I. INTRODUCTION

Osteoporosis is defined as ‘a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in enhanced bone fragility and consequent increase in fracture risk’ (Kanis, 1997). It is increasingly important public health problems in older men. The prevalence of low bone density (osteopenia) and osteoporosis was shown to be as 33% and 6%, respectively, in men aged 50 years old or above (Looker et al., 1997). In addition, the estimated lifetime risk of experiencing osteoporosis related fractures (vertebral, hip, and wrist fracture) was up to 13% for men (Melton et al., 1992), which is similar to the lifetime risk of prostate cancer (Merrill et al., 1997) Compared to the study of postmenopausal osteoporosis, however, male osteoporosis has not been well described.

With aging, men also suffer from cardiovascular disease. Cardiovascular disease claimed more than 900,000 lives in the United States in 1997 (Hoyert et al.1999). Specially, coronary heart disease is a leading cause of death and disability in older men. Death rates from cardiovascular disease are declining, but there is slowing tendency of this decreasing death rates. Men suffer more from cardiovascular disease at most age groups compared to women. Coronary/aortic calcification in atherosclerotic plaques has been correlated with coronary artery disease (CAD) (Rumberger et al., 1995). Furthermore, coronary calcification was a significant predictor of coronary events (e.g. myocardial infarction) in asymptomatic and symptomatic study populations (Arad et al., 2000; Detrano et al., 1999).

Until recently, both osteoporosis and cardiovascular disease were considered as unrelated diseases concomitantly occurring to aging process. New evidences indicated that coronary calcification and bone mineralization share similar mechanisms. Studies

on the molecular mechanisms of vascular calcification have supported a possible link to the process of bone formation and resorption (Fitzpatick et al. 1994, Bostrom et al.1993, Hirota et al 1993). Several epidemiological studies have supported molecular evidences that both low bone mass and increased osteoporotic fracture risks are associated with atherosclerotic calcification (Fujita et al., 1984; Ouchi et al., 1993; Byers et al., 2001) or cardiovascular mortality (Browner et al., 1993;Browner et al.,, 1991; von der Recke 1999). However, there were no consistent results on the relationship between cardiovascular mortality, cardiovascular disease, or aortic/coronary calcification and osteoporosis. In some studies, investigators have suggested that observed association would be just aging related processes (Frye et al., 1992; Anderson, 1964; Vogt et al., 1997), whereas others have supported a causal relationship (Browner et al., 1993; von der Recke et al., 1999; Barengolts et al., 1998; Kiel et al., 2001). Furthermore, only few studies were conducted on men.

Some potential mechanisms, such as estrogen deficiency, vitamin D and vitamin K deficiency (Moon et al., 1992; Aoyagi et al., 2001) and oxidized low-density lipoprotein (LDL-c) (Parhami et al., 1997), have been proposed to play an important etiologic role to link both diseases. Epidemiological studies suggest that estrogen deficiency may be a risk factor for decreased BMD (Bauer et al., 1993) and increased risk of CVD risk in women (Barrett-Connor, 1997). However, recent evidences also support that estrogens as well as androgens are also an important determinant on bone mineral density (BMD) or bone loss in elderly men (Riggs et al., 1998; Khosla et al., 1998). In addition, recently cloned osteoprotegerin (OPG), an essential cytokine for osteoclastogenesis, was associated with both of vascular calcification and osteoporosis (Bucay et al., 1998). For instance, OPG deficient mice showed severe osteoporosis and arterial calcification (Bucay et al., 1998). There have been relatively few clinical studies of OPG and cardiovascular disease. Serum levels of OPG were related to increased cardiovascular mortality (Browner et al., 2001) and severity of coronary artery disease (Jono et al., 2002).

Thus, we explored the association between coronary calcification and bone mineral density, and bone loss in older men. In addition, we studied the possible etiologic links between coronary calcification and osteoporosis to test the following hypotheses: 1) men with low bone density, high bone turnover rate, greater bone loss will have higher coronary calcification; 2) men with lower estrogen level and higher CRP will have lower BMD, and higher coronary calcification; 3) men with OPG T-950C SNP C/C genotype will have higher bone density and lower bone loss, lower coronary calcification compared to men with T/T genotype; 4) men with OPG G-1181C SNP C/C genotype will have higher bone density and less bone loss, and higher coronary calcification.

II. REVIEW OF THE LITERATURE

A. Osteoporosis in men

1. Pathophysiology of Osteoporosis

a. General Bone biology

Bone supports multiple mechanical and metabolic functions. The major functions of bone are: 1) structural supports for the body and for mechanical loading, 2) protection of vital organs, 3) the reservoir of essential ions, especially calcium and phosphate for the body fluid homeostasis, and 4) housing the bone marrow responsible for hematopoiesis (Einhorn 1996; Guyton and Hall 1998).

Bone is a mineralized connective tissue that is mainly composed of collagen fibers, noncollagenous proteins, and crystalline hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). 90% of bone matrix is collagen. It is enclosed by a fibrocelllular layer, the periosteum. The matrix consists of collagen fibers (mainly type I collagen) arranged in parallel and mineralized substances. Cross-linked bone collagen provides gaps between the fibers so that bone crystals are packed between the gaps to create the mineralized tissue (Einhorn, 1996). Noncollagenous proteins, osteocalcin or bone r-carboxyglutamic acid containing protein (Bone Gla Protein), are important for calcium or mineral binding, and collagen mineralization (Einhorn, 1996).

Bone is a unique calcified tissue unlike other connective tissues. Calcium and phosphorus are essential inorganic components of the body. About 1 % of calcium ion is for the maintenance of internal cellular structure and the passage of signal between cells. 99% of calcium is deposited in crystalline structure (Garner et al., 1996) In bone

minerals, HPO_4^{-2}, CO_3^{-2}, F^-, Mg^{+2}, Na^{+1} as well as Ca^{+2} contribute to mineral deposits, and crystal lattice. Within bone tissue, the neurovascular channels in concentric cylinders, osteons, which are surrounded by collagen fibers and mineral crystals, provide the space for capillaries to support the pathway for the diffusion of fluids, nutrients and gases (Einhorn, 1996).

About 80 % of the body skeleton comprises cortical (compact) bone and 20%, trabecular (cancellous) bone. Cortical bone is mainly found in the appendicular skeleton such as the shafts of long bones and surfaces of flat bones. Cortical bone accounts for approximately 80% of the skeleton but only covers about 20% of the surface area. Approximately 80 to 90% of cortical bone volume is mineralized crystal. Compact bone is laid down around haversian systems containing blood vessels, lymphatic tissue, and nerves (Comptson et al., 2001). Proximal forearm and mid-forearm are mostly consisted of cortical bone. 3% of cortical bone is renewed each year. Trabecular bone constitutes vertebral bodies, and is mainly found at the ends of long bones and inside of flat bones. Trabecular bone contributes to 20% of skeleton, but has 80% of the surface area. About 66~ 90% of vertebrae, and 50% of intertrochanteric region of the hip is composed of trabecular bone (Einhorn, 1996). Distal forearm and calcaneus sites are mostly trabecular bone. Trabecular bone is renewed about 25% every year. Although composed of the same cells and matrix, cortical and trabecular bone are structurally and functionally different. The networking structure of struts, and girders of bony tissue (the trabecuale) with hematopoietic marrow consists of trabecular or cancellous bone. This weaving arrangement gives the supportive strength for mechanical loading even with relatively great strain.

b. Bone growth and modeling

Bone is a living tissue that is tightly regulated by hormones (e.g. estrogen, PTH and testosterone), growth factors, other chemical factors and genetic influences. During skeletal development, intramembranous ossification occurs in flat bones, and

endochondral ossifcation in long bones. Three types of cells are found in bone, such as osteoblasts, osteoclasts, and osteocytes. Bone marrow plays a role in interconnecting these cells, in the production of osteogenic cells, and in regulation of bone modeling, and remodeling.

During growth, bone mass increases by linear growth, cortical apposition, and cancellous modification (epiphyseal closure). These processes are referred to as modeling. Bone modeling often occurs in response to altered mechanical stimuli, and as parts of the fracture healing process in the mature adult skeleton. Growth in length of bones occurs in the layer of epiphyseal plates (the growth plate) by a process of chondrogenesis followed by ossification. Longitudinal bone growth stops after puberty. Bone growth in length is impossible after the closure of epiphyseal plates of long bones, which occurs around the age of 20. Growth in the width of bones occurs by sub-periosteal bone formation and continues at a slow rate during lifetime. Endosteal resorption also continues over the lifespan. Bone mineral deposition during growth is influenced by various factors (sex steroids) and different rates (Einhorn, 1996).

Bone modeling (linear growth and shaping of bone) occurs during adolescence until growth plates remain open. By about the age of early 20s', bone mass of the body reaches to it's 'peak bone density or mass' (Bonjour and Rizzoli, 1996). After reaching its' highest point, peak bone mass is maintained for a while and then decreases. Peak bone mass appears to be reached differently at cortical bone and trabecular bone. Trabecular bone reaches peak values by the age of 20 while the timing of peak bone mass in cortical bone is varied by from 17~18 years of age to 35 years of age (Gilsanz et al., 1999). Factors associated with achieving maximal peak bone mass are genetic heritability, physical activity, and nutrition specially, intake of calcium and vitamin D (Heaney et al., 2000).

In adults, after cessation of growth, bone formation and resorption are coupled in a process called remodeling. In each modeling cycle in the young adults, bone formation equals the amount of bone removed during resorption. The purposes of

remodeling are to renew aging bone, to remove fatigue fractures, to release the calcium ions, and to adapt the skeleton to physical stress due to physical activity or load bearing work (Dempster et al., 1995).

The amount of bone in later life is determined by the bone mass accumulation (peak bone mass) during youth and the subsequent rate of bone loss. Low bone mass results either from failure to achieve peak bone mass during the first 30 years of life, or from rapid, or accelerated bone loss later in life. Both processes are thought to be equally important in determining bone mass at age 70. Women, however, have an additional rapid period of bone loss around the menopause due to the sharp decline in level of estrogen. Sex hormonal changes (gonadal insufficiency e.g. menopause or premenopausal oophorectomy in women, hypogonadism in men), age-related changes (e.g. declining activity, decreased intestinal calcium absorption), adverse effects of medical conditions (gastrectomy, alcoholism) and medications (use of corticosteroids, and anticovulsants) can contribute to the low bone mass (Heaney, 2000).

c. Bone formation by osteoblasts

Osteoblasts originate from mesenchymal stem cells and are responsible for the formation and mineralization of bone. Osteoblasts share the same origin (mesenchymal cells) with chondrocytes, adipocytes, myoblasts, and fibroblasts. The stromal stem cells undergo differential transcription and they are differentiated to different cells. Differentiation to osteoblasts is regulated by the expression of core-binding factor (*Cbfal),* namely*,* a transcription factor, bone morphogenetic factors (BMPs), glucocorticoids, 1,25-dihydroxyvitamin D (1,25$(OH)^2$D), and transforming growth factor-β (TGF-β) (Lian 1996). Cbfal regulated the expression level of osteocalcin, a secreted protein that inhibits osteoblast function (Ducy et al, 2000). Sox9 and cbfa1 are associated with differentiation of chondrocytes. Cbfal also leads fibroblasts by osteoprogenitor lineage to osteoblast (osteocytes). Peroxisome proliferator-activated

receptor (PPAR) gamma is believed to derive osteoblasts or adipocytes (Zangani et al.,1999; Satomura et al.,2000).

Recent studies reported the accumulation of adipocytes in osteopenic bone, and switching factors ($1,25(OH)_2D_3$, IL-11, TNFs, IGFs, PTH, or prostagladins) between adipocytes and osteoblasts/osteocytes supporting the contribution of adipocytes in osteoporotic bone. A hormone controlling adiposity, leptin, is also known be a regulator of the bone formation indirectly (Ducy, 2000).

Osteoblasts synthesize the proteins, and secret collagen and non-collagenous proteins. Non-collagenous proteins create osteoid, uncalcified pre-bone tissue. Osteoid contains collagen type I, osteocalcin, osteopontin, bone sialoprotien, and other bone matrix protein. Osteoid mineralization occurs approximately 10 days after the secretion with regulatory factors; the bone matrix proteins and matrix vesicles. Osteoblasts have membrane or nucleus receptors for various steroid (estrogen receptor, vitamin D receptor, or PTH) and cytokine receptors. Several adhesion molecules e.g. integrins are also synthesized by osteoblasts. Osteoblasts induce the calcification of the osteoid through a mechanism involving the secretion, of bone-specific alkaline phosphatase, osteocalcin and osteonectin. The precipitation of hydroxyapatite crystals from the matrix fluids is dependent on various factors including inorganic ion concentrations and local pH (Stein and Lian, 1993). Molecular regulation of mineralization follows these steps; 1) begin with inhibition of proliferation, 2) reduce activity of the transcription factor, activator protein-1 (AP-1), 3) induce the expression collagen type I, alkaline phosphatase, osteopontin, and osteocalcin, 4) deposit hydroxyapatite mineral with collagen, mainly, type I collagen.

Some osteoblasts are embedded in the matrix of bone to become osteocytes (Lian et al., 1996). Osteocytes are small-flattened cells within the bone matrix, and are connected to each other and to osteoblasts through extensive canalicular network. Osteocytes have specific features. They form cellular network with gap junctions, and probably respond to external mechanical and biochemical loading. Osteocytes mediate

cellular signaling through nitric oxide (NO), glutamate, and modulate estrogen, and prostaglandin (E2). In vitro studies have shown that osteocytes lead to apoptosis after exposure to glucocorticoid, which might be responsible to glucocorticoid- induced osteoporosis.

d. Bone resorption by osteoclasts

Osteoclasts are derived from the mononuclear/phagocytic cell lineage. Osteoclasts are phagocytic cells responsible for resorption of bone tissue. Osteoclasts are rich in lysosomes and they are able to resorb collagen and absorb matrix debris by pinocytosis (Teitelbaum et al., 1996). Osteoclasts derived from hematogenous mononuclear precursors are stimulated by local cytokines (eg, macrophage colony-stimulating factor (M-CSF) and src) and are directly inhibited by calcitonin. Osteoclasts are reservoirs of variable enzymes: carbonic anhydrase II, cathepsins B, L, & K, metalloproteinases, collagenases, acid phosphatase (type V). The ruffled-border of osteoclasts is operated via ATP driven H^+ pump. In addition, PTH, estrogens, and cytokines stimulate or inhibit osteoclast production only indirectly via the receptor activator of nuclear factor kappa B (NF-κB)(RANK) and ligand (RANKL) system.

An important inhibitory factor, osteoprotegerin (OPG) produced by the osteoblast act as a soluble receptor that competes with RANK for RANKL. Binding of OPG to RANK inhibits osteoclastogenesis. OPG deficient mice have shown increased osteoclastogenesis and severe osteoporosis (Teitelbaum, 2000). Sex steroid hormones e.g. estradiol limited the osteoclast differentiation and bone resorption. With proteases, bone growth-promoting cytokines are released including bone morphogenic protein (BMP-2), fibroblast growth factor (FGF), insulin-like growth factors (IGF), IGP-binding protein (IGFBP-5), transforming growth factor (TGF)β1 and TGT-β2.

e. Bone remodeling

1) Normal regulation and unbalanced coupling

The basic processes of formation and turnover of the skeleton is referred to modeling and remodeling. Bone health is maintained by replacement of old bone with new bone. These ‘coupled’ steps are processed by osteoclasts and osteoblasts. Basic multicellular unit (BMU) is a working team of cells that remove and replace bone tissue. Osteoclasts resorb bone in microscopic cavities and osteoblasts then reform the bone surfaces, filling the cavities. The initial development of bone structure happens through new bone formation on a cartilage template, either in the form of endochondral or membranous bone formation. After bone is fully formed, it begins to undergo continuous remodeling processes. The balanced activity of osteoblasts and osteoclasts means for rapid release and resorption of calcium ions, the repair of injuries and alterations in bone due to mechanical stress.

Remodeling consist of four steps-- 1) Activation, 2) Resorption, 3) Reversal, 4) Formation (mineralization) (Dempster et al., 1995). Damage to bone by mechanical stress leads to increased levels of PTH, IGF, IL-1, IL-6, PGE, and vitamin D3 ($1,25(OH)_2D_3$) (Dempster, 1995; Einhorn, 1996) (Origination). Due to increased levels of cytokines and hormones except 1l-6, the lining cells are activated and secrete RANK-ligand. Activation of osteoclast is the initial event in bone remodeling. Activation involves with the recruitment of cells into differentiated osteoclasts. From monocyte-macrophage cell lineage, pre-osteoclast having membrane receptor (RANK) can be differentiated into multinuclear osteoclast by binding to RANK-L. During osteoclastogenesis, OPG as a free-floating decoy receptor, can bind to RANK-L and block the interaction of RANK-L and RANK. After activation, resorption is followed. Mature osteoclasts dissolve the mineral component and hydrolyze the bone matrix with help of integrins, and interleukins. The average resorption cycle by osteoclast varies at cortical and trabecular bone, 27 days and 42 days, respectively (Dempster et al., 1995). Then osteoclast undergoes apoptosis. Estrogen deficiency can prolong the lifespan of osteoclast, which

results in excess bone resorption. Reversal occurs when osteoclastic resorption ceases. During bone resorption, the hydroxyapatite crystals are mobilized by detachment from collagen, and dissolved by acid environment. Dissolved hydroxyapatites helps to maintain calcium and inorganic phosphate levels in plasma.

Derived from marrow stromal cells, osteoblasts are recruited by bone-derived growth cytokines (TGF-β, BMP-2, FGF, and IGFs). Active osteoblasts build up layers of osteoid and slowly fill up the cavity, secreting osteopontin, and osteocalcin. Bone mineralization occurs in presence of calcium phosphate regulated by osteoblasts, and mineral maturation follows. Finally osteoblasts turn into lining cells and osteocytes which remain in the bone responding to mechanical stresses on bone. At any time, 10 to 15% of bone is undergoing bone remodeling (Heaney 1996) Remodeling occurs on trabecular surfaces by the formation of Howship's lacunae, which become filled in by plate-like bone structural units, and on the cortex by Haversian remodeling, in which an osteoclast cutting cone removes a cylinder of bone that is replaced by a new cylinder, called an osteon.

In general, two bone loss mechanisms occur with aging. An increase of the activation frequency causes increasing number of remodeling units on the bone surface. This results in a large number of bone remodeling units while this remodeling balance is maintained. In other mechanism, bone formation lags behind bone resorption, causing a net loss of bone mass with each remodeling cycle. Increased bone resorption without compensation by bone formation results in irreversible bone loss.

2) Endogenous regulators of remodeling

Sex steroids, parathyroid hormone (PTH), thyroid hormone, growth hormone, and 1,25$(OH)_2$D regulate and modulate bone remodeling (Compston 2001). Moreover, bone remodeling regulated by mechanical forces indicates that local factors must regulate bone resorption and formation. These factors include cytokines such as

interleukin (IL)-1, IL-6, and tumor necrosis factor; small molecules such as prostaglandins, and nitric oxide; and growth factors such as TGFß, IGF-1, and fibroblast growth factor (FGF), which are produced locally by bone cells. These local factors include both stimulators and inhibitors of bone resorption and formation. Their action can be altered by changes in their production and changes in their receptors or in cofactors that enhance or limit their action. Skeletal growth in children and bone remodeling in adults can be stimulated by the growth hormone (GH)/IGF factor system. Age-related decreases occur in GH secretion and in the levels of IGF-1 and its major binding protein, IGFBP-3. IGF can stimulate both resorption and formation of bone, but the major long-term effect is to increase formation. Decreased levels of IGF-1 and its binding proteins have been reported in osteoporosis, particularly in men. The factors produced by osteoblasts that regulate osteoclast formation and function, OPG and RANK ligand, are under the control of both systemic and local factors. Differences in their production or activity may also play an important role in accelerating or slowing bone loss.

Animal studies shows that these cytokines and growth factors can play a role in bone loss associated with sex hormone deficiency. Moreover, interactions between systemic hormones and local factors also play a role. For example, PTH can stimulate IL-6 and prostaglandin production in bone, and GH can stimulate local IGF-1 production while glucocorticoids can inhibit such production. PTH levels tend to increase with age, probably secondary to the decrease in calcium intake and absorption in older individuals. This secondary hyperparathyroidism will tend to increase bone remodeling. In many individuals, the increases in resorption and formation are approximately equal and there is no progressive bone loss. However, cortical bone loss and porosity could be increased by PTH. The ability of calcium and vitamin D supplementation to decrease fracture risk is probably dependent on the ability to reduce PTH levels. On the other hand, in postmenopausal women with vertebral crush fracture syndrome, PTH levels are not elevated and parathyroid responsiveness may be blunted. Estrogen may decrease both PTH secretion and the skeletal response to PTH.

f. The Pathogenesis of osteoporosis in men

Osteoporosis or bone fragility is involved with multiple levels of pathogenesis that involve genetic factors, bone development, aging (bone loss and fragility), and environmental factors. Bone strength is determined by a number of important factors, including bone mass, bone architecture (connectivity and remodeling), and bone geometry. A reduction in bone strength is clearly related to fracture. Decreased bone mass and changes in structure that predispose to fragility fractures can occur by 3 separate mechanisms (Steiniche and Eriksen, 1999). The first is failure to achieve optimal peak bone mass during skeletal growth. Skeletal structure and mass are largely determined genetically, but poor nutrition and limited activity during childhood and adolescence, as well as delayed puberty, may impair the ability to achieve optimal peak bone mass.

The second is excessive bone resorption, which can decrease bone mass and strength sufficiently to produce osteoporosis. Increased bone resorption is associated with estrogen deficiency at menopause and may also be associated with estrogen deficiency in older men. Resorption not only leads to loss of mass, but weakened trabecular bone by producing irregular trabeculae and cortical bone by increasing porosity. Moreover, once a portion of bone has been completely removed, there is no template for formation of new bone to repair that lesion.

The third mechanism is relative impairment of bone formation. The absolute rates of bone resorption in adolescents, who are gaining bone mass, are actually higher than those in osteoporotic patients. In osteoporosis, there is a decrease in the capacity of osteoblasts to form new bone, thus even though the absolute rates of bone formation may be increased because of the increased number of remodeling sites, bone loss occurs.

Osteoporosis in men is categorized into age-related, and secondary. Age-related osteoporosis, called primary osteoporosis, is not well defined (Seeman, 1995). Age-

related, and idiopathic osteoporosis is recognized as causes of primary osteoporosis in men (Ebeling et al., 1999; Seeman, 1993). Many factors have been proposed to influence the pathogenesis of osteoporosis in aging healthy men. These includes: 1) low peak bone density, 2) decreased trabecular and cortical bone mass, 3) reduced bone formation, 3) systemic hormonal changes (Seeman, 1993). Abnormality of growth hormone, reduced levels of insulin-like growth factor-I (IGF-1), and sex steroid hormones have also been significantly related to the pathogenesis of osteoporosis in men (Bilezikian et al., 1999). However, secondary causes of osteoporosis in men are indeed possible risk factors contributing to the development of primary osteoporosis (Compston et al., 2001). For instance, these include: subclinical hypogonadism associated to changes in hypothalamic-pituitary function, 2) vitamin D deficiency associated with decrease intestinal calcium absorption and vitamin D receptor function, 3) hyperparathyroidism, 4) alcohol excess, and 5) smoking (Seeman 1993; Ebeling et al., 1999).

However, there are only a few data to recognize risk factors for primary osteoporosis or idiopathic osteoporosis in men. For instance, hypogonadism that has significant adverse effect for osteoporosis, but the definition, prevalence, causes of hypogonadism, and its' relationship with male osteoporosis are still inadequately defined (Seeman et al., 2001).

2. Osteoporosis and measurements of Osteoporosis

a. Definition of Osteoporosis

Osteoporosis is the most common human metabolic bone disorder. It has been defined as 'a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk' by Consensus Development Conference (Conference, 1991). Recently, NIH consensus re-defined more detailed definition of osteoporosis incorporating bone quality factors (bone architecture, turnover, damage accumulation, and mineralization) into bone density aspects (2000). Osteoporosis is defined by an intermediate outcome (BMD), not a clinical manifestation (fracture). Changes in bone fragility and fracture risk can be assessed indirectly by noninvasive measurements of bone mineral density (BMD). Bone density explains about 70% to 85% of the variance in the ultimate strength of bone tissue and is closely correlated with the load-bearing capacity of the skeleton.

BMD is surrogate measure of bone weakening and a major determinant of future fracture risk along with other risk factors. The clinical manifestations of osteoporosis relate exclusively to the fracture risk. Fractures of the proximal femur (hip), vertebrae (spine), and distal forearm (wrist) are linked with osteoporosis (low bone mass) (Thiebaud et al., 1997; Boonen et al., 1997;Stewart et al., 1995; Nguyen et al., 1996; Ross et al., 1996; Melton et al., 1997). In the Dubbo Osteoporosis Epidemiology study, for instance, femoral neck bone mineral density was independent predictor of hip fracture with a risk of 2.3 (95% CI 1.2 – 4.5) for each standard deviation decrease of BMD in men (Nguyen et al., 2001). Moreover, femoral neck BMD in men was a significant predictor of forearm and wrist fractures along with dietary calcium intake, and height loss. A 1 SD (-0.1 g/cm^2) decreased in femoral neck BMD was associated with a relative risk of 1.52 (1.01 to 2.29) of forearm and wrist fractures (Nguyen et al., 2001).

1) Osteoporosis and WHO criteria

In women, WHO proposed guidelines (1994) for the diagnosis of osteoporosis have been used based on bone mineral density (BMD). BMD is a good surrogate measurement of bone strength. The diagnostic advantages based on BMD are: 1) BMD is normally distributed at all ages, 2) mean BMD decreases with age, 3) measuring BMD allows diagnosis of osteoporosis in asymptomatic persons prior to fracture (Kanis et al., 1994). There are strong associations between BMD and the likelihood of fractures in many large prospective studies (Cummings et al., 1995; Mussolino et al., 1998; Marshall et al., 1996). Decreasing in mean BMD value is parallel to increasing in fracture incidence. Furthermore, low bone mass or osteoporosis is predictive of future fracture risk at single or multiple sites (Black et al., 1992; Cummings et al., 1993; Looker et al., 1997). An important benefit of BMD based diagnostic criteria is the evaluation of future fractures risk similar to the use of blood pressure to diagnose hypertension, a major risk factor for stroke (Kanis et al., 2000). The WHO approach was based on arbitrary fracture threshold of BMD where a majority of women will experience with osteoporotic fractures (WHO, 1994). Osteoporosis in postmenopausal Caucasian women is defined as a bone mineral density or bone mineral content (BMC) more than 2.5 standard deviations below the young average female population value using Central DXA measurements. The WHO criteria to define osteoporosis and osteopenia as follows:

- Normal: BMD or bone mineral content (BMC) less than or equal to one standard deviations (SD) below average young adult
- Osteopenia: BMD or BMC greater than 2.5 SD and less than 1 SD below the average young adult
- Osteoporosis: BMD or BMC more than 2.5 SD below average peak young adult
- Severe osteoporosis: BMD or BMC more than 2.5 SD below average young adult with one or more fragility fracture

It was recognized that standardized cut-off values (T-score) would help clinicians and researchers to evaluate patients' status, and assess the effect of treatment (Genant et al., 1996). T-score is a comparison value to mean peak bone mass, which is expressed, as number of standard deviations that an individual's value falls below that of a gender matched mean young normal reference value. It is calculated as (BMD of patient – BMD young-normal reference)/SD of young-normal reference. With using T-score less than –2.5, approximately 15-30% of postmenopausal women aged 60 or above were identified as having osteoporosis measured at the spine, hip, or forearm. This prevalence is approximately similar to the lifetime fracture risk of at any these sites (Kanis et al., 1994; Nguyen and Eisman 1999).

However, limitations exist using WHO criteria based on BMD of postmenopausal Caucasian women. It has been shown that a T-score, and subsequent diagnosis of osteoporosis in a given population as well as its prevalence, varies dramatically with the measurement technique used, with the selection of the normal reference population, or with the variability of BMD measurement sites (Greenspan et al., 1997; Abrahamsen et al., 1997; Jergas and Genant, 1997; Faulkner et al., 1999). The accuracy of various techniques other than DXA ranged from 10% to 50% depending on the technique and site used for measurement and protocol involved (Kanis et al., 2000). Faulkner et al (1999) estimated the T-score and prevalence of osteoporosis in women with age using different measurement techniques (QCT, DXA, or QUS), and sites of measurement (Spine, heel, or total hip). BMD of lumbar spine measured with quantitative computed tomography (QCT) yielded the highest rates of prevalence compared to lower rates with ultrasound techniques at heel. At the age of 60 years the average T-score by QCT of the spine is –2.5, but average T-score by Sahara ultrasound (QUS) of the heel is as low as –0.7. Estimated proportions of women with spine fracture or without fracture based on T-score of –2.5SD or lower were differed in sensitivity and specificity (Kroger et al., 1999). Capturing fractures using T-score (-2.5 SD or below) ranged from 17.7 % by QCT of radius to 94. 2% by QCT of spine whereas 24.9% of the femoral neck to 71.2% of spine for DXA (Kroger et al., 1999).

The WHO based diagnosis is also limited by using younger populations as a reference data. BMD in younger populations is subject to changes in bone size during skeletal growth. Therefore, the conventional measurements of areal bone density (BMD), which do not account for bone size, or bone thickness, need to be applied cautiously (Seeman 1999). Another limitation is racial differences in bone density. Many manufactures reference data attempted to resolve this issue for generating quantitative data for specific races (e.g. African American, Asian). However, there is still a paucity of normative reference data for many races. Use of single reference data for Asian is problematic since, for example, Chinese and Japanese women different BMD and bone size.

Of importance of male osteoporosis, many researchers challenged that risk assessments in men using same criteria as women even though population based male reference data are available for many BMD measurement techniques (Kanis et al., 1994; Melton et al., 1998; De Laet et al., 1997; Selby et al., 2000; Cauley et al., 2000). Prediction of fracture or detection of low bone mass in men will be discussed in later section.

2) Application of WHO criteria in men

With emerging concerns of male osteoporosis, many studies have confirmed that BMD is a determinant of fracture risk in men as well (Kanis et al., 1994; Nguyen et al., 1996; Looker et al., 1997; Orwoll et al., 1999). BMD was measured in men who have suffered low trauma factures or have overt risks such as hyperparathroidism, hypogonadism, or glucocorticoid therapy for preventive methods (Orwoll 2000). BMD criteria for the diagnosis of osteoporosis, however, were established based on postmenopausal Caucasian women data (paradigms for WHO criteria). Currently, population based male reference ranges for many BMD measurement techniques are available, and same risk assessment protocols are used. However, there have been

various questions on using the application of BMD measurements (T-scores) in women unto men.

First of all, there are concerns about an underestimate of prevalence of osteoporosis in men using T-score cutoff (WHO) because it is considerably less than average estimated lifetime fracture risk of 13% for men. From the NHANES III study, the prevalence of low bone density and osteoporosis were observed as 33% and 6%, respectively, in men aged 50 years old or above using male reference data (Looker et al., 1997). Whereas in the Dubbo Osteoporosis Epidemiology Study in Australia, the prevalence of low bone mass (osteopenia) was estimated as 42% of men aged 60 or above, and osteoporosis was estimated as 11% in men (Nguyen et al., 1996). According to Selby and colleagues, and others (Faulkner et al., 2000), a T-score cutoff of -2.5 in men, using male normalization data, is not appropriate to define low bone mass or osteoporosis. In addition, the selection of a cutoff in men should be linked to a measure of fracture risk. This would require different T-score cutoffs depending on the skeletal site and device used. Faulkner and Orwoll (2000) suggested that the use of BMD T-scores in men suffers from the same problems (various techniques and sites of measurement) in women (Faulkner et al., 1999). Using various manufacturers' male BMD reference data for different skeletal sites, they estimated the proportion of men over the age of 50 who would have T-scores below selected values, ranging from 1.0 to 3.0 SD below the young normal reference values for men. As in women (Faulkner et al., 1999), the prevalence estimates varied from 4% to 28% in men having a T-score below –2.5 by skeletal site and technique. For dual x-ray absorptiometry (DXA) measurements at the hip and spine, the prevalence of T-scores below 2.5 ranged from 4% to 9%.

Another problem in the application of BMD measurement in men is the lack of data on the risk assessment of fracture in terms of BMD. If the relationship between BMD and fracture risk in men is similar to women, this would facilitate the selection of appropriate diagnostic and treatment thresholds in men. Fracture prevalence increased with decreasing BMD in both genders, however, fracture risk might be different in women and men at the same value of BMD. Cauley and colleagues (2000) studied 314

men (age range, 58-91; mean, 73 years) and 2067 women (age range, 66-95; mean, 73 years) with hip BMD measured at the total hip with DXA and prevalent vertebral fractures determined from lateral spine x-rays. Adjusting for age, weight, and height, the mean total hip BMD (g/cm^2) among men with a fracture (0.84) was significantly higher than the BMD among women with a fracture (0.71). Over 75% of the men, and 58% of the men having a history of fracture, had a BMD value above the 75^{th} percentile of BMD in women (representing 25% of the women). Only 1% of men had a BMD value below the 25^{th} percentile for women. The investigators concluded that male-specific reference values and BMD cutoffs should be used for identifying men at increased fracture risk.

b. Invasive assessments for Bone Mineral Density

Measuring bone mineral density at various skeletal sites by bone densitometry, is powerful to predict fractures. The rationale for BMD as a predictor for fractures is that approximately 70-80% of the variability in bone strength (ability to withstand compressive, torsional and bending forces) in vitro is associated with its mass or apparent density (Dalen et al., 1976). Biomechanical testing on cortical and trabecular bone material properties supported the rationale (Bouxsein and Augat, 1999). These methodologies have been used to assess bone mass in the whole body and at specific sites in the appendicular (peripheral: forearm, radius, or calcaneus) or axial (central: vertebral spine, hip) skeleton. The consumer selection of a measurement technique may be influenced by various factors, including site of bone measurement, radiation exposure, availability of instrumentation, and cost. In the health market, there are several techniques to measure the bone mineral density (BMD) or bone mineral content (BMC), including radiographic absorptiometry, single photon absorptiometry (SPA), dual energy X-ray absorptiometry (DEXA), quantitative computerized tomography (QCT) and quantitative ultrasound (QUS).

Two major different technology principles are used to the assessment of BMD; one is based on attenuation of absorption of ionizing radiation by bone (e.g. DXA), and

the other is based on the velocity or attenuation of sound wave propagation through bone (QUS). In techniques employing ionizing radiation, bone density is proportional to the attenuation of radiation, e.g. the less radiation is ascertained in the presence of the more bone mass. Alternatively, the speed of ultrasonic waves through bone is proportional to the mass density and elastic modulus of bone in using sound wave techniques. It provides estimates of bone density and bone structure or bone quality.
Accuracy and precision in bone densitometry need to consider in various imaging techniques. Accuracy is an ability to measure true value. It is important for diagnosis and for assessment of fracture risk. In other word, accuracy is % error between true value and measured value, and is expressed as % coefficient of variation. Accuracy ranges between 2 to 15% varied by technology. Precision is the measure of the device's ability to reproduce the parameters. It is important for serial measurements to look if there has been change. It also discriminates between the measurement error and rue biologic changes. This reproducibility is generally expressed as the percentage coefficient of variation (CV) of repeated measurements. The precision ranges from 1 to 4% based on densitometric techniques (Genant et al., 1996).

The following sections are adapted from Genent et al. (1996) and others (Kanis 1997; Marcus et al., 1996; Ross et al., 1999).

1) Conventional Radiography

Skeletal radiography is simple and low cost techniques (approximately $ 20-80). Radiographs of the spine are most widely used. However, bone mass is decreased by up to 40-50% before bone loss on radiographs can be measured. Therefore, radiographs alone cannot be used as a sensitive tool for diagnosing osteoporosis. Changes like wedge-shaped, biconcave, and compression in vertebral body are detected by radiography. Thinning and attenuation of cortices are measured as well. Singh index, one of semiquantitative indices of loss for diagnosis of osteoporosis in the proximal femur (Singh, Nagrath, and Malni., 1970), improves the sensitivity of

radiography. Yet, the usefulness of the measurement is limited (Marcus, Kelsey, and Feldman 1996). The most valuable feature of radiography is its ability to reveal bone morphology, such as vertebral deformities or fractures, rather than changes in bone density. Radiographic absorptiometry (RA) integrate radiographic films and optical densitometer. Recently, development of digital radiography reduced the radiation dose, and improved precision (Genant et al., 1996; Buckwalter et al., 1992; Huang et al., 1998). Another disadvantage of radiography is high radiation dose compared to other densitometric techniques. Effective radiation dose of lateral lumbar x-ray is 700 μSv (μ Sievert) compared to 1 ~ 3 μSv of central DXA examination (Genant et al, 1996)

2) Single photon and X-ray Absorptiometry (SPA and SXA)

Single Photon Absorptiometry (SPA) was used widely in the past to measure BMD at the forearm, femur, humerus, metacarpal, hand and foot. SPA provides an integral measure of both cortical and trabecular bone in the region. Bone masses are calculated from differences in photon absorption between bone and soft tissues, and bone alone (Wahner et al., 1988). For instance, this technique requires subjects to immerse their limb in water to compress the soft tissue and to standardize it to constant thickness. Thus, this technique was often applied to the forearm and heel. The bone mass (BMD) is obtained by the bone mineral content of the segment which is divided by bone width and area (g/cm2). The accuracy of measurement is mediated by the fat mass, and the computational software assumes that fat distributed uniformly through bone. However, there is various heterogeneity of the surrounding tissue in appendicular sites limiting the accuracy of SPA. Precision of SPA is ranged from 1-2%. BMD is detected with low radiation, high accuracy (3-6%), and low cost. However, SPA method is limited to appendicular sites such as calcaneus or forearm, which is mostly cortical bone (Eckert et al., 1996). In addition, there is variability with respect to maintain the radiation source, which needs to be replaced every 3 or 4 months.

SPA was replaced by SXA for scanning appedicular sites. SXA is mostly used for peipheral sites (radius or calcaneus sites) with a precision of 1-2% and accuracy of 4-6 %. Advantages of SXA include low cost, and accessibility, and reduced radiation exposure. However, SXA does not separate the integrated values of the trabecular and cortical bone area. Measurement of the radial shaft provides cortical bone and calcaneous bone with singly energy source techniques. SXA is also being replaced by peripheral DXA systems.

3) Dual photon and X-ray Absorptiometry (DPA and DXA)

Densitometry using single energy method could not measure BMD at sites with variable soft tissue thickness, and integrated composition (mixed at different proportion of cortical and trabecular bone) such as hip, or lumbar spine. The dual energy algorithm makes it possible to eliminate the assumption of constant soft tissue thickness underlying in the scan path. The use of second energy source (x-ray photon) can correct the tissue thickness difference. Dual photon Absorptiometry (DPA) based on radionucleide source of photons (usually gadolinium-153) emitting two distinct energies as of 44 and 100 KeV, measures mainly spine and hip. It may be used to measure total body mass. However, scan time of DPA is quite long and scan cost is expensive. The precision ranged from 2-5%.

DPA has replaced by Dual Energy X-ray Absortiometry (DXA). The 5 min measurement time using DXA is faster than 15~20 min using DPA. Because no isotopes are involved for DXA, patients receive low radiation dose compared to other methods. Unlike SPA, DPA and DXA can measure BMD of multiple sites. Currently the DXA is considered as “Standard” tool to measure BMD. Advantages of DXA measurements are: good precision (ranged from 1.5- 3% in spine, and femur, and less than 1% in forearm and whole body), accuracy (ranged from 3 to 15% at various sites), and low radiation exposure (1-3 μSv per site or less) (Boonen et al., 1997; Lafferty et al., 1996). Disadvantages of DXA are medium cost and interference with other disease,

such as osteoathritis and aortic calcification at lumbar sites. Bone density is most often expressed as areal density (g/cm^2).

A major criticism against the DXA and DPA technique is that bone density is measured as an areal or two-plane density (g/cm^2) rather than a real volumetric value (g/cm^3) accounting for bone size and bone depth. For instance, bigger bones appear to have greater BMD even if wider bones are thick but having similar actual tissue density. To reduce this problem, additional adjustments were made to compensate the true volumetric effect of bone using DXA or DPA. BMD divided by height (Reid et al.,1992) and bone mineral apparent density (BMAD)(Carter et al., 1991). BMAD (g/cm^3) is often used. This calculated values assumes proportional vertebral thickness to its height and width (Carter et al 1991). In a study of Rochester, investigators measured BMD, BMD/height, BMAD values in 348 men (aged 22-90) and 351 women (aged 21-93) (Melton et al., 2000). BMD values in men where greater in most body regions compared to women ($p<0.001$). Male excess of total body BMD and femoral neck were 14.5%, respectively. However, adjustment for height (e.g. total body BMD/height = 5.5%) and BMAD (e.g. Femoral neck BMAD –4.4%) reduced or eliminated the gender difference. Using these surrogate values for fracture risk assessment, Cumming et al (1994) found that BMAD compared to BMD had similar predictive value for hip fracture. Controversy remains about to use these values, but at least BMAD, or corrected BMD can reduce the problem aroused by areal DXA measurements. BMD measurements by DXA at antero-posterior lumbar spine also need attention because of the differences in bone size (areal density not adjusting for bone size) or the presence of calcification outside antero-posterior lumbar spine.

4) Quantitative Ultrasound Technology

Quantitative ultrasound (QUS) methods have been recently developed and introduced for the assessment of skeletal condition in recent years. Even though bone density explains 30-80% of the variance in bone strength, other skeletal properties such

as bone quality and geometry are also important determinants of bone strength (Faulkner et al., 1994). Quantitative Ultrasound (QUS) is a useful technique to evaluate skeletal integrity at peripheral sites such as calcaneus, patella, tibia, finger and forearm as well as bone density. QUS uses sound waves to assess skeletal status (Bauer et al., 1995). QUS is based on the difference in velocity and attenuation of the interaction between ultrasound and bone. However, QUS techniques have largely varied by skeletal measurement sites, QUS parameters of velocity and attenuation, or transducer coupling (gel coupled or water coupled). Thus it needs to be evaluated according to different methods (Gluer CC et al., 1997).

In ultrasound velocity techniques, for example, speed of sound (SOS) is the speed (m/sec) in which the sound wave passes from one transducer through the heel whereas the velocity of sound (VB) through bone estimates speed of sound through the bone alone and thus corrects for differences in sound transmission through water and soft-tissue. Broadband ultrasound attenuation (BUA, dB/MHz) is a parameter of difference of signal amplitude through medium (i.e. water). The amplitude of the ultrasound signal through bone is compared to the signal in transit through water, and the slope of the linear portion of the difference is plotted against frequency.

QUS has been successfully employed for many years for nondestructive material testing. Both scattering characteristics and ultrasound velocity changes have been used to evaluate mechanical competence and detect the presence of damage in both materials and structures. Nevertheless, the applicability of this technology to the requirements of medicine and specifically for fracture risk prediction has to be validated (Gregg et al., 1997). QUS was expected to compensate the weakness of BMD measurements, but recent studies showed that QUS is same or quite similar as to hip or calcaneal BMD measurements for prediction of fractures (Huopio et al.,2000; Hartl et al.,2000). Lower heel ultrasound is associated with lower BMD at the heel and at the hip. Heel ultrasound attenuation is also an independent risk factor of higher risk of hip, spinal fracture, and vertebral deformities (Pluijm et al., 1999; Gregg et al., 1997). Bauer et al. (1997) compared the relative predictability of femoral neck BMD by DXA and

broadband ultrasound attenuation (BUA) measurements of the calcaneous for hip fracture. While bone densitometry showed an eightfold increase of relative risk in hip fracture, QUS had a sevenfold increase risk of fracture among the highest predictive quartile compared to lowest. The short-term precision of BUA of the calcaneus with BMD at various sites reported as ranged from 0.93 to 10 % as compared that the CV of DEXA ranged 1-2% (Prins et al., 1998). Advantages of ultrasound are: no radiation exposure, relative low cost, and portability.

5) Quantitated Computed Tomography (QCT)

Quantitative Computed Tomography (QCT) provides volumetric images of body (g/cm^3), and evaluates separately trabecular and cortical BMC and BMD. For example, this technique is independent of the vertebral body so that size of vertebrae does not affect the precision error. Bone volume is achieved by using each thin traverse slice through the body. Low precision error at the radius and high resolution are merits of this method. Measurement time is about 10 to 20 minutes. QCT is also useful for individuals who are at the extremes of weight.

QCT measurements can measures not only bone strength, but also different aspects of bone quality such as bone size, bone microarchitecture, and microfracture.
The disadvantage of QCT is the exposure to high radiation dose. Because QCT is X-ray based technology, effective radiation dose for measurement is several times higher than using absorptiometry. Radiation dose is 50-60 μSv for central QCT and 10 μSv at peripheral sites. Also, high measuring cost and maintenance cost are another problem (Genant et al., 1996).

3. Epidemiology of Osteoporosis and Fractures in Men

a. Prevalence of osteoporosis and osteoporotic fractures

Despite the importance of the problem, until recently, there has been little information available on the etiologic causes, diagnosis and treatment of osteoporosis in men. From the third National Health and Nutrition Examination Survey (NHANES III) study, the prevalence of low bone density and osteoporosis were observed as 33% and 6%, respectively, in men aged 50 years old or above (Looker et al., 1997). Whereas in the Dubbo Osteoporosis Epidemiology Study in Australia, the prevalence of low bone mass (osteopenia) was estimated as 42% of men aged 60 or above, and osteoporosis was estimated as 11% in men (Nguyen et al., 1996).

Low bone density is one of the best predictor of future fracture risk even though concurrent fragility fractures and other clinical risk factors of fracture predict future risk as well (Cummings et al., 1995). As BMD decreases, the risk of fracture increases exponentially (Jacobsen et al., 1990). In addition, relative risk of fracture increases as the number of skeletal regions found to have BMD increases in older invididuals. Investigators of Rotterdam study reported that the age adjusted relative risk for hip fractures was 3.0 (95%CI; 1.7-5.4) per 1 standard deviation decrease in femoral neck BMD among 2778 Dutch men followed for an average of 3.8 years (De Laet et al., 1999). Approximately 1.5 million osteoporotic occurs each year, and this includes 700,000 spine fractures, 300,000 hip fractures, and 250,000 wrist fractures (Riggs et al., 1995). Estimated lifetime risk of experiencing one of osteoporosis related fractures (vertebral, hip, and wrist fracture) estimated to 13% for men at the age of 50 year old (Melton et al., 1992). For instance, approximately 150,000 hip fractures occur in men in the United States each year, and the incidence of hip fracture is projected to increased more than three times within the next 50 years (Gullberg et al., 1997). Furthermore, lifetime risk of a non-traumatic fracture in 60-year old men is to be 25% in one

prospective study (Nguyen et al., 1996). This lifetime risk of osteoporotic fracture is greater than the risk of prostate cancer (Melton et al., 1995).

b. Consequences of osteoporosis and osteoporotic fractures in men

Many studies have shown that bone density is an independent predictor of all cause morality in women (Cooper et al., 1993; Browner et al., 1991; Browner et al., 1996) and only a few studies reported the significance of bone density in mortality of men (Johansson et al., 1998; Trivedi and Khaw, 2001). An decrease of one standard deviation (0.144 $g.cm^2$) of total hip bone density was significantly associated with increased age-adjusted all cause mortality ratio in a study of 1002 men aged 65 to 76 years (Trivedi and Khaw, 2001). Calcaneal bone density was also related to mortality ratio in 653 men during 7 years of follow-up. Independent of covariates (e.g. age, smoking, blood pressure), an increase of bone density was related to decrease of mortality ratio (RR=0.81; 95%CI 0.71-0.91) (Johansson et al., 1998). The investigators from the Rotterdam Study reported that the risk of mortality was two fold higher among men with a hip BMD t-score of - 2.0 than those with normal BMD after adjusting for age and weight (van der Klift et al., 2000).

Osteoporotic fractures are related to increase morbidity and mortality. Most common osteoporotic fracture is vertebral fractures. Most vertebral fractures were asymptomatic (Cooper et al., 1992), but often associated with the loss of height, decrease in pulmonary function, chronic back pain, and loss of self-esteem (Ross, 1997). Cooper et al. (1993) studied the survival rate of 3334 men and women after vertebral fractures. Survival rates were poor in men (0.72; 95%CI 0.51-0.98) than in women (0.84; 95%CI 0.71-0.96) during 5 years. Currently, the scope of vertebral fractures are underdiagnosed and underestimated.

Mortality after different types of osteoporotic fractures has also been reported. Of all fractures, hip fractures cause the greatest number of deaths and lead to the most

severe health problems. Mortality increases with the age. As the number of comorbid conditions increase, mortality after hip fracture also increase. People 85 years or older are 10 ~ 15 times risks for hip fractures than people aged 60 and 65 years. While women sustain 75 ~ 80% of hip fractures and men showed excess mortality. The mortality after hip fractures is higher in men than in women (Poor et al., 1997; Center et al., 1999). The case fatality in men and women was 20.7% and 7.5% respectively among those over 75 years or above (Poor et al., 1997). Center and colleagues reported that age standardized mortality ratio for hip-proximal femur fracture was 2.18 (95%CI, 2.03-2.32) for women and 3.17 (95%CI; 2.90-3.44) for men in 5 year-prospective study. Rates of hospitalization for hip fracture differ by age and race for men and women. A similar study by Lu-Yao and colleagues reported that mortality 1 year after hip fracture was higher in men (OR=1.7) among 131,678 femoral neck fracture cases. For other major fractures except hip and vertebrae, the standardized mortality ratio was greater in men (2.22, 95%CI; 1.91-2.52) than in women (1.92, 95%CI; 1.70-2.14) (Center et al., 1999).

The osteoporosis related costs in U.S. were $13.8 billion per year and it includes hospitalization, and nursing home care. Economic cost of osteoporotic fractures in men was estimated as $2.53 billion, representing 20% of the total cost of osteoporosis in 1995 (Ray et al., 1997).

c. Risk Factors for Osteoporosis and fractures

The approach to the identification of risk factors in male osteoporosis has differed from that used for women. Most male osteoporosis has been regarded as of result of idiopatic or secondary reasons whereas hormonal depletion (estrogen) in women was the major risk factor for postmenopausal osteoporosis. Secondary causes of osteoporosis seen in men include glucocorticoid excess, hypogonadism, excessive alcohol consumption, smoking, and hyperparathyroidism (Orwoll, 1995; 1999). From a clinical study (Legroux-Gerot et al., 1999), authors reported that 28.1% of men had

idiopathic osteoporosis, 22.5% had alcoholic osteoporosis, 19.4 % had glucocorticoid-induced osteoporosis, 12.5% had osteoporosis due to moderate idiopathic proximal tubule dysfunction, and 8.8% had senile osteoporosis. However, less than 40% of male osteoporosis is described as secondary osteoporosis in other studies (Estell et al., 1998). The natural history of peak bone mass (PBM), maintenance of bone mass, or bone loss has been linked to a number of influences including genetic and familial factors, race and ethnicity, nutritional intakes, mechanical loading and hormonal factors (e.g. sex steroid hormones). For, example, femoral neck BMD (Nguyen et al., 2001;Alonso et al., 2000; Pande et al., 2000), height loss (Nguyen et al., 2001; Center et al, 1999), and dietary calcium intake were consistent risk factors for hip, or wrist fracture in men.

1) Bone mineral density and Peak Bone Mass

There is no evidence for gender difference in bone density at birth, and before the pubertal onset (Glisanz et al., 1997). The gender difference in bone mass becomes noticeable after puberty (Glisanz et al., 1997). Bone mineral mass increases during adolescence, and reach 'peak bone mass' in early adulthood (Glisanz, 1999). Thus most of peak bone mass has been achieved by the age of 17 or 18 in both males and females. Szulc et al (2000) measured bone mass in 934 men aged 19-85 years, peak bone density was achieved at 25 and 29 years at the lumbar spine and hip, respectively, but only at 40 and 37 years at the distal forearm and whole body, respectively. While increases of bone persist up to the age of 17 years old in boys, the rate of increase in bone mass decrease rapidly after the menarche in girls (Bonjour and Rizzoli, 1996). Longer period of bone mass gain in boys results in a larger increase in bone size and cortical thickness (Seeman 1997). Therefore the areal bone mineral density (BMD, g/cm^2) at the femoral neck is greater in males than females whereas volumetric bone density (g/cm^3) does not significantly differ between men and women (Seeman 1999).

Peak areal bone density is also greater in the lumbar spine in boys than girls, primarily because boys have larger vertebral cross-sectional area and volume compared with girls (Gilsanz et al., 1997). Vertebral width was 17% greater in boys than in girls by Tanner stage 1. If these differences in vertebral body size are accounted for, gender differences in areal bone density are no longer apparent with similar tabecular number and thickness (Gilsanz et al., 1997; Seeman et al., 1999). However, there is racial difference in vertebral height. Trabecular bone density at the spine increases more in black compared in whites (Gilsanz et al., 1998). Volumetric bone density at the lumbar spine is approximately 10% greater in black compared with white boys and girls at the end of pubertal maturation due to less vertebral height (Gilsanz et al., 1998). This racial difference is largely due to greater trabecular thickness in black compared with white children (Gilsanz 1998). Greater volumetric bone density at the spine in black compared with white men and women may contribute to their lower vertebral fracture risk. Similarly, bone mineral apparent density (BMAD, g/cm^3) adjusting for bone size also reduce the gender differences in bone density (Melton III et al., 2000).

In male, periosteal expansion accelerates probably due to androgen-mediated increase (Seeman, 1999). In female, periosteal expansion ceases while endocortical contraction narrows the medullary cavity. Femoral cortical width is similar in men and women because greater medullary expansion, and less medullary contraction in men during puberty (Seeman, 1999). The greater peak vertebral size in men due to wider vertebral body may be attributable to greater bone strength in men. Femur length and width is also greater in men (Seeman, 1999). The influence of body size on bone density and different patterns of bone changes at different sites with age had significant effect on the gender differences of osteoporosis (Melton III, et al., 2000).

2) Bone loss

Men lose bone mass with age like women. The mechanisms of age-related trabecular and cortical bone loss, however, differ in men and women. Bone density

declines after the achievement of peak bone density around the third decade of life in cross-sectional studies of men and women (Looker et al., 1997). Women experienced accelerated trabecular bone loss due to higher bone remodeling activity. Bone loss in women mainly results from loss of connectivity due to trabecular plate perforation and disappearance (Seeman, 1999). The pattern of bone loss in men results from the thinning of trabeculae (Compston et al., 1989). In male, the decrease in the trabecular node count and strut count indicate less removal of trabeculae than in female (Compston et al., 1989). Cancellous bone volume was decreased by 40% in men aged 20-80 years (Clarke et al., 1996). Age-related cortical bone loss is related to two mechanisms: thinning of the cortices and an increase in the cortical porosity. In male the thinning of cortices was 14%, and an increase of cortical porosity was 2.5-7% between 20 and 70-80 years where in females the thinning was 38%, and the porosity was 2.8-10% (Chavassieux and Meunier, 2001). The rate of cortical bone loss in men may not be as rapid as women. Also, cortical bone loss is less than in women because of less endocortical resorption and greater periosteal apposition (Martin et al., 1999). A significant decrease in the osteoid surfaces in men was reported in literatures (Rehman et al., 1994; Clarke et al., 1996). Osteoclast surface was relatively preserved and osteoblast function was decreased. The osteoblast-osteoid interface was decreased by 19.2 % in the sample of 43 men (Clarke et al., 1996). Overall, reduced bone formation with trabecular bone loss by thinning in men may serve as the cause of age-related bone loss.

In the third National Health and Nutrition and Examination Survey (NHNES III) showed that bone density at the femoral neck was 25% lower among men and 33% lower among women aged 80-85 years compared to those aged 20-29 years (Looker et al., 1997). A report from 1,856 men (mean 66.7 years) enrolled in the Rotterdam Study showed 0.19, 0.25, 0.33% of bone loss at the trochanter, triangle, and neck, respectively (Burger et al., 1998). Similar, but higher acceleration of bone loss with age was also seen in the Dubbo Study (Jones et al., 1994). Among 427 elderly men, femoral neck BMD with 25(OH)D, and sex steroid hormone binding globulin were independent predictors of major fracture (hip, pelvis, proximal tibia, multiple rib,

vertebral, and proximal humerus). The odds ratio of femoral neck BMD was 2.7 (95%CI, 1.5-4.7) per 1 SD decrease (Center et al., 2000).

Some studies of older men have not shown a similar age-related decline in lumbar spine bone density assessed with DXA (Blunt et al, 1994) because measurements are interfered by aortic calcification, osteophytes, and other spinal degenerative disease (Hopkins et al., 1988; Jones 1995b; Szulc et al., 2000). For example, average lumbar spine BMD increased after the age of 55 years, due to the development of osteoarthritis. In men without arthritis, lumbar spine BMD continued to decrease with aging (Szulc et al, 2000). Small change of bone (-0.09% per year) in lumbar spine was detected in aged 67 to 90 years (Hannan et al., 2000). In a cross sectional study of 934 French men, bone loss between peak bone mass and 80 years of age was linear at most sites by averaged13%-18% (SD 1.1-1.8 from peak bone density) except for Ward's triangle (43% bone loss; 2.5 SD from peak bone density) (Szulc et al., 2000). Height-adjusted partial correlations demonstrate that both the mineral content and the area of long bones of the limbs increased with age up to 50 years, followed by a decrease of BMD without change of bone surface. Thus, authors suggest that age-related change of BMD varied by site with peak bone mass achieved earlier at sites rich in trabecular bone and bone loss varied by site.

There are few prospective data on the magnitude and variations of bone loss with age in men. Age specific bone loss rate for men at the femoral neck was –0.38%/ yr among 278 men in Framingham osteoporosis study (Hannan et al., 2000). Bone loss at femur neck, trochanter, lumbar spine, radial shaft were greater among 486 women ranging from 0.86 - 1.21% per year compared to the those of men (0.09-0.90 % per year)

3) Body weight and weight loss

Body weight correlates positively with bone density in middle-aged and elderly men (Felson et al., 1993; Bell et al., 1995; Nelson et al., 1995; Glynn et al., 1995; Orwoll

et al., 2000). Low body weight is a risk factor for low BMD in men (Bendavid et al., 1996; Nguyen et al., 1994). Cross sectional analysis of the Dubbo Osteoporosis Epidemiology Study reported that body weight accounted for 10% and 17% of the total variance in BMD of the lumbar spine an femoral neck, respectively (Nguyen, and Eisman, 1999). Previous analysis on participants (n=523, mean 67 years) in the Study of Osteoporotic Risk in Men (STORM) presented approximately 5% increase in hip BMD was associated with every 25 pound increase in weight (Glynn et al., 1995). Similar observation has been made in a study of 355 men aged 60 years. Each 10 kg increase in body weight was associated with from 5.4% (95%CI, 4.2-6.5) and 5.2% (95%CI, 3.6-6.8) higher BMD at the femoral neck and spine, respectively.

The results from longitudinal studies of fracture consistently support that a higher body weight or high body mass index (BMI) is related to lower fracture risk (Nguyen et al, 1996; Poor et al., 1995; Meyer et al., 1993). Each 12.7 kg decrease in body weight was associated with 23% (95% CI: 1.09-1.39) increase in the risk of subsequent low trauma fractures among men aged 60 years and older (Nguyen, 1996). This effect was no longer statistically significant, however, after controlling for bone density. Ismail et al., showed the significant relationship of low body mass index to vertebral deformities in the European Vertebral Osteoporosis Study (Ismail et al., 2000). In 6937 men (mean age 64.4 $\pm$8.5 years), low body mass index was associated with 2.5 times increased vertebral deformities.

Weight may be another major determinant of low bone mass, accelerated bone loss, and increase fracture risk among older men. A 5% or greater gain in body weight during the 4-year follow-up significantly increased tranchanter BMD of hip, but 5% loss of weight was related to greater bone loss at femur neck (Hannan et al., 2000). 5% gain of weight-group showed –1.85$\pm$1.4 % annual changes while 5% loss of weight-group showed greater bone loss (-4.34$\pm$1.0%, $p<0.05$) at the femoral neck This study suggested that men showed stronger association between weight gain and bone loss at weight bearing sites compared to that of women. Similarly, weight loss greater than or

equal 10% was related to significantly higher hip fracture rate (RR= 2.27, 95%CI 1.13-4.59) in the NHANES I Epdiemiologic Follow-up Study (Mussolino, 1998).

The positive association between high body weight and greater BMD is closely related to the fat and lean mass, two major components of weight. Both fat and lean mass has found to be positively related to BMD in men as well as pre- and postmenopausal women (Reid et al., 1994; Ensrud et al., 1997;Salamone et al., 1995). In 62 healthy men (age range, 60 to 86 years), no significant correlation was found between fat mass and BMD. However, the lean body mass were significantly associated with the BMD of the proximal femur (r^2=0.21, P<0.001) (Kirchengast et al., 2001). In the Health, Aging, and Body Composition (Health ABC) Study, lean mass was also consistently associated with BMD at the femoral neck among 827 white men, and 455 black men aged 70-79 years. A unit (7.5kg) increase in lean mass was related to a 5.6% increase in BMD among white men, and a 5.9% increase among black men (Taaffe et al., 2001).

4) Physical activity and exercise

Physical activity and exercise are important for skeleton (Beck and Marcus, 1999). The literatures consistently report significant relationships between physical activity and exercise and bone. External weight-bearing forces stimulate bone formation and bone remodeling, and change the distribution of bone mass to accommodate the mechanical forces (Chilibeck et al., 1995; Rubin et al., 1985). Without weight-bearing exercise, bone loss occurred at both axial and appendicular skeletal sites. For instance, a study of bone loss in astronauts showed that cancellous (BMD) loss at the tibia occurred after the first month in space due to lack of gravitation and mechanical loading on skeleton. Subsequently, bone loss ranged from 0.4 to 23% loss with mission duration (6 months) (Vico et al., 2000).

Physical activity has been related to peak bone mass in children and adolescent (Kroger et al., 1993). Physical activity can also play a beneficial role in the maintenance of bone mass. A short period of immobilization results in rapid bone loss with more in trabecular bone than that of cortical bone (Mazness and Wheadon, 1983). Cross sectional studies in middle and elderly men have shown positive relationships between greater physical activity levels and higher bone density, heel ultrasound attenuation or fracture risk (Glynn et al., 1995; Grisso et al., 1997). The positive association between exercise and BMD were reported at weight bearing sites (hip, $p<0.02$; spine, $p=0.05$) in 218 men aged 50-64 of Racho Bernardo Cohort (Bendavid et al., 1996). In the Dubbo Osteoporosis Epidemiology Study, 1075 elderly men (mean age 69.4 $\pm$ 4 years) who engaged in recreational or home-based activity (physical activity index: PAI) showed positive association with femoral neck BMD not lumbar spine with age adjustment (Nguyen et al., 2000). Physical activity was also related to bone quality measured by quantitative ultrasound parameters. Wareham and colleagues assessed the relationship between types of physical activity and heel ultrasound attenuation in 2143 men (mean age 64.6 $\pm$ 8.3 years) and 2631 women (mean 62.9 $\pm$8. 4 years). Men who spent at least 2 hours per week of high impact activity (e.g. step aerobics, tennis, or football) showed 9.5% higher levels of ultrasound attenuation (BUA) compared with men who reported no activity.

There are little data with regard to longitudinal studies of physical activity. Study of Australian men (n=442, aged 60 years and older) did not confirm an cross-sectional association between current physical activity level and the bone loss at the hip or lumbar spine (Nguyen et al., 1996). Consistently, another longitudinal study (Hannan et al., 2000) also reported that physical inactivity calculated with Framingham physical activity score among 278 men did not show a strong relation with bone loss at various skeletal sites. One randomized clinical trial of physical training on 140 men (age range 53-62 years) demonstrated no effect of long-term regular aerobic physical activity on the age-related bone loss of femoral BMD. Long-term regular aerobics physical activity in men had no beneficial effect on the femoral ($r=-0.10$, $p>0.05$) and lumbar spinal BMD loss ($r=0.09$, $p>0.05$). Inconsistent findings, however, could be explained by recall bias,

difficulties in measuring physical activity levels, and different physical activity assessment (questionnaires).

There are a few studies demonstrating the relationship between physical activity and reduced fracture risk. High activity involved in one hours per day or heavy physical activity associated with significantly reduced risk of hip fractures compared to the groups of moderate activity (OR = 0.3; 95%CI 0.2-0.5), or low activity group (OR = 0.2; 95%CI 0.1-0.3) (Grisso et al., 1997). A European study showed 33% risk reduction of hip fractures (Jake et al., 2001)

5) Smoking

Tobacco use among high school students in the United States increased 32% in 1997 compared with 1991(CDC, 1998). Smoking during adolescence is associated with continued and heavier use of tobacco during adulthood (US Department of Health and Human Services, 1994). It is also related to other unhealthy lifestyle practices, such as alcohol use and lower levels of physical fitness. The relationship between smoking and lower bone density in young adults has been inconsistent. Hopper and Seeman reported that a difference of discordant tobacco use in twins is attributable to 5-10% of bone mass by menopause (1994). Continued smoking is related to an increasing cumulative negative effect on bone mineral density. Even though there is few data available for men, the tobacco effect on hip fracture risk is same as women (Law and Hackshaw, 1997)

Several explanatory mechanisms between the tobacco smoking and BMD have been proposed including direct toxic effect on bone cells, lower body weight, lower levels of sex steroid hormone, reduction of calcium absorption and greater risk of falling among smokers (Heaney et al, 2000; Seeman 1996). The impact of smoking on peak bone mass attainment may result in significant small reductions in bone mass. However, the long-time use of smoking on bone is cumulative, thus smokers are more

likely to experience an increasing, cumulative decrement in bone, which is significantly related to risk of osteoporosis in later life. Recent meta analysis of effect of smoking on BMD showed smoking had significantly reduced bone density compared with non-smokers (Ward and Klesges, 2001). They studied 40,753 pooled participants from 86 studies, and found that lifetime risk of developing vertebral fracture and hip fracture in men was increased by 32% and 40%, respectively for smoking.

In the Framingham Osteoporosis study, men who smoked cigarettes at baseline lost more BMD at the trochanter site (-4.37 mg/cm2/ yr vs 0.56 in never smoker, or 0.94 in former smoker) compared to baseline non-smoker during 4 year follow-up (Hannan et al. 2000). This smoking association was independent of age, weight, weight change, height, and alcohol intake. Men who smoked experienced twice the rate of hip bone loss compared to non-smoker (-7.0 mg/cm2/yr vs –3.0 mg/cm2/yr, $p < 0.05$) during an average of 2 years of follow-up (Buger et al., 1998).

6) Dietary Calcium & Vitamin D Intake

Calcium is the major mineral component of bone, and calcium deficient diets result in increase calcium transport from bone, thus decreasing bone calcium content (Nordin, 1997). Calcium needs change during our lifetime. The body's demand for calcium is greater during childhood and adolescence, when the skeleton is growing rapidly, and during pregnancy and breast-feeding. Postmenopausal women and older men also need to consume more calcium. The recommended daily allowance for elderly men (over 64 years) is 1500mg/day (NIH expert panel, 1994). The most recent recommendations are to advise all adults over the age of 50 to consume at least 1200 mg/day of elemental calcium (1998).

In addition, adequate vitamin D is essential for optimal calcium absorption, and vitamin D insufficiency can contribute to impaired intestinal calcium absorption, secondary hyperparathyroidsm, increased bone loss, and osteomalacia with impaired

bone mineralization (Dawson-Hugh et al., 1999). Vitamin D production decreases with age. As the skin ages, it is less efficient at synthesizing vitamin D3 ($1,25(OH)_2 D_3$) under the influence of sunlight because the thickness of the epidermis declines with age and the amount of the vitamin D precursor, 7-dehydrocholesterol, is reduced. Gastrointestinal absorption of vitamin D is also less efficient in older people. Aging decrease the ability to absorb calcium from the diet in cross-sectional studies of older men (Agnusdei, 1998;Bullamore, 1970), and this decreased capacity to absorb calcium may be exacerbated by low calcium and vitamin D intakes. Vitamin D status is related to seasonal variation. It is the lowest in fall and winter. It also varies with different geographic areas worldwide. From North to South, the vitamin D status decreases according to UV light. For example, deficiencies of vitamin D are quite common in northern latitudes where production of vitamin D on skin decrease because of short winter sunlight.

The relationship between dietary calcium and peak bone mass is not consistent in population studies. A higher dietary calcium intake was associated with significantly greater peak bone mass among men in one study (Kell, 1990), but not in another (Valimake et al., 1994). Bone density at the lumbar spine, but not at the hip, was significantly greater among older men with calcium intakes above 800 mg/day compared to below 800mg/day (Bendavid et al., 1996). High intakes of dietary calcium (>1300 mg/day) were significantly associated with slower femoral neck bone loss (~ -4.0 $mg/cm^2/yr$) in a study of 1578 men aged 60 years and older (Burger et al., 1998).

Some of inconsistencies in relating dietary calcium intake to bone density, bone loss, or fracture risk in observation studies may be due to the inaccuracies in measuring dietary calcium and age related to changes in calcium absorption. Moreover, the ability to absorb calcium from the diet varies considerably among individuals, and is inversely related to dietary calcium intake (Dawson-Hughes, 1999). Differences in calcium absorption efficiency have not been considered in population-base studies. Weight loss has been related to increased bone loss both in men (Hannan et al., 2000) and postmenopausal women. Jensen et al (2001) and other (Ricci et al.,2001) studied the

bone loss in obese women resulting from moderate weight loss. In a Denmark study, a 4.0% reduced BMD in the hip was related to a 5.5% weight loss during 6 month trials, but the loss of BMD was attenuated by calcium supplementation.

A recent trial suggest that increasing the calcium and vitamin D intake of older men may decrease age-related bone loss (Dawson Hughes et al., 1997). Calcium and vitamin D supplement was related to significant decline in the incidence of osteoporotic fracture (changes, -60%, 95%CI, 0.2-0.8) among 176 men and 213 women combined (Dawson Hughes et al., 1997). Reduced vitamin D levels have been reported in patients with hip fracture and hence attempts have been made to investigate the effect of vitamin D supplementation on prevention of fracture. In a three-year study of 3270 institutionalized older persons, supplementation with cholecalciferol and calcium resulted in a significant reduction in fracture rate. Protection was apparent after 6-12 months of treatment with a reduction of fractures of more than 30% by 18 months (Lips et al. 1996). The only randomised placebo controlled clinical trial of vitamin D supplementation alone and fracture incidence showed that after 3 years of supplementation with 10 μg of vitamin D, there was no difference in fracture rates between the supplemented and unsupplemented groups (Chapuy et al., 1992).

7) Other nutritional intake

Caffeine increases urinary calcium excretion in metabolic studies (Barger Lux et al. 1990), and higher caffeine intake has been associated with reduced bone mass and increase hip fracture risk in several, but not all, studies of older women (Cummings, 1995). In a study of 92 white women with normal weight, aged 55 and 70 years, dietary caffeine consumption are not related to change in bone density after controlling for hormone replacement therapy, diuretic, corticosteroid use, and alcoholic drink (Lloyd, 2000). A lifetime caffeine intake equivalent to about 2 or more cups of coffee per day was associated with a 0.5 standard deviation reduction in hip and lumbar spine bone

density, only among women who did not drink milk on a daily basis (Barrett Conner, 1994).

Soy consumption referring to soy isoflavones, and soy protein has been noted to be beneficial effect of bone in several animal, and cultural studies. Soyfoods contain isoflavones, compounds that are similar in chemical structure to estrogen. Genistein, one of two primary soybean isoflavone, have shown direct inhibitory effects on bone resorption in animal studies. Compared to animal protein, soy protein favorably affects calcium metabolism (Arjmandi, Khalil DA, and Hollis, 2002). In Japanese women, BMD adjusted to years since menopause and weight were significantly different in the highest isoflavone intake group compared with the lowest intake category, within the early and late postmenopausal groups. (Somekawa et al., 2000).

8) Alcohol consumption

Alcohol causes some unfavorable changes to bone mass. Acute alcohol intoxication results in lower levels of serum PTH, and increased levels of urinary calcium excretion (Laitinen et al., 1991) Chronic heavy alcohol consumption have related to lower serum calcium and higher serum PTH levels, as well as reduced rates of bone formations in postmenopausal women (Rapuri et al., 2001). The relationship of alcohol consumption with development of peak bone mass (adolescent and young adulthood) shows a biphasic mode, with higher bone mass for moderate alcohol consumer and then declining bone density at higher intakes (Neville et al., 2002)

Chronic alcohol abuse is associated with reduced bone mass in men (Klein, 1999), and is a common (~7%) occurrence among men presenting with symptomatic vertebral fractures (Cauley and Zmuda, 1999). In the Framingham study, the relative risk of hip fracture increased by 28% (95%CI, 1.05,1.56) for every 7 ounces per week intake of alcohol in women and men combined (Felson et al., 1988). Alcohol abuse decreased the spinal BMD and increased hip fracture risk by 2.8 fold mainly due to

increased tendency of falling (Poor et al., 1995). However, moderate, current alcohol consumption was significantly related to higher BMD at the spine, radial, or femoral neck in 355 men aged 60 years or over (Orwoll et al., 2000). The investigators concluded that bone density might be affected in dose dependent manner.

The mechanisms responsible for alcohol-induced osteoporosis are not known, but there is some evidence that alcohol may have a direct acute effect on osteoblast functions. Alcohol has been shown to decrease the bone formation by decreasing the osteoblast number, osteoid formation, and osteoblast proliferation (Klein et al., 1996). The concentration of ethanol that inhibits osteoblast proliferation in vitro is within the physiologic range observed in alcoholic subjects (Klein, 1999). In addition, the production of osteocalcin and numbers of osteoblast were significantly reduced with alcohol (Crilly et al., 1988). These effects of ethanol on osteoblast function and serum osteocalcin levels appear to normalize promptly upon alcohol withdrawal (Linholm, 1991). Bone resorption appears to be normal in alcoholic patients (Klein, 1999)
In summary, excess alcohol intake appears to have a moderate unfavorable effect on the bone density in adult men and premenopausal women, mainly by suppressing bone formation shile modest intake may actually have favorable effects on bone.

9) Medical Conditions

The relationships between various medical conditions and BMD have been studied. A recent publication by Orwoll and his colleagues (2000) demonstrated that the significant association of several medical conditions with BMD at the proximal radius, distal radius, femoral neck, and spine. Gastrectomy was related to 6 to 14% lower BMD at the proximal radius or spine. History of hyperthyroidism, and hypertension was related to radial BMD by –10.0 % (95%CI, -19.1~ -0.9), and –2.3% (95%CI; -4.1 ~ -0.4), respectively. However, hypogonadism was not related to BMD at any of skeletal sites. Hypogonadism has been an important risk factor in the development of osteoporosis in men. Hypogonadism before puberty has shown a big effect on cortical bone

development. Bertelloni et al. (1995) reported that short- term testosterone treatment resulted in 26% increased BMD, and 41% increased BMC of boys with constitutional delayed puberty compared to untreated controls. Long periods of hypogonadism in adult men has been related to reduced bone remodeling, decreased bone formation and low serum 1,25 $(OH)_2D_3$ levels (Francis et al., 1986; Smith et al.,1994). A number of medical conditions have been associated with bone density and fracture risk in men. Some of these conditions are uncommon, such as hyperparathyroidism (Larsson, 1993), and probably make only a minor contribution of osteoporosis risk among elderly men.

10) Medications

Chronic use of several types of medications may reduce bone density and increase the risk of hip fracture. Chronic corticosteroid use is the most common cause of secondary osteoporosis among men, and is present in about 15% of men suffering from vertebral fractures (Cauley and Zmuda, 1999). Corticosteroid use was not associated with an increase risk for hip fracture in two case-control studies of men (Grisso, 1997; Poor, 1995c), but current use of oral, but not inhaled, corticosterids was associated with significantly lower bone density and two-fold greater bone loss and hip fracture risk among older men (Baltzan et al., 1999). Men taking corticosteroids showed significantly lower bone density at the hip compared with non-users in one study (Glynn et al., 1995). In many of these studies, sample sizes were small and power was compromised because of the relative small number of steroid users.

Several large, prospective epidemiological studies in elderly men and women have shown that thiazide use is associated with higher bone mass and a reduced risk (30%) of hip fracture (Glynn et al., 1995; Morton et al., 1994; Wasnich, et al, 1990;Felson et al., 1991 etc). Thiazides as anti-hypertensive medication may act directly on the distal nephron to enhance calcium reabsorption and lower calcium excretion in hypercalciuria resulting improved calcium balance. In men with hypercalciuria, thiazides lower urine calcium and lead to positive calcium balance. In a

vitro study, thiazides reduced osteoclastic activity, possibly by inhibiting carbonic anhydrase. Men who used thiazide diuretics had 4% higher bone density at the femoral neck compared with non-users in the Study of Osteoporotic Risk in Men (Glynn et al, 1995). Men who used thiazide diuretics in the Hawaii Osteoporosis Study experienced a 30-50 % slower bone loss at the calcaneous and radius compared with men who did not use thiazides (Wasnish, 1990). Thiazide diuretic use has also been associated with a lower risk of hip (Grisso et al., 1997, Poor et al., 1995) and vertebral fractures in men (Wasnich et al., 1983), but these associations have not been statistically significant. A recent three year randomized trial of low dose of thiazide in normotensive men and women aged 60-79 years showed significantly positive changes on spine BMD but not on hip BMD (LaCroix et al., 2000). In addition, use of thiazide for hypertensive participants showed that the subjects who took thiazide had increased bone mass, whereas those on other forms of antihypertensive medication showed decreases in bone mass. A recent meta-analysis reported a pooled relative risk of 0.8 for thiazide use and the risk of hip fracture among women (Jones et al., 1995a). Thus, it is possible that previous studies in men lacked sufficient power to detect an effect of this magnitude.

Long-term thyroid hormone use was not associated with bone density among 685 older men (Schneider et al., 1995). Anticonvulsants may reduce bone density (Ebeling et al., 1999) and their use was associated with a three-fold increased risk of hip fracture in men that approached statistical significance (Poor et al., 1995). Recently, several studies showed that use of HIV protease inhibitor therapy is related to increased bone loss compared to other HIV therapy, or control male group. Men receiving protease inhibitors had a higher incidence of osteopenia and osteoporosis (RR =2.19, 95%CI, 1.13-4.23) (Tebas et al., 2000).

11) History of falls

The increase in fall frequency with age accounts some of the increased risk of hip fracture incidence with age (Melton et al., 1988; Cummings & Nevitt, 1988). About 90% of hip and wrist fractures occur because of falls but only about 5% of falls result in

a fracture and only 1% result in hip fractures (Cummings, 1994). One of every three older persons (aged over 65 years) living in community falls every year. This trend increases to 50% by the age of 80 years (Blake et al., 1988; O'Loughlin et al., 1993; Nguyen et al.,1996). Falls account for approximately 90% of all fractures for people 65 years and older. An estimated 1 ~ 2 % of falls cause hip fractures accounting for the majority of fall-related morbidity and mortality (Cummings and Nevitt, 1994). 3~ 5 % of falls result in other type of fractures, e.g. hand, and ankle fractures (Sattin, 1992). More than 60% of fall related deaths occurred in the persons aged 75 years or older. Fall related deaths for men and women increase with advancing age (Nguyen et al., 1999). More than 60% of fall related deaths are occurred to persons aged 75 years or older. The physiologic changes with aging such as slower reflexes, increased postural sway, and declined visual ability, contribute to instability and increased likelihood of experience a fall. Weak muscle strength and balance, gait reaction time as well as decreased activities of daily living had been consistently implicated in falls in the elderly (Tinetti, 1988; Nevitt, 1989). A recent summary of literatures about falls in elderly demonstrated that muscle weakness (Odds ratio, 4.4), and history of falls (Odds ratio, 3.0) was consistently related to the risk of falls (AGS Panel, 2001).

Independent of bone density, orientation of fall, characteristics of fall (a fall to the side), and impairment in mobility were strongly related with the risk of hip fractures (Schwartz et al., 1998; Greenspan et al., 1998). Schwartz et al. (1998) demonstrated that hitting the hip or thigh in a fall resulted in a significant risk of hip fracture (OR 48.6; 95% 22.5-105). After adjustment for age, state of residence and others, risk of hip fracture tremendously increased. However, hitting the knee in a fall (OR= 0.26, 95%CI 0.14-0.49), or falling forward (OR=0.22, 95%CI 0.12-0.38) was related to decreased risk of hip fractures. Few prospective data shows the direct relationship of fall-related risk factors and fractures in men. Women and men may have different outcomes from a fall. For instances, women may fall often on their hips and absorb mechanical energy differently from men. Nguyen et al. (1996) found that 1 SD (10kg) increase in quadriceps strength was associated with reduced risk of hip fracture (OR = 0.88; 95%CI, 0.75-0.99) in 820 men aged 60 years or above. They also found that men

experienced non-traumatic fractures exhibited more body sway (OR=1.13; 95%CI, 1.01-1.27).

4. Sex steroids and bone metabolism in men

a. Estrogen and bone in men

Androgens had been regarded as predominant hormones influencing the male skeleton and this concept has been dramatically changed by recent researches. In this section, we reviewed the role of estrogen and estrogen receptors in skeletal maturity, growth and bone loss in men.

1) Estrogen receptors

Estrogen is related to a number of actions involving differentiation, proliferation, and function in many target tissues. Estrogen mediates those mechanisms through genomic pathways interacting with estrogen receptor as well as non-genomic pathways with plasma membrane receptors (Compston, 2001; Wehling et al., 1997). Estrogen receptors (ER) are a family of steroid hormone receptors to bind to estrogen and it is regulated by various transcription factors. The estrogen receptor has several functional domains; 1) DNA binding domain, 2) ligand-biding domain (estrogen response element, ERE), 3) activation factor-1, and 4) activation factor-2 (Webster et al., 1988; Berry et al., 1990). There are two subtypes of estrogen receptor called estrogen receptor α (map position, 6q25) and estrogen receptor β (map position, 14q22-24), and ER α and β share approximately 47% structural domain to each other (Kuiper et al., 1997; Enmark and Gustafsson 1999). Estrogen receptor α is expressed on osteoblasts, osteoclast, growth plate chondrocytes and bone marrow stromal cells, and is mainly regulated by 17-β estradiol (Kusec et al, 1998; Grandien et al., 1995; Oreffo et al., 1999). Gender difference in number of estrogen receptor α in osteoblasts was reported in a vitro study

(Colvard et al., 1989). Less amount of ERα was detected in osteoblasts from male than from female donor in vitro studies. However, the numbers of estrogen receptor α were greater than number of androgen receptors found in osteoblasts (Colvard et al., 1989).

2) Effects of estrogen on bone cells – osteoblasts, and osteoclasts

During puberty and up to the third decade, estrogens are related to an anabolic effect on the osteoblast and an apoptotic effect on the osteoclast. Specifically, estrogens stimulate bone mineral acquisition in axial and appendicular bone. In the adult, estrogens are important in maintaining the constancy of bone mass through its effects on remodeling and bone turnover (Doran et al.,1999).

There is an evidence of decreased estrogen receptor α activity on male osteoporosis. Braidman and colleagues (2000) compared the localization of ERα and AR protein expression in bone biopsies from a small number of patients with male idiopathic osteoporosis with age-matched control men. However, the deficient expression levels of estrogen receptor α in osteoblasts and osteocytes of patients were reported. (Braidman et al., 2000) even though the estrogen receptor mRNA was still expressed (Braidman et al, 1998). Previously, they were unable to link between declined levels of circulating estradiol and idiopathic male osteoporosis in a case-control study (Selby et al., 1996). Only 1±5% of osteocytes, and 2±1% of osteoblasts were expressed the estrogen receptor α in men with idiopathic osteoporosis, whereas 14% of osteocytes, and 23% of osteoblasts expressed the estrogen receptor α in normal men. Most patients and controls showed normal estradiol, testosterone, and sex hormone binding globulin levels. Therefore, the authors concluded that reduced estrogen receptor α protein expression might explain male idiopathic osteoporosis.

3) Effects of estrogen on cytokines and growth factors

Estrogen modulates the expression and activity of various cytokines and growth factors produced in bone (Pacifici 1996; Manolagas and Jilka 1995). Estrogen

suppresses the synthesis of interleukin-1 (IL-1β) (Kitazawa et al., 1994), IL-6 (Kassem et al., 1996), tumor necrosis factor-α (TNF-α) (Kimble et al. 1997; Kimble et al., 1996), and prostaglandin E2 (PGE2) (Kawaguchi et al., 1995). Additionally, estrogens suppress the production of IL-6, and type I collagen by osteoblasts (Bodine et al., 1998). Reduced estrogen levels resulted in increased levels of IL-1, TNF-α, IL-6, GM-CSF, which were related to increased bone turnover and bone loss. Elevated levels of IL-1 and tumor necrosis factor were reported to the rapid bone loss after menopause. According to Pacifici et al. (1989; 1993), secretion of IL-1 and IL-1 beta from cultured monocytes was higher in cells from untreated postmenopausal women than in cells from pre-menopausal or estrogen treated postmenopausal women. Jilka et al. (1992) demonstrated in ovariectomized mice that increased bone loss can be prevented by treatment with either estrogen or antibodies that neutralize interleukin(IL)-6. IL-6 production by bone marrow-derived stromal cells and osteoblast-like cells was inhibited by estradiol treatment although the magnitude of this inhibition was variable (Jilka et al.,1995; 1998). These cytokines appeared to modulate the rate of osteoclast differentiation, and estrogen regulates bone resorption by directly regulating osteocalst activity and indirectly influencing osteoclast formation.

Estrogen stimulates the expression of IL-1 receptor antagonist (IL-1ra) (Pacifici et al., 1989), transforming growth factor-β (TGFβ) (Oursler et al., 1991), insulin-like growth factor-1 (IGF-1), insulin-like growth factor-binding protein (IGFBP) (Kassem et al., 1996), and bone morphogenetic protein-6 (BMP-6) (Rickard et al., 1997). IL-1 receptor antagonist (IL-1ra), and soluble TNF receptors negatively modulated bone loss. Serum IL-1 receptor antagonist (IL-1ra) levels were inversely related to bone loss and serum osteocalcin in women. Kimble et al. (1994) showed that IL-1ra treatment of ovariectomized rats blocked bone loss.

Estrogen also modulates directly or partly the induction of apoptosis of osteoclasts and osteocytes (Tomkinson et al., 1997; Kameda et al., 1997) by the estrogen receptor α mediated pathway. It has been reported that the responsiveness to estrogen exists through differential expression levels of estrogen receptor (Pederson,

1997). However, there are inconsistent evidences that estrogen may relate to influence bone matrix proteins, alkaline phosphatase, osteocalcin, and osteonectin (Bodine et al., 1998).

4) Estrogen and bone – Animal studies

Vanderschueren and his coworkers (1997, 1998) demonstrated a significant effect of aromatase inhibitor treatment or orchidectomy on skeletal modeling in older male rats. Treatment with an aromatase inhibitor significantly increased bone resorption, and reduced the bone mineral content, and bone density of the femur and lumbar vertebrae in growing male rats (Vanderschueren et al., 1997). Estrogen prevented the bone loss resulting from aromatase inhibition. In aged orchidectomized rats, estrogen treatment also prevented trabecular bone loss due to a decrease in both bone resorption and bone formation of the trabecular (Vanderschueren et al., 1992). These evidences demonstrated that the conversion (aromatization) of androgens to estrogens appeared to play an important role in bone metabolism. (Vandershueren et al., 1998).

5) Effects of estrogen on male skeleton – peak bone mass

Bone mass increases during childhood and adolescence, and gains in bone mass are closely related to pubertal stage (Krabbe et al., 1979). However, there is increasing evidence suggesting that estrogens may play an important role in the pubertal bone gain in male (Lee and Witchel, 1997). In males, approximately 20% of estrogen is derived from direct testicular secretion from 80% of estrogen derived from extragonadal aromatization of testosterone and androstenedione.

Estrogen is the critical sex hormone involved in the pubertal growth spurt, skeletal maturation, accrual of peak bone mass, and the maintenance of bone mass in the adult. Estrogen stimulates chondrogenesis in the epiphyseal growth plate increasing pubertal linear growth. At puberty, estrogen promotes skeletal maturation and the

gradual, progressive closure of the epiphyseal growth plate through estrogen-induced vascular and osteoblastic invasion and the termination of chondrogenesis (Doran et al.,1999). Many studies have shown that estrogen involved with the increase of normal bone density as the result of an increase in trabecular bone mass, and in periosteal and endosteal bone mineral apposition in males (Seeman, 1999). Estrogens are also related to the closure of the epiphysis in males (Smith et al., 1994; Bilezikian et al., 1998). Men with defective mutations on the estrogen receptor α and aromatase raised the possibility that estrogen plays an important role on the male skeleton. A 28 year-old man with estrogen receptor mutation showed estrogen resistance and un-fused epiphyseal plates, and severe osteopenia despite normal serum testosterone levels, and high circulating gonadotrophin level (Smith, 1994). In the studies of young men with aromatase deficiency (null homozygous mutation), Bilezikian et al. (1998) and Carani et al. (1997) reported of osteopenic bone mass with unfused epiphyses. All three patients showed similar characteristics of tall stature, marked osteopenia, and increased rates of bone turnover. Treatment with testosterone failed to improve skeletal maturation or bone turnover in the aromatase deficient individual (Carani et al., 1997) while estrogen treatment produced marked increases in bone density (10-20%), and decreases in bone turnover rates in estrogen receptor defective men and aromatase deficient individuals (Bilezikian et al., 1998; Carani et al., 1997). Estrogen treatment also completed the epiphyseal closure and ceased the linear growth. These studies support the hypothesis that estrogen is an essential hormone for normal linear growth and peak bone mass in male. In study of transsexual men with cyproterone acetate, Lip et al. (1989) demonstrated that estrogen also prevented the loss of apparent bone density.

6) Epidemiologic studies supporting a unitary model for involutional male osteoporosis

Men do not seem to undergo periods of rapid bone loss during their lifetime (Riggs et al., 2002). However, continuous bone loss (Hannan et al.,2000) with increment in plasma level of PTH (Sherman et al.,1990; Ledger et al., 1995), and

increased bone resorption might cause osteoporosis in men, similar to that observed in older women.

Serum total testosterone levels in male decrease with aging but in small quantity until men reaches in theirs 80's (Khosla et al., 1998). Serum bioavailable testosterone and estradiol decrease in elderly men, and values are 30 to 50% of the values in young adult men (Khosla et al., 1998). For instance, Carlson et al (2000) demonstrated the prevalence of estrogen deficiency in male osteoporosis (n = 63;age 20-76 years) (2000). Only 5 % (n=2) out of confirmed male osteoporosis (n=42) were classified as male hypogonadism whereas 14% of patients had serum estradiol values below the normal range ($p < 0.001$). Even though men do not experience rapid hormonal changes like menopause, they have gradual, age-related decreases in both bioavailable testosterone and estradiol levels, mainly due to age-related increase in serum SHBG levels (Legrand et al., 2001).

The unitary model for osteoporosis by Riggs et al. (1998) summarized that estrogen deficiency is a main cause of bone loss for both postmenopausal women and aging men.

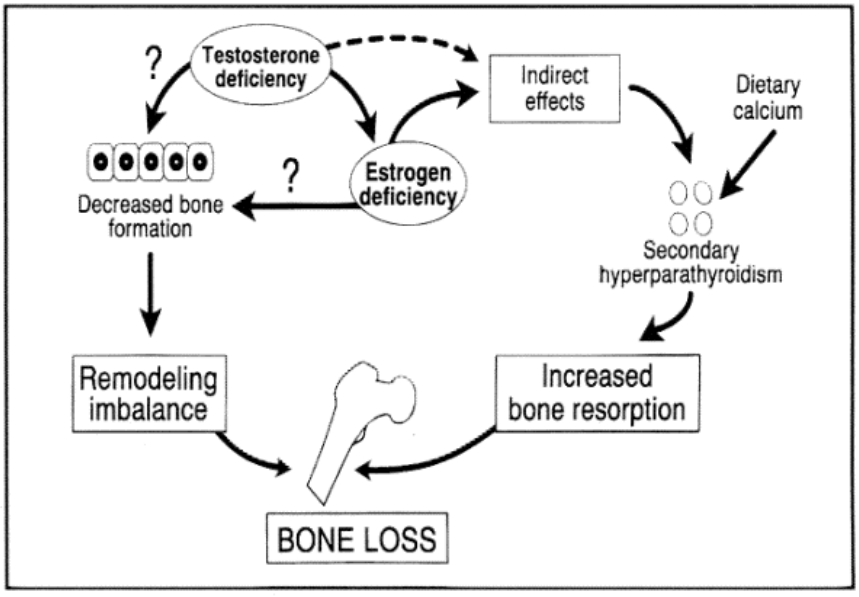

Figure1. Unitary model for bone loss in aging men (Riggs et al. 1998. J Bone Miner Res 13:763-773)

A number of cross-sectional studies have reported a relationship between BMD in adult and elderly men and sex steroid levels (Slemeda et al., 1997; Greendale et al., 1997; Khosla et al., 1998; Ongphiphadhanakul et al., 1998; Szulc et al., 2001). Low serum estradiol is associated with low BMD (Greendale et al., 1997), vertebral fractures (Barrett-Connor et al., 2000), and high bone turnover (Khosla et al., 1998; Szulc et al., 2000) in elderly men. These studies suggest that male osteoporosis is mediated by estrogen deficiency as much as, or perhaps more than, androgen deficiency. Slemenda et al. (1997) initially reported that in men over age 65 years, BMD was significant associated with serum estradiol levels at all skeletal sites (correlation coefficients of 0.21–0.35), with testosterone actually being negatively associated with BMD. 10~30% of the variance in BMD were explained by estrogen (Slemenda et al., 1997). Among 534 men aged 50 ~89 years enrolled in the Rancho-Bernado study, Greendale et al. (1997) found that serum bioavailable estradiol levels was strongly associated with BMD at radius, lumbar spine, and total hip ($p<0.001$). Khosla and colleagues also found that serum bioavailable estrogen levels predicted BMD better than testosterone levels in both young (less than 50 years) and older (over 50 years) men (1998). These results confirmed by others (Center et al., 1999; Amin et al., 2000).

A French study on 596 men aged 51 to 85 years, showed bone mass of the hip increased with increasing levels of total and free estradiol in cross-sectional analysis (Szulc et al., 2001). Biochemical markers of bone metabolism, which reflect the rate of bone turnover, were also associated with endogenous estradiol levels. Markers of both bone resorption and bone formation were 11% to 36% higher among men in the lowest quartile of estradiol compared with those in the highest quartile. Testosterone levels, on the other hand, were not correlated with either bone mass or markers of bone turnover. This study further supports the role of estrogen metabolism in the skeletal health of men and suggests that alternative approaches to hypogonadism, such as low doses of estrogen-like compounds, might be effective.

Khosla and colleagues (2000) studied the association of bone density and serum sex steroid levels in age-stratified groups. In this study, both the rate of increase in mid-radius and ulna BMD in the young men (age < 40 years) as well as the rate of decrease in BMD at these sites in the elderly men (age > 60 years) were more strongly associated with serum bioavailable estradiol levels than with serum testosterone levels.

A summary table of selected literatures related to sex steroid hormone and bone metabolisms is shown Table 1.

Table 1. Epidemiologic studies of sex steroids and bone density

Investigators	Designs	Populations	Age (years)	Skeletal site (method)	Hormones	Results	Comments
Szulc (2001)	Cohort	Caucasian European (n=596)	51-85 (mean 65)	LS (DXA) Hip (DXA) TB (DXA) Forearm (SXA)	Fasting E_2, $BioE_2$, T, FT, Andros, SHBG	E_2, $BioE_2$ correlated with all sites; Hip, forearm BMD lower with lowest vs upper quartiles of $BioE_2$; T, FT, SHBG not related	Adjusted for age, weight
Barett-Connor (2000)	Cohort (Nested CC)	Caucasian American (n=352)	50-87 (median 66)	Vertebral fractures (Lateral radiograph)	Fasting AM E_2, $BioE_2$, T BioT, DHT, DHEA, DHEAS	E_2, Bio E_2: Negative association with Vertebral fractures	Adjusted for age, BMI, smoking, alcohol, thiazide and thyroid use
Carlsen (2000)	Cross sectional	Caucasian European, (n= 42 w/w primary OP, n=21 secondary OP)	20-76 (mean 56)	LS (DXA) Hip (DXA)	N/A E2, FE2, BioE2, SHBG, T, FT, DHT	33-38% of primary OP patients low or undetectable estradiol levels, 3% of male hypogonadism,	Not adjusted for age, weight for prevalence
Center (1999)	Cohort	Caucasian (n=437)	Mean 69 $\pm$ 6	LS (DXA) FN (DXA)	Nonfasting FT, E2, SHBG	E2, FT positively related on LS, FN (E2 only); SHBG negatively on LS, FN.	Adjusted for age, weight

Table 1 (Continued)

Investigators	Designs	Populations	Age (years)	Skeletal site (method)	Hormones	Results	Comments
Rapado (1999)	Cross sectional	Caucasian European (n=140)	55-90 (mean 68.8)	LS (DXA) Hip (DXA)	Fasting AM T, FT, BioT, SHBG, DHT	No association for all sites	None
Gillberg (1999)	Case Control	Caucasian European (n =12 with MIO vs. n=12 healthy control)	Cases 27 – 55 (mean 41.5) ; control 27-62 (mean 43)	LS (DXA) Hip (DXA) Calcaneous (QUS)	Fasting AM E_2, SHBG, T, DHEAS, E_2/SHBG, FAI	E2, E2/SHBG Ratio, FAI lower (16-43%), but SHBG higher (59%) in MIO. E2/SHBG associated with FN in cases	Normal ranges for all parameters (even in MIO) ; Adjusted for age and BMI
Ongphiphadhanakul (1998)	Cross sectional	Asian (n=81)	20-79	LS (DXA) Hip (DXA)	Fasting AM FT, E2	FT associated with FN.	Adjusted for age, height, weight
Khosla (1998)	Cohort	Caucasian American (n=346)	23-90	TB (DXA) LS (DXA) Hip (DXA) Forearm	Fasting AM E2, BioE2, T, BioT, FT, SHBG, DHEAS	All hormones associated with on sites in univariate BioE2 positively associated with FN (20% variation)	Age stratified sample (< 50 vs ≥ 50 yrs)
Greendale (1997)	Cohort	Caucasian American (n=534)	50-89 (mean 68.6)	Forearm (SPA) LS (DXA) Hip (DXA)	N/A E2, BioE2, T, BioT, DHEA, DHEAS, DHT	BioT, BioE2 ($p<0.001$) related to all sites	Adjusted for age, BMI, alcohol, exercise, smoking, thiazides & thyroid hormone use

Table 1 (Continued)

Investigators	Designs	Populations	Age (years)	Skeletal site (method)	Hormones	Results	Comments
Slemenda (1997)	Cohort	Caucasian American (n=93)	Mean 67.3±4.3	LS (DXA) Forearm (SPA) Hip (DXA)	Not standardized E1, E2, T Andros, FE2, FT, SHBG, DHEA, DHEAS	E2 positively associated with all skeletal sites, T negatively correlated with LS & Trochanter; 10-28% of BMD variance	Adjusted for age, weight
Wishart (1995)	Cross sectional	Caucasian (n=147)	20-83	LS(DXA) Hip(DXA) forearm	Fasting AM FAI	No association at all sites	No adjustment, decreased fall in FAI with aging
Drinka (1993)	Cross sectional & longitudinal	Caucasian American (n= 112)	65-91 (mean 71.7)	LS (DPA, DXA), Hip (DPA, DXA), Forearm (DPA)	Fasting AM FT	No association of FT at all sites	Adjusted for age
Murphy (1993)	Cross sectional	Caucasian (n=134)	65-76 (mean 69.5)	LS (DXA) Hip (DXA)	Not standardized FT, T, DHEAS, SHBG, FAI	FAI associated with Hip (r=0.20-0.22) (FT associated with FN)	Adjusted for age, BMI

Nested CC, nested case control; OP, osteoporosis; MIO, male idiopathic osteoporosis; LS, lumbar spine; FN, femoral neck; Hip, total hip; WB, whole body ; N/A, not available

E_2, estradiol; $BioE_2$, bioavailable estradiol; FE2, free estradiol; E1, estrone; T, total testosterone; BioT, bioavailable testosterone; FT, free testosterone; SHBG, sex hormone binding globulin; DHEA, dyhydroepiandroserone; DHEAS, dehydroepiandrosteone sulphate; DHT, dihydrotestosterone; E2/SHBG, estradiol/SHBG ratio; FAI, free androgen index (Total testosterone/SHBG ratio); Andros, androstenedione

b. Androgen and Bone in men

1) Androgen receptors

A direct effect of androgen on bone metabolism through androgen receptors has been suggested. Androgen receptors (map position, Xq11-13) (Brown et al., 1989) are expressed in active osteoblasts at the sites of bone formation, osteocytes, bone marrow-derived stromal cells, and epiphyseal chondrocytes (Abu et al., 1997). They are detected in marrow mononuclear cells and endothelial cells in blood vessels (Wiren and Orwoll, 1999). The number of androgen receptors in human osteoblasts is similar between men and women (Orwoll, 2001). However, the expression levels of androgen receptors in osteoblasts seem to be different according to the skeletal site of origin and androgen responsiveness (Kasperk et al., 1997). For example, androgen receptor expression is up-regulated by androgens in osteoblasts, but down-regulated in prostate cell (Wiren and Orwoll, 1999). The studies of androgen receptor support a role of androgens in bone metabolism. An animal study provides the functional importance of androgen receptor in bone metabolism. Vanderschueren (1994) demonstrated that the androgen resistant male rat had small bone size and mass than in control animals. In human studies, the CAG repeat length polymorphism in the androgen receptor has also supported that the importance of androgen receptor in male skeleton. Subjects with longer repeat lengths were related to higher rates of bone loss and higher fracture prevalence (Zmuda et al., 2000)

2) Effects of androgen on bone cells – osteoblasts and osteoclasts

Androgenic hormones are produced by the testis and adrenal glands in men. Leydig cells produce testosterone in men, and approximately 7 mg of testosterone is produced daily (Luke et al. 1994). Testosterone, the major gonadal androgen, act on target cells, and it can be metabolized into 5α dihydrotestosterone (DHT) and

androstenedione by the 5α-reductase (Schweikert et al., 1980). Aromatase in bone converts testosterone to 17β-estradiol (Veldhuis 1991; Nawata et al., 1995).

Testosterone and dihydrotestosterone (DHT) bind to the androgen receptor with different affinity (Benz et al., 1991). Dihydrotestosterone, non-aromatizable androgens, is more potent because of higher affinity to androgen receptor (Luke et al. 1994). 50% ~ 60% of Testosterone is transported by sex hormone binding globulin (SHBG) in plasma, where 40~50 % is transported by albumin. Only 1 ~ 2 percent of free testosterone is available (Dunn et al. 1981). 5α-reductase is localized in prostate, skin, and other reproductive tissues while aromatase enzyme complex is abundant in adipose tissue, and liver (Saito and Yanaihara 1998). Androstenedione and dehydroepiandrosterone (DHEA) are converted to estrone. Dehydroepiandrosterone (DHEA) is metabolized to DHEA-sulphate in perpheral tissues by the enzyme, steroid sulfotransferase (Fujikawa et al., 1997). DHEA can also be converted to androstenedione by the enzyme, 3β-hydroxysteroid dehydrogenase (HSD), and further metabolized to testosterone by 17β-hydroxysteroid dehydrogenase (Bruch et al., 1992). Thus, the bone microenvironment has the ability to form biologically potent androgens and estrogens. Androgens stimulate the proliferation of bone cells in vitro. It has been speculated the beneficial effect of androgens either the androgen itself or to the estrogen converted from androgen. Both testosterone and non-aromatizable androgens (e.g. DHT) affect major functions including proliferation, differentiation, and production of growth factors in osteoblasts (Hofbauer and Khosla, 1999; Kasperk et al., 1997).

Androgens have been shown to affect bone metabolism by several mechanisms. These pathways include inhibition of bone resorption through a reduction in interleukin-6 (IL-6) production by osteoblasts, inhibition of the production of prostaglandin (PGE), and inhibition of the effect of PTH on osteoblasts. Androgens reduce osteoblastic IL-6 production and hence rates of osteoclastic bone resorption. It is probably important that androgens appear to increase osteoblastic IGF-1 production and, as a result, osteoblast proliferation. In addition, androgens may improve calcium balance by increasing intestinal calcium absorption, decreaseing renal excretion, and increasing circulating

levels of free 1, 25-dihydroxyvitamin D3. A recent in vitro study reported that androgens (5α-DHT) suppressed osteoclast formation mediated by receptor activator of NF-κB ligand (RANKL) and selective regulation of c-JUN (Huber et al., 2001). Other important roles of androgens are: 1) to reduce PTH-induced cyclic AMP production, 2) to increase TGF-β levels, 3) to increase production of matrix proteins, 4) to increase rates of cellular proliferation and differentiation, and 5) to modulate osteoblast apoptosis.

3) Androgenic effects on male skeleton

Androgens stimulate the proliferation of bone cells in vitro. It has been speculated the beneficial effect of androgens either the androgen itself or to the estrogen converted from androgen. Androgens are important for linear and periosteal apposition during the normal pubertal growth. Longitudinal bone growth and bone mass accretion are accelerated and correlated with increase in testosterone during the pubertal period and (Finkelstein et al., 1987; Orwoll, 1999). In younger men with androgen resistance, hypogonadism has been shown to be important risk factor in attaining peak bone mass, growth rate and maintenance of BMD after puberty. Remarkably reduced bone density was reported in these patients because peak bone mass was not achieved (Soule et al., 1996; Bertelloni et al, 1998). Short-term testosterone treatment in these patients showed the increase in epiphyseal growh plate width, long bone growth rates, and resulted in rapid increase in bone mass (Finkelstein et al., 1989). Testosterone has an anabolic effect on bone directly or can be aromatized into estrogen in skeletal tissue. This suggests that testosterone by itself or through conversion to estrogen may be important factor for maintaining bone mass, and regulating bone turnover. Adipocytes and stromal cells in fat tissue also express P450 aromatase gene, and are capable of converting adrenal estosterone and androstenedione to 17 beta estradiol and estrone, respectively.

c. Treatment of men with estrogen and testosterone

Though the result is not consistent, findings from eugonadal men with androgen treatment suggest that androgens preserve bone mass by reducing bone turnover (Anderson et al., 1997). Falahati and colleagues (2000) studied 59 healthy elderly men (mean age, 68 years) at baseline after pharmacologically suppressing endogenous testosterone and estrogen production with a GnRH agonist (Leuprolide acetate) and inhibiting the conversion of androgens to estrogen with an aromatase inhibitor. Physiologic source of estradiol and testosterone were only established with patch implantation and men were randomly assigned to continue the patches, or to discontinue the testosterone patch, the estrogen patch, or both in a factorial design. Bone formation and resorption markers were examined 3 weeks after the removal of patches. Men who discontinued the estrogen patch but continued the testosterone patch had significant increases in bone resorption, whereas those who discontinued the testosterone patch but continued the estrogen patch had no change in bone resorption markers. On the other hand, circulating levels of osteocalcin, an osteoblast-specific protein that reflects the number and/or activity of this cell type, were not affected when either the E_2 or the testosterone patches were removed. However, circulating osteocalcin levels decreased dramatically when both patches were removed. This result provides that estrogen is more likely to be more potent steroid than androgen as well as both estrogen and androgen are needed for skeletal homeostasis in men.

Androgen replacement therapy in osteoporotic males with hypogonadism is associated with an increased bone mass (Diamond et al., 1991, Finkelstein et al., 1989). Aromatase deficient man with estrogen replacement therapy has also shown to increase bone density (Bilezikian et al., 1998). For instance, Tenover (1992) found that elderly men with testosterone supplementation during 3-month period were associated with a significant decline in urinary hydroxyproline excretion without any change in osteocalcin levels. Snyder et al. (1999) also reported an increase of BMD in older men with borderline low testosterone levels using transdermal testosterone or placebo. Increase of bone mass was the greatest among who had the greatest increases in

testosterone levels. This suggests that testosterone replacement may be useful in older men without complete hypogonadism.