NUTRITIONAL INFLUENCES ON NET ACID EXCRETION

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ABSTRACT

Net acid excretion (NAE) is implicated in bone loss, as increased calcium loss is seen with high NAE. Protein is the main source of dietary acid load and fruit and vegetables provide potassium salts which counteract this effect. Two studies investigated how dietary factors affect NAE and markers of bone loss. The purpose of Study 1 was to determine if pH paper strip measurement of first morning urine reflected NAE and to investigate dietary effects on NAE and markers of bone loss in free-living individuals. Twenty-three subjects recorded 24-hour food records and collected 24-hour urine, as day (~7 a.m. to 11 p.m.) and overnight (~11 p.m. to 7 a.m.), and fasting second morning urine collections. NAE was measured as titratable acidity minus HCO_3^- (TA) plus NH_4^+. pH paper strip measurement of first morning urine was significantly correlated with 24-hour TA ($r = -0.466$, $p < 0.025$), but not with 24-hour NAE. The expected relationship between NAE and dietary protein or potassium intake was not evident, instead there was an association between protein and potassium intake ($r = 0.679$, $p < 0.005$). Nor was the ratio of protein to potassium associated with NAE. A positive association was found between urinary sodium (reflecting dietary sodium) and fasting urinary calcium excretion (indirect measure of bone loss). A surprising significant negative correlation was found between NAE and urinary cross-linked N-telopeptides (NTx), suggesting that NAE may not be a significant factor in bone turnover. The log transformation of urinary sodium versus NTx indicates a possible effect of sodium on bone turnover ($r = 0.407$, $p = 0.084$). Although pH paper strips are a good estimate of NAE, they measure a factor that appears less important than sodium intake. The purpose of Study 2 was to determine if fruit intake (a source of alkalinity) would lower NAE and thereby urinary calcium loss. A crossover, acute load study was designed to investigate if processed fruit was as effective as fresh fruit in reducing NAE and protein induced hypercalciuria. Fifteen volunteers completed 3 dietary treatments on 3 different days. A fasting urine sample was collected before consuming one of the following 3 isocaloric high protein treatments: control (C), sugar and protein; fresh (F), apples, sugar and protein; and processed (P), applesauce and protein. Fruit treatments were designed to each provide 9 mmol of potassium, according

to published food labels. Urine was collected at 1.5 hour, 3 hour, and 4.5 hour. The mean NAE at 3 hour was (mmol/mmol Cr): C, 366 ± 2.18; F, 2.05 ± 2.05; and P, 1.63 ± 2.56, ($p = 0.082$), indicating a trend for lower NAE with fruit. The change in calcium excretion at 3 hour was (mmol): C, 0.239 ± 0.20; F, 0.126 ± 0.11; and P, 0.079 ± 0.21, ($p = 0.048$). Post hoc LSD test did not show a significant difference between treatments. Therefore, fruit intake is able to reduce protein induced hypercalciuria, and processed fruit appears to be as effective as fresh fruit, although a larger serving had to be consumed. While protein has received much attention for its role in increasing NAE and urinary calcium, these studies support other current literature which indicate that protein may not be harmful to bone when the diet is adequate in fruits and vegetables. Therefore, a diet generous in fruits and vegetables, adequate in protein, and low in sodium appears to be a dietary pattern which would promote bone health.

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LIST OF ABBREVIATIONS

BMD	bone mineral density
BMR	basal metabolic rate
DASH	dietary approaches to stop hypertension
DRI	dietary reference intake
EI:BMR	estimated intake:basal metabolic rate
FFQ	food frequency questionnaire
NAE	net acid excretion
NCI	National Cancer Institute
NEAP	net endogenous acid production
NHANES	National Health and Nutrition Examination Survey
NTx	urinary cross-linked N-telopeptides
PBH	Produce for Better Health Foundation
RDA	recommended dietary allowance
REE	resting energy expenditure
SD	standard deviation
TA	titratable acidity
WHO	World Health Organization

1. INTRODUCTION

1.1 Rationale

Bone provides the human body with structure and support but is not an unchanging, rigid system. This dynamic system is regulated by many nutritional and lifestyle factors. When dietary calcium intake or absorption is inadequate, calcium from bone can be removed to provide the body with the necessary calcium (Fardellone, Brazier, Kamel, Guéris, Graulet, Liénard, Sebert, 1998). Therefore, calcium homeostasis is of high interest when considering the regulation of bone remodeling. Continual bone resorption without adequate formation can lead to osteoporosis, which is the loss of bone tissue that results in low-density bones that are thin and substandard (Groff, Gropper, & Hunt, 1995). This disease is most prevalent among elderly women, as considerable bone loss occurs with estrogen depletion. Osteoporosis causes severe losses in quality of life and creates a burden on health care systems, as elderly patients often cannot sufficiently recuperate to regain their independence.

Contrary to past belief, preventing osteoporosis is not as simple as increasing calcium intake. While calcium is well known for its important role in ensuring healthy bone (Heaney, 2000), other dietary factors are implicated in bone gain and bone loss. Although North Americans consume very high amounts of milk and calcium compared to many other countries, there is a greater prevalence of osteoporosis (Brown, 2000). A positive association has been found between a country's dietary calcium intake and fracture incidence (Abelow, Holford, & Insogna, 1992). Furthermore, Abelow et al. implicated protein intake with poor bone health, as they found a positive association between the country's per capita intake of animal protein and the incidence of hip fracture among the country's female population (R^2=0.72; P<0.001). Though a significant association was found, it was believed that other causal factors, such as environmental or genetic factors, could not be ruled out and it was suggested further study be conducted.

Experimental studies have found that increasing a subject's protein intake results in increased calcium loss and it is widely accepted that protein increases urinary calcium by raising net acid excretion (NAE) (Kerstetter, Mitnick, Gundberg, Caseria, Ellison, Carpenter & Insogna, 1999; Barzel & Massey, 1998). On the other hand, a review of several prospective studies has shown that protein intake is associated with higher BMD and decreased fracture incidence in elderly women (Bell & Whiting, 2002). Due to the conflicting findings, it is reasonable to investigate further which dietary factors, in the free-living individual consuming their typical diet, are associated with increased urinary calcium loss or bone turnover markers.

Researchers have tried to predict the acid load of the diet by calculating the ion content of food (Remer & Manz, 1995; Weinstein, Austic & Schwartz, 1992). Remer and Manz attributed increased acidity primarily to protein intake. However, Weinstein et al. (1992) determined that cation excess of the diet was not negatively associated with protein content and that all cations and anions were important in estimating diet acidity. Other researchers determined that protein and potassium content of the diet alone could significantly predict the effect of the diet when subjects were acclimated to the diet (Frassetto, Todd, Morris, & Sebastian, 1998). However, the ability of the protein to potassium ratio to predict NAE in free-living individuals has not been examined.

Counteracting the acid-producing effects of protein is endogenously produced base, such as bicarbonate production from dietary potassium salts of organic acids (Frassetto et al., 1998). Because fruits and vegetables contain large amounts of the base producing organic acid salts, the intake of these foods in relation to bone density has been studied and found to reduce BMD loss. Therefore, potassium rich foods are promoted among the public for reducing the risk of osteoporosis. For example, "Better Bones, Better Body" (Brown, 2000) emphasizes consumption of fresh fruits and vegetables and avoidance of processed foods, especially those high in salt. It is generally assumed that fresh foods are better than processed foods. However, no one has determined if the processing of fruit actually reduces its ability to be an alkalizing agent. Therefore, the proposed research will examine this question.

Along with Brown's alkaline diet recommendations, it was recognized that people would need to be able to monitor their acid/alkaline balance. Brown published a simple method, which involves measuring urine acidity with pH paper strips. First morning urine is collected, into which a pH paper strip is immersed until there is no further color change. From the color chart, a pH value is determined. Brown recommends a pH value of 6.5-7.0 to ensure a healthy, alkaline diet is being consumed. Because pH paper strips measure excess H^+, but not necessarily ammonium and titratable acids, this method has been in question. Furthermore, urine acidity is increased during fasting, so a first morning sample may be a false measurement. Therefore, the usefulness of this measurement will be investigated.

1.2 Objectives and hypotheses

1.2.1 Objectives and hypotheses of Study 1

There were four objectives in Study 1: firstly, to investigate whether a pH strip measurement can determine dietary net acid load by comparing it to total (24-hr) NAE; secondly, to examine if a urine sample less than a 24-hour collection, such as overnight, could be used to accurately determine net acid excretion; thirdly, to examine if dietary protein and potassium intake is reflected in net acid excretion in the free-living individual; and finally, to examine the relationship between dietary factors, NAE and bone loss (measured as fasting urine calcium and NTx).

It was hypothesized that measurement of first morning urine acidity with a pH paper strip would accurately reflect NAE. It was also hypothesized that overnight NAE could be used to accurately determine total NAE without having subjects carry out a complete 24-hour urine collection. It was expected that urinary potassium would be negatively correlated and urinary sulphate would be positively correlated with total NAE. Finally, it was also hypothesized that NAE and the measurements of bone loss would be positively correlated.

1.2.2 Objectives and hypotheses of Study 2

There were two objectives in study 2: firstly, to determine if dietary treatment of processed fruit lowers NAE to a lesser extent than would a dietary treatment of fresh fruit; and secondly, to determine if a dietary treatment of fresh fruit reduces protein induced hypercalciuria to a greater extent than a dietary treatment of processed fruit.

It was hypothesized that processed fruit would not lower NAE to the same extent as fresh fruit, due to loss of potassium salts being reduced during processing. It was also expected that there would be greater urinary calcium retention during fresh fruit treatment than with the processed fruit treatment, where there is protein-induced hypercalciuria.

2. LITERATURE REVIEW

2.1 Osteoporosis

2.1.1 Overview

Osteoporosis is a disease characterized by thinning of the bone tissue, resulting in an increased risk of fracture. Bone is made of a dynamic matrix of organic and inorganic compounds that depend on various factors to ensure strength and health to provide structure and support for the body. When bone becomes thin and brittle, the clinical and public health implication is the increased rate of fractures, particularly hip fractures.

The most commonly used definition for diagnosis was established by the World Health Organization (WHO), where osteoporosis is considered to be present at bone mineral density (BMD) value more than 2.5 standard deviations below the normal mean for young white adults. However, the act of defining and diagnosing osteoporosis is plagued by discrepancies. It has been reported that body size, method of BMD measurement, and site of BMD measurement have significant impact on diagnosis of osteoporosis (Melton, Khosla, Achenbach, O'Connor, O'Fallon, Riggs, 2000; Garnero, Dargent-Molina, Hans, Schoot, Breart, Meunier, Delmas, 1998). Among 351 postmenopausal women, diagnosis of the disease varied from 2%-45%, depending on the site measured (spine vs. Ward's triangle) (Melton et al., 2000). These variations make diagnosis difficult and the accepted mean BMD values used may need to be reassessed. Measurement should occur at the proximal femur or at the spine, as the T-score cutoff selected by WHO does not apply to all bone sites (Roux, 2001). Therefore, diagnosis of osteoporosis by current standards must be done carefully. Measurement of BMD has been found to have high specificity but low sensitivity. Diagnosis is often associated with fracturing, but fractures may occur in people with normal BMD (Roux, 2001). Current literature often uses fracture incidence as an indicator the presence of osteoporosis.

Due to the mentioned discrepancies, reported rates of osteoporosis vary widely. It

has been estimated that one out of every two women and 1 in 8 men over the age of 50 will have an osteoporosis related fracture in his or her lifetime (Avioli, 2000). In the early 1990s it was estimated that 25 million Americans were affected by osteoporosis, evident primarily by distal radius, vertebral and hip fractures (Anderson, 2000). Rates of incidence and projected incidence in Canada has been estimated from data reported by the Canadian institute for Health Information in 1993-94. It was found that among people aged 65 years or older, females incurred 17 823 hip fractures and males incurred 5552 hip fractures. When these rates were age-adjusted, hip fractures were found to occur in 479 per 100 000 females and 187 per 100 000 males. With Canada's population aging, the reported rate has been used to estimate that by year 2041 the number of hip fractures would increase from 23 375 per year to 88 124 per year (Papadimitropoulos, Coyte, Josse, Greenwood, 1997). This exponential increase would have serious implications for Canada and cause significant strain on health care. In the United States in 1995, an estimated 547 000 hospitalizations due to osteoporotic fractures resulted in a $13.8 billion cost (Cummings & Melton, 2002). Therefore, research of the etiology of osteoporosis to enhance prevention of the disease is essential for the health of our society.

2.1.2 Bone physiology

The body relies on the skeletal system for its strength and support, but bone must also have tensile properties to handle stresses. The composition of bone consists of inorganic and organic components that allow these structural needs to be met. The inorganic matrix consists mainly of crystals of hydroxyapatite, which contains calcium and phosphate, and may be written as: $(Ca_{10}[PO_4]_6[OH]_2)$ (Baron, 1996; Groff et al., 1995). This hydroxyapatite forms a hard tissue that provides strength. The organic matrix is known as osteoid and provides the necessary tensile properties. Osteoid consists primarily of type I collagen and small amounts of proteoglycan, lipids, and several noncollagenous proteins (Green & Kleeman, 1991). These collagen fibers are usually organized in a preferential direction and have hydroxyapatite attached. The organization results in lamellar structure, as every layer alternates direction, which provides optimal

strength (Baron, 1996).

There are essentially two types of bone tissue, which are cortical and trabecular. While each type is formed of the same elements, hydroxyapatite and osteoid, these components are found in different proportions. Cortical bone has a greater proportion of hydroxyapatite than trabecular bone. Trabecular bone, which comprises approximately 20% of the skeleton, has greater amounts of collagen and is found primarily in the ends of the long bones (Anderson, 2000). Trabecular bone is only 15-25% calcified, whereas cortical bone is 80-90% calcified. The trabecular bone is also occupied by connective tissue, bone marrow, and blood vessels (Baron, 1996). Cortical bone is primarily responsible for providing mechanical strength, however, the microarchitecture of trabecular bone is also essential to prevent bone fragility.

Bone is not only essential for structural support, but it also plays a major role in storage of and regulation of minerals. For example, bone is essential in maintenance of calcium balance, as it contains approximately 99% of the 1000 g of calcium which the adult human body contains. The other 1% is found in extracellular fluid and soft tissues, which is critical for several biochemical processes and therefore, the concentration must be maintained within a narrow range. Bone also plays a role in the regulation of serum concentration of other minerals. For example, bone contains approximately 85% of the body's 600 g phosphorus content, and 66% of the body's 25 g magnesium content (Broadus, 1996). Bone has compartmentalized extracellular fluid, with a membrane that controls ion exchange. The cells composing the membrane around bone are believed to be morphologically similar to osteocytes. These membrane cells have regulatory functions, as receptors for PTH have been identified and communication with osteocytes has been acknowledged (Mundy, 1990). Hydroxyapatite interacts with the water in the bone matrix; therefore, calcium and phosphate from the bone may interact with the extracellular fluid (ECF) through bone ECF and this membrane (Green & Kleeman, 1991). Calcium may be transported by active transport or by passive movement along an electrochemical gradient. Although the mechanism has not yet been determined, the movement of calcium has been suggested to be due to the following. Firstly, the ECF has

a much greater calcium concentration than the bone surface, suggesting calcium may move into bone due to a concentration gradient. Secondly, potassium ions are actively pumped from ECF into bone, and it has been suggested that calcium may move by an electrochemical gradient into ECF (Mundy, 1990). Several mechanisms are likely responsible for the control of these ion fluxes.

Bone is not a rigid, static system and even after growth is complete, bone tissue is constantly being remodeled. As already discussed, some changes can be due to ion exchange. However, bone remodeling occurs primarily through the action of osteoblasts and osteoclasts. The process of remodeling begins when lining cells on bone surface retract and osteoclasts resorb mineral and organic material, which occurs as the osteoclasts secrete hydrogen ions and lysosomal enzymes (Kenny & Raisz, 2002). Osteoblasts are complex cells that form the structural components of bone, thereby counteracting the osteoclastic action. Osteoblasts are responsible for the production of almost all bone matrix constituents and for the organization of the mineralized bone matrix (Rodan & Rodan, 1995). Osteoblasts are also involved in the regulation of bone formation and resorption by producing regulatory factors (Puzas, 1996). Bone formation is somewhat regulated by bone turnover, as osteoblasts have been shown to have receptors for hormones and factors that stimulate bone resorption, such as PTH, $1,25(OH)_2D_3$, and interleukin-1 (Rodan & Rodan, 1995). Factors affecting the remodeling process, although numerous and complicated, are briefly summarized below.

Several polypeptide hormones, steroids, and local factors have various effects on the action of osteoclasts and osteoblasts (Canalis, 1996). Some of the most significant factors are parathyroid hormone (PTH), vitamin D, estrogen, and insulin-like growth factor-1 (IGF-1). IGF-1 is a polypeptide that is produced by skeletal cells and enhances bone formation by stimulating replication and differentiation of osteoblast cells (Canalis, 1996). This process is regulated by several of the hormones which are summarized below.

Estrogen is important for bone regulation, as its absence following menopause results in a great increase in bone remodeling and a subsequent loss in bone mass (Kenny

& Raisz, 2002; Groff et al., 1995). Estrogen receptors have been found on osteoblasts, indicating that estrogen likely stimulates bone formation. Also, estrogen has been shown to stimulate TGF-β and IGF-1, which stimulates osteblastic action (Kenny & Raisz, 2002; Lindsay, 1995). Estrogen also decreases bone resorption by inhibiting factors which have been implicated in the activation of osteoclasts, such as, cytokines, prostaglandins, and tumor necrosis factor and stimulates production of osteoclast inhibitors, such as osteoprotegerin (Lindsay, 1995). Therefore, the absence of estrogen may allow for greater bone resorption and result in decreased formation.

Vitamin D plays an important role in bone mineralization by various pathways. The active form of vitamin D, $1,25(OH)_2D_3$ or calcitriol, enhances the synthesis of the peptide osteocalcin produced by osteoblasts (Canalis, 1996; Groff et al., 1995). It also increases the binding of IGF-1 to osteoblasts. However, calcitriol is also known to stimulate bone resorption and inhibit bone collagen synthesis (Canalis, 1996). Likely, one of the largest roles of $1,25(OH)_2D_3$ is to enhance gastrointestinal calcium absorption to ensure the mineral is available for bone mineralization (Mundy, 1990).

PTH is a polypeptide that has a very significant role in bone remodeling regulation. Its primary function is to regulate serum calcium and phosphorus levels, which is achieved by stimulating renal calcium resorption, renal vitamin D synthesis, and release of calcium and phosphate from bone (Kronenberg, 1996). PTH stimulates both bone formation and resorption through its mitogenic effect, by enhancing IGF-1 synthesis, and by decreasing collagen synthesis at a transcriptional level (Canalis, 1996). PTH not only appears to control bone remodeling through osteoblast proliferation, but also through its effect on osteoblast apoptosis (Hock, Krishnan, Onyia, Bidwell, Milas, Stanislaus, 2001). Therefore, the significant effect of PTH on bone is through various mechanisms. Other factors which have influence on the regulation of bone remodeling include insulin, growth hormone, thyroid hormones, glucocorticoids, other growth factors, and cytokines, including interleukin-1, -4, -6, -11, and tumor necrosis factors (Canalis, 1996).

2.1.3 Risk factors

In the past, osteoporosis was regarded as an inevitable disease of the old. Fortunately, this view is changing as many modifiable factors are identified. Furthermore, although the disease may be seen in the elderly, it has its origins among the young. Most bone mass in accumulated by late adolescence, notably at the proximal femur and vertebral body. While some bone mass accumulation occurs after this time, it is believed to be primarily periosteal (outer bone) formation (Matkovic, Jelic, Wardlaw, Jasminka, Ilich, Goel, Wright, Andon, Smith, Heaney, 1994). Bone loss with age occurs at a somewhat similar rate, and it has been shown that those who start with more, end up with more. Therefore, peak bone mass indicates how much reserve there is for later in life (Heaney & Matkovic, 1995). Because peak bone mass is a primary determinant of BMD later in life, it is essential to ensure bone mass accumulation throughout childhood (Matkovic, et al., 1994). Therefore, less than optimal peak bone mass is a risk factor for the development of osteoporosis.

Although osteoporosis should not exclusively be considered a disease of the old, ageing is a large risk factor. Trabecular bone resorption increases significantly during ageing, and although it is somewhat offset by periosteal (outer) bone formation, significant structural changes occur. Bone densiometry provides a measure of the width and length of the bone but not depth, so periosteal thickening hides the loss of trabecular bone (Seeman, 2002). Therefore, even when BMD measurement does not indicate bone loss, structural changes increasing fracture risk may have occurred. It has not been determined if the loss of density is due to a decrease in the matrix production of osteoblasts or a decrease in the number of osteoblasts (Dempster, 1995). Similarly, cortical bone resorption with inadequate formation occurs during ageing, although it is not noted to be as significant a factor as trabecular bone loss in the microarchitectural changes of bone that occur which lead to osteoporosis (Dempster, 1995).

Genetics are recognized as a risk factor since having a family member with osteoporosis has been shown to increase the disease risk of the individual. The role of heredity is evidenced by studies that show daughters of women with osteoporosis tend to

have lower BMD. However, no genotype has been identified to account for endosteal (inner bone) remodelling or periosteal apposition. Furthermore, the phenotype for bone fragility is difficult to identify (Seeman, 2002). Several genetic factors likely play a role in the accretion and remodeling of bone tissue. Peak bone mass is one phenotype which has been considered hereditary, as determined by twin studies (Heaney & Matkovic, 1995).

A genotype that has been associated with increased BMD is the vitamin D receptor genotype. The primary role of vitamin D in intestinal intracellular Ca^{+2} transport is a function of calcitriol genomic action (Issa, Leong, Eisman, 1998). Calcitriol interacts with the intestinal vitamin D receptor (VDR) to mediate induction of calbindin-D9k (Raval-Pandya, Porta, Christakos, 1999). Calbindin-D9k plays an important role in the transcellular calcium absorption as it transports Ca^{+2} across the cell, buffers cytoplasmic Ca^{+2}, and stimulates Ca^{+2} basolateral extrusion (Weaver & Heaney, 1999). The calcitriol genomic action is also important in the basolateral extrusion of Ca^{+2} as it initiates transcription of plasma membrane calcium pump mRNA. Furthermore, when calcitriol binds to VDR, the complex interacts with vitamin D response element (VDRE), which is able to initiate transcription. For example, a VDRE has been identified as a PTH gene promoter, which is important in calcium homeostasis (McCary & DeLuca, 1999).

Polymorphisms of VDR expression show an effect on calcium absorption, calcium accretion, and bone mass. Subjects with the desired genotype have positive indicators of increased calcium absorption (Nakano, Oshima, Sasaki, Yamaoko, Matsumoto, Hirao, Ozono, Matsuura, Kajiyama, Kambe, 2000). Certain polymorphisms have been associated with calcium absorption and bone mineral density (BMD) in children. Children with desirable genotypes absorbed on average 115 mg more calcium per day and also had significantly higher BMD than those children with undesirable genotypes (Ames, Ellis, Gunn, Copeland, Abrams, 1999). It has been found that VDR gene polymorphisms correlate with bone mass but do not correlate with bone loss (Gomez, Naves, Barrios, Diaz, Fernadnez, Salido, Torres, Cannata, 1999) . Desirable VDR genotype does not appear to override other significant factors causing bone loss,

especially menopause. While these are some studies that have had positive findings, there are some that have not found significant associations. These discrepancies are believed to be due to the numerous confounding factors involved in bone health. Therefore, more research needs to be done to confirm the significance of VDR genotype and other genotypes involved in bone health to predict a person's risk of developing osteoporosis (Eisman, 2001). This area of research is one of the most promising areas of genetic research regarding identification of those who may be genetically at risk for osteoporosis.

Gender is another significant risk factor, as it is clear more females suffer from osteoporosis. Men generally have greater periosteal apposition than women, which partially explains why fracture incidence is lower among men (Seeman, 2002). Hormones, such as estrogen, play a major role in bone remodelling. Estrogen inhibits bone resorption and stimulates bone formation; therefore, after menopause, bone turnover increases significantly (Kenny & Raisz, 2002; Groff et al., 1995). Therefore, postmenopausal women are at greater risk of developing osteoporosis than men. Furthermore, late onset of puberty or infrequent menstrual cycles in females are risk factors for low BMD (National Institutes of Health, 2001).

As previously mentioned, parathyroid hormone and calcitriol play a significant role in bone health (Holick, 1994; Dawson-Hughes, Harris, Krall, Dallal, Falconer, Green, 1995). PTH moderates serum calcium and phosphorus levels by increasing bone resorption and renal resorption (Groff et al., 1995). The circulating concentration of PTH is mediated by calcitriol, which is influenced by dietary vitamin D and sun exposure (Anderson, 2000). Calcitriol is also involved in calcium homeostasis through action on intestinal calcium absorption. Age decreases the intestinal responsiveness to calcitriol (Ebeling, Sandgren, DiMagno, Lane, DeLuca, Riggs, 1992). Therefore, inadequate vitamin D intake, sun exposure, and age are risk factors for osteoporosis. While age is a non-modifiable risk factors, along with genetics and gender, diet and sun exposure are modifiable factors.

Other modifiable factors increasing osteoporosis risk include inadequate physical