RELATIONSHIP BETWEEN BONE MINERAL DENSITY AND MUSCLE STRENGTH RELATED TO PROTEIN INTAKE AND POLYPHARMACY: ELDERLY, GREATER THAN 55 YEARS OF AGE.

A THESIS

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ABSTRACT

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RELATIONSHIP BETWEEN BONE MINERAL DENSITY AND MUSCLE STRENGTH RELATED TO PROTEIN INTAKE AND POLYPHARMACY: ELDERY, GREATER THAN 55 YEARS OF AGE

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This study is part of a fall prevention study on osteoporosis and parameters relating to bone mineral density. The purpose of this study was to determine the relationship between protein intake, and polypharmacy (number of medications consumed) on bone mineral density and muscle strength in the elderly, 55 years and older.

Thirty-one members from the Seniors in Motion facility completed a 3 day diet analysis to determine protein intake and had bone mineral density measured. The number of medications varied from one to nine medications daily. The most common types of medications consumed included: blood pressure medications (12%), antacids (8%), and blood thinners (8%). In this study there was no significant difference between those consuming a low protein intake (< 0.8 g/kg), moderate protein intake (0.8 – 1.1 g/kg), and high protein intake (> 1.2 g/kg) and total bone mineral density and total hip bone mineral density. There was also no correlation between bone mineral density and polypharmacy.

TABLE OF CONTENTS

Page

LIST OF TABLES

Tables Page

LIST OF FIGURES

Figure Page

CHAPTER I

INTRODUCTION

Falls among older adults, 65 years and older, are detrimental to health and lead to many problems including financial stress. In 2010, there were approximately 2.3 million nonfatal falls. Among these falls, 662,000 individuals were hospitalized. According to the Centers for Disease Control and Prevention (CDC), 1 out of 3 adults, 65 years and older, fall each year (CDC, 2010). In 2000, the cost of falls for the U.S. health care system was 19 billion, and in 2010, this number increased to 30 billion. The total cost of fall related injuries in the elderly, 65 years and older, for males was $160 million, and for females was $189 million in 2005 (CDC, 2012). Preventative actions are important to keep these numbers from rising.

There are multiple factors that increase the chance of a fall occurring: decreased bone mineral density (osteoporosis) leading to hip fracture, muscle atrophy (sarcopenia), and alterations in balance and mechanics, possibly due to number of medications prescribed. Controlling these factors can decrease the chance of falling. Diet, exercise, and monitoring individuals on certain medications prescribed may help prevent osteoporosis, hip fractures, and falls. Adequate protein (0.8 g/kg/day; Bern, 2011) intake may prevent osteoporosis and muscle catabolism. Controlling prescriptions for certain medications (sedative-hypnotic and anxiolytic drugs, tricyclic antidepressants, major tranquilizers [phenothiazines and butyrophenones], antihypertensive drugs, cardiac

medications, corticosteroids, nonsteroidal anti-inflammatory drugs, anticholinergic drugs, and hypoglycemic agents) can prevent dizziness and disturbances in balance (Fuller, 2000). In this study, protein intake, muscle strength, and polypharmacy will be evaluated to determine the relationship to bone mineral density. This study will also determine if there is a difference between high, moderate, and low protein intakes and bone mineral density.

Purpose of the Study

The purpose of this observational, correlation study is to determine if there is a difference between protein intake (high, moderate, and low) on bone mineral density, the relationship between polypharmacy, consuming five or more medications daily, and bone mineral density, and the relationship between muscle strength and polypharmacy in the elderly, 55 years of age and older, participating in regular, monitored exercise at the Seniors in Motion facility located in Denton, Texas. This study is part of a longitudinal, comprehensive therapeutic exercise program for elderly fall prevention started in the Fall 2010 at Texas Woman's University, Denton campus and Seniors In Motion (SIM) facility.

Statement of the Problem

Protein Intake

Protein is involved in numerous metabolic processes including: bone health, preservation of energy balance, cardiovascular function, and wound healing (Wolfe, Sharon, & Miller, 2008). The current minimal protein recommendation for the healthy elderly population is 0.8 g/kg/day, which is the same for younger adults. However, the

protein requirement to optimize bone health may be higher in the elderly (Bern, 2011). The optimal upper end of protein recommendations for bone health is 1.5 g/kg/day. Elderly individuals need closer to 1.0 g/kg/day, plus the additional requirements associated with wound healing (Chernoff, 2004).

Excessive consumption of protein can increase the acid load causing urinary calcium loss and negative calcium balance. Bone acts as a buffering system in presence of a high acid load leading to bone degradation, or osteoporosis (Rapuri, Gllagher, & Haynatzka, 2003). Bern et al. (2011) found that a protein intake of 2.0 g/kg body weight increases the acidic environment.

Inadequate protein intake can be detrimental to bone metabolism. Less than 0.8 g/kg/d protein is associated with malnutrition and also decreases bone mineral density (Kerstetter, O'Brien, & Isongna, 2003). A low protein diet induces changes in calcium metabolism resulting in hyperparathyroidism and a reduction in calcium absorption (Kerstetter et al., 2003). Inadequate protein consumption also decreases the levels of insulin-like growth factor (IGF-1). IGF plays an essential role in growth and development through growth promoting polypeptides (Yakar et al., 2002). IGF is a growth-promoting agent synthesized and retained in bone tissue (McCarthy, Centrella, Canalis, 1989). IGF-I and IGF-II stimulate the synthesis of protein, DNA, and collagen in bone (McCarthy et al., 1989). Inadequate protein consumption decreases the metabolic clearance of this protein and does not promote the growth and maintenance of tissues required to build and sustain muscle and bone structure (Schurch et al., 1998).

Consuming adequate protein as a percentage of energy intake is important. The elderly should consume 10-35% protein of their total energy consumed (Genaro & Martini, 2011). Consuming enough protein without the recommended energy intake will compromise protein anabolism. Hormones, specifically insulin and testosterone, aid in the transfer of protein into the muscle. Consumption of carbohydrates (CHO) and proteins will decrease muscle breakdown (Tipton & Wolfe, 2001). A diet deficient in CHO consumption, but adequate in protein consumption may not prevent osteoporosis or aid in muscle anabolism.

Increasing protein intake will increase lean body mass, and increased lean body mass is associated with an increase in bone mineral density (Whiting, Boyle, Thompson, Mirwald, & Faulkner, 2002). In addition, additional protein intake can decrease sarcopenia, a loss of bone mass and development that occurs with ageing (Morley, Baumgartner, Boubenoff, Mayer, & Nair, 2001). Sarcopenia is also associated with a change in body composition in the elderly population. Muscle tissue contains 50-75% of the amino acids contained in the body; therefore it is vital to replenish muscle stores (Genaro, 2011).

In elderly population, aged 55 and older, protein intake to meet requirements may be difficult to achieve, due to the cost of these foods, intolerance to different food groups, difficulty tearing or chewing protein rich foods, and fear of consuming too much cholesterol (Chernoff, 2004).

Polypharmacy

Polypharmacy, taking five or more drugs per day, is defined as the concurrent use of multiple medications and has been linked to an increase in falls among the elderly population (Chan, 2009; Lai, et al. 2010). The risk of falling is two times greater in patients using at least 4 drugs per day compared to those not taking medication (Ziere, et al. 2006). Lai et al (2010) found that the odds ratio increased to 8.42 for those who used >10 drugs per day, compared to those using 0-1 drugs per day. Increases in drug use cause a cascade of effects due to the drugs including: drug-drug interactions, electrolyte imbalances, decreased drug clearance rates, and impaired balance (Lai et al., 2010).

Muscle Strength

Muscle strength is the ability of the muscle to produce force (Ford-Smith, Wyman, Elswick, & Fernandez, 2002). The decline of functionality associated with normal aging, disuse, and disease, increases atrophy of muscles, thus placing an individual at a greater risk for falls (Ford-Smith, Whyman, Elswick, & Fernandez, 2002; Hopp, 1993). Fourteen percent of deaths in the United States in 1993 were associated with inactivity and inadequate nutrition (McGinnis & Foege, 1993). In the year 2000, 28 – 34% of adults aged 65 to 74 were inactive, and 35 – 44% of adults greater than 75 years of age were inactive (U.S. Department of Health & Human Services, [U.S. HHS], 2002). The number of elderly is growing and the cost of inactivity is going to continue to increase with time.

Exercise and healthy eating habits are essential in sustaining activities of daily living, especially among the elderly populations. A sedentary lifestyle can cause atrophy

of muscles and thus a decrease in bone mineral density. Incorporating weight-bearing exercises into daily exercise can increase muscle strength resulting in an increase in muscle stress on the bone (Bocalini, Serra, Santos, Murad, & Levy, 2009). Stress on the bone can cause collagen synthesis producing greater bone mineral density. Non-impact resistance training can decrease the degradation of bone mineral density. Strength training exercises, such as weight lifting or body weight circuit training, can build muscle strength, and if completed regularly can stimulate muscle turnover and maintain muscle mass (Chernoff, 2004). Exercise can increase peak BMD and decrease muscle atrophy, or sarcopenia (Korpelainen et al., 2006). The natural aging process related to degradation of the muscle, genetics, hormonal changes, undernutrition, and inactivity can cause sarcopenia; a decrease in muscle mass. However, applied resistance to muscle, specifically strength training, is shown to be associated with a decrease in muscle breakdown (sarcopenia) and an increase in muscle strength (Tipton, 2001). In the elderly, individuals 65-83 years of age, a decrease in the contractile tissues (muscle) and an increase in the non-contractile tissue (fat) when compared to younger individuals, 26-44 years of age have been observed (Williams, Higgins, & Lewek, 2002). Increasing strength-training exercise is vital to combat the decreased number of muscle fibers. Muscle strength increases with applied force and without daily resistance training there can be a decrease in the cross-sectional area (CSA) of the muscle (Williams et al., 2002). Combining the effect of physiological change and a decrease in exercise causes a cascade of effects on the muscle furthering sarcopenia (Williams et al. 2002). The intrinsic factor of the aging process is inevitable, but the extrinsic factor, exercise, can help decrease the

breakdown of muscle strength and make activities of daily living easier, more enjoyable, and decrease chance of osteoporosis.

Hypotheses

Null Hypotheses

1. H_0: There will be no significant difference between groups consuming < 0.8 g/kg/d protein, 0.8 – 1.0 g/kg/day, and > 1.0 g/kg/d on total hip bone mineral density.
2. H_0: There will be no relationship between muscle strength and polypharmacy.
3. H_0: There will be no significant difference in individuals consuming 5 or more medications and those consuming less than 5 medications on total hip bone mineral density.
4. H_0: There will be no relationship between polypharmacy and total hip bone mineral density.

Definitions

Bone mineral density*:* The measure of the structure and composition of the bones that comprise the skeletal system, usually expressed as g/cm^2 (Heaney, 2009).

Bone mineral content: the amount of mineral in the specific site scanned (Kanis, 2002).

Lumbar Spine*:* five vertebras in the spinal column, L1-L5 (Thorpe, Mojtahedi, Chapman-Novakofski, McAuley, & Evans, 2008).

Exercise: a subset of physical activity that is planned, structured and repetitive and has a final or intermediate objective of the improvement or maintenance of physical fitness (Caspersen, Powell, & Christenson, 1985).

Elderly – individuals aged 55 and older (WHO, 2013)

Total body bone mineral density*:* The average measurement of bone structure and composition using all regional areas of the body (Wells & Fewtrell, 2006).

Three-day diet analysis*:* a record of food consumption over a 3-day period (one-weekend and two week days (Yang et al., 2010).

Muscle Strength: maximum force generation capacity of an individual (Kim, 2005).

Osteoblasts*:* Bone cells functioning in the buildup and formation of bone matrix, also recognized as fibroblasts (Yoshitake et al., 1998).

Osteoclasts: Type of bone cell involved in the breakdown of bone tissue, collagen. The process is commonly recognized as bone resorption (Yoshitake et al., 1998).

Physical Activity: occupational, sports, conditioning, household, or other activities that increase movement of the body (Caspersen et al., 1985)

Polypharmacy: five or more different medications consumed on a daily basis (Lai et al., 2010)

Sarcopenia: age associated loss of skeletal muscle mass and function (Fielding et al., 2011).

T-scores: represent the number of SDs from the mean of normal/young individuals of the same age and ethnicity by US standard. A score less than – 1 is considered normal, between -1 and -2.5 is osteopenic, and -2.5 or greater is considered osteoporotic (NIH, 2012)

Assumptions

The assumptions of the study were:

1. All participants recorded 3-day diet analysis accurately and honestly.
2. All participants answered questionnaires honestly.
3. All measurement and evaluation tools were used correctly.

Limitations

Limitations of the study were:

1. Assessing nutrient intake using a 3-day diet analysis.
2. No supervision required by facilitator of food intake.
3. Number of participants that returned the 3-day diet analysis.

Delimitation

The delimitation of this study was:

1. NutritionPro® software was used to analyze nutrient intake.

Significance of the Study

The significance of this study was to obtain a better understanding of the relationship of protein intake and bone mineral density, polypharmacy and bone mineral density, and polypharmacy and muscle strength. Osteoporosis and sarcopenia are prevailing problems in the elderly population found to lead to falls or hip fractures. There is controversy concerning protein intake and bone mineral density that remains inconclusive. Minimal research been completed on polypharmacy and bone mineral density and muscle strength. Additional research on these topics will enhance knowledge on protein and polypharmacy as factors in the maintenance and prevention of falls and osteoporosis.

CHAPTER II

REVIEW OF LITERATURE

This study is part of a program aimed to decrease falls among the elderly. There are many factors that may increase the chance of a fall occurring: decreased bone mineral density (osteoporosis), polypharmacy (increased number of prescribed drugs, specifically drugs altering psychomotor capabilities), poor nutrition (calcium, vitamin D, vitamin C, trace minerals, and protein intake), as well as decreased activity or concentration of hormones that regulate bone metabolism (PTH and estrogen).

Cost of Problem

According to the World Health Organization (WHO, 2008), the world's population of individuals, 60 years and older, will triple in the next 50 years. The subpopulation of this group, individuals aged 80 years and older, is one of the fastest growing subpopulations in the world (Koopman & Loon, 2009). According to the US census, those 60 years and older increased 30% from 2000 to 2010. This trend is predicted to continue (U.S. Census Bureau, 2010).

The rise in the number of senior citizens in Western society is increasing medical expenses due to falls (Granacher, Lrene, Wehrle, Bridenbaugh, & Kressig, 2010); 20 to 30% of the individuals that fall suffer extensive medical complications due to lacerations, hip fractures, and head traumas (CDC, 2012; Stevens, Corso, Finkelstein, & Miller, 2006). Among older adults, aged 65 and older, falls are the most common cause of injury

and trauma resulting in hospital admission (CDC, 2012; Hausdorff, Rios, & Edelber, 2001). In 2010 there were approximately 2.3 million nonfatal injuries and 662,000 hospitalizations resulting in medical costs of roughly $30.0 billion after adjustment for inflation due to falling (CDC, 2012; Hornbrook, et al. 1994).

Fall prevention is key to decreasing medical costs and enhancing quality of life. Prevention of falls includes: increasing physical activity, consuming daily calcium vitamin D and protein (if deficient), controlling polypharmaceuticals, reducing tripping hazards, and screening for osteoporosis (CDC, 2012; Karlsson, Magnusson, von Schewelov, & Rosengren, 2013).

The amount of protein intake and type of protein consumed related to bone density is still a controversial topic. In this study we will further explore the effect of protein intake and polypharmacy on bone mineral density in individuals aged 55 years and older.

Osteoporosis

Osteoporosis is a bone condition defined as a decrease in bone architecture causing micro-fractures. Micro-fractures within the bone gradually may cause a bone fracture (Heaney, 2009). The diagnosis of osteoporosis is bone mineral density greater than 2.5 standard deviations below the young adult mean (National Institute of Health [NIH], 2012). Approximately 44 million Americans suffer from osteoporosis, 10 million over the age of 50 years; it is three times more prevalent in women than in men. Eight million women and two million men are currently diagnosed with osteoporosis (Dempster, 2011; International Osteoporosis Foundation [IOF], 2010).

Osteoporosis increases the risk of an individual suffering from a hip fracture. In the United States, osteoporotic hip fractures in 50-year-old women make up 17.5% of all osteoporotic hip fractures (Munger, Cerhan, & Chiu, 1999). The number of hip fractures associated with osteoporosis are estimated to double reaching approximately 2.6 million by 2025, with a greater percentage increase in men than women (McNeely, 2012).

Not only is osteoporosis detrimental to health, the cost of osteoporosis in the United States is estimated to rise dramatically as baby boomers age. If the problem of osteoporosis is not addressed, the prevalence of osteoporosis will continue to increase. Furthermore, as the number of individuals with osteoporosis increases, so does the risk of bone fractures. Once a bone fracture has occurred, an individual has an increased risk of developing secondary health issues that increase the cost of medical care.

Bone

Bone is composed primarily of protein. Approximately 50% of bone volume is protein matrix (Heaney & Layman, 2008). Proteins are not reused to strengthen the matrix following proteolysis resulting in the need for daily dietary protein consumption (Heaney & Layman, 2008). Osteonectin and osteopontin are two primary bone proteins that contribute to bone matrix. Both proteins promote healthy bone turnover. Osteonectin is a protein specific to bone that binds hydroxyapatite and collagen (Termine et al., 1981). Osteopontin is a non-collagenous bone matrix protein produced by both osteoblasts (bone forming cells) and osteoclasts (bone-resorbing cells) and aids in bone mineralization (Yoshitake, Rittling, Denhardt, & Noda, 1998). Cell recycling of these two proteins occurs in areas of the bone where the greatest force is applied resulting in an

increase in bone density in that location. On the other hand, areas with lower force applied will have decreased cell turnover and lower bone density (Einhorn, 1996).

Bone Remodeling System

Bone status depends primarily on the role of osteoblasts and osteoclasts, and the stimulus that drives the activity of these cells, both physiologically and mechanically. The physiological stimulus of bone is regulated by: hormone levels, intake of calcium and vitamin D, cytokines, sex, and genetics, to continue growth, or maintain integrity. The mechanical stimulus is the force produced by the muscles and tendons acting on the bone. Harold Frost proposed a theory known as the mechanostat theory that describes bone mineral content related to thresholds of the physiologic stimuli to skeletal health/disease (Frost, 1996). Bone health is dependent on the physiological force acting on the bone, which increases the density of the bone structure. Exceeding a minimum effective strain (MES) will cause an adaptive response from the bone directly related to the mechanical overload (Frost, 1996). This minimum effective strain is the minimum amount of force produced on the bone to promote the activation of osteoblast cells, causing an increase in BMD. During growth, longitudinal and circumferential bone growth occurs faster than remodeling; therefore an increase in bone mass occurs. However, as bone growth declines, remodeling continues and cortical bone mass declines with age, unless mechanical stimuli is applied (Frost, 1996). Therefore, those engaging in strength training will continue to produce force against the bone leading to the maintenance of BMD.

The mechanostat theory states bone growth is not linked to a set point during the aging process, but based more on physiological strains produced by the muscle. The more mechanical usage, the greater the strength of the muscle, thus increasing the force applied to the bone, leading to an increase in bone mineral density (Burr, 1997). Muscle strength begins to decrease after the age of 30 unless stimulated by strength training. The timing of decline in strength varies by anatomical region, usually occurring later in the lower extremities than in the upper. Strength training and exercise become vital to maintaining not only muscle strength, but also BMD.

Physiological Factors Affecting Bone Health

Cellular Proteins

As stated previously, bone structure is strictly regulated by a system of osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells). Osteoblasts are derived from marrow stromal cells; they function to synthesize, deposit, and orient fibrous proteins of the bone matrix to promote bone mineralization (Heaney, 2006). Osteoclasts derived from monocyte-macrophage type cells, are multinucleated, and resorb bone. Osteoclasts secrete acid and proteolytic enzymes to digest bone matrix. Bone metabolism occurs through these cells causing bone resorption or bone formation.

Growth Hormone

Growth hormone (GH) helps regulate bone formation. GH promotes the release of insulin like growth factor-1 (IGF-1), which stimulates synthesis of bone proteins and osteoblastic proliferation (Johansson et al., 1997); therefore an increase in IGF-1 is related to greater BMD. Messenger RNA of IGF-1 has been found in cultures of human

osteoblasts as well as other growth factors associated with bone formation: parathyroid hormone, estrogen, 1,25-dehydroxyvitamin D_3, cortisol, and prostaglandin E_2 (Schmid, 1993).

Vitamin D

Vitamin D is a fat-soluble, secosteroid hormone, obtained from daily exposure to the sun, also found in food products such as: cod, swordfish, salmon, tuna, and vitamin D fortified foods. Vitamin D is absorbed and utilized in the form of D_3. Vitamin D is necessary for bone growth and metabolism. The elderly have only 30% as much circulating vitamin D when compared to younger adults (Holick, 2006) further exposing the elderly to possible deficiency. When vitamin D is absorbed, it is first hydroxylated to 25 (OH) D in the liver and released into the blood. The kidneys and the placenta have the capability of hydroxylating 25(OH) D to $1,25(OH)_2D$. Inadequate calcium intake increases the release of parathyroid hormone, causing calcium reabsorption from the renal tubules and increasing renal production of $1,25(OH)_2D$. $1,25(OH)_2D$ travels to the small intestine leading to increased calcium absorption. Osteoclasts mobilize calcium from the bone via receptor activator of NFκB ligand (RANKL), stimulating RANK and increasing serum calcium levels (Holick, 2006). RANKL is a ligand for osteoprotegerin and activates osteoclast activity (Wada, Nakashima, Hiroshi, & Penniinger, 2006). Phosphorus is mobilized from bone by $1,25(OH)_2D$ when calcium levels in blood are low (Holick, 2006). A complete diagram of vitamin D metabolism and the effect on calcium homeostasis is shown in Figure 1.

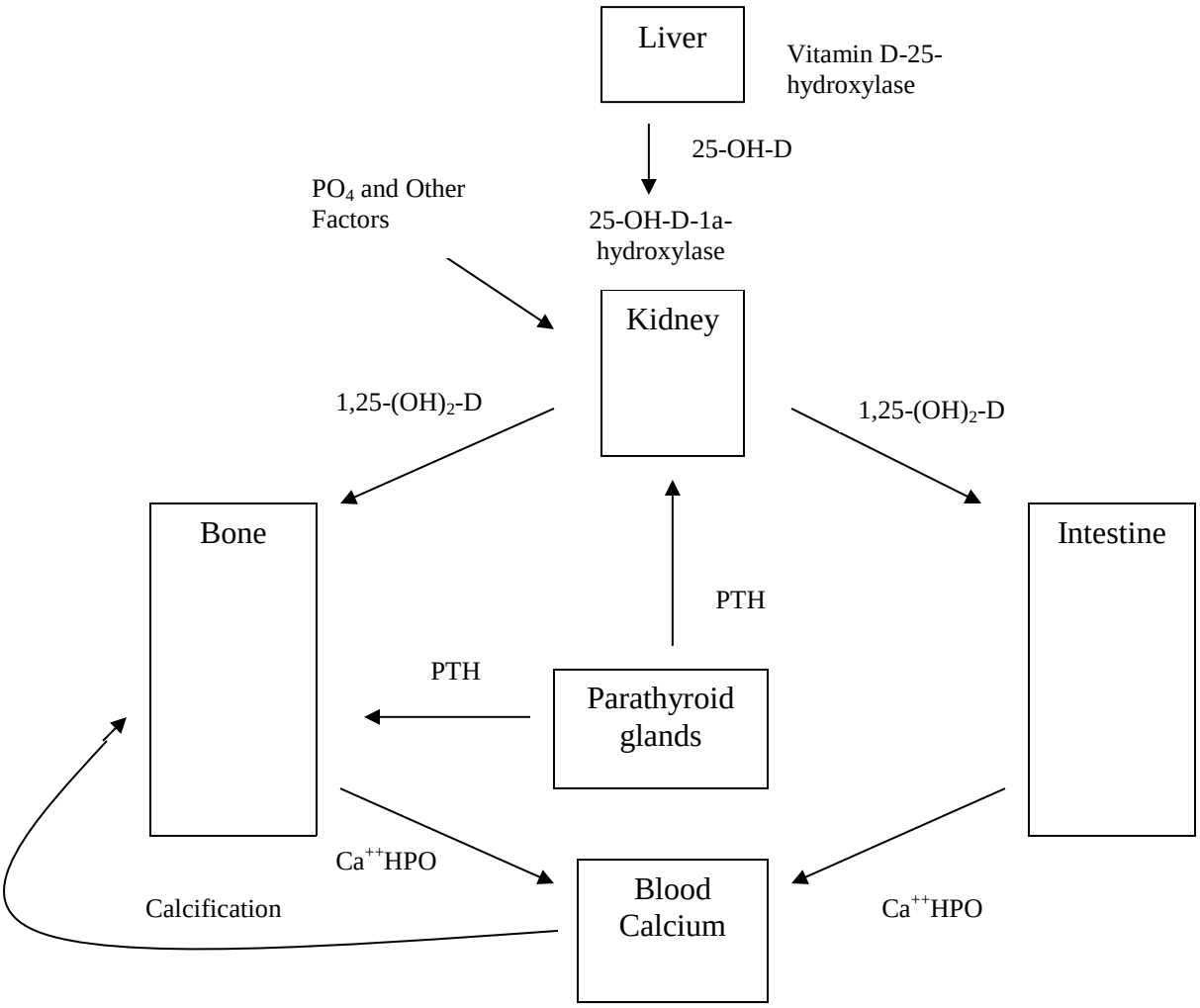

Figure 1. Vitamin D Metabolism (Buchman, 2007)

Note: Vitamin D metabolism and calcium homeostasis for cell growth. Vitamin D from the diet or the sun metabolized in the liver by the enzyme D-25-hydroxyase (25-OHase) to 25-hydroxyvitamin D_3 [$25(OH)D_3$]. $25(OH)D_3$ enters circulation and converted in the kidney to 1,25-dihydroxyvitamin D_2 [$1,25(OH)_2D_3$]. $1,25(OH)_2D$ regulates metabolism of calcium through interactions with the bone and the intestine.

Calcium

Calcium exists in the body primarily as insoluble hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$. Calcium comprises 39.9% of the weight of bone (Weaver & Heaney,

2006). Mature healthy women have approximately 920 to 1000 g of calcium in the body and the mature healthy man has about 1200 g calcium in the body. The body is designed to retain adequate amounts of calcium as bony tissue. In periods of deprivation calcium is removed from the bone and used to maintain calcium balance (Heaney, 2009). Physiological changes in the elderly such as decreased efficiency of calcium conservation, physical inactivity, gonadal hormones, decreased circulating levels of $1,25(OH)_2D$, and resistance to circulating $1,25(OH)_2D$ all cause an increased need for calcium intake for regulation.

Dietary calcium intake recommendations by The Panel on Calcium and Related Nutrients, for older individuals is 1200 mg/day, and for the prevention of bone loss and decreased risk of hypertension is likely to be up to 500-600 mg/day (Heaney, 2006). Meeting these recommendations is important in the elderly due to the increase in bone loss after the reproductive years in both males and females. Bone loss occurs approximately at a prevalence of 1% each year for men and women 65 years and older. However, in women after menopause there is a rapid increase in bone loss that occurs for 3 - 5 years following.

It is important to remember calcium may be excreted in the presence of a high protein diet; therefore if dietary protein consumption his high, it is important to maintain circulating calcium levels by consuming at least the recommendations for calcium intake daily (Kerstetter, O'Brien, Isongna, 2003).

Parathyroid Hormone

Parathyroid hormone (PTH) is responsible for the maintenance of calcium homeostasis and guards against hypocalcaemia (Kerstetter et al., 1997). PTH is responsible for stimulation of bone resorption. In the presence of decreased calcium levels in the blood, PTH is released into the blood stream causing the renal tubules to reabsorb calcium, decrease phosphorus reabsorption, increasing calcium released from the bone (Kerstetter et al., 1997). PTH stimulation also affects the enzyme, 1-α-hydroxylase, associated with the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D leading to an increase in calcium absorption in the intestines (Kerstetter et al., 1997). PTH receptors are located on osteoblast cells so when PTH is released it binds these receptors. The binding of these receptors stimulates osteoclasts, osteoclastic activity, resulting in bone resorption. PTH is directly responsive to levels of circulating calcium in the body. When calcium is needed, PTH is released and whole fragments of bone are removed; calcium is scavenged from the fragments for calcium utilization (Heaney, 2006).

Estrogen

Estrogen influences bone cell turnover and has been linked to the estrogen receptors located on osteoblast-like bone cells in vitro (Heaney, 2006). Estrogen directly influences calcium absorption through 1,25 $(OH)_2$ D receptors on the bone. Estrogen replacement therapy is linked to a decrease in BMD loss. Hormone replacement therapy is indicated primarily for women, who hit menopause prior to the age of 40, have moderate to severe hot flashed and/or other menopausal symptoms, and have severe bone

loss and have osteoporosis. However, hormone replacement therapy should be evaluated in regards to treating bone disease, unless indicated, due to some of the side effects: myocardial infarction, stroke, invasive breast cancer, pulmonary embolism, and deep vein thrombosis (Heaney, 2006).

Trace Minerals and Vitamin C

Trace minerals, copper, zinc, and manganese, along with vitamin C are important cofactors in forming the cross-links of matrix proteins that aid bone formation. Copper is a cofactor for lysyl oxidase, an enzyme responsible for cross-linkage in collagen (Heaney, 2006). Manganese plays a functional role in bone, enhancing bone turnover by stimulating osteoclastic function (Gur et al., 2002). Bone is comprised of proteins that require zinc to function; zinc is a cofactor for osteoblastic activity promoting bone formation and reducing risk for osteoporosis, and zinc is required for every step in bone metabolism (Molokwu & Yang, 2006). Vitamin C also aids in cross-linkage of bone structures. Vitamin C stimulates conversion of pro-collagen to collagen, stimulating alkaline phosphatase activity, a marker for osteoblastic activity (Morton, Barrett-Connor, & Schneider, 2001).

Protein

Dietary protein consumption is essential for bone remodeling within the recommendations of 0.8 – 1.0 g protein/kg BW for healthy individuals. Excess consumption of protein, > 2.0 g/kg/day paired with inadequate calcium intake, has been shown to cause calcium loss through the urine, negative calcium balance, and bone loss in elderly men and women (Bern, 2011; Rapari, Gallagher, & Haynatzka, 2003).

Adequate protein intake, 0.8 g/kg/day, is essential for bone remodeling, although amino acids removed from bone matrix cannot be reutilized following posttranslational modification (Bern, 2011; Heaney, 2006). Safe protein intake in the elderly ranged from 1.0 to 1.35 g/kg (Hannan et al., 2000), but most recommendations are 0.8 g/kg (Bern, 2011; Rapari et al., 2003).

Low protein intake affects insulin like growth factor-1 (IGF-1) activity (Bourrin, Ammann, Bonjour, & Rizzoli, 2000). IGF-1 is a polypeptide that promotes growth and development (Yaker et al., 2002). Adequate protein intake has been linked to an increase in IGF-1 and a decrease in dihydroxypyridinoline, which is a bone marker for bone growth. IGF-1 stimulates the proliferation of osteoblastic cells promoting bone formation (Heaney, 2006). A majority of studies observing the relationship of protein intake and bone mineral density have determined that inadequate protein intake (< 0.8 g/kg BW) often contributes to decreased bone mineral density. Low protein intake is linked to malnutrition, and malnutrition causes a decrease in insulin IGF-1, which initiates bone resorption (Bonjour, 1996; Geinoz et al., 1993; Promislow et al., 2002). Low protein diets, < 0.7 g/kg, are also hypothesized to activate 1-α-hydroxylase, a reaction that occurs in the kidneys, and causes increased active calcium transport into the intestines by resorption of the bone (Stewart & Broadus, 1987). Hannan et al. (2000) completed a 4 year longitudinal study on men and women 68 to 98 years of age to determine rate of bone loss. Those consuming a lower percentage of protein (7.3 – 15.5%) in their overall diet had reduced bone mineral density at the femoral neck and spine sites ($p < .01$). The

average percentage of protein intake for the Hannan el al. (2000) study was 16 ± 3%, similar in the present study, which was 16 ± 3%.

Decline of Protein Intake in the Elderly

Daily protein intake as a preventative measure for decreasing the risk of osteoporosis has gained importance over the past decade, however the amount of protein consumption in this population has not followed the trend. Among the elderly, > 65 years of age, diets low in protein are common, especially in women (Castaneda, Charnley, Evans, & Crim, 1995). According to the National Health and Nutrition Examination Survey (NHANES II), American women > 55 years of age consumed < 30 g protein/day (Castaneda et al., 1995). White women, from 50 to 80 years of age had a decline in the consumption protein intake, from > 65 g/day to a mean of 52 g/day (Bales & Ritchie, 2006). Furthermore, Whitehead & Finucane (1997) found that 2 - 16% of community-dwelling individuals aged 65 to 70 had protein and energy malnutrition. Low protein intake in the state of malnutrition is associated with hip fracture and lower bone mineral density (Bonjour, Schurch, & Rizzoli, 1996).

Acid-Base Proteins

Amino acids have a carboxyl-carbon group and an amino-N group attached to one central α-carbon. Amino acids are grouped by their functional groups based on their chemical structure: non polar, uncharged, but polar, acidic, and basic. Within these classes amino acids are grouped by their functional groups. Amino acid groups are as follows: neutral amino acids (glycine, alanine, valine, leucine, isoleucine, serine,

threonine), sulfur amino acids (cyctein and methionine), cyclic amino acids (proline), aromatic amino acids (phenylalanine, tyrosine, tryptophan, histidine), basic amino acids (Lysine, ornithine, arginine), and acidic amino acides and amides (glutamic acid, glutamine, aspartic acid, asparagines; Matthews, 2006).

The average American diet is high in meat protein and low in fruits and vegetables and can produce about 100 mEq acid daily (Brazel & Massey, 1998). A diet high in animal protein resulted in 6.8 mmol more sulfate than did those consuming a non animal based protein diet (Breslau, Brinkly, Hil, & Pak, 1988). This acid generating diet causes an increase in the potential renal acid load (PRAL). Bone responds to the acid environment by rapid release of carbonate, citrate and sodium from the hydrogen shell. In the presents of a low calcium, low alkali (low fruit and vegetable), and acid (protein) diet, bone mineral density may be compromised (Brazel & Massey, 1998).

Protein Intake and Bone Mineral Density

Protein intake related to net calcium balance is associated with potential risk of osteoporosis related to bone mineral density and increased risk of hip fractures. Excess protein intake, > 2.0g/kg BW, is possibly associated with negative calcium balance (Hannan et al., 2000). Protein consumption from non-dairy sources, such as meat, fish, and eggs may lead to a decrease in calcium intake and potentially an increase in calcium excretion (Meyer, Pedersen, Loken, & Tverdal, 1997). Meyer et al. (1997) conducted an observational prospective study to determine relative factors influencing calcium balance and incidence of hip fractures. There was an elevated risk of fracture for women who consumed the highest quartile of protein intake from nondairy protein foods and those

who consumed the lowest quartile of calcium intake from dairy (< 1 glass of milk per day; relative risk – 1.96; 95% CI interval, 1.09-3.56). However, in the presence of high protein intake (those in the highest quartile) and high calcium (≥ 5 glasses of milk a day), there was not a significant risk for hip fracture. The skeleton is the calcium reservoir, and in the presence of a high protein diet, calcium is removed creating "metabolic acid-osteoporosis" (Abelow, Holford, & Insogna, 1992). Increasing net protein consumption, specifically from animal protein intake, will increase phosphorus in the blood creating an increase in acid excretion from the kidneys, leading to chronic bone loss to buffer this system with calcium (Wachman & Bernstein, 1968). Many studies have focused on protein and calcium intake on bone metabolism, but there are no conclusive answers. Following is a review of previous research related to the topic.

High protein intake, may cause a negative calcium balance contributing to brittle bones (Hannan et al., 2000; Kerstetter, O'Brien, & Isongna, 2003; Rapuri, Gallagher, & Haynatzka, 2002). Excess protein, consumption may cause a highly acidic environment requiring calcium to be released from the bone to buffer the blood. These buffering substances include: citrate, carbonate, and sodium from the hydration shell of the bone (Barzel & Massey, 1998). For every 50 g increase in protein consumed, an extra 60 mg of calcium is excreted (Kerstetter & Alen, 1994). Intakes of protein greater than 2.0 g protein/kg body weight per day, especially of animal protein, cause a decrease in BMD due to the amino acid-induced decreased pH level of the blood (Breslau, Brinkly, Hill, & Pak, 1988; Rapuri et al., 2003). The human kidney can only excrete urine with a minimum pH of 5. The increased consumption of meat and fish may cause the pH to

drop below 5, resulting in a substantial release of calcium and other buffering compounds to counteract this change in acid-base chemistry. It is hypothesized that bone will buffer this acid environment by increasing calcium urinary excretion, causing a negative calcium balance and an increase in bone loss in elderly men and women (Rapuri et al., 2003).

In a meta-analysis of studies on protein intake related to calcium and bone mineral density, for every 25g increase in protein intake, there was a 0.8 mmol rise in urinary calcium (Kerstetter, O'Brien, Caseria, Wall, & Isogna, 2005). The increased rise in calcium excretion may cause detrimental effects on bone because bone is a calcium reservoir. When blood calcium levels drop below normal ranges, altered hormonal status signals changes that ultimately affect BMD. It is important to note that most of Kerstetter's studies are short term studies (Kerstetter & Allen, 1994; Kerstetter et al., 1997; Kerstetter, O'Brien, & Isongna, 2003). Short term acute effects of high dietary protein intake may not be a detriment to bone density, but affects calcium excretion (Kerstetter, O'Brien, Caseria, Wall, & Isogna, 2005). However, chronic effects of high dietary protein intake may be a detriment to bone mineral density.

Hannan et al. (2000) completed a four year, population-based study on the effect of dietary protein and bone loss in elderly men and women, as part of the Framingham Osteoporosis Study. Subjects consisted of 391 women and 224 men; mean age was 75 years (68 – 91 years of age). Femoral spine and radial BMD were measured and measurements were adjusted for age, weight, height, weight change, total energy intake, smoking, alcohol intake, caffeine, physical activity, calcium intake, and for women,

estrogen use. Protein consumption was measured as percentage of intake; mean intake of protein was 16% of calories (± 3.4: range, 7-30%) and 68 g/d (± 24.0; range, 14-175 g/d). A significant difference in BMD of the femoral and spine sites ($p \leq .04$) in both males and females consuming less protein was observed, and also an increase in bone loss in those in the lower quartile of protein intake. No significant difference in bone mineral density of the radius between the groups was observed ($p = .23$). In addition, high intakes of animal protein, 58 – 132 g/d, were not associated with fractures in this population ($p > .05$).

Contrary to high protein diets having an effect on bone mineral density, diets low in protein have been shown to be equally detrimental to bone mineral density. The US Department of Agriculture found that approximately 30% of women ≥ 20 years of age consumed less than adequate protein recommendations (Kerstetter et al., 2000). Low protein diets, < 0.7 g/kg, are hypothesized to affect the activation of the 1-α-hydroxylase, a reaction that occurs in the kidneys and increases active calcium transport into the intestines by resorption of the bone (Stewart & Broadus, 1987). This enzyme converts calcidiol to calcitriol, the active form of vitamin D. Kerstetter and colleagues conducted multiple studies from 1997 to 2003 on low protein diets related to parathyroid hormone and calcium metabolism in young females (Kerstetter et al., 1997; Kerstetter, O'Brien, & Insogna, 1998; Kerstetter, Svastisalee, Caseria, Mitnick, & Insogna, 2000; Kerstetter, O'Brien, & Insogna, 2003). All studies were short-term studies lasting approximately 2 weeks or less, and were completed in young, healthy women ranging from 20 to 40 years

of age. The number of participants studied ranged from 7 to 16 subjects for each study. One of the main objectives was to determine concentrations of parathyroid hormone and calcium absorption with low protein diets. Parathyroid hormone release is thought to increase in the presence of low protein intakes causing excess calcium to be released from the bone. Subjects in the Kerstetter et al. (1998) study developed hypocalciuria and secondary hyperparathyroidism by Day 4 of the low protein diet.

In the Kerstetter et al. (2000) study, protein intakes were graded and participants placed in groups based on protein consumption per kilogram of body weight, 0.7 g/kg, 0.8 g/kg, 0.9 g/kg, and 1.0 g/kg, and calcium metabolism was monitored to determine the amount of protein needed to maintain normal calcium balance. Following a 2-week period, individuals in the lowest protein intake group had higher PTH concentrations, 1.8 - 2.2-fold above the upper normal concentration and those in the high to normal protein intake groups had normal concentrations of PTH-1-∝-hydroxylase. Absorption of calcium was also lower in the 0.7 g/kg group when compared to normal population by 25%. In conclusion, those consuming a diet low in protein will have alterations in calcium metabolism related to the release of PTH. In this study, Kerstetter et al. (2000), recommends protein intakes be at least 0.9 g/kg/day to preserve PTH metabolism on calcium absorption and excretion. These results were similar to Gienoz et al. (1993) who found a significant increase in BMD with increased protein intake above 1 g/kg body weight. An increase in the femoral neck site BMD in female participants and a significant increase in both the spine and the femoral neck for the males in those who had increased protein intakes were observed.

As part of a longitudinal, cross-sectional study, Rapari et al. (2003) investigated protein intake on bone mineral density in elderly women, > 65 years of age. The main objective was to determine the rate of bone loss over a period of time related to percentage of protein consumption in the diet. This cross-sectional study used data from a placebo group to evaluate protein intake and rate of bone loss in 92 elderly women, 65 to 77 years of age, over a 3-year period. A 7-day diet analysis was obtained from each individual and protein intake was determined as a percentage of total calories consumed. BMD and biochemical indexes were measured and compared to protein consumption in quartiles and percentage of protein kilocalories to total kilocalories consumed for the day (Q1, 13.1 ± 0.12%; Q2, 15.1 ± 0.11%; Q3, 16.7 ± 0.12%; Q4, 19.8 ± 0.12%). A series of additional tests were completed including: calcium absorption test, biochemical analyses, serum and urine chemistry measurements, serum calciotropic hormones, bone biomarkers, and measurement of bone mineral density. There was no significant differences in age ($p = .3781$), height ($p = .9425$), and calcium consumption ($p = .0774$) between the quartile groups of percentage of protein intake to calories. There was a significant difference in the weight of women between the quartiles of protein percentage consumption ($p = .0003$), dietary protein intake as grams per day ($p < .0001$), grams or protein per kilogram body weight ($p < .0001$), and vitamin D intake ($p < .0001$). Weight and protein intake increased linearly. Those in the lowest quartile consumed an average 54 g protein/day or 0.8 g protein/kg body weight, and approximately 13% total calories as protein. Those in the highest quartile consumed, on average, 71 g/day of protein, 1.02 g/ kg of protein, and approximately 19.8% of total calories in protein. Bone mineral density

at baseline for the women in the highest quartile of protein intake was significantly greater in the spine (7.5-8%), midradius (5.5-7%), and total body (5%) compared to those in the lower three quartiles; however this was only significant when calcium availability from the diet exceeded 408 mg/day. There was not a significant difference between the groups related to rate of bone loss, possibly due to the size and the length of the study.

Wengreen et al. (2004) conducted a case-controlled study to determine protein intake related to hip fractures. They analyzed data using odds ratio analysis to determine the amount of protein intake associated with a reduced risk for hip fractures. A food frequency questionnaire (FFQ) consisting of 137 items was used to assess the diet. Percentages of total calories were used to evaluate protein intake. Participants included males and females with a history of hip fractures, and were part of the Utah Study of Nutrition and Bone Health (USNBH), a hip fracture study. The control subjects were randomly selected using driver licenses and medical databases. The age range for this study was 50 – 89 years of age, including 785 male participants: 336 cases and 449 controls, and 1716 females: 831 cases and 885 controls. Mean percentage of carbohydrate, fat, and protein intakes between the case and control groups did not differ; however women consumed a greater percentage of carbohydrates than males ($p < .001$), and males consumed a greater percentage of calories from fat ($p < .001$). Females consumed approximately 126 g/day CHO (50% kcals) compared to males 121 g/day CHO (48% kcals) and males consumed 41 g/d fat (37% kcals) compared to females 40 g/day (36% kcals). Mean calcium consumption did not differ between groups or sex; however females consumed more calcium from supplements compared to males.

Furthermore, those consuming adequate calcium included 68% of case women, 71% of control females, 42% of case males, and 43% of control males. Protein intake related to risk of hip fractures decreased as total percentage of protein intake increased in those aged 50-69 years (OR: 1 [reference]; 0.51 [95% CI 0.30-0.87]; 0.53 [95% CI 0.31-0.89]; 0.35 [95% CI 0.21-0.59], *p* trend = .06), but not for those aged 70-89 years (OR: 1 [reference]; 1.01 [95% CI 0.78-1.32]; 1.15 [95% CI 0.88-1.51]; 1.28 [95% CI 0.97-1.70], *p* trend = .06). The greater consumption of animal protein decreased risk of hip fractures between the highest and the lowest protein consumption quartiles in the 50 – 69 aged group (OR: 0.35; 95% CI: 0.21, 0.59) and vegetable protein had a marginal effect (OR: 0.52, 95% CI: 0.27, 0.997). There was no significant difference between animal and vegetable protein consumption in the highest and lowest quartiles for those in the 70 – 89 years of age group. In conclusion, major risk factors for hip fractures included: BMI, smoking status, alcohol use, and physical activity, calcium, vitamin D, and potassium intake. The odds ratio for hip fractures increased as the percentage of protein intake decreased in patients 50-69 years of age, but not in those aged 70 – 89 years.

Ilich, Brownbill, and Taborini (2002) reviewed multiple factors related to bone health, protein intake being one of the measures. Ilich et al. (2002) used multiple regression models to study the relationship between BMD and other nutrients: energy, protein, calcium, magnesium, zinc and vitamin C. They further examined confounding variables using stepwise regression models to determine the significant effect of calcium and protein on bone mineral density and/or bone content. Subjects included 136 generally healthy Caucasian women, 68 ± 7.1 years, all post-menopausal. Nutrients were

assessed using a three-day diet analysis administered by a registered dietitian. Following dietary intake analysis, multiple regression models were used to determine correlations between each nutrient and bone mineral density. There was a positive, significant relationship between most nutrients (phosphorus, Mg, Fe, Se, Zn, Cu, K, Na, and vitamins C, D, & K) and bone mineral density (r between .170 and .2; $p < .05$). However energy, protein, and calcium overall showed the highest correlations with bone mass. Participant data was divided into two groups based on the mean, lower median and upper median values compared with bone mineral density. The independent variables included: energy (median = 7089 kJ/day or 1693 kcals/day), protein (median = 68.9 g/day), and calcium (median = 750 mg/day). Lean body mass and weight were considered prior to comparing variables to total bone mineral density and Ward's triangle bone mineral density. Protein and calcium intake were also considered independent of each other; these nutrients were compared based on upper and lower protein intakes compared to upper and lower calcium intakes. Individuals consuming protein above the median (68.9 g/day) had significantly greater bone mineral density at all sites measured, and these were not related to calcium intake. There was a moderately strong correlation found for protein intake and BMD ($r = .607$). Energy, protein and calcium intakes were all independently related to BMD. Contrary to this research, high intakes of non-dairy, animal protein in the presence of a low daily calcium intake were found to increase the risk of hip fractures (Dargent-Molina, et al. 2008; Meyer, Pedersen, Loken, & Tverdal, 1997), which indicated there is a relationship between calcium and protein intake.

Promislow, Goodman-Gruen, Slymen, and Connor (2002) completed a population-based study using The Rancho Bernardo Study information and prospectively examined the associations of total, animal, and vegetable protein intake on bone mineral density in postmenopausal women (n = 882) and men (n = 644) aged 55 to 92 years. The Harvard-Willet diet assessment questionnaire, a type of food frequency questionnaire, was used to determine portion size and frequency of consumption of 128 different types of food. Demographic, health history, lifestyle, vitamins, and medications were all determined using the questionnaire. For every 15 g/day increase in animal protein, the participants had a significant BMD increase in hip (0.016 g/cm^2; p = .005), femoral neck (0.012 g/cm^2; p = .02), spine (0.015 g/cm^2; p = .08), and total body (0.010 g/cm^2; p = .04); however, there was a negative impact on BMD with vegetable protein intake. Also, in this study there was no effect of calcium intake on BMD for those consuming more animal or vegetable protein. In fact, when comparing vegetable protein intake to BMD, those with a greater amount of vegetable protein intake and calcium, there was decrease in BMD of the spine. In conclusion of this study Promislow et al. (2002) found, individuals eating diets with greater protein intake may benefit from consuming less calcium, and animal protein will support bone mass in elderly women.

Munger et al. (1999) also evaluated protein intake and the risk of hip fracture in a cohort of women aged 55 – 69 years. Hip fractures were determined by participant response of number of hip fractures in the initial questionnaire and in the follow-up questionnaire and one year later (n = 44 confirmed hip fractures by physician). The relationship of hip fractures and protein intake was determined by comparing mean daily

protein intake of those who suffered a hip fracture and those who did not suffer from a hip fracture. There was no significant difference in calories consumed between the hip fracture group and the non-hip fracture group. The hip fracture group had decreased total protein intake when compared to the non-hip fracture group ($p = .01$), however when body weight was considered, protein intake was the same (1.2 g/kg) in both groups; the hip fracture group consumed less animal protein ($p = .002$) and higher vegetable protein ($p = .01$) and they also had higher carbohydrate intake ($p = .01$). Non-hip fracture group consumed 1799 kcals/d and the hip fracture group consumed 1753 kcals/day. Furthermore, there were no associations between intakes of total fat, saturated fat, calcium, and vitamin D and hip fracture. Bone mineral density measurements were not available and correlation of protein intake and bone mineral density was made using hip fracture reports only.

Animal protein consumption in the presence of low vegetable intake is associated with lower bone mineral density. Animal protein increases the acidic environment, increases urine calcium excretion, and promotes negative calcium balance especially in the presence of low vegetable intake (Hannan et al., 2000; Kerstetter, O'Brian, & Isongna, 2003; Rapuri, Gallagher, & Haynatza, 2002). Calcium is removed from bone to buffer the acidic environment, compromising bone mineral density (Barzel, 1998). However, protein consumption from animal proteins versus vegetable protein was associated with a higher bone mineral density in women, age 55 years and older ($p < 0.05$; Promislow et al., 2001). In the Hannan et al. (2000) study, there was no significant bone loss between the two types of protein consumed.

Diets associated with weight loss (high protein intake, low carbohydrate, and low calorie intake) have been associated with low bone density. In one study completed by Thorpe et al. (2008), there was an increase in bone loss in those consuming > 1.4 g/kg/day of protein (30% PRO, 40% CHO, and 30% FAT) compared to those that consumed the recommended 0.8 g/kg/day of protein and macronutrient consumption (15% PRO, 55% CHO, and 30% FAT) over a 12 month period. Those in the high protein group consumed 387 ± 72 mg calcium compared to those in the recommended macronutrient intake group 261 ± 81.6 mg calcium per day. In a similar study on protein and weight loss in post-menopausal women, bone turnover was greater in those consuming 34% of energy from protein (Campbell & Tang, 2010). Consumption of calcium (> 2,000 mg/d) with diets higher in protein intake (34% kcals) did not prevent bone loss during weight loss. In the Thorpe et al. (2008) study, high protein (> 1.4 g/kg/day) group had greater urinary calcium excretion compared to the lower protein, higher carbohydrate, lower protein group (0.8 g/kg/day protein + 261 ± 81.6 mg/day calcium) + 55% CHO intake. Urinary calcium excretion was negatively associated with total body BMC ($p < .01$) indicating urinary calcium excretion remained high in those with the higher protein intake. The indicators used for bone turnover were urinary deoxypyridinoline and plasma osteocalcin. These measures remained high for those consuming high protein and calcium consumption in both studies. Overall, Thorpe et al. (2008) concluded even if calcium intake is adequate, a diet high in protein exacerbates bone loss and Campbell and Tang (2010) saw a decrease in BMD after weight loss in the high protein group, whereas the normal protein group did not see a decrease in BMD.

Physiological Decline of Aging

In the elderly there is a decrease in basal metabolic rate (BMR) and protein utilization, which lessens the ability to increase muscle mass without exercise and adequate protein intake. Typically, more lean body mass results in higher metabolic rate, which is important in this population. Total body mass is composed of lean mass (muscles, tissues, and organs) and fat mass (adipose tissue). Lean body mass is the powerhouse to metabolic rate. The physiological effects of aging are associated with a decrease in lean body tissue and increase in adipose tissue (Chernoff, 2004). Therefore, the decrease in lean muscle tissue and the increase in adipose tissue lead to a decrease in basal metabolic rate (BMR) causing a decrease in total energy utilization. Total energy requirements for the elderly diminish by about 100 kcal/day per decade over 65 years of age (Wells & Dumbrell, 2006), therefore it is important to sustain muscle mass to compensate for the decrease in BMR.

Protein intake aids muscle metabolism. Protein intake helps to repair and build muscle after a workout. Protein turnover in the elderly, over the age of 70, decreases from 30% to 20% resulting in an increased need for adequate and consistent protein intake (Chernoff, 2004). After exercise, muscles require additional protein to increase hypertrophy. This makes it even more important to consume adequate protein.

Muscle strength declines with age at the rate of 1 to 2% per year after 70 years (Seene & Kaasik, 2012). Basal protein synthesis also gradually declines 3 to 8% per decade after 30 years and even more after the 60 years (Volpi, Nzemi, & Fujita, 2004). After the age of 50, muscle mass is lost at a rate of 6% per decade (Lynch et al., 1999)

and muscle strength decreases approximately 12-14% each year (Larsson et al. 1979). Strength training coupled with adequate protein intake is extremely important for this population to maintain protein balance and prevent the muscle atrophy.

Sarcopenia is prevalent in the elderly, aged 65 and older. Sarcopenia is the age related loss of muscle mass, strength, and function (Morley, Baumgartner, Roubenoff, Mayer, & Nair, 2001). The prevention of muscle catabolism will decrease the reduction of muscle mass and functional capabilities in this population. Sarcopenia can be prevented through diet and exercise (Tipton, 2001). However, for muscle growth to occur, force must be applied to the muscle (resistance training) and they must be used on a daily basis. Resistance training exercises, at least 1 set of 15 repetitions of 8 to 10 exercises that use a variety of muscle groups at a moderate to hard intensity will prevent sarcopenia (Kravitz, 2007).

To achieve muscle growth, net muscle protein synthesis must exceed net muscle protein breakdown. During normal feeding cycles, increased protein consumption plus increased muscle use will result in muscle synthesis, and vice versa; starvation will result in muscle catabolism, resulting in sarcopenia (Tipton, 2001). Muscle loss occurs when the net protein balance is negative making adequate protein consumption important (Tipton, 2001).

Muscle strength is not only important for metabolism and muscle synthesis, it also aids in bone mineral density. Resistance training leada to an increase in muscle strength and, it has also been shown to decrease the normal physiological decline in bone density and bone mass (Wilmore, 1991).

Muscle Strength and Protein Intake

Protein synthesis can occur in the elderly during a monitored exercise regimen with adequate protein intake (Yarashesk et al., 1999). In the Yarasheck et al. study (1999), muscle amino acid metabolism, exercise bouts, and consistent food intake were monitored in individuals aged 76- to 92- years (n = 17). Individuals received an exercise program and meals on a daily basis (18% protein, 49% CHO, and 33% fat); food intake was recorded for reliability. Exercise regimens were supervised and unsupervised (at home). Supervised exercise programs consisted of prescribed exercise regimens 3 days/week focusing on improving range of motion and improvement of muscle strength. Individuals were assessed prior to the study, obtaining 1-RM values and increasing the routine from 65% 1-RM to 100% 1-RM at the conclusion of the program. The unsupervised group received exercise programs and explanation, but no supervision. Following three months exercise, individuals in the supervised group had a significant gain in muscle strength ($p < .05$). The unsupervised group had little gain in muscle mass, 0.0 ± 0.5 kg (males and females combined for results; 1 male, 4 females). The supervised exercise group, women increased muscle mass by 1.0 ± 0.6 kg, and the supervised group men increased muscle mas 2.2 ± 0.2 kg. The three-month exercise program did increase protein synthesis of the vastus lateralis in men and in women after resistance training. This was measure by monitoring amino acid metabolism in the vastus lateralis of nonoxidative leucine disposal rate, an estimate of whole body protein synthesis rate.

The above study discusses muscle hypertrophy associated with a positive nitrogen balance. Inversely, prolonged periods of negative nitrogen balance can lead to a decrease in bone mineral content (BMC) and muscle tissue, increasing the risk for osteopenia and osteoporosis. Consuming adequate amounts of protein may restore nitrogen balance, preventing the decrease in muscle mass and BMC (Castaneda et al., 1995). Castaneda et al. (1995) conducted a 9-week study on 12 women evaluating the effect of a low protein diet (0.45 g/kg) vs. an adequate protein diet (0.92 g/kg) on muscle cell mass, muscle function, and immune response. The lower protein group had significant losses in lean tissue, immune response, and muscle function; whereas, the group that consumed adequate amounts of protein maintained lean tissue, and improved immune response, and muscle function. Limitations to this study were length of study and number of participants.

Welle and Thornton (1997) studied myofibrillar synthesis induced by exercise and the incorporation of protein in the diet. They compared elderly men and women, 62 to 75 years of age. The subjects consumed diets high in protein (28% energy intake), moderate in protein (14% of energy intake), and low in protein (7% of energy intake); all individuals were exercising. There was an increase in myofibrillar protein synthesis, but there was no difference between the groups thus indicating amount of protein did not affect muscle growth, but exercise did have an effect.

Dietary protein recommendations for prevention of sarcopenia are no different than recommended for all healthy individuals, however consistency is key according to Paddon-Jones & Rasmussen (2009). Consistency of protein intake and amount (% of

protein consumption) are equally important. Spreading protein intake throughout the day will help maintain protein status and promote a positive nitrogen balance. The most appropriate recommendation for protein consumption in the elderly is to consume moderate amounts of high quality protein, including all essential amino acids at each meal. The recommended dietary allowance (RDA) is 60 g protein/d day, or 20 g/high quality protein per meal in the elderly (CDC, 2012; Paddon-Jones et al., 2009). Protein intake accompanied by resistance training has been related to hypertrophy if consumed post weight training in the elderly (Esmarck et al., 2001). This study was completed with 13 elderly men, 70 – 80 years of age. These men were untrained prior to testing procedures. All participants completed a 12-week resistance-training program. Participants were divided into two groups; both groups consumed a protein supplement. The supplement was in liquid form and consisted of 10 g protein, 7 g carbohydrates, and 3 g fat. The timing varied between the groups: group one consumed protein within 5 min of completion of resistance workout and group two consumed the protein 2 hr after workout completion. The group consuming protein directly following the workout had a significantly greater gain in muscle protein synthesis in the quadriceps femoris (54.6 ± 0.5 to 58 ± 0.5 cm^2; $7 \pm 1\%$; $p < .05$), but there was no significant difference in the post 2-hr protein group (53.2 ± 0.2 to 53.3 ± 0.3 cm^2; $p > .05$). Furthermore, there was no significant increase in mean fiber area in the protein consumed immediately after exercise group (4041 ± 320 to $5019 \pm 615 \mu m^2$; $p < .05$) and no significant change in the protein consumed 2-hour post workout (4300 ± 338 to 4088 ± 415). In the group consuming

protein immediately following the exercise, an increase in both dynamic and isokinetic strength were observed (46% dynamic and 15% isokinetic) compared to the group consuming protein two hours later, which had only 36% improvement in dynamic strength and no improvement in isokinetic strength. In conclusion, it is more beneficial for individuals to consume protein immediately following strength training. This research also indicates the significance of protein consumption and muscle hypertrophy in the elderly, but timing is significant.

The above studies suggest that exercise and protein intake will positively affect muscle strength. However, Verdijk et al. (2007) found protein supplementation pre- and post- exercise does not affect muscle hypertrophy. Verkijk et al. (2007) looked primarily at timed protein supplementation. This differs from the previously discussed studies where protein was assessed over the entirety of the day based on grams per kilogram body weight. In this study, 26 elderly men, aged 72 ± 2 years, were provided a 12 week resistance exercise program. Twenty grams of protein was supplemented immediately prior to exercise and immediately following the exercise bout. The data collected included: muscle hypertrophy, muscle strength, body composition, muscle fiber typing, dietary intake records, and blood urine collection. The difference in results between this study and the previously reported one may be due to lack of carbohydrate provided with the protein to facilitate amino acids uptake into the muscle; however there is no way to measure the association. Lastly, the immediate ingestion of protein pre- and post-exercise does not seem to be associated with an increase in muscular hypertrophy,

whereas the total amount of protein intake related to body weight has a greater effect on muscle strength and hypertrophy.

Muscle Strength and Bone Mineral Density

Not only is muscle strength important for maintenance of activities of daily living, but also reduces the degradation of bone. There is a strong correlation between muscle strength and bone mineral density (Sinaki, Wahner, Offord, & Hodgson, 1989; Shimegi et al., 1994; Stanely, Marshal, Tilyard, & Taylor, 1994). Mechanical stress placed on localized bone increases bone mineral density (Shimegi et al., 1994). Increased muscular stress prior to menopause will lead to increases in BMD, decreasing risk of osteoporosis once menopause occurs (Ballard, McKeown, Graham, & Zinkgraf, 1990). Increased amounts of physical activity in postmenopausal women aged 50 to 68 years significantly increased BMD compared to those participating in low intensity workouts. A regular high load (60-85% 1RM) training three or more times per week will significantly increase BMD in elderly adults, aged 65 and older (Howe et al., 2011).

Polypharmacy and Bone Mineral Density

Polypharamacy is increasing in the US due to the diagnosis of multiple disease states. The more diseases controlled with drugs, the greater the drug prescription rate. In addition, the greater the number of individual providers, the greater the number of prescription drugs. Following a physician's visit, approximately 75% of individuals leave with another drug prescription (Vyas, Pan, & Sambamoorthi, 2012).

Polypharmacy linked to falls is becoming a more significant topic for study, especially concerning certain types of drugs (sedative-hypnotic and anxiolytic drugs,

tricyclic antidepressants, major tranquilizers [phenothiazines and butyrophenones], antihypertensive drugs, cardiac medications, corticosteroids, nonsteroidal anti-inflammatory drugs, anticholinergic drugs, and hypoglycemic agents; Fuller, 2000). However, there are few published studies evaluating polypharmacy related to bone mineral density. Polypharmacy is defined as consuming multiple drugs during the course of a day; for the present study, greater than five medications a day was considered polypharmacy. Lai, Liao, Liu, and Sung (2010) recently evaluated polypharmacy and the correlation to hip fractures in the elderly. The population-based study identified 2328 elderly patients newly diagnosed with a hip-fracture between the years of 2005-2007. Random selections of 9312 individuals within a database were selected to be in the control group. Odds ratio statistical analysis was used to determine the association of hip fractures to number of medications individuals were using. Hip fractures were found to increase as the number of medications increased on a daily basis. On average, elderly >75 years take eight different prescribed drugs; for every decade, there is approximately one new medication prescribed per year for individuals >80 years. Gosch, Jeske, Kammerlander, and Roth (2012) found that individuals above the age of 80 consume up to 10 medications daily. Selective drugs can affect bone metabolism directly or indirectly: antihypertensive agents, diuretics, beta-blockers, sedatives, neuroleptics, antidepressants, benzodiazepines, narcotics, and NSAIDs; regardless of the drug type, individuals with polypharmacy are at a higher risk of fractures (Gosch et al., 2012). Gosch et al. (2012) notes, regardless of the amount and type of medications provided, one should not be refused medication for the treatment of osteoporosis. The following table

represents the different types of drugs, the effect they have on bone metabolism, and the research completed to date.

Table 1

Medications and Bone Metabolism

Drug Type	Effect on Bone Metabolism	Research Results
Glucocorticoids	- Inhibitory effect on osteoblasts - Inhibit production of IGF -1 and testosterone - Increase apoptosis of osteoblasts and osteocytes and raise the secretion of PTH (Gosch, 2012)	- Intake of 20 mg prednisolone reduced lumbar spine BMD 21% (Reid & Heap, 1990)
Loop diuretics	- Raise loss of calcium, blocking the reabsorption in the loop of Henle. (Gosch, 2012)	- 87 healthy postmenopausal women - A significant decrease by 2% in total hip and 1.4% total body BMD compared to placebo. - Biochemical markers for bone turnover significantly differed by 20% compared with placebo group (Rejnmark, Vestergaard, Heickendorff, Andreasen, & Mosekilde, 2006)
Antidepressants & serotonin reuptake inhibitors (SSRIs)	- Increase facture risk. - SSRIs interfere with 5-HTT receptor in bone metabolism (Gosch, 2012)	- Daily intake of SSRIs significantly increased fracture risk (HR 2.1, 95% CI 1.3-3.4). - Effect of SSRIs was dose dependent - Increased risk for osteoporosis (Richards et al., 2007; Verdel et al., 2010).
Vitamin K antagonists	- Reduces fracture risk - Vitamin K antagonist may inhibit γ-carboxylation of osteocalcin (Gosch, 2012)	- Reduced fracture risk in postmenopausal women by 25% (Gajic-Veljanoski, Bayoumi, Tomlinson, Khan, & Cheung, 2012)
Thyroid hormones	Thyroid hormones may interfere with calcium metabolism. Triiodothyroinine receptors, located in the nucleus of osteoblasts and osteoclasts may be stimulated in the presence of more circulating thyroid hormone causing and increasing bone resorption (Gosch, 2012).	- Only one trial currently completed to date. - 5 year study, women >65 years of age. - Those with lower circulating TSH levels had greater risk for hip fractures, however results were not significant (Leese, Jung, Guthrie, Waugh, & Browning, 1992).

(Continued)

Proton pump inhibitors (PPI)	PPIs decrease hydrochloric acid (HCL) production. HCL aids calcium absorption in small intestine (Gosch, 2012).	- Study results vary; most studies indicate there is a greater risk of hip fractures, however recent studies do not agree (Gosch, 2012).
Thiazoldineione (TZD)	Agonist to peroxisome proliferator-activated receptor gamma (PPARγ), which have been found in bone cells, affects osteoblasts (Heikkinen, Auwerx, Argamann, 2007).	- Significant decrease in bone mineral density in postmenopausal women (Grey, 2008). - In a study specific to diabetics, Analysis from a Diabetes Outcome Progression Trial (ADOPT), a 4-6 year study, there was a significant increase of bone fractures in women (Kahn, et al., 2008) - Case controlled study resulted in a 2.5-fold increase in fracture risk in those taking TZDs in both men and women (Meier, Kraenzlin, Bodmer, Jick, Jick, & Meier, 2008)
Chemotherapeutics	- Effect on bone is multifaceted; one relationship is the blockage of estrogen synthesis by aromatase inhibitors. - Direct, negative effect on bone metabolism specifically with aromatase inhibitors (Gosch, 2012).	- Consumption of Anastrozole and Tamoxifen caused significant decrease in bone mineral density of lumbar spine (median decrease of 4.1%) and of total hip (median decrease of 3.9%) in postmenopausal women (Eastell et al., 2006).
Antiepileptic agents	Affects vitamin D metabolism (Gosch, 2012).	Individuals on antiepileptic agents increase risk of hip fracture by 2- to 3-fold (Bartl, Bartl, & Gradinger, 2009).
Cholestyramine	Effects absorption of vitamin D (Gosch, 2012)	May induce osteomalacia (Bartl et al., 2009).
NSAIDS and analgesics	Unclear (Gosch, 2012)	None of the medication influenced bone mineral density; however NSAIDS were associated with an increase in fractures. Study was conducted on 2,016 postmenopausal women over a 10 year period (Vestergaard, Hermann, Jensen, Eiken, & Mosekilde, 2012).
Statins	Possibly increase bone density through inhibition of HMG-CoA reductase and activation of BMP-2.	Currently no studies show a significant increase/decrease in BMD in those consuming statin type drugs (LaCroix et al., 2003).

(Continued)

Thiazides	Affect calcium excretion through the urinary tract (Gosch, 2012).	A randomized, double-blind, placebo-controlled study on 320 healthy, normotensive men and women age 60 to 79. No significant differences in total bone mineral density between the treatment groups (LaCroix, Ott, Ichikawa, Scholes, & Barlow, 2000).
Beta-Blockers	Inhibit osteoclastic bone resorption and increase in osteoblastic bone formation (Togari, Arai, & Kondo, 2005).	Population based study on beta-adrenergic blockers reduced risk of osteoporosis. Beta-blockers associated with significant increase in BMD of hip & ultradistal (UD) forearm, 2.5% increase BMD in the hip and 3.6% increase in the UD than controls. (Pasco et al., 2004).

The primary drug type affecting bone metabolism is the antiliepiletic (AED) drug. These drugs are associated with abnormalities in calcium and bone metabolism by affecting vitamin D levels (Farht et al., 2002). AED drugs are seizure preventatives used for those with epilepsy. The mechanism that causes osteomalacia in patients consuming the drug is unknown. It is speculated that pheophytin causes an acceleration of vitamin D metabolism directly inhibiting calcium absorption (Fraht et al., 2002). Fraht et al. (2002) conducted a cross-sectional study on ambulatory individuals consuming the drug. Participants included 71 individuals, 42 adults and 29 children. All participants included in the study had been on the drug for at least 6 months. Calcium intake was determined using a detailed questionnaire. Individuals consuming AED medications had low 25-OHD, but this did not significantly affect bone mineral density.

Drugs that affect muscle synthesis, or amino acid metabolism include: beta-adrenergic blockers, beta-agonists, Ca channel blockers, and corticosteroids. Diseases

that affect amino acid metabolism are metabolic diseases (diabetes), or neuromuscular diseases (Parkinson's, peripheral neuropathy, sciatica; Yarasheski et al., 1999).

Polypharmacy and Muscle Strength

Currently there are minimal studies looking directly at polypharmacy and muscle strength, however, as medication consumption increases there is a decrease in appetite and a decrease muscle growth and maintenance due to decrease in protein and calorie consumption (Doherty, 2013). However, some disease processes do affect muscle protein synthesis, more specifically, amino acid metabolism leading to a decrease in muscle hypertrophy and an increase in muscle atrophy (Ziere, 2005). These diseases include diabetes, neuromuscular diseases such as Parkinson's and peripheral neuropathy, and sciatica.

Specific drugs that affect muscle metabolism include: beta-adrenergic blockers (Sectral, Tenormin, Tenoretic, Kerlone, Zebeta, Ziac, Coreg, Coreg CR, Brevibloc, Trandate, Lopressor, Troprol XL, Lopressor HCT, DUTOPROL, Corgard, Corzide, Bystolic, Levaltol, Inderal LA, InnoPran XL, and Betapace; Health and Human Services [HHS], 2013) beta-agonists (Airolin, Airomir, Asmasal, Buventol, Inspiryl, Proventil, Salbulin, Salbutamol, Ventodisk, Ventolin Ventolin Evohaler, Bambec, Berotec, Bronkosol, Bronkometer Isuprel, Xopenex, Alupent, Metaprel, ProMeta, Maxair, Breathaire, Brethine, Bricanyl, and Bitolerol; American Thoracic Society, 2013), Ca channel blockers (Adalat, Calan, Cardene, Cardizem, Cardizem CD, Cardizem SR, Cartia, Covera-HS, Dilacor XR, Diltia XT, DynaCirc, Isoptin, Lotrel, Nimotop, Norvasc, Plendil, Procardia, Procardia XL, Sular, Tiamate, Tiazac, Bacor, and Varelan; Texas

Heart Institute, 2013), and corticosteroids (Aclovate, Desowen, Verdeso, Desonate, Derma-smoothe-FS, Capex, Synalar, Cortifoam, Anusol-HC; HHS, 2013). In this study, participants used Cardizam, Coreg, Troprol XL, Tenormin, Isoptin, and Avapro for blood pressure regulation. These drugs are the only drugs related to muscle metabolism that our participants consumed.

Channel blockers are used to depolarize cardiac and vascular smooth muscle in the heart. Calcium channel blockers are used specifically for heart conditions that dilate the coronary arteries to inhibit coronary artery spasms. Cardizem can help increase exercise tolerance due to reductions in heart rate and systolic blood pressure. However, calcium channel blockers have been found to decrease isometric peak torque of the muscle during exercise (Beaton, Tarnopolsky, & Phillips, 2002). In this placebo controlled trial, 9 healthy men, age 23 ± 2.5 years participated.

Beta-blockers work to reduce blood pressure by blocking receptors for epinephrine, or adrenaline. Few studies have been completed with beta-blockers specifically related to muscle strength. In one study, Levinger, Bronks, Cody, Linton, and Davie (2005) found that in those individuals using beta-blockers participating in a strength training program did see an increase in capacity (peak VO_2) and muscle strength. This study indicates muscle strength can increase even when beta-blockers are prescribed. Subjects were men, age 57 ± 10.2 years, diagnosed with heart failure greater than 3 months and prescribed beta-blockers for management.

Avapro is part of a group of drugs known as angiotensin II receptor antagonists (ACE) inhibitors. These help to lower blood pressure by inhibiting the conversion of

antiotensin I to angiotensin II. This type of drug is effective in preventing physical decline (Ondera, Vedova, & Pahorc, 2006); ACE-I aids mechanical, metabolic, anti-inflammatory, nutritional, neurological, and angiogenetic actions of skeletal muscle. Carter el al. (2004) found ACE-I contributes positively to exercise performance and improved lean body mass in aged rats.

The interaction of polypharmacy and nutritional deficiencies is a growing concern in the elderly population as medicine consumption continues to increase. The prevalence of polypharmacy indicated that 51.1% of 1,100 participants consumed more than 5 drugs per day (Heuberger & Caudall, 2011). Heuberger and Caudall (2011) reviewed the relationship between number of drugs consumed on a daily basis and lifestyle habits and food choices. There was a positive correlation between amounts of cholesterol consumed, refined carbohydrate consumed, and saturated fat consumed and the number of drugs prescribed. There was a negative correlation between the number of drugs prescribed and the number of supplements consumed, indicating even though individuals are on medication, lifestyle modifications do not occur to change the initial problem.

CHAPTER III

METHODS

The purpose of this observational, correlation study was to analyze the relationship between protein intake, exercise, and polypharmacy on muscle strength and bone mineral density in elderly individuals, both men and women, 55 years and older, participating in regular exercise at Seniors in Motion (SIM) facility in Denton, Texas. This study is an ancillary study based on information gathered during a previous longitudinal fall prevention study started in the fall of 2010 at Texas Woman's University, Denton campus and Seniors In Motion rehab facility.

Overview

Prior to the initial data collection, the Institutional Review Board at TWU approved the research study (*Appendix A*). All data files were kept in a closed and locked file cabinet located in the Institute for Woman's Health. Only approved individuals involved in the study had access to the keys and preserved confidentiality of the participants. The data were collected at two locations, TWU and the Seniors in Motion, both in Denton, Texas. Anthropometric measurements were completed in the Exercise and Sports Nutrition Clinic, located in the Human Development Building, room 011. The Lunar Prodigy (Lunar DPX-IQ software version 4.6c; Lunar, Madison, WI) dual-energy X-ray absorptiometry (DXA) scans were performed in the Institute for Women's Health

(IWH) laboratory, which is located in the Human Development Building (HDB), room 017B.

Participants

The original study was conducted on 50 volunteers, both male and female, recruited from Seniors in Motion. All individuals were age 55 and older. All participants exercised at the SIM facility. Recruitment of the original population was completed by the staff at SIM and by the staff at the Institute for Woman's Health. Only 31 individuals were included in this study. Twenty five participants were excluded due to lack of compliance to complete the diet analysis. Prior to data collection, all participants sign the informed consent form (*Appendix B).*

The participants were screened prior to admission to the study. The screening process included: 1) measurement of current hip related pain on a pain scale of 1 to 10 and had a 5 or lower, 2) assessing a strength score of at least 3 out of 5 or higher using the manual muscle strength test, 3) the absence of related injuries and surgeries within the past year, and/or 4) identifying any determining previous health related issues which may intervene in outcome data. The measurement of past and current hip related pain was based upon the participant's individual perception of pain. The manual muscle test is a test used in physical therapy to determine resistance to pressure and is measured on a scale from one to five. A 0 out of 5 indicated there is no muscle contraction visible (ie: the muscle is paralyzed), a score of 1 represented muscle contraction, but there was no movement against gravity. A score of 2 indicated there was a muscle contraction, but still no movement against gravity; however, when gravity was eliminated, the individuals

would move their limb through full range of motion. A score of 3 indicated the body could move a limb through full range of motion when gravity is applied, however when resistance was applied the muscle could no longer hold contraction. A score of 4 indicated the individual could hold a contraction in the presence of both minimal resistance and gravity. Lastly, a score of 5 indicated a normal functioning muscle (Dutton, 2009).

Equipment and Procedures

Health History and Demographics

A health history (*Appendix C*) was obtained using the health history questionnaire used in the clinic at the Institute for Woman's Health on the TWU, Denton campus. The questionnaire asked about the incidence of a variety of diseases or disorders that a participant may have or had including medications, surgeries, and history of hospitalizations. The medication section included the name of the medication, dose, start date, and reason listed. All surgeries and hospitalizations were listed with year and reason. An additional, optional section was located at the end of the survey for any additional information the participant wished to provide.

Demographic questionnaire (*Appendix D*) was also completed prior to data collection. The demographic questionnaire gathered contact information regarding date of birth, sex, ethnicity, education level, and present work situation.

Anthropometrics

Weight and height were measured for all participants at the IWH. Height measurements, to the nearest quarter inch, were completed using a stadiometer

manufactured by Perspective Enterprises, Portage, Michigan. Weight measurements, to the nearest tenth of a pound, were determined using a Tanita Scale by TANITA Corporation, Japan. All weights were obtained with clothes on, shoes off. To refrain from measurement discrepancy the same researcher obtained all height and weight measurements.

Bone Mineral Density

Bone mineral density was measured using the dual energy x-ray absorptiometer (DXA; Lunar DPX-IQ software version 4.6c; Lunar, Madison, WI). Prior to all examination procedures, a quality assurance scan was completed. Total body, lumbar spine, and hip measurement scans were completed in the same session. Prior to all scans, participants were required to remove all attenuating materials (buttons, jewelry, zippers, etc.). Lumbar scans (L1-L4) were completed with the patient laying in the supine position in the middle of the table: center line on the table bed lengthwise down the center of the participant's body, the participant's head directly below the horizontal line at the top of the table, the participant's arms against their sides with palms flat against the table pad, or with the patient's hands resting on the upper chest, the patients legs were secured using a strap provided with the scanner and placed around their feet and their knees.

Total body scans were completed with the participant laying in the supine position in the middle of the table: center line on the table pad running lengthwise down the center of the participant's body, their head directly below the horizontal line at the top of the table pad, approximately 1.3 cm between the top of the participant's head and the line,

arms snug against their sides with palms facing the scanning table, entire body within the scan lines on the table pad, if necessary the participant's hands tucked slightly under their hips, but not under pelvis bones, feet strapped together with the shorter strap provided with the system, and knees strapped with the longer strap provided with the system, the participant relaxed their legs into the straps prior to scan and participant remained motionless until scan was complete.

Left, total hip measurement was completed with the participant in the center of the table: centerline on the table pad running lengthwise down the center of the participant's body, participant's head directly below the horizontal line at the top of the table pad, participant's leg moved gently through a small range of movement to ensure leg is in a completely neutral position without rotation, slightly flexed with patella directly above the join, using the knee positioner under the leg being scanned (knee toward participant's thigh) the knee centered between the raised areas and the positioner, the strap of the foot of the leg being scanned straight, vertical side of the femur foot brace, the participant's toes pointing to the ceiling, not toward the end of the scan table and the sole of the participant's foot perpendicular to the top, the femur foot brace and the participant's leg until the femur of the leg being scanned is parallel to the centerline of the table pad. Following positioning, the scan arm was moved to the approximate starting position and the greater trochanter was located to ensure precision of measurement. If the left hip was artificial, the right hip was measured instead. The same registered technician completed all scans to ensure accuracy and precision.

Nutrition Analysis

Protein intake was determined using a 3-day diet analysis. All participating individuals completed a detailed 3-day diet analysis, two weekdays and one weekend day. All participants received instruction of procedure and description of correct serving sizes for accuracy in recording diet related data. Nutrition analyses was be completed using Nutritionist Pro analysis software (version 1.3; Axxya Systems) located in the Sports Nutrition Clinic on the TWU, Denton campus.

Medications

The current medication usage was determined using the Health History Questionnaire developed by the IWH. All participants signed and consented that all information and medications were currently being consumed. Polypharmacy was defined as the consumption of 5 or more different types of medications (McCloskey, 2002). The participants were separated into two groups, those consuming greater than five different types of medications and those consuming less than five different types of medications. Supplements were listed with the medications if they consumed supplements on a daily basis. Vitamins and minerals associated with bone mineral density consisted of calcium, phosphorus, vitamin D, and magnesium. Individuals consuming multivitamins, or vitamins containing these minerals were assessed.

Muscle Strength

Muscle strength was determined using a hand-held dynamometer (Jamar; Jackson, MI). A dynamometer is an instrument used to measure force. The hand-held dynamometer has been shown to correlate with the isokinetic strength scores, thus

adequately predicting muscular strength in a field setting (Ford-Smith et al., 2001; Reed et al., 1993). Muscle strength was measured for handgrip strength and knee flexion and extension. Handgrip strength was measured by placing the dynamometer in the participant's hand with the base resting on the first metacarpal, the fingers holding the handle. The participant held their arm by their side, elbow bent at 90°. The participant was asked to forcefully grip the dynamometer for 3 to 5 s with no other movement to obtain accurate results. To obtain the knee flexion, the participant was placed in the lateral recumbent position on the side to be tested, with the hip of the lowermost limb extended and knee flexed to 90°. The practitioner resisted force produced by stabilizing the femur. The dynamometer was placed on the posterior aspect of the distal leg joint. The location was marked for consistency in recording data. Resistance was applied in the perpendicular direction of knee extension and held for 3 to 5 s. Knee extension was determined with the participant in the lateral recumbent position with hip of lowermost limb extended and knee in approximately 10° flexion. The practitioner placed a hand on the posterior side of the knee for resistance and the participant resisted pressure from the dynamometer. The dynamometer was placed on the anterior aspect of the distal leg just proximal to the ankle. Resistance was applied perpendicular to the leg in the direction of knee flexion and held for 3 to 5 s.

Inclusion Criteria

Participants were > 55 years of age, healthy and physically active, exercising at SIM facility under the supervision of the SIM staff. Participants were successfully able to walk without assistance and have the ability to sit and stand without extreme difficulty.

Female participants had to be postmenopausal. All participants completed exercises on a weekly basis determined by a physical therapist and monitored by employees at the SIM facility. All participants agreed to complete procedures involved with this research, including muscle strength evaluation, balance evaluation, demographic questionnaire, health history form, activities-specific balance confidence (ABC) scale, bone mineral density scan, and a three day diet analysis. All participants signed an informed consent agreement prior to data collection.

Exclusion Criteria

Participants under the age of 55 years were excluded from the research procedure. Women who had a menstrual cycle were not able to participate due to predicted, normal hormone levels and the fact that hormone status has an effect on BMD in women (Neer et al., 2001). Participants had not experienced a fall-related or otherwise serious injury within the last year requiring surgery or hospitalization. Individuals who could not balance on their own for at least 30 seconds were excluded. Eligible individuals possessed strength scores of 3 out of 5 or higher as determined by manual muscle testing, range of motion in any joint that was 50% or greater than what was typically anticipated, pain of 5 or lower on the Numerical Rating Pain Scale, or dorsal kyphosis of less than 40° curvature. Lastly, participants had to be ambulatory and only use a straight cane, if any assistance was needed.

Statistical Analysis

All analyses were conducted using SPSS statistical software program (version 19.0; SPSS Inc, Chicago, IL). To determine the significance between protein intake and

bone mineral density: high, moderate, and low protein intakes were compared using one-way ANOVA with post hoc comparisons. F-tests were used to determine relationships between groups. Student t-tests were used to determine the difference in total hip bone mineral density in those consuming 5 or more drugs and less than 5 drugs. Linear regression analyses were used to determine the relationship between protein intake and muscle strength, protein intake and bone mineral density, polypharmacy and muscle strength, polypharmacy and bone mineral density, and micronutrient consumption (zinc, magnesium, calcium, vitamin D) and bone mineral density. Significance values were set at $p < .05$.

CHAPTER IV

RESULTS

Summary

This study examined protein intake and polypharmacy and the effects on bone mineral density in individuals aged 55 years and older. The study was part of a fall prevention study completed earlier at Texas Woman's University. Beginning in the Fall of 2010, the original study was a year long study evaluating exercising and non-exercising individuals and protein intake and exercise effects on bone mineral density. Thirty-one male and female participants from the longitudinal study completed the requirements for the present study. Participants were included in the present study if they completed the following: three-day diet analysis used to determine nutritional information, the health questionnaire to determine number of medications consumed, and the strength assessment, completed at the Seniors in Motion facility.

Demographics

Average age of the individuals was 73 ± 8 years with a range of 55 to 91 years. There were 21 female participants and 10 male participants; average weight for males was 90 ± 14 kg (198 ± 32 lb) and females, 76 ± 19 kg (167 ± 41 lb). Overall, average height was 64 ± 3.6 inches and weight was 178 ± 40 pounds. The average BMI was 30 ± 7 kg/m^2 which is the upper end of the over weight category. Percent body fat was determined using the results of the DXA scan. Average percent body fat (% BF) for both

males and females was 43 ± 10 %. Separately, average % BF for males was 42 ± 7 % and average for females was 44 ± 11 %. According to the American College of Sports Medicine (ACSM) guidelines, the average range for % BF in the elderly, age 60 years and older, for females is 29 – 32% and for males is 22– 25%. It is common for lean body mass to decline with age and fat mass to increase in this age group.

Table 2

Demographic Description of Participants

Participants (n = 31)	Mean ± SD
Age (years)	73 ± 8.5
Height (in)	65 ± 4
Weight (lb)	178 ± 40
Body fat (%)	43 ± 10
BMI (kg/m^2)	30 ± 4

Macronutrient Consumption

The average daily calorie intake was 1901 kcals ± 538 kcals. Males consistently consumed greater number of calories than females (males 2064 ± 686 kcals and females 1827 ± 451 kcals). Average carbohydrate consumption was 238 ± 78 g/day and 49 ± 7 percent total kcal. Average fat intake was 75 ± 6 g/day and 35 ± 6 percent total kcals. Average total protein intake was 75 g/day, 15% kcals, and 1 g/kg/day. Table 3 describes macronutrient average macronutrient and calcium consumption.

Table 3

Macronutrient Content of Participants' Diets

Macronutrient*	Mean ± SD
Calories (Kcals)	1901 ± 537
Carbohydrates (g/day)	243 ± 79
Carbohydrate (% Kcals)	49 ± 7
Fat (g/day)	75 ± 25
Fat (% Kcals)	35 ± 6
Protein (g/day)	76 ± 22
Protein (g/kg BW)	1.0 ± 0.3
Protein (% Kcals)	16 ± 3
Calcium (mg; food alone)	859 ± 367

Note:* n = 31 for this analysis

Protein Intake, Total Hip and Total Bone Mineral Density

An ANOVA was used to determine the difference between protein intake and bone mineral density. There was no significant difference between the groups in our study; low protein (< 0.8 g/kg), moderate protein (0.8 – 1.2 g/kg), and high protein (> 1.2 g/kg) intakes and total hip bone mineral density (F = 0.726, p = 0.494) and total bone mineral density (F = 2.06, p = 0.15). Overall mean total bone mineral density was 1.11 ± 0.11 g/cm^2 and the overall mean total hip bone mineral density was 0.88 ± 0.15 g/cm^2. Results showed mean total BMD to be slightly higher in the low and moderate protein intake groups, but not statistically significant.

Table 4

Total BMD and Hip BMD Protein Intake Groups

Protein Group*	Total BMD (g/cm^2)	Total Hip BMD (g/cm^2)
Low (< 0.8 g/kg, n = 10)	1.18 ± 0.12	0.96 ± 0.17
Moderate (0.8 – 1.2 g/kg, n = 11)	1.10 ± 0.09	0.88 ± 0.13
High (> 1.2 g/kg, n = 10)	1.00 ± 0.93	0.90 ± 0.51

Note:* *n* = 31

Polypharmacy, Muscle Strength, Supplements and BMD

Linear regression analyses were used to determine the relationship between muscle strength and total hip and total bone mineral density. Leg flexion and extension were used to determine the relationship between muscle strength and total BMD and total hip BMD. There was a significant relationship between muscle strength. Results are shown in Table 5.

Linear regression analyses were also used to determine the relationship between total number of medications used and total hip bone mineral density and total bone mineral density. There was no significant relationship between the number of medications used and bone mineral density at either site.

Lastly, supplement intake was evaluated to determine if total number of supplements consumed had an impact on bone mineral density. Linear regression analyses were used to determine the relationship between total hip bone mineral density and total bone mineral density. There was no significant relationship between the two variables. Results are depicted in Table 5.

Table 5

*Correlations between Variables and BMD**

	Total BMD (*r*)	Significance *(p)*	Total Hip BMD (*r*)	Significance *(p)*
Muscle strength				
Right Leg Flexion	.446	.002*	.483	.008*
Right Leg Extension	.589	.001*	.215	.037*
Left Leg Flexion	.414	.026*	.265	.165
Left Leg Extension	.522	.004	.405	.029*
Medications	.017	.920	.133	.470
Supplements	.146	.424	.168	.358

Note:*Significant at $p < .05$; $n = 31$

Polypharmacy and Total Hip Bone Mineral Density

Polypharmacy (consuming multiple drugs) did not have an impact on total hip bone mineral density. The participants were separated into two groups, those taking less than 5 drugs/day and those taking 5 or more drugs/day. Total hip bone mineral density was compared between the groups and there was no significant difference ($p = .84$). Two participants consumed zero medications and one participant consumed 13 medications, which was the highest consumer. The list of medication types and the number of individuals consuming the type of drugs are listed in the table below. Further description of drugs types can be found in *Appendix E*.

Majority of the individuals consumed blood pressure, lipid-lowering, and heart rate lowering drugs. The top three medications consumed included blood pressure lowering medications ($f = 20$; 12%) followed by antacids ($f = 13$; 8%), and aspirin ($f = 13$; 3%).

Table 6

Type of Medications Consumed

Type of Drug	Number of participants (*f*)*	Percent
Blood pressure	20	12%
Antacid	13	8%
Aspirin	13	8%
Nasal spray steroid	9	5%
Cholesterol/lipid lowering	7	4%
ACE inhibitor	7	4%
Thyroid	7	4%
Asthma/allergy	6	4%
Anti-depressant	6	4%
Diuretic	5	3%
NSAID	5	3%
Insulin	5	3%
Pain reliever	4	2%
Arthritis	4	2%
DM	4	2%
Beta-blocker	3	2%
Prescribed Eye drops	3	2%
Anxiety	3	2%
COPD	3	2%
Sleep aid	3	2%
Prostate	3	2%
Osteoporosis	3	2%
Calcium channel blocker	2	1%
Topical anti-inflammatory	2	1%
Estrogen	2	1%
Blood thinner	2	1%
Dementia	2	1%
Anti-seizures	2	1%
Antibiotic	1	< 1%
Expectorant	1	< 1%
Lactose	1	< 1%
Sickle cell anemia	1	< 1%
Corticosteroid	1	< 1%
Crohn's	1	< 1%
Fibromyalgia	1	< 1%
Steroids	1	< 1%
Anti-histamine	1	< 1%
PPI- inhibitor	1	< 1%
Progesterone	1	< 1%
Pancreatic enzyme	1	< 1%

Note:* $n = 31$ for this analysis, f = frequency

Supplements Intake

Many individuals consumed dietary supplements including: a daily multivitamin (*f* = 16; 18%) followed by calcium (*f* = 13; 15%) and vitamin D (*f* = 12; 14%). The average number of supplements consumed was 3 ± 2. A list of supplements and the number of individuals consuming the supplements per day can be found in Table 7.

Table 7

Type of Supplements Consumed

Type of Supplement	Number of Participants Consuming Supplements/ Day (*f*)*	Percent
Multivitamin	16	18%
Calcium	13	15%
Vitamin D	12	14%
Fish oil	7	8%
Vitamin C	6	7%
Folic Acid	5	6%
Glucosamine	4	5%
B12	3	3%
B-complex	2	2%
CoQ10	2	2%
Lutein	2	2%
Chromium	2	2%
Magnesium	2	2%
Probiotics	1	1%
Zinc	1	1%
Saw Palmetto	1	1%
Cranberry	1	1%
Niacin	1	1%
Thiamin	1	1%
Vitamin E	1	1%
Chromium	1	1%
Biotin	1	1%
Iron	1	1%
Benefiber	1	1%
Lecithin E	1	1%

Note:* *n* = 31 for this analysis, *f* = frequency

Calcium Intake

Calcium intake in each protein group varied, with those in the lower protein group consuming an average of 941 mg/day of calcium daily, the moderate protein group consuming an average of 1049 mg/day, and the high protein group consuming an average of 1485 mg/day calcium daily. The maximum calcium intake was 2813 mg/day, found in the highest protein intake group and the lowest calcium intake was 512 mg/day mg found in the low protein intake group. The recommended calcium intake for individuals over 51 years of age is 1000 mg/day for males and 1200 mg/day for females. The majority of the participants (n = 19) met these recommendations through food plus supplements. There was no significant difference between the groups in calcium intake.

Table 8

*Calcium Intake**

Calcium	Mean (mg/d)	SD (mg/d)	Range (mg/d)
Low Protein (< 0.8 g/kg, n =10)	941.2	352.3	689.2 - 1193
Moderate Protein (0.8 – 1.2 g/kg, n =11)	1049.5	301.2	770.9 – 1328.1
High Protein (> 1.2 g/kg, n = 10)	1385.4	575.5	1119.8 – 1851.0
Total	1192.5	503.8	1000.9 – 1384.2

Note:* n = 31 for this analysis

Micronutrients and BMD

Multiple linear regression analyses were used to determine the relationship between micronutrients and total bone mineral density and total hip bone mineral density. There was no significant relationship between calcium, zinc, vitamin D, or magnesium intake. Intake recorded was only determined by food intake. However, there was a significant relationship between energy intake and total BMD and energy and protein intake and total hip BMD. Supplement intake was excluded from this analysis. Results are displayed in Table 9.

Table 9

*Linear Regression Results BMD & Micronutrient Intake **

	Total BMD (*r*)	**Significance *(p)***	**Total Hip BMD (*r*)**	**Significance *(p)***
Calcium	.024	.902	.129	.475
Zinc	.283	.137	.088	.625
Vitamin D	.220	.251	.037	.839
Magnesium	.084	.666	.241	.178
Protein	.341	.052*	.431	.017*
Energy	.345	.049*	.427	.013*

Note:* p = significance > 0.05; n = 31

CHAPTER V

DISCUSSION

To date, multiple studies have explored the relationship of bone mineral density and protein intake in individuals over the age of 55 years. However, results remain inconclusive. There has been minimal research completed on polypharmacy and its relationship to muscle strength and bone mineral density. This study was completed to further examine the relationship between protein intake and bone mineral density in individuals over the age of 55 years and provide additional information on the relationship of polypharmacy, bone mineral density, and strength. In this study, no significant differences in high, moderate, and low protein intakes and bone mineral density, relationship between pholypharmacy and bone mineral density or muscle strength, and between muscle strength and bone mineral density where observed.

The following decisions were made regarding the null hypotheses tested at a 0.05 significance level:

1. H_0: There will be no significant difference between groups consuming < 0.8 g/kg/d protein, 0.8 – 1.1 g/kg/day, and > 1.2 g/kg/d on total hip bone mineral density. FAILURE TO REJECT
2. H_0: There will be no relationship between muscle strength and polypharmacy. FAILURE TO REJECT

3. H_0: There will be no significant difference in individuals consuming 5 or more medications and those consuming less than 5 medications on total hip bone mineral density. FAILURE TO REJECT
4. H_0: There will be no relationship between polypharmacy and total hip bone mineral density. FAILURE TO REJECT

Protein Intake and Bone Mineral Density

The effect of protein intake on bone mineral density is not conclusive. Inadequate consumption of dietary protein may lead to frail bones and excessive consumption can cause a high acid environment, and as a result, may lead to low bone mineral density. However protein intake as a direct indicator of bone mineral density remains questionable. In this study, there was a significant relationship between protein intake and bone mineral density, but there was no significant difference between protein intake groups of high, moderate, and low intake. This study was an observational study, solely evaluating the participants' usual protein intakes. No nutrition education or diet intake information was provided.

Mean protein intakes were within the Acceptable Macronutrient Distribution Range (AMDR) set by Dietary Reference Intakes (DRIs) as a percentage of total calories. These recommendations are set to ensure individuals meet the correct amount of macronutrient needs. Carbohydrate recommendation is 45 – 65% total kcal intake, fat recommendation is 20-35% total calorie intake, and protein recommendation is 10 to 35% of total kcal consumption (Sizer & Whitney, 2008). In this study, participants consumed an average of 15% total calories per day in protein. Another way to measure

protein intake is protein per kilogram of body weight. Recommendation of protein per kg in a healthy individual is 0.8 g/kg/day. During stress, protein requirements increase, for example: injury, burn, malnutrition, or growth. However, the participants in this study were healthy and non-stressed. Participants consumed an average of 1.0 g/kg/day, greater than the recommended intake.

Low Protein Intake

In this study, the low protein intake group did not have a significantly lower BMD when compared to the other groups. There were only ten individuals consuming less than 0.8 g/kg BW. However, the one participant with the lowest protein intake did have the lowest bone mineral density at two of the sites measured. This individual's protein intake was only 0.5 g/kg total body weight. Bone mineral density measures included total bone mineral density (0.93 g/ cm^2) and total hip bone mineral density (0.67 g/cm^2). There have been no recent studies specifically evaluating the long term effects of low protein intake, however, Kerstetter and colleagues conducted multiple short term studies from 1997 to 2003, evaluating a low protein diet and the effect on bone mineral density. The hypothesis was low protein intake impacts parathyroid hormone and calcium metabolism, ultimately compromising bone mineral density (Kerstetter et al., 1997; Kerstetter, O'Brien, & Insogna, 1998; Kerstetter, Svastisalee, Caseria, Mitnick, & Insogna, 2000; Kerstetter, O'Brien, & Insogna, 2003). It is important to note that young healthy individuals were used in the Kerstetter studies. In the Kerstetter et al. (1998) study participants developed hypocalciuria and secondary hyperparathyroidism by Day 4 of the low protein diet, this persisted for 2 weeks. The onset of hyperparathyroidism induced by

the low protein intake is still unknown, however it is known that low protein intake does compromise bone mineral density Kerstetter et al. (2003). The present study did not look specifically at calcium levels in the blood, however it was hypothesized that low protein intake will compromise bone mineral density. In further research on this topic, evaluating calcium levels in the blood may be beneficial.

High Protein Intake

In the present study, there was no difference in BMD between participants in the high protein group and the low protein group. Only one participant consumed 1.4 g/kg per day and the highest percentage of protein intake was 20% total calories consumed. Hannan et al. (2000) found excess protein intake, > 2.0g/kg BW, is possibly associated with negative calcium balance and Thorpe et al. (2008) found high protein intake (> 1.4 g/kg/day) had greater urinary calcium excretion. In the Thorpe et al. (2008) study urinary calcium excretion was negatively associated with total body bone mineral content ($p <$ .01). Overall, Thorpe et al. (2008) and Hannan et al (2000) concluded even if calcium intake is adequate, a diet high in protein exacerbates calcium excretion. In further research, obtaining calcium excretion would determine the effect of high protein intake in an acute setting. It is important to note, the variety of individuals in this study was limited. All individuals were exercising; therefore it is hard to determine if the bone mineral density measure was an effect of protein intake or exercise. Also, in this study there were no participants who consumed protein >2.0 g/kg, like the Hannan et al. (2000) study.

Total Energy, Protein, and Micronutrient Correlations to BMD

In the present study there were correlations between energy and protein intake and total BMD, energy (r = .345; p = .049) and protein (r = .341; p = .017). However, there were no correlations between any micronutrients: calcium (r = .024; p = *.475*), vitamin D (r = .220; p = .251), magnesium (r = .084; p = .666), and zinc (r = .283; p = .137). Ilich, Brownbill, and Tamborini, (2003) found correlations of specific nutrients and bone mineral density using multiple linear regression analyses. They found that the intake of energy, protein, calcium, magnesium, and zinc were significantly related to multiple skeletal sites.

The present study was similar to the Ilich, Brownbill, and Tamborini, (2003) study in cross-sectional nature and they used linear regression analysis to determine the correlation between variables. In the Ilich, Brownbill, and Tamborini, (2003) study, participants were postmenopausal women (68.7 ± 7.1 years). All participants completed three-day dietary records that were analyzed by Food Processor®. They found weak, but positive relationships between some nutrients and bone mineral density such as calcium, magnesium, zinc, and vitamin C (all $p < .05$). Regression models were controlled for age, fat, and lean tissue, physical activity and energy intake.

To evaluate protein intake, Ilich, Brownbill, and Tamborini, (2003) separated participants into only two groups based on nutrient consumption, those consuming greater than median, and those consuming less than median for protein intake. The median for protein consumption was 68.2 g/day. They found those consuming greater than the median protein intake had significantly greater total body bone mineral density,

Wards triangle, and hand BMD ($p < .05$). They also found those consuming above the median for calcium (> 750 mg/day) and protein (> 68.2 g/day) had greater measures of bone mineral density of Ward's Triangle and total body BMD than those consuming less than the median. However, it is important to note, to compare other data with these results is difficult, because protein intake was set at median consumption and this consumption may not be adequate for everyone. A better measure of protein intake is by determining protein intake by kilogram of body weight.

Protein Intake and Calcium Metabolism

In the present study, there was no significant relationship between protein intake and BMD in the presence of adequate calcium intake. The participants in this study consumed a minimum of 292 mg calcium and a maximum of 1357 mg of calcium through food alone. When supplements were considered, the minimum intake was 512 mg and the maximum was 2813 mg calcium consumed daily. Calcium intake in the presence of higher protein intake can prevent loss of BMD (Dawson-Hughes & Harris, 2000), and is associated with a higher total BMD (Ilich, Brownbill, & Tamborini, 2003), and decrease in risk of bone fractures (Meyer, Pedersen, Loken, & Tverdal, 1997; Wengreen et al., 2004). Higher protein intake (79.1 ± 25.6 g/day) with supplemental calcium (1346 ± 358 mg/day) was associated with a decreased BMD loss (or greater gain; Dawson Hughes & Harris, 2000). In the present study calcium intake did not have an effect on BMD between the three groups of protein intake.

Polypharmacy and Bone Mineral Density

Polypharmacy in those over the age of 55 years is associated with falls leading to bone fractures (Ziere, 2005), specifically hip fractures. However, bone mineral density directly associated with polypharmacy has not been well studied. In this study there was no correlation between the number of drugs consumed and total bone mineral density or total hip bone mineral density. Other research does indicate polypharmacy is related to an increase in falls and hip fractures due to certain "risk-increasing drugs" (Ziere, 2005). These risk-increasing drugs include: sedative-hypnotic and anxiolytic drugs, tricyclic antidepressants, major tranquilizers, antihypertensive drugs, hypoglycemic agents (Fuller, 2000) diuretics, antiarrhythmics and psychotropics (Ziere, 2005). In the present study Cardizam and Isoptin (calcium channel blockers), Coreg and Troprol (beta-blockers) were the only drugs from the list used. Further research on bone mineral density and polypharmacy should be completed to determine the effects associated with the consumption of multiple drugs on bone mineral density.

Polypharmacy and Muscle Strength

In the present study there was no significant relationship between the number of medications consumed and muscle strength. Currently, there have been few studies looking at polypharmacy and muscle strength in individuals over the age of 55 years. In the present study t-tests, were used to determine the difference between participants in the lower drug consumption group and those in the higher drug consumption group. There was no significant difference between polypharmacy (more than 5 drugs) and those consuming less than 5 drugs/day and muscle strength (p = .84). Also, a linear regression

analysis was used to determine the correlation between medications consumed and muscle strength. In theory, bone mineral density will decrease as number of drugs consumed increases. There was no correlation in this study between number of medications and total hip bone mineral density and total body BMD (p = .920; total; p = .470; hip). Further research on this topic should be completed and compared between exercising and non-exercising populations.

There were multiple limitations to this study. The major limitation was the response rate of the 24-hr recall, limiting the number of participants. The original goal was to obtain participation from 100 individuals, however only 56 responded and of that 56, only 31 completed the 3 day diet record. The original study was projected to be a year long study with at least two groups of individuals, exercising and non exercising individuals. However, recruitment was not completed and only a cross-section of the data was obtained. The participation group was limited to those participating at the Seniors in Motion facility, also limiting variety of subject participation. All participants were actively participating in exercise therefore limiting the variety of activity levels to one specific group. To gain a better understanding of picture intake and calcium regulation on bone metabolism, additional analyses would be of benefit. Extensive studies have been completed specifically relating protein intake to bone mineral density. To obtain a better understand of protein and calcium metabolism of bone tissue, lab values of calcium blood and urinary calcium excretion would have been beneficial to determine calcium levels in the blood or calcium excretion through the urine

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APPENDIX A
(IRB)

TWU
TEXAS WOMAN'S UNIVERSITY
DENTON DALLAS HOUSTON

Institutional Review Board
Office of Research and Sponsored Programs
P.O. Box 425619, Denton, TX 76204-5619
940-898-3378 FAX 940-898-4416
e-mail: IRB@twu.edu

May 3, 2012

Dr. Nancy DiMarco
Institute of Women's Health

Dear Dr. DiMarco:

Re: A Longitudinal Study of a Comprehensive Therapeutic Exercise Program for Elderly Fall Prevention (Protocol #: 16150)

The request for an extension of your IRB approval for the above referenced study has been reviewed by the TWU Institutional Review Board (IRB) and appears to meet our requirements for the protection of individuals' rights.

If applicable, agency approval letters must be submitted to the IRB upon receipt PRIOR to any data collection at that agency. A copy of all signed consent forms and an annual/final report must be filed with the Institutional Review Board at the completion of the study. A copy of the approved consent form with the IRB approval stamp is enclosed. Please use a copy of this stamped consent form when obtaining consent from your participants.

This extension is valid one year from May 7, 2012. Any modifications to this study must be submitted for review to the IRB using the Modification Request Form. Additionally, the IRB must be notified immediately of any unanticipated incidents. If you have any questions, please contact the TWU IRB.

Sincerely,

Rhonda R Buckley

Dr. Rhonda Buckley, Co-Chair
Institutional Review Board - Denton

cc. Dr. Chandan Prasad, Department of Nutrition & Food Sciences

APPENDIX B
(CONSENT FORM)

postural alignment and head position during quiet stance, 4. current pain scale and threshold levels, and subjective fall risk assessment on a scale of 1-5 from least to most likely to fall. Following the assessment you will be assigned to one of three groups: 1. Physical Therapy-based exercise program, 2. Physical Therapy-based exercise program plus Bidirectional Hip Strengthening Machine, and 3. Control Group. Participants will be randomly assigned to one of the two exercising groups by the Physical Therapist. If you are part of the Control Group, you will not participate in the Physical Therapy-based exercise program; however, you will be asked to come back every 0, 6, and 12 months for data collection; if you are part of the exercising groups, you will also be required to participate in a weekly exercise program; as well as data collection at months 0, 6, and 12.

The Physical Therapy-based exercise program will be developed and monitored by Seniors in Motion that will adhere to all principles governed within the discipline of Physical Therapy. You will be required to meet with the staff at Seniors in Motion a minimum of twice and no more than three times a week. You will be asked to follow a generalized program that will be customized to meet your specific needs based on your most recent assessment.

The Bidirectional Hip Strengthening Machine provides direct force in two directions with stabilization. Therefore, muscle contraction will be required in both hip joint bending and extending with outward rotation. This concept is unique in the fitness equipment industry and may promote strength and stability in the hip joint and possibly contribute to elderly balance/stability. Given this exercise to a common fracture site, femoral neck, it is further believed that an improvement in bone mineral density will result over this 12 month study.

The assessments that will be performed by the Physical Therapist will take 1 hour or less to complete. The exercise program (2-3 sessions per week) which will be developed by a Physical Therapist and monitored by the Seniors in Motion staff will take 3 hours or less per week.

Once you have been assessed and assigned to one of three groups you will be required to visit the campus of Texas Woman's University: 1. Institute for Women's Health located in 011 and 017 of the Human Development Building and 2. Biomechanics Motion Analysis Laboratory located in Pioneer Hall.

While at the Institute for Women's Health, you will participate in a balance analysis survey and three bone scans and percent body fat and muscle measurements. In addition, you will also pick up the materials and instructions to complete the food diary. The food diary will be recorded over three days (72 hours), including one weekend day. You will be asked to record all food consumption over a 72 hour period, which includes the type and portion size. The balance analysis survey will be assessed using The Activities-Specific Balance Confidence (ABC) Scale. The ABC Scale is a graded 16-item survey which will assess your confidence of your balance under various activity conditions. Finally, a bone scan will be used to measure Bone Mineral Density at the following three sites: 1. spine 2. hip joint and 3. total body scan and percent body fat and muscle measurements.

You will be asked to wear loose fitting clothing and remove all metal items, such as jewelry, zippers, snaps, buttons, glasses, etc. for the bone scan. In addition, you will be asked

Initials: _____

to remove your shoes. Once properly attired, you will be comfortably positioned by the practitioner on the scanning table where you will remain motionless for the duration of each of the scans.

The three bone scans will take 30 minutes or less to complete. The ABC scale takes 5 minutes or less to complete. The food diary is recorded over 3 days; however it will take 1 hour or less to complete.

The Biomechanics Motion Analysis Laboratory will perform the balance and gait assessments. The gait assessment will include both normal walking and walking over objects. A gait analysis for normal walking will be conducted to assess your normal walking patterns. In addition, walking over objects will determine your ability to walk up a normal step or curb. Laboratory measurement of your balance will be use a Neurocom Balance Master for the following clinical balance tests: 1. sit-to-stand, 2. modified Clinical Test of Sensory Interaction on Balance, and 3. Limits Of Stability.

During the gait analysis you will enter the laboratory and change into clothing conducive to Biomechanical research – dark and form-fitting, provided by the laboratory. You will be asked to wear your own shoes that you would normally walk or exercise in for the data collection. Twenty-four reflective markers will be strategically adhered to outline your body. The following anatomical sites will be used: upper body (2), pelvis (3), hips (2), outer thigh (2), knees (4), outer lower legs (2), ankles (4), toes (2), heels (2), with the last marker being used to determine right versus left side of the body at shoulder blade level. You will be given plenty of time to warm-up and self report once completed. Fifteen or less walking trials will be collected with a minimum of five "good" trials collected for both normal walking and walking over an object.

The assessment of balance will be conducted in the Biomechanics Laboratory (Pioneer Hall, Room123) with the use of a Neurocom Balance Master. You will be asked to remove your shoes and socks and step on a platform based on height and then harnessed into the machine to prevent a fall from occurring. Each test: 1. sit-to-stand, 2. modified Clinical Test of Sensory Interaction on Balance, and 3. Limits Of Stability has a set procedure. During sit-to-stand you will start in a seated position and rise to a standing position until the test is completed. The modified Clinical Test of Sensory Interaction of Balance is a four-step test that determines the source of loss of balance. Limit of Stability is a multi-directional test used to establish balance in eight separate directions. All three balance tests will compare your results over time as well as to others of your same age.

The measurement of balance will take 30 minutes or less to complete. The gait assessment will take 45 minutes or less to complete.

The proposed study is longitudinal training study in which each variable will be measured three times: 0, 6, and 12 months. The time commitment per each participant will be no less than 13.5 hours for all testing conditions and 156 hours for the Physical Therapy based exercise program; therefore, a total time commitment of 170 hours will be required to complete the 12 month study.

Initials:_____

Potential Risks

Loss of Confidentiality: Confidentiality will be protected to the extent that is allowed by law. All your paperwork and computer files associated with this study will be identified by a randomly assigned identification number. Only the co-principal investigators will know which data is associated with you. Research assistants will participate in the data collection, processing, and data reduction/analysis. All data will be obtained specifically for research purposes. All data collected will remain confidential. The data from testing will be kept in locked cabinets at Texas Woman's University – Human Development Building 013. The master list which cross-references your name to identification number will be stored separately from all other information and data. Data will be destroyed after three years or upon publication of results. Paper files will be destroyed by shredding. Computer files and video tapes will be destroyed by erasure. Computer disks will be destroyed by breakage. There is a potential loss of confidentiality through all email transactions.

Embarrassment: We will place reflective markers over anatomical landmarks on your body for gait analysis data collection sessions. These reflective markers are necessary to track your walking motion through our laboratory. A research assistant of the same sex will be present to place the reflective markers on your body. Reflective markers will be conducted in private, with no other participants present. If for some reason you become uncomfortable with the data collection conditions please advise the research assistants or principal investigators.

Possibility of Injury: Potential of injury will be minimized by allowing you adequate time for each testing condition. If you should feel uncomfortable with any of testing condition, you are free to discontinue your involvement in this research project. In addition, assistants at both SIM and in the Biomechanics lab will be strategically positioned to assist you in maneuvering in and around the walking surfaces. In the event of an injury, accident, or changes of condition involved in performance of research testing procedure:

1. Research assistance and staff will follow emergency procedure as established by the American Red Cross.
   a. The emergency response system (ERS) will be activated as indicated by the nature of the accident, injury or condition of the participant.
2. You will be instructed to report following occurrence:
   a. Onset pain greater than minimum or three on the pain scale
   b. Onset of shortness of breath (dyspnea) that causes a distress or feeling nausea that you are unable to articulate appropriately.
   c. A feeling of dizziness or fairness
   d. Chest pain
   e. Pain that is experienced which is still present 24 hours after activity.
   f. Feeling nausea or illness
3. Non-emergency procedure will be followed up by your contact with your physician as needed

Initials _____

4. In the case of a fall, you will not be moved from floor to stand without professional staff first assessing the extent of your injury and cause of fall. In case of a suspected fracture or serious injury, a call to 911 will be activated.

Muscle soreness: About 24-48 hours after participating with a bout of exercise, you may experience muscle soreness. This is normal after participating in a new physical activity, and can range from mild to moderate. There is no additional risk over and above the normal risk you would encounter when exercising or walking. Muscle soreness will be minimized by having you warm-up and stretch at the beginning of the exercise and data collection session. If muscle or joint soreness should happen to occur, then you will be instructed through a post-event cool-down and stretching routine. If soreness persists, then you will be advised to seek medical attention. However, TWU does not provide medical services or financial assistance for injuries that might happen because of participant participation in the current research.

Skin irritation due skin preparation: Reflective markers are used to assist the laboratory in determining your movement in our laboratory. Marker placement is necessary to ensure good skin-reflective marker contact to ensure that marker placement is maintained throughout data collection. Erroneous results can occur if this step is not taken. Care will be taken in skin preparation to minimize this risk; however, if you are sensitive to such treatments please let a research staff member know and the circumstances will be addressed on an individual basis.

Radiation exposure: We will determine the bone mineral density of your spine (lower back), hip (femur), total body, and body composition (total fat, non-fat, and bone tissue) using a dual energy x-ray absorptiometer (DXA). This procedure will be conducted 3 times (pre-study screening and at 5 & 12 months). Only certified technicians will perform these procedures. You will feel no pain or other sensation while on the machine. The only risk is exposure to a minimal amount of radiation. The amount of radiation from the DXA scan (<5 mR) is far less than the 100 mR of a chest x-ray and the 600 mR of a lumbar X ray.

Coercion: Steps will be taken by the staff at Seniors in Motion to ensure you do not have the feeling of being coerced into participating in the study. Participation is completely voluntary and you may withdraw at anytime for any reason.

Fatigue: The nature of this study is a training study and fatigue is a byproduct of your effort. If you should start to feel fatigue, you may rest. If excessive fatigue should occur, you will be instructed to sit or lie down, and the staff will monitor your situation. Standard CPR and First Aid requirements will apply if the you happen to worsen and/or 911 will be called. You may withdraw from the study at any time for any reason.

The researchers will try to minimize any problem that could happen because of this research. You should let the researchers know at once if there is a problem and they will help you. However, TWU does not provide medical services or financial assistance for injuries that might happen because you are taking part in this research.

Initials _____

Participation and Benefits

There is a positive direct benefit of this study to you in that you will learn more about your standing balance, walking gait characteristics, ability to negotiate an obstacle course relevant to walking in the normal world, bone mineral density, body composition, and dietary intake. This may assist you in identifying your risk of falling and make you aware of possible risks. Also, you will benefit from the exercise, walking ability, balance, strength, risk of falls, and performance should be improved. Any questions will be answered so that the maximum amount of understanding and medical use of the information will be achieved.

Participation in this study is voluntary and you are free to withdraw at any time without penalty. You will not be monetarily compensated for your time in this study. Your time is completely voluntary. A copy of the abstract of the final published research will be mailed to you if you so desire.

Questions Regarding the Study

You will be given a copy of this signed and dated consent form to keep. If you have any questions about the research study you should ask the researchers; their phone numbers are at the top of this form. If you have questions about your rights as a participant in this research or the way this study has been conducted, you may contact the Texas Woman's University Office of Research and Sponsored Programs at 940-898-3378 or via e-mail at IRB@twu.edu.

Signature of Participant _____ Date _____

If you would like to receive a copy of the abstract of the published research, provide the following information.

Full Name _____

Mailing Address _____

City, State, Zip Code _____

Initials: _____

APPENDIX C
(HEALTH QUESTIONNAIRE)

IWH Wellness & Sport Evaluation Program
Health Questionnaire

Name _____ Date ____/____/20_____
(Last) (First) (Middle)

		Circle One	Notes
(1)	Have you been under the care of a physician during the past 2 years?	Yes No	
(2)	Are you allergic to penicillin, any drugs, medicine, or latex?	Yes No	
(3)	Have you ever had excessive bleeding which required special treatment?	Yes No	
(4)	Women: Is there a chance you might be pregnant?	Yes No	
(5)	Women: Are you taking any birth control medication?	Yes No	
(6)	Have you had adverse reaction to local anesthetics?	Yes No	
(7)	Do you use recreational drugs?_____ If yes, what?_____		
(8)	Do you use tobacco? _____ If so, what form? _____		
(9)	Date of last medical exam _____		

(10) Circle Yes to any of the following which you have had or have at present. Circle No to those that you have not had.

Yes	No	High Blood Pressure
Yes	No	High Blood Cholesterol
Yes	No	Chest Pain or Pressure (Angina)
Yes	No	Heart Disease or Attack
Yes	No	Heart Pacemaker
Yes	No	Heart Failure
Yes	No	Heart Surgery
Yes	No	Fainting or Lightheadedness
Yes	No	Artificial Heart Valve
Yes	No	Congenital Heart Lesions
Yes	No	Mitral Valve Prolapse
Yes	No	Stroke
Yes	No	Transient Ischemic Attack
Yes	No	Lupus
Yes	No	Rheumatic Fever
Yes	No	Scarlet Fever
Yes	No	Chronic Fatigue
Yes	No	Artificial Joints
Yes	No	Kidney Dialysis
Yes	No	Kidney Disease
Yes	No	Eating Disorder
Yes	No	Rheumatoid Arthritis
Yes	No	Arthritis
Yes	No	Chronic Head, Neck, or Back Pain
Yes	No	Diabetes Requiring Insulin
Yes	No	Diabetes Not Requiring Insulin
Yes	No	Hypoglycemia
Yes	No	Hyperthyroidism (High)
Yes	No	Hypothyroidism (Low)
Yes	No	Ulcers
Yes	No	Pulmonary Disease

Yes	No	Unexplained Shortness of Breath
Yes	No	Chronic Cough or Bronchitis
Yes	No	Tuberculosis (TB)
Yes	No	Emphysema
Yes	No	Asthma
Yes	No	Hay Fever
Yes	No	Allergies or Hives
Yes	No	Sinus Trouble
Yes	No	Cancer
Yes	No	Leukemia or Lymphoma
Yes	No	Radiation or Chemotherapy
Yes	No	Anemia
Yes	No	Bruise Easily
Yes	No	Bleeding Disorders
Yes	No	Sickle Cell Disease
Yes	No	Alcoholism
Yes	No	Drug Addiction
Yes	No	Blood Transfusion
Yes	No	Liver Disease
Yes	No	Yellow Jaundice
Yes	No	Hepatitis
Yes	No	AIDS / HIV Infection
Yes	No	Cold Sores / Fever Blisters
Yes	No	Psychiatric Treatment
Yes	No	Depression / Bipolar
Yes	No	Nervousness / Anxiety
Yes	No	Dizzy Spells
Yes	No	Epilepsy or Seizures
Yes	No	Condition Requiring Cortisone Medicine
Yes	No	Glaucoma
Yes	No	Spine or Hip Fractures

List all prescription medications that you are currently taking.

Medication/Dosage/Date Started/Reason _____
Medication/Dosage/Date Started/Reason _____
Medication/Dosage/Date Started/Reason _____
Medication/Dosage/Date Started/Reason _____
Medication/Dosage/Date Started/Reason _____
Medication/Dosage/Date Started/Reason _____

Please list all non-prescription medication or vitamins or nutritional supplements you are currently taking.

Name/Dosage/Date Started/Reason _____

Name/Dosage/Date Started/Reason _____

Name/Dosage/Date Started/Reason _____

Name/Dosage/Date Started/Reason _____

Name/Dosage/Date Started/Reason _____

Name/Dosage/Date Started/Reason _____

List all surgical procedures that you have had in the past.

Year _____ Type of Surgery/Reason _____

Year _____ Type of Surgery/Reason _____

Year _____ Type of Surgery/Reason _____

Year _____ Type of Surgery/Reason _____

List all hospitalizations of 24 hours or more for any reason.

Year _____ Reason for hospitalization _____

Year _____ Reason for hospitalization _____

Year _____ Reason for hospitalization _____

Year _____ Reason for hospitalization _____

Other Health Information

Please use this space to record any other personal health information that was not listed above.

_____

_____

"I Attest To The Fact That The Information Given Above Is Correct And I Consent To Receive Clinical Services."

_____

(Parent or Guardian must sign for patient under age 18.)

This section for office use only:

Comments:

_____

_____

_____

_____

_____

APPENDIX D
(DEMOGRAPHIC QUESTIONNAIRE)

IWH Wellness & Sport Evaluation Program
Demographic Questionnaire

Name: _____ Date: ____/____/20____
(Last) (First) (Middle)

Phone: (____) _____ Email: _____

Address: _____ City _____ ST _____ Zip _____

How would you prefer we contact you? ❑ Phone ❑ Email ❑ Mail

Date of Birth: ____ / ____ / ____ Gender: ❑ Male ❑ Female

Ethnicity: (Check all that apply)
❑ African American
❑ American Indian
❑ Asian/Pacific Islander
❑ Caucasian (non-Hispanic)
❑ Hispanic
❑ Scandinavian
❑ Other: _____

What is the highest level of education you have attained? (Please mark only one)
❑ Less than a high school diploma
❑ High school graduate
❑ Some college or technical training
❑ Associate's degree or equivalent
❑ Bachelor's degree
❑ Graduate degree

What is your present work situation? (Check all that apply)
❑ Employed full-time
❑ Employed part-time
❑ Semi-retired
❑ Fully-retired
❑ Self-employed
❑ Unemployed
❑ Homemaker
❑ Student
❑ On disability
❑ Other: _____

Are or were you a student at Texas Woman's University?
❑ Yes, I am a current student
❑ Yes, but I am not currently enrolled in any courses
❑ Yes, I am a TWU alumnus
❑ No

Are you a current employee of Texas Woman's University?
❑ Yes ❑ No

Please provide the name of a close relative or friend that we may contact, if necessary.

Name: _____ Phone: (____) _____

Please provide the name of your physician.

Name: _____ Phone: (____) _____

For office use:
Is physician clearance required?
❑ Yes ❑ No
Proof of physician clearance provided:
❑ Yes ❑ No
Approved by: _____

Proof of TWU employee/student status provided:
❑ Yes ❑ No
Approved by: _____

APPENDIX E
(MEDICATION LIST)

Name of Drug, Drug Type, and the Number of Participants Consuming the Name Brand

Name of Drug	Type of Drug	Number of Participants *(f)*
Aspirin	Anti-inflammatory/pain med/blood thinner	12
LEVOTHYROXINE (levoxy, synthroid)	Thyroid medication	6
NEXIUM (esomeprazole)	Antacid	5
PRINIVIL (lisinopril)	ACE inhibitor	5
ZOCOR (simvastatin)	Lipid-lowering	3
FLONASE (fluticasone)	Steroid – nasal spray	3
PRAVACHOL (Pravastatin)	Cholesterol lowering	3
NORVASC (Amlodipine Besylate)	Blood pressure	3
FUROSEMIDE (lasix)	Diuretic	2
DIOVAN (valsartan)	Beta-blocker	2
PRED FORTE ® (prednisolone acetate)	Topical anti-inflammatory	2
FLONASE (Fluticasone nasal)	Nose spray	2
LOSARTAN (Cozaar)	Blood pressure	2
ZANTAC ® (Ranitideine)	Antacid	2
XANAX (Alprazolam)	Anxiety	2
ALLEGRA ® (fexofenadine hydrochloride)	Allergy	2
ADVAIR (fluticasone & Salmeterol)	COPD	2
TYLENOL ® (Acetaminophen)	Pain reliever	2
Ibuprofen	Anti-inflammatory	2
TRAZODONE (deseryl)	Sleep	2
Prilosec OTC	Heart burn	2
FLOMAX (Tamsulosin Hydrochloride)	Prostrate	2
HUMALOG (Insulin lispro)	Insulin	2
HCTZ (hydroclorothiazide)	Diuretic	2
JALYN (Dutasteride & Tamsulosin hydrochloride)	Testosterone	2
CITALOPRAM (Celexa)	Antidepressant	2
LIPITOR (atorvastatin calcium)	Cholesterol lowering	2
ZYRTEC®	Allergy	2
COSOPT (Dorzolamide/Timol0l)	Sterile ophthalmic solution	2
LUMINGA ®	Ophthalmic solution	2
RAMIPRIL (Altace)	ACE inhibitor	2
LANTUS (insulin)	Insulin	2
GLUCOPHAGE (metformin)	Blood glucose	2
ACTOSE (pioglitazone)	Blood glucose	2
VASOTEC ® (enalapril)	Blood pressure	1
AFEDITAB CR (nifedipine)	Calcium channel blocker	1
TEKTURNA (aliskiren)	Blood pressure	1
RESTASIS ® (cyclosporine)	Eye Dropper	1

(Continued)

ASTELIN ® (azelastine hydrochioride)	Nasal spray	1
AMOXIL (amoxicillin)	Antibiotic	1
PREMARIN ® (conjugated estrogen)	Estrogen	1
NASALCROM (Cromolyn sodium)	Nasal spray	1
ENTEX LA (guaifenesin & Phenylephrine)	Expectorant	1
SINGULAIR ® (montelukast sodium)	Asthma/allergy	1
MONOPRIL (Fosinopril sodium)	Blood Pressure	1
PATANASE (olopatadine)	Nasal spray – anti-histamine	1
Oxymetazoline (nasal route)	Nasal spray – allergies	1
ENBRE ® (etanercept)	Arthritis	1
METHOTREXATE (Rheumatrex, trexall)	Arthritis	1
PROTONIX (pantoprazole)	Antacid	1
MAALOX ®	Antacid	1
LACTAID ®	Lactose intolerance	1
MAXIDE (Triamteren & hydrochlorothiazide tablets)	Blood pressure	1
LANSOPRAXOLE (Prevacid)	Antacid	1
REGLAN (Metoclopramide)	Antacid	1
TRAMODOL (tramadol)	Narcotic	1
RELAFEN (Nabumetone)	NSAID	1
WELCHOL ® (Colesevelam Hcl)	Cholesterol lowering	1
CARDIZEM (Diltiazem)	Blood pressure	1
COUMADIN (Warfarin)	Blood thinner	1
ARMOUR THYROID (Tyroid tablets)	Thyroid tablets	1
HYDREA (Hydroxyurea)	Sickle cell anemia	1
COREG (Carvedilol)	Beta-blocker	1
Hydrocortisone	Corticosteroid	1
PLAVIX (clopidogrel)	Anticoagulant	1
NIFEDICAL XL (nifedipine)	Blood pressure	1
LOPRESSOR (metoprolol tartrate)	Blood pressure	1
TRIAMTERENE (Dyrenium)	Thiazide diuretic	1
Aleve ®	NSAID	1
TROPROL XL (metoprolol succinate)	Blood pressure	1
ELAVIL (Amitriptyline)	Depression	1
VYTORIN (Ezetimibe & Simvastatin)	Cholesterol	1
BONIVA (lbandronate sodium)	Osteoporosis	1
LEVEMIR ® (Insulin detemir)	Insulin	1
VESICARE (solifenacin)	Bladder control	1
ARICEPT (Donepezil Hydrochloride)	Dementia	1
NAMENDA (memantine HCL)	Dementia	1
ADOVART ® (dutasteride)	Prostate hyperplasia	1

(Continued)

Hydrocodone	Pain reliever	1
REMICADE® (infliximab)	Crohn's disease	1
LUNESTA ® (esopiclone)	Sleeping aid	1
LYRICA®(pregabalin CV)	Fibromyalgia	1
ATROVENT (Ipratropium bromide)	COPD	1
NASONEX (mometasone furoate)	Allergies	1
FIORINAL (aspirin, butalbiatal & caffeine)	Tension headaches	1
KLONOPIN (Clonazepam)	Anxiety	1
TENORMIN (atenolol)	Blood pressure	1
EFFEXOR (venlafaxine)	Antidepressant	1
ACTONEL (Risedronate)	Bone density	1
Advil	NSAIDS	1
PREMARIN (estrogens)	Estrogen replacement	1
DELTASONE (prednisone)	Steroids	1
WELLBUTRIN SR	Antidepressant	1
DEPAKOTE (divalproex sodium)	Anti-seizure	1
NEURONTIN (Gabapentin)	Anti-seizure	1
CLARITIN (loratadine)	Anti-histamine	1
PREVACID (lansoprazole)	PPI-inhibitor	1
Progesterone	Hormone replacer	1
MOBIC®(meloxica,)	Rheumatoid arthritis	1
CREON®(pancrelipase)	Pancreatic enzyme	1
ISOPTIN SR (verapamil)	Blood pressure	1
AVAPRO®(irbesartan)	Blood pressure	1
PAMELOR(nortriptyline)	Antidepressant	1
FOSAMAX (Alendronate sodium)	Osteoporosis	1
INDOCINE(indomethacin)	Rheumatoid arthritis	1
DYAZIDE (hydrochlorothiazide/triamterene)	Blood pressure	1
NAPROSYN(naproxen)	Rheumatoid arthritis	1

Note: n = 31 for this analysis.