the loading varied in this experiment (i.e. since the frequency of applied load was either 0.05- 2.0 Hz, the duration of loading varied from 12 mm/day (0.05 Hz) to 18 s/day (2.0 Hz)) (112). To address this, Turner et al. performed another experiment in which strain rate was altered, but the frequency, duration, and peak strain magnitude were kept constant

by altering the range of strain (113). In this follow-up experiment, Turner found that that bone formation was significantly increased in the experimental groups with the highest strain rates compared with the lower strain rates, and that bone formation rate was directly proportional to strain rate (113).

**Duration and frequency – bone response to stress saturates quickly.** Nearly 20 years ago, Rubin and Lanyon conducted a classic experiment that showed that only 36 cycles/day at physiologic strain magnitudes were just as effective in promoting bone formation as 1800 cycles/day at the same strain magnitude (96). Specifically, Rubin and Lanyon used applied loads (waveform 0.5 hertz) to 50 week old male turkey ulnas. Groups consisted of not loaded, or 4, 36, 360, 1800 consecutive cycles (occupying 8 s, 72 s, 12 min, and 1 hr, respectively). They found that with the removal of applied load, a negative balance caused remodeling endosteally, intracortically, and periosteally, leading to bone loss (96). Specifically, the bones that did not receive applied loads had a steady decline in BMC content to 88% of the original value by the end of the study (96). Rubin and Lanyon also found that the four consecutive cycles of applied load per day that produce normal physiological strain magnitudes, but an altered strain distribution, prevented remodeling and was associated with no change in bone mass (BMC) (96). Furthermore, the turkeys that were subjected to 36 loading cycles per day showed extensive sub-periosteal and endosteal new-bone formation (96). Interestingly, over a six week period, BMC increased to between 133 -143 % of the original value (96). Moreover, the data on histology and BMC content in the turkey ulnas receiving 360 or 1800 strain cycles revealed no significant difference in either the arrangement or mass of bone tissue when compared with the 36 strain cycle group (96). They concluded that these findings suggest that 1) functional load-bearing application can prevent a remodeling process that would otherwise lead to disuse osteoporosis;

2) a small exposure to a suitable dynamic strain regimen appeared to be sufficient to prevent a negative balance in remodeling that is responsible for disuse osteoporosis; and 3) physiological levels of strain imposed with an abnormal strain distribution (dynamic) can produce an osteogenic stimulus that is capable of increasing bone mass (96).Thus, these results show that the magnitude of the bone response was not enhanced by additional loading cycles beyond 36, implying that the cellular response to mechanical loading saturates quickly. In addition, Umemura et al. also showed that only a few strain cycles are required to induce bone formation, as well as saturate bone response (117). Umemura et al (117) conducted a study in 344 female rats were trained to jump between 5 and 100 jumps/day for eight weeks. They found that only 5 jumps/day were sufficient to cause a significant increase in cortical area and bending rigidity (117). However, area and rigidity were not increased significantly more by 100 jumps/day than by 10 jumps per day (117). These results further indicate that a large number of strains per day is not necessary for bone hypertrophy to develop in rats (117). In a human example, Karlsson et al (50) examined the relationship between the duration of exercise and BMD by measuring the BMD of the axial and appendicular skeleton in 67 active male soccer players. The duration the athletes trained per week was 12 h/week, 8 h/week, and 6 h/week (50). Karlsson found that BMD was higher in all weight-bearing regions for each group participating in the sport compared to age-matched inactive controls (50). In addition, there were no differences in BMD measurements when comparing soccer players exercising for different activity durations, and the BMD needed to attain bone strength proportionate with that of duration of activity is achieved by 6 h/wk of exercise (50). Karlsson concluded that beyond this duration of training, additional exercise confers no higher BMD, and that the skeleton adapts to the prevalent level of exercise intensity required and no further (50). Thus, increasing the duration of a loading bout therefore results in

diminishing returns in bone formation, suggesting that cells may become desensitized to repeated mechanical stimuli (115).

**Duration and frequency – mechanosensitivity.** In order to investigate the amount of time required to restore mechanosensitivity to desensitized bone cells in vivo, Robling et al (88) hypothesized that more frequent, shorter duration loading bouts would elicit a greater osteogenic response than a single 3-minute bout. Sixty-three adult female Sprague-Dawley rats were subjected to 360 bending cycles per day of a 54 N force delivered in 1, 2, 4, or 6 bouts on each of the 3 loading days. Rats in the 6-bouts/d group received 60 bending cycles per bout (60 x 6), separated by a 2 h recovery period from the previous bout; rats in the 4-bouts/day group received 90 bending cycles per bout (90 x 4), each bout separated by 3 h; the 2- and 1-bouts/day groups received 180 (180 x 2) and 360 (360 x 1) bending cycles per bout, separated by 6 h recovery and no recovery, respectively (88). Endocortical bone formation rate in the right tibia of the 4-, 2-, and 1-bout bending groups exhibited 8-, 4-, and 4-fold increases, respectively, over the control side (88). Relative values for endocortical BFR/BS, mineralizing surface (MS/BS), and mineral apposition rate (MAR) were 65-94% greater in the 90 x 4 and 60 x 6 bending groups compared to the 360 x 1 bending group (88). The results presented by Robling et al (88) reveal that 360 daily loading cycles applied at intervals of 60 x 6 or 90 x 4 represent a more osteogenic stimulus than 360 cycles applied all at once, and that mechanical loading is more osteogenic when divided into discrete loading bouts. In a follow up experiment, Robling et al inserted recovery periods (0, 0.5, 1, 2, 4 or 8 h) between loading bouts for 144 female adult Sprague-Dawley rats (89). In addition, Robling et al also investigated the osteogenic effectiveness of shorter-term recovery periods (0.5, 3.5, 7 or 14 s) introduced between each of 36 identical daily loading cycles (89). Robling found that in the rats receiving recovery periods between loading bouts,

histomorphometric measurements from the endocortical surface of the tibiae revealed more than 100 % higher relative bone formation rates in the 8 h recovery group than in the 0 and 0.5 h recovery group (89). In the rats allowed time to recover in between loading cycles, 14 s of recovery resulted in significantly higher (66-190 %) relative bone formation rates compared to any of the three shorter recovery periods ( 0.5, 3.5, 7 s) (89). Robling et al (89) concluded that approximately 8 h of recovery was sufficient to restore full mechanosensitivity to the cells, and that their results further demonstrate the importance of recovery periods for restoring mechanosensitivity to bone cells, as well as maximizing the osteogenic effects of mechanical loading treatments.

In addition, Umemura et al (118) investigated the frequency per week or day of high-impact, low-repetition (10 jumps) exercise for osteogenic response in two experiments. The first experiment examined frequency of exercise per week in 48 Wistar rats. The rats were divided into five groups including: a sedentary control (W0), one exercise session per week (W1), three exercise sessions per week (W3), five exercise sessions per week (W5), and seven exercise sessions per week (W7). In the second experiment, 30 rats were randomly divided into three groups: a sedentary control (D0), one exercise session per day (D1), and two exercise sessions per day (D2). After eight weeks of exercise, histomorphology revealed that the exercise increased the fat-free dry weight of the tibia in the W1 (7.5%, n.s.), W3 (12.6%, $P < 0.01$), W5 (12.0%, $P < 0.01$), and W7 (19.8%, $P < 0.001$) groups compared with the W0 group (118). In the daily jump experiment, fat-free dry weight in the D1 (12.0%, $P < 0.001$) and D2 (13.0%, $P < 0.001$) groups were increased compared with the D0 group (118). These increases were also accompanied by increased bone strength and cortical area at the mid-shaft. The results presented by Umemura et al (118) suggest that it is not always necessary to do high-impact exercise every

day for bone gain. However, exercising every day proved to have the greatest effect (118). The results in this study also suggest that there is little additional benefit if bones are loaded by two separate exercise sessions daily (118). However, only two sessions were included, thus an increase in frequency (i.e. 4 sessions per day) may prove to have a greater effect, as shown by Robling et al previously. For instance, Robling et al (92) again examined the effects of shorter, more frequent mechanical loading on the bone mass of female Sprague-Dawley rats. The rats were put into two loading groups where the right ulnae was subjected to 360 load cycles per day, 3 days per week, for 16 consecutive weeks. Load was applied as a haversine waveform at a frequency of 2 Hz and peak load magnitude of 17 N of the 360 load cycles received throughout each load day. One group was administered all 360 cycles in a single, uninterrupted session (360x1), which lasted 3 min. The other loaded group was administered the 360 cycles in four discrete bouts of 90 cycles per bout (90x4), with 3 h of recovery inserted between each of the brief (45 s long) loading bouts. After 16 wk of loading, BMC, aBMD, vBMD, and mid-shaft cross-sectional area were significantly greater in right (loaded) ulnae compared with left (nonloaded) ulnae in the two loaded groups (92). When the daily loading regimen was broken into four sessions per day (90x4), BMC, aBMD, midshaft cross-sectional area improved significantly over the loading schedule that applied the daily stimulus in a single, uninterrupted session (360x1) (92). Specifically, the percent difference between right and left ulnar aBMD in the 90 x 4 group was approximately 60% greater ($P = 0.012$) than the right versus left difference in the 360x1 group (92). Additionally, the 90x4 group exhibited 37% greater ($P = 0.012$) right versus left difference in cross-sectional area than the 360 x1 group (92). Robling (92) concluded that when 360 load repetitions are administered to the rat ulna 3 times x wk, for 16 wk, the anabolic response is much greater if the repetitions are divided into four smaller bouts of 90

repetitions per bout, separated by 3 h recovery periods, than if they are applied in a single, uninterrupted bout.

In combination, these experiments show that bone response saturates quickly in response to mechanical loading, and that a period of recovery either between cycles or between loading sessions can optimize the adaptive response.

Overall, previous research has revealed the many factors that are needed produce an osteogenic stimulus. Thus, in order to be most effective, the exercise regimen must include the appropriate type, intensity, frequency, and duration of exercise to obtain the most beneficial osteogenic gains. Specifically, dynamic loads are necessary for gains in bone mass, as static loads not only lack an osteogenic effect, they may indeed suppress normal bone growth. In addition, the intensity of the exercise must involve a large enough magnitude to surpass the "minimal effective stimulus," and the rate of strain development on the skeleton is more effective if it is applied rapidly. Furthermore, exercise programs aimed at maintaining or improving bone mass might achieve greater success if the daily exercise regime is broken down into several smaller sessions separated by recovery periods.

**Mechanism of how exercise affects bone.** The human skeleton contains an intrinsic biological control system that directs bone formation to areas that experience high mechanical stress, or strains, thus strengthening the skeleton in highly stressed regions (31, 115). Julius Wolff (125) first recognized that bone‟s architecture can be affected by mechanical loads, and as a result, he developed "Wolff‟s law" in 1892. Wolff‟s law states that bone adapts its form and function to the stimuli applied to the skeleton (125). This system responds to strains detected by bone is also called the bone‟s "mechanostat" (31). The mechanostat involves cells within the

bone tissue detecting and responding to mechanical loads in regions of high mechanical strain (31). It is necessary for the applied mechanical load to exceed a "minimally effective strain (MES)" threshold to provide the necessary stimulus to activate bone remodeling (31).

At the cellular level, this mechanosensory function operates by a network of bone lining cells, osteoblasts, and osteocytes that transduce stress signals to activate resorption and/or formation (15, 22, 61). Specifically, osteocytes within the mineralized matrix are in direct communication with one another and surface osteoblasts (including bone lining cells) through gap junctions due to an extracellular fluid shift when mechanical stimulus is applied (15, 31, 61, 115). This fluid shift associated with mechanical strain produces a rapid flux of intracellular calcium across these junctions, which is thought to facilitate the transmission of information regulating modeling and remodeling between osteoblasts and osteocytes (22, 61). The mechanosensory response in areas of high strain that surpass this threshold causes bone formation to increase and reduced bone resorption, resulting in increased cross-sectional area and reduced porosity, both of which strengthen the bone (31, 61, 115). Therefore, in order to have an effective exercise intervention, mechanical loading must past the threshold that causes stimuli to regulate bone remodeling, such as resistance training or plyometrics. Passing this threshold is crucial to preserve, or even improve, bone integrity and strength by positively regulating the balance between formation and resorption. Thus, the type of exercise participated in during adulthood is a crucial factor in promoting positive, osteogenic response in bone.

**The effects of exercise based interventions on bone mineral density in men.** Exercise continues to have benefits throughout the lifespan. There have been several studies examining the effects of weight-bearing, high-impact activities during young adulthood, middle-adulthood, and late-adulthood in men.

**Young adulthood.** Young adulthood has shown to also be an important time to accrue bone mineral to optimize peak bone mass before adulthood. For example, Casez et al (19) investigated BMD and BMC at the lumbar spine and tibial diaphyses at the beginning and at the end of a 15-week military training period for 151 male recruits of the Swiss army, ages 20-22 years old. The troops belonged to one of five different categories (infantry grenadiers, tank drivers, tank gunners, signalmen, and privates) who each participated in physical training of varying intensity. At baseline, height, BMI, and degree of physical fitness independently correlated with vertebral and tibial BMD. BAP, gamma-glutamyl-transferase, OC, and PTH were measured at the beginning and end of the military training period. DXA was used to assess BMD and BMC of the lumbar spine, which revealed over the 15 weeks of physical training, BMD at tibial diaphyses increased (2.2%) at the left leg ($p$ = <.001) and by 1.1% at the right leg ($p$ = 0.002) with differences between troop categories. Interestingly, lumbar spine BMD decreased significantly in tank drivers (−1.2%, $p$ = 0.001) and particularly in infantry grenadiers (−2.1%) who had the most strenuous weight-bearing training, but not in other troop categories (19). Furthermore, these BMD changes were associated with increments in serum levels of osteocalcin and BAP activity. In addition, 48 subjects volunteered for a third investigation carried out 2 years after the end of military training. At this time, lumbar spine BMD and BMC had returned to baseline, whereas bone width and BMC, but not BMD, increased by 5.8% and 6.2 %, respectively, vs. baseline ($p$ = <.001 for both) at the tibial diaphyses (19). Casez et al concluded that 1) bone mass appears to be determined by both anthropometric parameters and the degree of physical fitness; 2) an acute four-month physical exercise period leads to increased BMD tibial diaphyses and to increased bone turnover, resulting in a transitory bone loss at lumbar spine with

complete recovery within two years; and 3) diameter of tibial diaphyses increases after age 20, leading to a rise in absolute tibial bone mass (19).

In addition, Cohen et al (25) examined the effects of rowing on BMD and BMC of 17 college-aged males (mean age 19.5 y) over a seven month period. The subjects had no previous rowing experience, and were compared with eight age-matched controls. Cohen et al (25) measured the lumbar spine (L1-L4), femoral neck, greater trochanter, and wards triangle by DXA to determine BMD and BMC. The rowing training program consisted of approximately 8 h of rowing, 1 h of resistance training, and 1 h of running per week. After 7 months, BMD of the lumbar spine (L1-L4) had increased significantly by 2.9% and the mean BMC had increased by 4.2% in the exercise intervention group (25). Furthermore, no significant change was found in the control group. In addition, neither group showed a significant change in BMD or BMC in the femoral neck, greater trochanter or Ward's triangle (25). During the drive phase of the rowing stroke, maximal force on the proximal femur is exerted almost exclusively by muscle activity without gravitational contributions, which may not exceed the threshold necessary to cause a significant osteogenic response (25). They concluded that these results provide further evidence that exercise, including rowing intervention, plays an important role in bone mineral formation (25).

Furthermore, resistance training has shown to possibly be a useful exercise modality to increase bone mass in young adults. For example, Ryan et al (98) conducted a six month whole-body resistive training (RT) exercise intervention in a cohort of 20-29 year old men (n=10) and women (n=7); and 65-74 year old men (n=10) and women (n=10). The RT program consisted of 3 exercise sessions/wk on non-consecutive days for approximately six months using 11 exercises of pneumatic variable-resistance machines. The training included the following exercises: leg

press, chest press, leg curl, latissimus pull-down, leg extension, military press, seated row, triceps pushdown, abdominal crunch, biceps curl, and sit-ups. DXA was used to assess total and regional BMD and BMC at the femoral neck, Ward's triangle, greater trochanter, total-body, and lumbar (L2-L4) spine before and after the 6 month study (98). Ryan et al (98) found a significant increase in BMD at the femoral neck, ward's triangle and greater trochanter, as well as total body BMC and leg BMC ($P<0.05$). However, total body and lumbar spine BMD did not change with RT (98). In addition, no gender differences in the training response between men and women for any of the BMD regions were found, and no age differences in the training response, except for a trend between young and older subjects for femoral neck ($P<0.08$) was found. Ryan et al (98) concluded that a six month RT program increases muscle mass and improves BMD of the femoral region in young (20-29 y) and healthy older (65-74 y) men and women as a group, with a trend for the positive response to be greater in young subjects.

**Middle- and late-adulthood.** Middle and late adulthood is a time when bone mineral density begins, and continues to decline with age. However, exercise interventions have shown that it is still possible to maintain, and possibly gain, BMD in middle-and late adulthood. For example, Menkes et al (74) examined the effects of resistance training (RT) on BMD and bone remodeling in middle-aged men. Eighteen previously inactive untrained males ages 54-61 years old underwent 16 weeks of either RT (n = 11) or no exercise (inactive controls; n = 7). The exercise training was 3 d/wk, 1-2 sets x 15 reps. Total body, lumbar spine (L2-L4), and femoral neck BMD were measured before and after the experimental period by DXA. In addition, serum concentrations of OC, BAP, and TRAP were measured before, during, and after the experimental program in all subjects. Menkes et al (74) found that BMD increased in the femoral neck by 3.8 % and 2% in the lumbar spine. However, changes in lumbar spine BMD were not significantly

different from those in the control group. Furthermore, no significant change in total body BMD was found (74). Osteocalcin increased by 19% after 12 wk of training and remained elevated after 16 wk of training (74). There was a 26% increase in BAP levels after 16 wk of training (74). In addition, no significant differences in TRAP levels were found. Moreover, there were no significant changes in BMD, or any of the serum markers in the control group. Menkes et al (74) suggest that these findings confirm that 16 weeks of RT in middle-aged and older men results in increased regional BMD.

Likewise, Bemben and Bemben (14) conducted a study which aimed to determine the dose–response effect of 40 weeks of resistance training on BMD in older men and women, aged 55–74 y. The training program consisted of 12 isotonic resistance exercises, including five upper body (forearm flexion/extension, shoulder press, latissimus pull-down, seated row) lifts, and seven lower body (knee flexion/extension, two-leg press, hip flexion/extension, hip abduction/adduction) lifts. Subjects were randomized into one of four groups: 1) high intensity (80%1RM), 2 d/wk (2HI); 2) low intensity (40% 1RM), 2 d/wk (2LI); 3) high intensity (80% 1RM), 3 d/wk (3HI); or 4) low intensity (40% 1RM), 3 d/wk (3LI). Bemben and Bemben (14) used DXA to observe changes in WB, LS, and proximal femur BMD. They found significant trial ($p<0.05$) effects, but no significant trial × training group interactions each BMD site. LS, trochanter, and total hip BMD increased from baseline to 40 wk. Men and women exhibited similar improvements for the trochanter and total hip sites, but the percent change in the spine tended to be higher for men (1.8%) than women (0.4%) ($p=0.054$).

In addition, Huuskonen et al. (47) investigated effects of regular aerobic exercise training on bone mineral density (BMD) in middle-aged men. A cohort of 140 men (n = 70 EX, n = 70 CON) aged 53-62 years was randomly assigned into the exercise (3-5x/wk, 60 min) and control

groups. Huuskonen measured BMD and apparent volumetric BMD (BMDvol) of the proximal femur and lumbar spine by DXA. Regardless of the group, there was no association between the increase in aerobic threshold and change in BMD. In the entire group, age-related bone loss was seen in the femoral neck BMD and BMDvol ($p < 0.01$), and both BMD and BMDvol values increased with age in L2-L4 ($p < 0.004$). In men with low energy-calcium adjusted intake, an increased rate of bone loss at the femoral neck was ($p = 0.003$). Furthermore, men who increased their alcohol intake during the study showed a decrease in the rate of bone loss at the femoral neck ($p = 0.040$) (47). Huuskonen et al (47) concluded that long-term low- to moderate-regular aerobic physical activity in middle-aged men had no effect on the age-related loss of femoral BMD. In addition, the increase seen in lumbar BMD reflects age-related changes in the spine, thus making it an unreliable site for BMD follow-up in men (47).

Combining both resistance training and jumping exercise, Kukuljan et al (60) examined the independent and combined effects of a multi-component exercise program (RT and impact exercise) and calcium with vitamin-$D_3$ fortified milk on BMD in 180 older men, ages 50-79 years old. The study was a 12 month randomized control trial, in which the men were randomized into one of four groups: 1) exercise + fortified milk; 2) exercise; 3) fortified milk; or 4) controls. The exercise consisted of 60-75 minutes of warm-up, progressive resistance training (PRT), core muscle stabilization exercises and a series of moderate impact weight bearing activities interspersed between the RT exercises, and cool-down. The impact training started with three sets of 20 jumps, and progressed to between 80-180/session. Jumps included: single and double foot multi-directional landings, bench stepping, and jumping off 15 and 30 cm boxes. The magnitude, rate and distribution (direction) of loads applied to the lower body were also progressively increased throughout the program by either increasing the height of jumps and/or

by introducing more complex movement patterns. To measure GRFs, force plates were used. GRFs varied from 1.5 x body for walking on the spot with knee lifts to a maximum of 9.7 x body weight for a forward leap off a 30-cm box with a rebound. Femoral neck, total hip, lumbar spine and trochanter BMD were measured via DXA. Kukuljan et al (60) found that exercise resulted in a 1.8% net gain in femoral neck BMD relative to no-exercise ($p < 0.001$). For lumbar spine BMD, there was a net 1.4-1.5% increase in all treatment groups relative to controls (all $p < 0.01$) (60). In addition, there were no main effects of fortified milk at any skeletal site. Kukuljan concluded that a multi-component exercise program involving weight-bearing, high-impact activities was effective for increasing femoral neck BMD in older men, but additional calcium-vitamin $D_3$ did not enhance the osteogenic response (60).

Similarly, Welsh et al (123) studied the effects of high-impact exercise on BMD in 15 men ($n = 6$) and women ($n = 9$) between the ages of 50 and 73 years old. The exercise was a part of an aerobics class called "keep-fit," where exercises consisted of step and jumping activities specifically to load the proximal femur and spine, and were performed 2-3 times per week. Subjects were matched for sex, age, menopausal status and mass to 15 non-exercising controls. The proximal femur, lumbar spine, and total body BMD were measured at before and after the study. Welsh et al (123) found that BMD increased non-significantly at the femoral neck (1.57%) and Wards triangle (1.97%) in the exercise group. In addition, greater trochanter BMD significantly increased (2.21%) in the exercise group, and femoral neck BMD decreased by -1.9% in the control group, which was significantly different from the change in the exercise group (123). Furthermore, BMD did not change at Wards triangle or trochanter in the controls, and lumbar spine BMD did not change in either group. Total body BMD did not change in the exercise group, but decreased by -0.79% in the controls (123). Welsh et al (123) suggest that this

study supports that high-impact aerobic exercise in postmenopausal women and men over 50 years old is reasonable and effective at increasing proximal femur BMD, but not spine or total body BMD (123). However, it may maintain BMD at the whole body.

In summary, the previous studies show that exercise interventions which involve weight-bearing or high-impact exercises can positively affect bone mineral density in males during all stages of the lifespan. Therefore, it should be recommended and encouraged that males of all ages participate in a form of exercise throughout life that incorporates skeletal loading. By doing this, peak bone mass can be optimized during growth and young adulthood, and maintained or even added upon during the adult years, resulting in a decreased susceptibility for osteopenia, osteoporosis, and fracture.

**The long-term effects of exercise on markers of bone turnover.** There is limited data on the long-term effects of exercise on bone turnover markers in males. Specifically, there are very few longitudinal studies that last more than six months. However, the data available is promising. For example, Fujimura et al (32) studied the effects of high intensity resistance exercise training on bone metabolism in 17 young adult males (23-31 years) by measuring sensitive biomarkers of bone formation and resorption. The subjects were assigned to a training group, which followed a 45 minute weight training program, three sessions per week for four months, or a sedentary control group. Total body, lumbar spine, femoral neck, and mid-radius BMD were assessed via DXA. Biomarkers including osteocalcin (OC), specific alkaline phosphatases (BAP), and procollagen type-I C-terminal concentration (PICP) were measured once a month during both exercise and resting days for the training group, and once every other month in the control. In the training group, serum OC concentration and serum BAP activity were significantly increased within the first month after the beginning of resistance exercise

training, and the elevated levels remained throughout the training period (32). There was no significant change in plasma PICP concentration. Furthermore, urinary deoxypyridinoline excretion was briefly suppressed and returned to the initial value but was never stimulated during the 4 months (32). These results suggest that the resistance exercise training enhanced bone formation without prior bone resorption. In addition, there was no significant change bone mineral density in either group. Fujimura et al concluded that resistance exercise training increased markers of bone formation, while it transiently suppressed a marker of bone resorption (32). In addition, the adaptive changes of bone metabolism caused by resistance training occurred during the early period of the training, before changes in bone density were observable through densitometry (32).

Woitge et al (124) investigated the changes in bone turnover induced by eight weeks of aerobic or anaerobic exercise in young males, aged 20-29 y. Thirty healthy young males were randomized into either an aerobic exercise (n = 10), anaerobic exercise (n = 10), or control group (n = 10). Each exercise group participated in 60 minutes of exercise per session, three times per week. The aerobic exercise group completed 40-60 minutes of running at a heart rate corresponding to 60-85% $VO_2$max. In the anaerobic group, two of the three weekly anaerobic sessions consisted of sprints at 90–100% of maximum speed (5 x 80–300 m) with 5–8 minutes of passive recovery between each interval. During the third weekly session, a 60-minute weight-lifting program for increasing leg strength and sprint ability was performed. Serum BAP, serum OC, and urinary PYD and DPD were determined as indices of bone metabolism. After four weeks of aerobic training, serum BAP, OC ($P < 0.01$), urinary PYD ($P < 0.001$), and DPD ($P < 0.01$) were significantly reduced (124). After eight weeks, BAP and OC levels had returned to baseline values, whereas the urinary cross-link excretion remained low. In the anaerobic training

group, elevated levels of BAP ($P < 0.05$ vs. week 4), OC ($P < 0.05$ vs. week 4), and PYD ($P < 0.01$ vs. week 0) were observed after 8 weeks of exercise, further suggesting the impact of physical activity on bone turnover may depend on the kind of exercise performed (124).

**Middle- to late-adulthood.** During middle-to late-adulthood, bone modeling has ceased, thus remodeling prevails. Thus, it has become of interest what the effects of weight-bearing exercise have on bone health during middle- to late-adulthood. Remes et al (87) conducted a four year longitudinal study examining the effects of low- to moderate-intensity aerobic exercise on markers of bone metabolism and BMD in middle-aged men (50-60 y). One-hundred and forty men were randomized into either an exercise group (n = 70), or a control group (n = 70). Participants in the exercise group were prescribed aerobic exercise (i.e., walking, jogging, corss-country skiing, swimming, or cycling), equivalent to 40-60% of maximal oxygen uptake (VO2max) for 30-60 minutes per session, five times per week. Serum TRAP5b and OC were measured to examine changes in bone turnover markers at baseline, one year, and four years. In addition, LS and hip BMD were measured via DXA. After one year of exercise, TRAP 5b activity was significantly reduced in the exercise group compared to the control group ($P = 0.006$). However, after four years of exercise intervention, the difference was no longer statistically significant. Furthermore, Remes et al (87) found no differences in the OC concentration between the study groups during the intervention.

In 2002, Vincent and Braith (121) investigated the effects of six months of high- or low-intensity resistance exercise on markers of bone turnover and BMD in older adults aged 60-83 years. Sixty-two men and women were randomly assigned to one of three groups: 1) control (n = 16); 2) low-intensity resistance training (n = 24); or high-intensity resistance training (n = 22). The exercise protocol was progressive, with subjects training at either 50% of their 1RM for one

set and 13 repetitions (low-intensity), or 80% of 1RM for one set and eight repetitions. Subjects completed this exercise three times per week, for 24 wks. Vincent and Braith (121) measured serum levels of BAP, OC, and PYD to assess bone turnover during the six months of exercise; while DXA was used to assess BMD of the WB, FN, and LS. At the conclusion of their study, they found a 25.1% and 39.0% increase in serum OC in the low- and high-intensity groups, respectively ($P < 0.05$). In addition, BAP increased by 7.1% ($P < 0.05$) in the high-intensity resistance training group. Following these changes in markers of bone turnover, FN BMD significantly increased in the high-intensity group ($P < 0.05$). However, no other changes in BMD were observed. Nonetheless, these results may suggest that low- and high-intensity resistance training is a plausible way to increase markers of bone formation, which may lead to increases in BMD in adults.

## APPENDIX C: INFORMED CONSENT

# CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

INVESTIGATOR'S NAME: PAMELA S. HINTON PH.D.
PROJECT # 1095877
DATE OF PROJECT APPROVAL: SEPTEMBER 12, 2007

| FOR HS IRB USE ONLY |
| --- |
| APPROVED |
| 9/27/10 |
| HS IRB Authorized Representative Date |
| EXPIRATION DATE: 09-12-2011 |

STUDY TITLE: EFFICACY OF PLYOMETRICS TO INCREASE BONE MASS IN MALES WITH LOW BONE MINERAL DENSITY

## INTRODUCTION

**This consent may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand.**

This is a research study. Research studies include only people who choose to participate. As a study participant you have the right to know about the procedures that will be used in this research study so that you can make the decision whether or not to participate. The information presented here is simply an effort to make you better informed so that you may give or withhold your consent to participate in this research study.

Please take your time to make your decision and discuss it with your family and friends.

You are being asked to take part in this study because you are a healthy male who participates in leisure time physical activity.

This study is being sponsored by the Department of Nutrition and Exercise Physiology, University of Missouri-Columbia.

In order to participate in this study, it will be necessary to give your written consent.

## WHY IS THIS STUDY BEING DONE?

The purpose of this research is to determine how effective long term (12 months) jump training (plyometrics) is at improving bone density and increasing hormones that promote bone formation, as

compared to long-term resistance training. This research is being done because the long-term benefits of regular plyometric exercise or resistance training on bone health in males with below normal bone density are unclear.

## How Many People Will Take Part In The Study?

About 250 people will take part in this study at the University of Missouri-Columbia.

## What Is Involved in the Study?

Visit 1: Begin the informed consent process and describe the study purpose and the requirements.

All participants must: 1) be males between 25 and 60 years of age who participate exclusively in leisure time physical activity at least 4 hours per week for the past 24 months; 2) be apparently healthy; 3) be physically able to perform plyometrics or resistance training; 4) be willing to keep daily records of physical activity and food intake; 5) be willing and able to provide accurate information about your medical history; 6) follow a normal sleep/wake cycle; and 7) be willing to take a calcium and vitamin D supplement daily.

All participants must not: 1) smoke, or have quit smoking within the last 6 months; 2) drink excessive amounts of alcohol (more than 3 drinks per day); 3) take medication that affects bone; 4) have a disease that affects bone; or 5) participate regularly in plyometrics or resistance training.

Visit 2: If you decide to participate in the study you will come back for Visit 2 and sign the consent form. Then you will undergo a dual X-ray absorptiometry (DXA) bone density test. You will be required to lie still for approximately 10 minutes during this procedure. You will be exposed to a small amount of radiation during the scan, equivalent to $1/10^{th}$ the radiation of a chest X-ray and about 1/1000 of a similar Computed Tomography scan. All study participants will undergo additional bone density tests at 6 and 12 months. **It is important to note that in order to be eligible to participate in this study, the DXA scan must indicate that you have below normal bone mineral density.** You will be provided with the results of your bone mineral density test. If you have any questions about the results you will need to contact your family practitioner. Interpretation of the results of your bone mineral density test must be performed by a physician.

You will also fill out a medical and physical activity history questionnaire. You must provide information about your medical history, including history of illness, injuries, and drug treatment that may affect your ability to safely and effectively participate in the study. You also must provide accurate information about your physical activity history.

If you meet the eligibility requirements of the study (i.e., age, activity level, no diseases or medications that affect bone, below normal bone mineral density), you will be provided a 7-Day diet record form to record your dietary intake and return at the next visit. You will also be given a form to record your physical training for 7 days.

Visit 3: You will have your blood drawn on five occasions during the study (0, 3, 6, 9, 12 months). Following an 8-12 hour fast, your height and weight will be measured and a blood sample will be taken from a vein in your forearm using the same procedure as would be followed at a health clinic. On three of

these occasions (0, 6, and 12 months) additional blood samples (3) will be collected during the 24 hours after your normally scheduled training. The amount of the blood sample is very small and will not affect your health (15 mL, 1 tablespoon). The blood will be used to measure markers of bone formation and breakdown and hormone levels. Your blood will be analyzed for factors that may affect your bone mass.

Your blood will be kept frozen for 5 years after the study is completed and the results are published in a research journal. No additional tests will be performed on your blood sample.

The study will require regular visits to the Exercise Physiology Laboratory, each visit lasting 30-90 minutes during the course of the exercise intervention. On several occasions (0, 6, and 12 months) during your normally scheduled training we will determine your feelings of pain, fatigue and exertion using surveys to help determine your experience with the training program and monitor your risk for pain and/or injury.

You will continue your normal exercise program throughout the study and you will maintain your normal life at home, work or school. You are allowed to quit at any time without penalty or loss of any benefits. You will be asked to discontinue the study if the research and medical staff determine it is in your best interest to do so.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in either group.

Interventions: All exercise training sessions will be conducted at the McKee Gym Fitness Center, under the supervision of trained exercise personnel.

**Group 1: If you are participating in the plyometric intervention you will attend 3 training sessions per week until you complete the 12-month exercise intervention.**

Participants will complete 10 repetitions of 10 different exercises to accumulate 40-120 loading cycles (jumps). The plyometric exercise sets will include: squat jumps, forward hops, split squat jumps, , lateral box push offs, bounding, bounding with rings (lateral), box drill with rings, lateral hurdle jumps, zigzag hops, single leg lateral hops, and progressive depth jumps (10-100cm). The intensity of plyometric training will progress, with low intensity jumps weeks 1-2, low and moderate jumps weeks 3-4, and high intensity jumps weeks 5-6, followed by a rest week. You will steadily increase the intensity and number of jumps over each training cycle.

**Group 2: If you are participating in the resistance training intervention you will attend 2 training sessions per week until you complete the 12-month exercise intervention.**

Each exercise session will be made up from the following resistance exercises: squats, bent over row, dead lift, military press, lunges, and calf raises. Prior to and every 6 weeks during the Resistance Exercise Training (RET) intervention, maximal strength testing will be performed. This will involve a warm-up set of 5-10 repetitions, equal to 40-60% of your perceived maximum for each exercise. After a brief rest period, a second set of 3-5 repetitions at an intensity between 60-80% of perceived maximum will be performed. Subsequent attempts will be conducted using incremental increases in weight until a failed attempt, typically within 3 to 5 maximal attempts. One repetition maximums (1RM) will be conducted

for squat, dead lift, and military press exercises, and modified maximums (10 repetitions) will be calculated for exercises in which 1RM are not commonly performed.

To account for strength adaptations as a result of strength training improvements, a progressive exercise program will be used. Weeks 1-2 will include one warm-up set (10 repetitions at 20% 1RM) and 3 moderate intensity sets (10 repetitions at 50% 1RM) for each exercise performed. Weeks 3-4 will be comprised of one warm-up set (10 repetitions at 20% 1RM), two sets at a moderate intensity (10 repetitions at 60% 1RM), and one set at high intensity (6-8 repetitions at 70-75% 1RM). Weeks 5-6 will be comprised of one warm-up set (10 repetitions at 20% 1RM), two sets at moderate intensity (10 repetitions at 60% 1RM), and one set at high intensity (3-5 repetitions at 80-90% 1RM). Week 7 will be a rest week.

## How Long Will I Be in the Study?

Completion of all exercise training and testing procedures will take approximately 12 months.

You can stop participating at any time. Your decision to withdraw from the study will not affect in any way your medical care and/or benefits.

## What Are the Risks of the Study?

While on the study, you are at risk for the side effects described below. You should discuss these with the investigator and/or your doctor. There may also be other side effects that we cannot predict.

Risks and side effects related to the study tests and procedures include:

There is a possibility of bruising and soreness at the site of the blood draw. Sterile procedures will be used so the chance of getting an infection is very remote.

There is a possibility of muscle and joint injury as a result of participating in the weight lifting exercises of the resistance training and the jumping of the plyometric training. Participants will be instructed in the safe and proper procedures for all exercise activities by qualified exercise physiologists and supervised by exercise personnel at all times. All exercise sessions will include warm-up and cool-down procedures to further minimize the risk of injury.

**Reproductive risks: The effects of the DXA scan on the male reproductive system are unknown but could cause harm. If you have any questions about the reproductive issues, please discuss them with the investigator or your doctor.**

You will be exposed to a small amount of radiation. Radiation effects are cumulative. You should always inform future doctors of your participation in this study.

For the reasons stated above the investigator will observe you closely during the study described above and, if you have any worrisome symptoms, notify the investigator immediately. Dr. Pam Hinton's telephone number is (573) 882-4137. For more information about risks and side effects, ask the investigator or contact Dr. Hinton at (573) 882-4137.

## ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. You may expect to benefit from taking part in this research to the extent that you are contributing to medical knowledge. We hope the information learned from this study will allow for more specific exercise prescriptions for men with low bone mineral density.

In addition, you will: 1) participate in a supervised exercise program; 2) potentially improve your bone mass, strength, and balance; 3) receive free bone mineral density screening and results; 4) receive free diet and physical activity analyses; 5) receive free calcium and vitamin D supplements; and 5) have free parking and access to the McKee Gym locker room and showers during exercise sessions.

## WHAT OTHER OPTIONS ARE THERE?

You have the option to not participate in this study.

## WHAT ABOUT CONFIDENTIALITY?

Information will be stored in the investigator's file and identified by a code number only. The code key connecting your name to specific information about you will be kept in a separate, secure location. Information contained in your records may not be given to anyone unaffiliated with the study personnel at the University of Missouri-Columbia in a form that could identify you without your written consent, except as required by law. If the investigator conducting this study is not your primary, or regular doctor, she must obtain your permission before contacting your regular doctor for information about your past medical history or to inform them that you are in this study.

It is possible that your medical and/or research record, including sensitive information and/or identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), the Food and Drug Administration (FDA), federal or state government agencies, University of Missouri Health Sciences Institutional Review Board or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor (and/or its agents), or by any of these agencies, the University of Missouri-Columbia will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

## WHAT ARE THE COSTS?

There is no cost to you for the study procedures. You will not be charged for blood tests that are part of this research study.

## WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

You will be compensated $1000 for completion of the study. You will be paid $300 for completion of the first six months of the study and an additional $700 upon completion of the entire study.

## WHAT IF I AM INJURED?

It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury. The University of Missouri, in fulfilling its public responsibility, has provided medical, professional and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff. The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri. In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

## What Are My Rights as a Participant?

**Participation in this study is voluntary. You do not have to participate in this study. Your present or future care will not be affected should you choose not to participate.** If you decide to participate, you can change your mind and drop out of the study at any time without affecting your present or future care in the University of Missouri-Columbia. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. In addition, the investigator of this study may decide to end your participation in this study at any time after she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed.

You will be informed of any significant new findings discovered during the course of this study that might influence your health, welfare, or willingness to continue participation in this study.

## Whom Do I Call if I Have Questions or Problems?

If you have any questions regarding your rights as a participant in this research and/or concerns about the study, or if you feel under any pressure to enroll or to continue to participate in this study, you may contact the University of Missouri Health Sciences Institutional Review Board (which is a group of people who review the research studies to protect participants' rights) at (573) 882-3181.

You may ask more questions about the study at any time. For questions about the study or a research-related injury, contact Dr. Pam Hinton at (573) 882-4137 or Dr. John Thyfault at (573) 882-9818.

A copy of this consent form will be given to you to keep.

## SIGNATURE

I confirm that the purpose of the research, the study procedures, the possible risks and discomforts as well as potential benefits that I may experience have been explained to me. Alternatives to my participation in the study also have been discussed. I have read this consent form and my questions have been answered. My signature below indicates my willingness to participate in this study.

| | |
|---|---|
| Subject/Patient* | Date |
| Legal Guardian/Advocate/Witness (if required)** | Date |
| Additional Signature (if required) (identify relationship to subject)*** | Date |

*A minor's signature on this line indicates his/her assent to participate in this study. A minor's signature is not required if he/she is under 7 years old. Use the "Legal Guardian/Advocate/Witness" line for the parent's signature, and you may use the "Additional Signature" line for the second parent's signature, if required.

**The presence and signature of an impartial witness is required during the entire informed consent discussion if the patient or patient's legally authorized representative is unable to read.

***The "Additional Signature" line may be used for the second parent's signature, if required. This line may also be used for any other signature which is required as per federal, state, local, sponsor and/or any other entity requirements.

"If required" means that the signature line is signed only if it is required as per federal, state, local, sponsor and/or any other entity requirements.

## SIGNATURE OF STUDY REPRESENTATIVE

I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts as well as potential benefits and have answered questions regarding the study to the best of my ability.

| | |
|---|---|
| Study Representative**** | Date |

****Study Representative is a person authorized to obtain consent. Per the policies of the University of Missouri Health Care, for any 'significant risk/treatment' study, the Study Representative must be a physician who is either the Principal or Co-Investigator. If the study is deemed either 'significant risk/non-treatment' or 'minimal risk,' the Study Representative may be a non-physician study investigator.

## APPENDIX D: HIPPA AUTHORIZATION FORM

UNIVERSITY OF MISSOURI-COLUMBIA
Institutional Review Board

# HIPAA AUTHORIZATION FORM

**Authorization for the Use and Disclosure of Personal Health Information Resulting from Participation in a Research Study**

| FOR IRB USE ONLY | |
|---|---|
| Acknowledged | |
| Dan Vellem | 3/18/09 |
| IRB Authorized Representative | Date |

**Principal Investigator's Name:** Dr Hinton
**Project #** 1095877
**Project Title:** Efficacy of Plyometrics to Increase Bone Mass in ~~Male Cyclists with Osteopenia~~ Males with Low Bone Mineral Density

You have agreed to participate in the study mentioned above. This authorization form gives more detailed information about how your health information will be protected.

1. Description of the information
My authorization applies to the information described below. Only this information may be used and/or disclosed in accordance with this authorization:
Demographic and anthropomorphic information, results of bone density scan, blood tests, and medical history

2. Who may use and/or disclose the information
I authorize the following persons (or class of persons) to make the authorized use and disclosure of my PHI:
Principal investigator and graduate students research assistants.

3. Who may receive the information
I authorize the following persons (or class of persons) to receive my personal health information
University Missouri IRB, publications, research collaborators, and current and potential funding agencies

4. Purpose of the use or disclosure
My PHI will be used and/or disclosed upon request for the following purposes:
Publications and presentation that will not identify me, auditing, administrative and billing reviews, study outcomes including safety and efficacy

5. Expiration date or event
This authorization expires upon:
☐ The following date: _____
☐ End of research study
☒ No expiration date
☐ Other: _____

6. Right to revoke authorization
I understand that I have a right to revoke this authorization at any time. My revocation must be in writing in a letter sent to the Principal Investigator at 106 McKee Gym, University of Missouri, Columbia, MO 65211. I am

- aware that my revocation is not effective to the extent that the persons I have authorized to use and/or disclose my PHI have already acted in reliance upon this authorization.

7. Statement that re-disclosures are no longer protected by the HIPAA Privacy Rule
I understand that my personal health information will only be used as described in this authorization in relation to the research study. I am also aware that if I choose to share the information defined in this authorization to anyone not directly related to this research project, the law would no longer protect this information. In addition, I understand that if my personal health information is disclosed to someone who is not required to comply with privacy protections under the law, then such information may be re-disclosed and would no longer be protected.

8. Right to refuse to sign authorization and ability to condition treatment, payment, enrollment or eligibility for benefits for research related treatment
I understand that I have a right not to authorize the use and/or disclosure of my personal health information. In such a case I would choose not to sign this authorization document I understand I will not be able to participate in a research study if I do not do so. I also understand that treatment that is part of the research project will be conditioned upon my authorization for the use and/or disclosure of my personal health information to and for use by the research team.

9. Suspension of right to access personal health information
I agree that I will not have a right to access my personal health information obtained or created in the course of the research project until the end of the study.

10. If I have not already received a copy of the University of Missouri Healthcare Privacy Notice, I may request one. If I have any questions or concerns about my privacy rights I should contact, the HS Privacy Officer at 573-882-9054 or the Campus Privacy Officer at 573-882-7254.

11. Individuals' signature and date
I certify that I have received a copy of the authorization.

_____ _____
Signature of Research Participant Date

_____ _____
Research Participant's Legally Authorized Representative Date

_____
Describe Representative Authority to Act for the Participant

## APPENDIX E: PHYSICAL ACTIVITY READINESS QUESTIONNARE (PAR-Q)

## Male Bone Intervention Study

### Physical Activity Readiness Questionnaire

Subject number _____

These questions ask about your readiness to participate in this research study's physical activity component. Please read each question carefully and answer each one honestly. Check **YES** or **NO**

| YES | NO | |
|---|---|---|
| ☐ | ☐ | 1. Has you doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor? |
| ☐ | ☐ | 2. Do you feel pain in your chest when you do physical activity? |
| ☐ | ☐ | 3. In the past month, have you had chest pain when you were not doing physical activity? |
| ☐ | ☐ | 4. Do you lose your balance because of dizziness or do you ever lose consciousness? |
| ☐ | ☐ | 5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity? |
| ☐ | ☐ | 6. Do you have high blood pressure (systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg)? |
| ☐ | ☐ | 7. Is your doctor currently prescribing drugs (for example, water pills) for blood pressure or heart condition? |
| ☐ | ☐ | 8. Do you know of any other reason why you should not do physical activity? |
| ☐ | ☐ | 9. Do you have a family history of heart disease (for example, heart attack or sudden death) in first degree relative (male <55 years or female <65 years old)? |
| ☐ | ☐ | 10. Currently a smoker or quit within previous 6 months? |
| ☐ | ☐ | 11. Do you have high cholesterol? (Total cholesterol > 200 mg/dl, high-density lipoprotein cholesterol < 35 mg/dl, low-density lipoprotein > 130 mg/dl) |
| ☐ | ☐ | 12. Do you have impaired fasting glucose? (for example ≥ 110 mg/dl) |
| _____ | | 13. During a typical week how many alcoholic beverages do you consume? |
| _____ | | 14. What is the greatest number of alcoholic beverages you may consume in a single day? |

## APPENDIX F: HISTORICAL LEISURE ACTIVITY QUESTIONNAIRE (HLAQ)

## Efficacy of Plyometrics to Increase Bone Mass in Men

Medical and Physical Activity History Questionnaire

Subject number _____
Date _____

These questions ask about your medical and physical activity history. Please fill in the blank or circle the appropriate response.

1. Date of Birth: __ __ / __ __ / __ __ __ __

2. Ethnicity: Hispanic or Latino Not Hispanic or Latino

3. Race: African-American/Black
   Alaskan Native
   American Indian
   Asian
   Caucasian/White
   Hawaiian or other Pacific Islander
   Other: _____ (specify)

4. Do you regularly consume soy foods? Yes No

5. Do you currently take a calcium supplement? Yes No

   What dose? _____mg

6. Are you currently taking any medications? Yes No

   If so, which ones_____(specify)

7. Are you currently taking any anti-inflammatory steroids? Yes No

   If so, which ones? _____ (specify)

   How long have you been taking them? _____ (specify)

8. Have you previously taken anti-inflammatory steroids? Yes No

   If so, which ones? _____ (specify)

   When and for how long? _____ (specify)

9. Do you have a family history of osteoporosis? Yes No

If so, please list affected family members, e.g., maternal grandmother.

_____

10. Have you ever been diagnosed with a disease that affects bone (Cushing's disease, hyperthyroidism, leukemia, Crohn's disease, chronic liver disease, rheumatoid arthritis, etc)? Yes No

What was the diagnosis? _____

When was the diagnosis? _____

What is your current treatment? _____

11. Have you had any sports related fractures or stress fractures in the past 5 years?

Fracture: Yes No
Number _____
Location on body_____

_____

Year_____

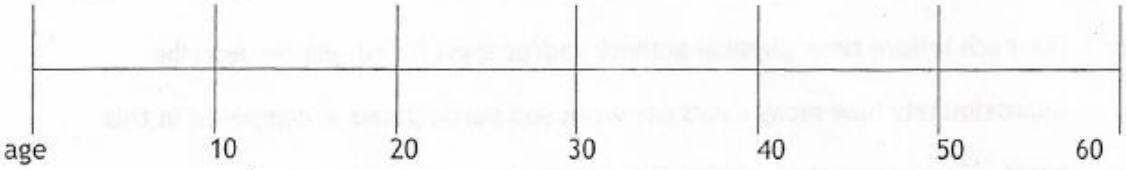
Stress Fracture: Yes No
Number _____
Location on body_____

_____

Year_____

12. Please use the timeline below to indicate what leisure time physical activity and/or sports (include strength training) you participated in or played during your lifetime.

14. Please use the timeline below to indicate job titles and physical activity you have had during your lifetime.




15. During the past 7 days, did you work for pay or as a volunteer (if yes, continue to questions 15-16)? Yes No

16. During the past 7 days, how many hours did you work for pay and/or as a volunteer?
_____ hours.

17. Which of the following categories best describes the amount of physical activity required on your job and/or volunteer work?

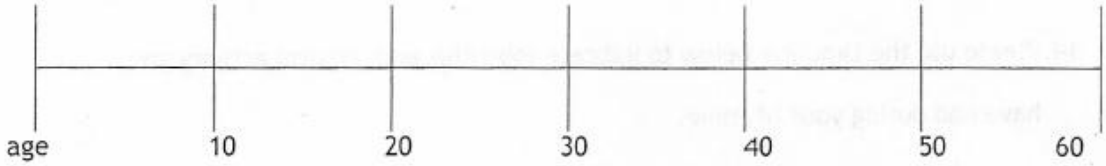
a. Mainly sitting with slight arm movements. [Examples: office worker, watchmaker, seated assembly line worker, bus driver, etc.]

b. Sitting or standing with some walking. [Examples: cashier, general office worker, light tool and machinery worker, etc.]

c. Walking with some handling of materials generally weighing less than 50 pounds. [Examples: postal worker, waiter/waitress, construction worker, heavy tool and machinery worker, etc.]

d. Walking and heavy manual work often requiring handling of materials weighing over 50 pounds. [Examples: lumberjack, stone mason, general laborer, etc]

18. Do you have a "normal" sleep pattern i.e., awake during the day, and asleep at night? Yes No




For each leisure time physical activity and/or sport listed, please describe approximately how many hours per week you participated or competed in this sport. If you competed, please indicate the level of competition.

| Physical Activity or Sport | Ages | Hours per week | Weeks per year | Level of Competition |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

13. What leisure time physical activities and/or sports do you participate in now (include strength training)? How many hours per week do you train for or compete in this leisure time physical activity and/or sport? If you compete, please indicate the level of competition.

| Physical Activity or Sport | Hours per week | Weeks per year | Level of Competition |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

## APPENDIX G: CONTROL SUBJECT FOLLOW UP FORMS

Dear_____,

My name is Andy Dawson and I am a graduate student working with Dr. Pam Hinton in the Department of Nutrition and Exercise Physiology at the University of Missouri - Columbia. I would like to thank you for previously participating in the screening for our study, **"Efficacy of Plyometrics to Increase Bone Mass in Males with Low Bone Mineral Density."** Based on your DXA results, you were eligible for our study. We have attached your DXA reports and have summarized your results from your previous screening.

We are currently in the process of inquiring if people who qualified to participate in our research study, but chose not to participate, would be willing to return for a follow up DXA scan to measure their bone density, as you did before. This would require less than 1 hour of your time in the lab, and would only involve a DXA scan and completion of a 7 day diet and exercise log. In addition to receiving an updated DXA scan, you would also be compensated for you time ($25) and travel expense if necessary.

I look forward to hearing from you, and hope you choose to participate in this follow up DXA scan. Please let me know if there are any questions I can answer. Thank you for your time and consideration.

Sincerely,

Andy Dawson, B.S.
Graduate Student
Dept. of Nutrition and Exercise Physiology
University of Missouri
107 McKee Gymnasium
Columbia, MO 65211

Email: awdqm2@mail.missouri.edu
Phone: 573-882-9917

# CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

**INVESTIGATOR'S NAME: PAMELA S. HINTON**
**PROJECT # 1140618**
**DATE OF PROJECT APPROVAL:**

| FOR HS IRB USE ONLY |
| --- |
| APPROVED<br>HS IRB Authorized Representative 11/2/10 Date<br>EXPIRATION DATE: 07-08-2011 |

## STUDY TITLE: FOLLOW UP BONE DENSITY ASSESSMENT OF MEN WITH OSTEOPENIA

### INTRODUCTION

**This consent may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand.**

This is a research study. Research studies include only people who choose to participate. As a study participant you have the right to know about the procedures that will be used in this research study so that you can make the decision whether or not to participate. The information presented here is simply an effort to make you better informed so that you may give or withhold your consent to participate in this research study.

Please take your time to make your decision and discuss it with your family and friends.

You previously participated in a screening for a project titled "*Efficacy of plyometrics to increase bone mass in men with osteopenia.*" You are being asked to take part in this follow-up study because you have previously been identified as having a hip and/or spine bone mineral density T-score of $\leq$ -1.0.

This study is being sponsored by the Department of Nutrition and Exercise Physiology, University of Missouri-Columbia.

In order to participate in this study, it will be necessary to give your written consent.

## WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine changes in your bone mineral density over time.

This research is being done because there is little information regarding the rate of change of bone density in non-weight bearing male athletes, who previously have been identified as having a hip and/or spine bone mineral density T-score of $\leq -1.0$.

## HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 50 people will take part in this study at the University of Missouri-Columbia.

## WHAT IS INVOLVED IN THE STUDY?

As a study participant you will make a total of 1 visit to McKee Gym at the University of Missouri-Columbia. The study visit will last approximately 1 hour. Prior to your study visit you will be provided a copy of the informed consent form and provided an oral explanation of the study purpose, protocol, and potential risks and benefits. You will be given time to read the consent form and ask questions of the study personnel.

If you choose to participate in the study, the informed consent document will be signed and witnessed at your study visit. At this visit, you will complete a written medical history questionnaire. This questionnaire will be reviewed by study personnel with you to verify accuracy of responses. You also will be provided a 3-Day Diet Record and 7-Day Physical Activity Log forms to record your dietary intake and return completed at your study visit.

At the study visit to the Exercise Physiology Lab, you will return the 3-Day Diet Record and Physical Activity Log. You will report to the lab between 06:00 and 09:00 hours after an overnight fast (10 hours) and prior to exercise (24 hours). You will have your weight and height measured using standard procedures. You will undergo a DXA (QDR 4500) scan for determination of BMC, BMD and body composition. A "whole body" scan requires that the subject lay still for 3 minutes.

The radiation you will receive is equivalent to $1/10^{th}$ of a chest X-ray.

## HOW LONG WILL I BE IN THE STUDY?

The one study visit will be completed with in 1 week after you have provided informed consent.

**You can stop participating at any time. Your decision to withdraw from the study will not affect in any way your medical care and/or benefits.**

## WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects described below. You should discuss these with the investigator and/or your doctor. There may also be other side effects that we cannot predict.

Risks and side effects related to the study tests and procedures we are studying include:

You will be exposed to a small amount of radiation from the bone density DXA scan. The radiation you will receive is equivalent to $1/10^{th}$ of a chest X-ray. Radiation effects are cumulative. You should always inform future doctors of your participation in this study.

Reproductive risks: The effects of the bone density DXA scan on the male reproductive system are unknown but could cause harm. If you have questions about the reproductive issues, please discuss them with the investigator or your doctor.

For the reasons stated above the investigator will observe you closely while participating in the study described above and, if you have any worrisome symptoms, notify the investigator immediately. Dr. Pam Hinton's telephone number is (573) 882-4137. For more information about risks and side effects, ask the investigator, Dr. Hinton at (573) 882-4137.

## ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may be direct medical benefit to you. Upon completion of the study, you will be provided measurement of your bone mineral density using a DXA scan body composition analysis, and a dietary analysis. You may expect to benefit from taking part in this research to the extent that you are contributing to medical knowledge. We hope the information learned from this study will benefit other individuals with low bone mineral density in the future.

## WHAT OTHER OPTIONS ARE THERE?

You have the option to not participate in this study.

## WHAT ABOUT CONFIDENTIALITY?

Information produced by this study will be stored in the investigator's file and identified by a code number only. The code key connecting your name to specific information about you will be kept in a separate, secure location. Information contained in your records may not be given to anyone unaffiliated with the study in a form that could identify you without your written consent, except as required by law. If the investigator conducting this study is not your primary, or regular doctor, they must obtain your permission before contacting your regular doctor for information about your past medical history or to inform them that you are in this trial.

It is possible that your medical and/or research record, including sensitive information and/or identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), the Food and Drug Administration (FDA), federal or state government agencies, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor (and/or its

agents), or by any of these agencies, the University of Missouri-Columbia will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

## WHAT ARE THE COSTS?

There is no cost to you for the study procedures.

## WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

You will be compensated *$25* for completion of the study.

## WHAT IF I AM INJURED?

It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury. The University of Missouri, in fulfilling its public responsibility, has provided medical, professional and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff. The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri. In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

## WHAT ARE MY RIGHTS AS A PARTICIPANT?

**Participation in this study is voluntary. You do not have to participate in this study. Your present or future care will not be affected should you choose not to participate.** If you decide to participate, you can change your mind and drop out of the study at any time without affecting your present or future care in the University of Missouri-Columbia. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. In addition, the investigator of this study may decide to end your participation in this study at any time after she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed.

You will be informed of any significant new findings discovered during the course of this study that might influence your health, welfare, or willingness to continue participation in this study.

## WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions regarding your rights as a participant in this research and/or concerns about the study, or if you feel under any pressure to enroll or to continue to participate in this study, you may contact the University of Missouri Health Sciences Institutional Review Board (which is a group of people who review the research studies to protect participants' rights) at (573) 882-3181.

You may ask more questions about the study at any time. For questions about the study or a research-related injury, contact Dr. Pam Hinton at (573) 882-4137.

A copy of this consent form will be given to you to keep.

## SIGNATURE

I confirm that the purpose of the research, the study procedures, the possible risks and discomforts as well as potential benefits that I may experience have been explained to me. Alternatives to my participation in the study also have been discussed. I have read this consent form and my questions have been answered. My signature below indicates my willingness to participate in this study.

| | |
|---|---|
| Subject/Patient* | Date |
| Legal Guardian/Advocate/Witness (if required)** | Date |
| Additional Signature (if required) (identify relationship to subject)*** | Date |

*A minor's signature on this line indicates his/her assent to participate in this study. A minor's signature is not required if he/she is under 7 years old. Use the "Legal Guardian/Advocate/Witness" line for the parent's signature, and you may use the "Additional Signature" line for the second parent's signature, if required.

**The presence and signature of an impartial witness is required during the entire informed consent discussion if the patient or patient's legally authorized representative is unable to read.

***The "Additional Signature" line may be used for the second parent's signature, if required. This line may also be used for any other signature which is required as per federal, state, local, sponsor and/or any other entity requirements.

"If required" means that the signature line is signed only if it is required as per federal, state, local, sponsor and/or any other entity requirements.

## SIGNATURE OF STUDY REPRESENTATIVE

I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts as well as potential benefits and have answered questions regarding the study to the best of my ability.

Study Representative****

Date

****Study Representative is a person authorized to obtain consent. Per the policies of the University of Missouri Health Care, for any 'significant risk/treatment' study, the Study Representative must be a physician who is either the Principal or Co-Investigator. If the study is deemed either 'significant risk/non-treatment' or 'minimal risk,' the Study Representative may be a non-physician study investigator.

UNIVERSITY OF MISSOURI-COLUMBIA
Institutional Review Board

# HIPAA AUTHORIZATION FORM

**Authorization for the Use and Disclosure of Personal Health Information Resulting from Participation in a Research Study**

| FOR IRB USE ONLY |
| --- |
| **Acknowledged** |
| Dan Vinson 7/6/09 |
| IRB Authorized Representative Date |

**Principal Investigator's Name: Pamela S. Hinton**
**Project #** 1140618
**Project Title: Follow up bone density assessment of men with osteopenia**

You have agreed to participate in the study mentioned above. This authorization form gives more detailed information about how your health information will be protected.

**1.** Description of the information
My authorization applies to the information described below. Only this information may be used and/or disclosed in accordance with this authorization: Demographic and anthropomorphic information, results of bone density scan, and medical history.

**2.** Who may use and/or disclose the information
I authorize the following persons (or class of persons) to make the authorized use and disclosure of my PHI: Principal investigator and student research assistants.

**3.** Who may receive the information
I authorize the following persons (or class of persons) to receive my personal health information: University Missouri IRB, publications, research collaborators, and current and potential funding agencies.

**4.** Purpose of the use or disclosure
My PHI will be used and/or disclosed upon request for the following purposes:
Publications and presentation that will not identify me, auditing, administrative and billing reviews, study outcomes including safety and efficacy

**5.** Expiration date or event
This authorization expires upon:
☐ The following date: _____
☐ End of research study
☒ No expiration date
☐ Other: _____

**6.** Right to revoke authorization
I understand that I have a right to revoke this authorization at any time. My revocation must be in writing in a letter sent to the Principal Investigator at 106 McKee Gym, University of Missouri, Columbia 65211. I am aware that my revocation is not effective to the extent that the persons I have authorized to use and/or disclose my PHI have already acted in reliance upon this authorization.

**7.** Statement that re-disclosures are no longer protected by the HIPAA Privacy Rule
I understand that my personal health information will only be used as described in this authorization in relation to the research study. I am also aware that if I choose to share the information defined in this authorization to anyone not directly related to this research project, the law would no longer protect this information. In addition, I understand that if my personal health information is disclosed to someone who is not required to comply with privacy protections under the law, then such information may be re-disclosed and would no longer be protected.

**8.** Right to refuse to sign authorization and ability to condition treatment, payment, enrollment or eligibility for benefits for research related treatment
I understand that I have a right not to authorize the use and/or disclosure of my personal health information. In such a case I would choose not to sign this authorization document I understand I will not be able to participate in a research study if I do not do so. I also understand that treatment that is part of the research project will be conditioned upon my authorization for the use and/or disclosure of my personal health information to and for use by the research team.

**9.** Suspension of right to access personal health information
I agree that I will not have a right to access my personal health information obtained or created in the course of the research project until the end of the study.

**10.** If I have not already received a copy of the University of Missouri Healthcare Privacy Notice, I may request one. If I have any questions or concerns about my privacy rights I should contact, the HS Privacy Officer at 573-882-9054 or the Campus Privacy Officer at 573-882-7254.

**11.** Individuals' signature and date
I certify that I have received a copy of the authorization.

_____ _____
Signature of Research Participant Date

_____ _____
Research Participant's Legally Authorized Representative Date

_____
Describe Representative Authority to Act for the Participant

## Follow up bone density assessment of men with osteopenia

Subject number _____

These questions ask about your medical and sports history. Please fill in the blank or circle the appropriate response.

1. Current age _____

2. Race/Ethnicity:

   Caucasian/White
   African-American/Black
   Hispanic/Latino/Mexican-American
   Asian American/Pacific Islander
   Other: _____ (specify)

3. Do you regularly consume soy foods? yes no

4. Do you currently take a calcium supplement? yes no

   What dose? _____mg

5. Are you currently taking any medications?

   _____(specify)

6. Are you currently taking any anti-inflammatory steroids?

   _____(specify)

7. Have you in the past 2 years been diagnosed with a disease that affects bone

   (Cushing's disease, hyperthyroidism, leukemia, Crohn's disease, chronic liver disease,

   rheumatoid arthritis, etc )? yes no

   What was the diagnosis? _____

   When was the diagnosis? _____

   What is your current treatment? _____

8. Have you had any sports related fractures or stress fractures since your previous visit?

   Fracture: yes no
   Number _____
   Location on body_____

   _____

   Date_____

   Stress Fracture: yes no
   Number _____
   Location on body_____

   _____

   Date_____

9. Have you significantly changed your diet or physical activity since your last visit?

   yes no

10. If yes please indicated what changes you have made:

11. Did you consult with a physician or seek medical treatment as a result of you previous bone density findings? yes no

12. If yes, please indicate:

13. Based on your previous bone density test, have you made any lifestyle changes?

14. Please use the table below to indicate what activities you participated in since you previous visits.

    For each activity listed please describe approximately how many hours per week and weeks per year you trained.

| Activity | Intensity | Hours per week | Weeks per year |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

# APPENDIX H: DIET AND PHYSICAL ACTIVITY LOGS

ID #: mbi-  Session: MD  Date:  Day of week:

| Time of Day | Food/Drink | Brand | Amount (tsp, cup, oz) | Condiments | Location/Place |
|---|---|---|---|---|---|
| **BREAKFAST** | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| **MORNING SNACK** | | | | | |
| | | | | | |
| | | | | | |
| **LUNCH** | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| **AFTERNOON SNACK** | | | | | |
| | | | | | |
| | | | | | |
| **DINNER** | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| **EVENING SNACK** | | | | | |
| | | | | | |
| | | | | | |
| **SUPPLEMENTS** | | | | | |

# University of Missouri-Columbia
## Exercise Physiology Lab

### Male Bone Intervention

### Physical Activity Log

Subject # _____
Week_____ Dates __/__/__-__/__/__ Weight (lbs)_____

| Day | Date | Exercise Mode | Total Time (hrs:min) | Distance (miles/yards) | Average Pace (min/mile, mph, yds/min) | Max HR | Avg HR | Intensity (L, M, H) |
|---|---|---|---|---|---|---|---|---|
| Mon | | | | | | | | |
| | | | | | | | | |
| Tues | | | | | | | | |
| | | | | | | | | |
| Wed | | | | | | | | |
| | | | | | | | | |
| Thur | | | | | | | | |
| | | | | | | | | |
| Fri | | | | | | | | |
| | | | | | | | | |
| Sat | | | | | | | | |
| | | | | | | | | |
| Sun | | | | | | | | |

# APPENDIX I: INTERVENTION EXERCISE LOG EXAMPLES

PLYO

SUBJECT ID_____
PLYOMETRICS TRAINING WORKOUT LOG

| Time Period | Cycle | Touches |
|---|---|---|
| Week 1 | Light | 40 |

Warm-Up: 10 min

| | Session #1, Date _____ | Session #2, Date _____ | Session #3, Date _____ |
|---|---|---|---|
| EXERCISE/MUSCLE GROUP | reps | reps | reps |
| Squat Jump | | | |
| Forward Hop | | | |
| Split Squat | | | |
| Lateral Box Push Off | | | |
| Bounding | | | |
| Lateral Bounding | | | |
| Box Drill | | | |
| Lateral Hurdle | | | |
| Zig Zag | | | |
| Single Leg Lateral Hurdle | | | |
| Depth Jump (Height: L M H) | | | |
| Jump off Box (Height: L M H) | | | |

Abdominals/Low Back: 2 sets of 15 reps
Cool Down (5 min)/Stretching (5 min): Quads, Hamstrings, calf, IT band, shoulders (2)
Notes:

RT

Subject ID_____
RESISTANCE TRAINING WORKOUT LOG

| Time Period | Cycle | Rest Periods |
|---|---|---|
| Week 4 | Moderate | 3 min |

Warm-Up: 10 min

| | | Session One; Date _____ | | | | Session Two; Date _____ | | | |
|---|---|---|---|---|---|---|---|---|---|
| Exercise | | 20% | 60% | 60% | 70-75% | 20% | 60% | 60% | 70-75% |
| | Load | | | | | | | | |
| Squat | | / | / | / | / | / | / | / | / |
| Military Press | | / | / | / | / | / | / | / | / |
| Dead Lift | | / | / | / | / | / | / | / | / |
| Bent Over Row | | / | / | / | / | / | / | / | / |
| Forward Lunge | | / | / | / | / | / | / | / | / |
| Calf Raise | | / | / | / | / | / | / | / | / |
| Abdominal Crunch | | / | / | / | / | / | / | / | / |
| Back Extension | | / | / | / | / | / | / | / | / |

Cool Down (5 min)/Stretching (5 min, hold for 30 sec): Quads, Hamstrings, calf, IT band, shoulders (2)

Notes:

**SUBJECT ID**_____
**1-RM TESTING WORKOUT LOG**

Warm-Up: 10 min

| | Warm-up #1 | Warm-up #2 | Attempt #1 | Attempt #2 | Attempt #3 |
|---|---|---|---|---|---|
| EXERCISE | wt/reps | wt/reps | wt/reps | wt/reps | wt/reps |
| Squat (1-RM) | / | / | / | / | / |
| Military Press (1-RM) | / | / | / | / | / |
| Dead Lift (1-RM) | / | / | / | / | / |
| Bent Over Row (10-RM) | / | / | / | / | / |
| Forward Lunge (10-RM) | / | / | / | / | / |
| Calf Raise (10-RM) | / | / | / | / | / |

Cool Down (5 min)/Stretching (5 min): Quads, Hamstrings, calf, IT band, shoulders (2)

Notes: