Osteoporosis in Men

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Abstract

Osteoporosis is a progressive bone disease that is characterized by a decrease in bone mass and density. Osteoporosis can occur in both genders. Women are more likely to be diagnosed with osteoporosis. Since men have larger bones than women, it is difficult to diagnose osteoporosis. However, presently, the occurrence rate of osteoporosis in men is increasing. It is very important to be aware of an increase of the true frequency of osteoporosis in men which is essential for prevention and long-term health. The purpose of this thesis is to examine pathogenesis of osteoporosis, hormone-related factors, lifestyle, diet, and exercise habits of men related to osteoporosis and how to prevent or treat it.

Osteoporosis in Men

Osteoporosis is a potentially debilitating disease that presents itself in excessive bone loss, usually during aging and results in fragile bones. Osteoporosis can be broken down into two words, the term "osteo" means bone and the term "porosis" which means porous or having pores. Osteoporosis refers to a disease causing the bone structure to become more open and porous resulting in fractures (Qalawa, Mohamed, & Aly, 2013). According to the National Institutes of Health (2012) osteoporosis is defined as "a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture" (para. 4). As known, osteoporosis is regarded as a type of a disease in women. However, this disease is becoming more of a concern as its prevalence continues to rise. Presently, one in four men will have a symptom of osteoporosis presented by fracture in their lifetime (Cleveland Clinic, 2012). Osteoporosis is increasingly recognized in men. Low bone mass, risk factors for falling, and factors causing fractures in women are also likely to cause fractures in men. Bone mass is largely genetically determined, but environmental factors also contribute. Since osteoporosis can cause fragile bones resulting in fracture and increases mortality rate in men, it is imperative that prevention and treatments for osteoporosis in men be recognized in order for it to be managed well (National Institutes of Health, 2012).

According to the research surrounding this topic, many patients do not understand the prevalence of osteoporosis in men because most people think osteoporosis occurs more in women (National Institutes of Health, 2014). As a result, this thesis will propose that this problem can be remedied in three ways. First, the recognition of risk factors of osteoporosis in men could significantly increase the knowledge to prevent or treat osteoporosis. Second, by identifying risk factors for

osteoporosis, prevention care needs to be initiated. With preventative care, there are three different preventing measures which can be applied to patients with osteoporosis: Dietary alteration, exercises, and the avoidance of harmful lifestyles. Third, treatment as pharmacologic and non-pharmacologic management would allow for reduced the risk factors of a fracture, better patient care, and improved patient outcomes (Rosen, 2014).

Epidemiology

In the past, osteoporosis was thought to affect only women; however, in the last decade many researchers found that osteoporosis is common in men, especially in elderly men. According to Cauley (2006), osteoporosis affects as many as two million men in the United States and eight to thirteen million have low bone mass. As in women, the risk of fracture in men is elevated with age. However, the peak occurrence of osteoporotic fractures occurs 10 years later in men than women because men have greater bone mass (Rao, Budhwar, & Ashfaque, 2010). One in four men over age 50 has an osteoporosis-related fracture in his lifetime (National Osteoporosis Foundation, 2011). The most serious osteoporosis-related fracture is hip fracture. Hip fracture is the most serious complication of osteoporosis and results in higher mortality in men than women. Men are twice as likely as women to die after a hip fracture occurs (Rao, Budhwar, & Ashfaque, 2010). The prevalence of osteoporosis is different depending on ethnic groups. In case of white men, the prevalence of osteoporosis is seven percent; in black men, it is five percent; it is three percent in Hispanic American men. Data on the prevalence of osteoporosis in Asian-American men and other ethnic groups are lacking (Michael, 2003). Osteoporosis is now responsible for more than two million fractures each year, and this number continues to grow (Cleveland Clinic, 2012).

Pathophysiology of Osteoporosis

To understand the pathophysiology of osteoporosis, it is necessary to review normal bone physiology first. Bone is a living tissue and its strength is made by the normal functioning of three bone cells: osteoclasts, osteoblasts, and osteocytes. According to Becker (2008), osteoclasts and osteoblasts are involved in the bone multicellular unit (BMU), where bone remodeling and reconstruction initiate. At the BMU, a part of old or damaged bone tissue is removed by the osteoclast in a process known as bone resorption. Then osteoblasts are recruited to the damaged site to fill it in with new, young, and healthy bone tissue (Becker, 2008). This mechanism continuously occurs throughout the skeleton and is critical for normal bone strength. Osteoblasts and osteoclasts functions are coordinated. Osteocytes, the most numerous and longest-lived bone cells act as the sensors for the skeleton and are derived from osteoblasts. They form an intricate communication with each other and the outer bone surface, therefore, are involved in bone remodeling. Since the time needed for osteoblast to form bone is long, while osteoclast to resorb bone is short, any process in men that increase the rate of bone remodeling will result in a net loss of bone. In addition, as the number of unfilled excavation pits increases, they elevate stress in bones, which are vulnerable sites that can perforate and cause micro-fractures (Becker, 2008). Excessive bone resorption can also result in complete dropout of trabecular plates, no template upon which bone formation can occur. In contrast to the pattern of complete loss of trabecular structures among postmenopausal women, aging men tend to have thinning of trabeculae rather than total dropout. With aging in men, for unknown reasons, the osteoblastic response to bone resorption is inadequate and resorption surpasses formation. This osteoblastic failure is the major factor in the pathogenesis of osteoporosis in men (Becker, 2008).

Risk Factors

Two types of osteoporosis occur in men: primary and secondary. Primary osteoporosis is a caused by either age-related bone loss, sometimes called *senile osteoporosis*, or the cause is unknown, called idiopathic osteoporosis. According to the National Institute of Health (2012), the term, idiopathic osteoporosis is used only for men who are younger than 70 years old; in older men, age-related bone loss is most likely to be assumed to be the cause. Up to 40 percent of cases of osteoporosis in men are primary or idiopathic (Rao, Budhwar, & Ashfaque, 2010). As men are aging, their bone resorption slowly begins to exceed new bone formation. Excessive bone resorption can do not only dropout of trabecular plates, no template upon which bone formation can occur, but also thinning of trabeculae. It is the cause of primary osteoporosis in men. In the case of idiopathic osteoporosis, causes are various. Currently, causes of idiopathic osteoporosis are unclear and still are researched (National Institute of Health, 2014).

Secondary osteoporosis occurs in at least half of men. In the case of secondary osteoporosis, the loss of bone mass is caused by certain lifestyle behaviors, disease or medications. According to Cleveland Clinic (2015), the most common causes of secondary osteoporosis in men are hypogonadism, low levels of testosterone, excess of glucocorticoid medication, smoking, alcohol abuse, immobilization, diabetes, inadequate amount of intake of vitamin D, and primary hyperparathyroidism. Male hypogonadism refers to abnormally low production of sex hormones. It is well known that loss of estrogen causes osteoporosis in women, but in men decreased levels of sex hormones may cause osteoporosis (Cleveland Clinic, 2015).

Male Hypogonadism

A main cause of osteoporosis in men is male hypogonadism and is a condition in which the body does not produce enough testosterone. An important cause of osteoporosis in men is reduced serum testosterone. The incidence of osteoporosis in men is directly correlated to the decrease in circulating testosterone (Dupree & Dobs, 2004). In aging men, the occurrence of partial androgen deficiency has been directly related to male age-related osteoporosis; thus, a mild to severe decline of androgens level with aging can directly or indirectly cause bone loss in men (Rochira et al., 2006). Gonadal androgens including testosterone act directly on osteoblasts, influencing growth, proliferation, and differentiation of osteoblastic cells in vitro by binding to an androgen receptor (Chen, Kaji, Sugimoto, & Chihara, 2001). Androgens also inhibit osteoclastic activity of recruitment and signaling, which results in decreased bone density in the body. However, the mechanism how androgens inhibits osteoclastic activity is unknown. As for bone resorption related with androgens, the recent study revealed that androgens regulated bone-resorbing activity of isolated chicken osteoclasts (Pederson et al., 1999). According to Dupree and Dobs (2004), in vitro studies also showed that androgen inhibit the activity of isolated osteoclasts. In addition, androgens have a role in inhibiting the production of interleukin (IL)-6, which is a cytokine that increases resorption in bone marrow stromal and mature osteoblastic cells. Science has not shown how much of the bone-building benefit is a direct testosterone effect, but it is clear that testosterone turns into estrogen through aromatase, an enzyme that coverts testosterone to estrogens (Taylor, 2015). If men do not have enough testosterone level in the body, there can be only small amount of estrogen, which causes osteoporosis and is a risk factor of low bone mass. Therefore, male hypogonadism, androgen deficiency, may result in

osteoporosis by enhancing osteoclastic activity, decreasing growth, proliferation, and differentiation of osteoblastic cells, and reducing the conversion of testosterone to estrogen in men (Clarke & Khosla, 2008).

Estrogen-related Osteoporosis

Estrogen-related osteoporosis is known as women's disease. However, in men estrogen-deficiency is also one of causes of osteoporosis and low bone mass. According to Khosla (2010), he refers that estrogen is also necessary for bone strength in men, and this has been clearly demonstrated in men who lack aromatase, the enzyme which converts testosterone into estrogen. The characteristic of these men is failure to close their epiphyses and has low bone density. New research at Washington University School of Medicine in St. Louis has found that "low amounts of active estrogen metabolites can increase men's osteoporosis risk. It also claims men actually have somewhat more estrogen on average than do postmenopausal women" which states estrogen hormone can affect the bone density in not only women, but men (Ericson, 2007, para. 2-3). Estrogen plays an important role in the growth and maturation of bone as well as the regulation of bone health in adult bone. Functions of estrogen in the body vary, but the major physiological effect of estrogen is to inhibit bone resorption. Basically, estrogen reduces bone resorption and increases bone formation as elevating osteoblast production. Estrogen induces osteoclast apoptosis and represses differentiation of osteoclast in the body (Washington, 2008).

The activities of osteoclasts and osteoblasts occur in defined anatomical spaces called bone multicellular units (BMUs). A remodeling cycle initiate from the activation of a new BMU (Weitzmann & Pacifici, 2006). As explained earlier, osteoclasts will cause bone resorption to remodel bones, and osteoblasts will be recruited that fills in the resorption cavity with new bone. Estrogen deficiency causes

increased amount of BMUs through increased activation frequency, which is the frequency of activated new remodeling units in each unit of time. Increased activation frequency expands the remodeling space; increases cortical porousness, and extends the area of resorption. This event results from increased osteoclast formation, which is a complex event including a variety of hematopoietic and immune cells, as well as increased osteoclast recruitment to bone surfaces to be remodeled. Estrogen deficiency also prolongs remodeling cycle in the resorption phase, which intensifies destruction of bones through increased osteoclast lifespan secondary to reduced apoptosis (Weitzmann & Pacifici, 2006).

When old bone is broken down faster than new bone is made, and then net bone loss occurs. The net bone loss in estrogen deficiency is limited in part by a compensatory increase of bone formation. According to Pacifici (2007), "It is a consequence of stimulated osteoblastogenesis fueled by an expansion of the pool of early mesenchymal progenitors and by increased commitment of such pluripotent precursors toward the osteoblastic lineage" (p. 102). Despite produced osteoblastogenesis, the increased amount of bone formation is insufficient to compensate for elevated bone resorption resulting from osteoblast apoptosis, induced by estrogen deficiency (Weitzmann & Pacifici, 2006). An additional event triggered by estrogen withdrawal is to elevate production of inflammatory cytokines such as interleukin 7 (IL-7) and Tumor Necrosis Factor (TNF). These inflammatory cytokines limits the activity of mature osteoblasts. So inflammatory cytokines reduces the effect of osteoblasts, but does not affect the activity of osteoclasts in the body, which augments bone resorption (Bussard, Venzon, & Mastro, 2010). The initial phase of rapid bone loss secondary to estrogen deficiency causes increased bone resorption and trabecular thinning and perforation. The initial phase is followed by a continuous

period of slower bone loss where trabecular thinning occurs. Eventually, this phase shows impaired osteoblastic activity resulting from increased osteoblast apoptosis and reduced osteoclast apoptosis (Weitzmann & Pacifici, 2006).

When estrogen circulates in the body, it goes through the liver where many enzymes convert hormones to other forms. In case of estrogen, the liver converts it to estrogen metabolites, which are active or inactive. Each has different processes in producing estrogen and estrogen metabolites in the liver, so the levels of estrogen metabolites will vary among people (Ericson, 2007). However, the Washington University researchers found that the amounts of active estrogen metabolites are a strong predictor of bone mineral density in men they studied. Testing hormone levels and bone density were measured by dual X-ray absorptiometry (DEXA) scans in 61 men age 50 or older. The researchers found that men with higher levels of active estrogen metabolites seemed to have higher bone density. On the other hand, men with lower levels of estrogen metabolites tended to have lower bone density (Ericson, 2007). Most people do not think about estrogen in men, but men actually have considerable amount of estrogen. In summary above information, estrogen could significantly affect health of the bone in men.

Another risk factor of secondary osteoporosis is excessive intake of glucocorticoid in men. Glucocorticoid is a steroid hormone released by the adrenal cortex to decrease inflammatory activation (Canalis, Mazziotti, Giusina, & Bilezikian, 2007). Glucocorticoid induces osteoporosis in direct and indirect ways. Glucocorticoids decrease the amount and the function of osteoblasts. These effects result in a suppression of bone formation, causing glucocorticoid-induced osteoporosis. These drugs decrease the duplication of osteoblastic cells, which reduces cells that may differentiate into mature osteoblasts. In addition,

glucocorticoids impair osteoblastic differentiation and maturation. Glucocorticoids inhibit the function of the differentiated mature cells. Glucocorticoids hinder synthesis of type I collagen, the major element of bone extracellular matrix. It results in continuous decrease of bone matrix available for mineralization in bone and makes bones weaker (Canalis, Mazziotti, Giusina, & Bilezikian, 2007). Glucocorticoids trigger apoptotic effects on osteoblasts and osteocytes through activation of caspase 3, stimulating apoptotic signaling pathways. When caspases are active, these contribute to apoptosis on osteoblasts and osteocytes by cleaving target cellular proteins. Therefore, glucocorticoids inhibits osteoblastic cell replication and differentiation, and apoptosis of mature osteoblasts increased by caspase 3, which deplete the osteoblastic cellular pool and decrease bone formation (Canalis, Mazziotti, Giusina, & Bilezikian, 2007).

Glucocorticoid-induced Osteoporosis

Glucocorticoids induce the apoptosis of osteocytes. Osteocytes have a role in the repair of bone micro-damage. Loss of osteocytes by the apoptosis of bone cells interrupts osteocyte-canaliculi network used to obtain nutrients from the blood supply and communicate among themselves and other cells on bone surfaces (Canalis, Mazziotti, Giusina, & Bilezikian, 2007). As a result, it causes failure to detect signals that normally occur in case of processes associated with the replacement of damaged bone. Disruption of this network system can interrupt fluid flow with the network affecting changes in bone remodeling. Glucocorticoids affect the function of osteocytes, by modifying the elastic part which surrounds osteocytic lacunae to cause osteoporosis in men (Canalis, Mazziotti, Giusina, & Bilezikian, 2007).

Glucocorticoids also enhance the activation of osteoclasts. Glucocorticoids enhance the expression of Interleukin-6, an osteoclastogenic cytokine, and suppress

the expression of interferon-beta, an inhibitor of osteoclastogenesis. Those drugs decrease the apoptosis of osteoclasts. As a result, there is increased number of osteoclasts, and the enhanced and prolonged bone resorption is observed in glucocorticoid-induced osteoporosis in men (Canalis, Mazziotti, Giusina, & Bilezikian, 2007).

Alcohol Consumption

Alcohol consumption can disrupt the balance of calcium level which affects condition of bones through hormones, vitamins, and local growth factors to regulate the distribution of calcium between blood and bone. The most representative hormone to control calcium level in bloodstream is parathyroid hormone (PTH). PTH is secreted into the bloodstream by four small glands located behind the thyroid gland in the neck. The hormone produced by parathyroid stimulates the activity of osteoclasts as response to decreasing levels of calcium in the blood. In addition, PTH inhibits the excretion of calcium by the kidney and activates vitamin D, which promotes the absorption of calcium from the intestine (Sampson, 1998). According to Laitinen and colleagues, even though it is not proven how exactly alcohol consumption affects the bone formation, their experiment showed that each person who receives approximately five to eleven standard drinks has increased PTH levels in their bloodstreams and results in loss of bone mass. They also found that long-term heavy drinking was associated with low blood calcium, called hypocalcemia, although PTH level in the bloodstream was normal. It demonstrates that alcohol administration impairs the ability of the parathyroid glands to increase PTH production in response to the presence of hypocalcemia (1998).

Smoking

One of the causes for bone loss in the body is smoking. When smoking occurs in men, nitric oxide (NO) is produced. Nitric oxide is a free radical involved in the regulation of many physiological processes, such as vascular relaxation, platelet aggregation, and immune regulation. During the last decade, it has become apparent that NO has important influences on bone cell function (Sheweita & Khoshhal, 2007). Accumulating evidences suggest that free radical causes oxidative stress, which presumably increases with age. Continuous oxidative stress in the body normally damage cells, organs, and hormones involved in keeping bones healthy or causes an imbalance between the production of free radicals and the ability of the body to eliminate their harmful effects through neutralization by antioxidants (Mandal, 2014). Oxidative stress caused by free radicals are involved in osteoblastogenesis, in apoptosis of osteocytes and osteoblasts and in osteoclastogenesis, which results in bone resorption as shown in animal and in vitro studies (Elsevier, 2009). Above information indicates there is a biological link between oxidative stress caused by free radicals and bone.

Another effect of smoking in the body is to increase serum cortisol level. Lewis (2013) states that smoking is considered as an unwelcoming guest in the body, called stressor. Smoking has multiple effects on hormone secretion including the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is used in the body's response to physical and mental stress. When the body is on stress such as smoking, the cerebral cortex recognizes physiologic stressor and activates limbic system to stimulate hypothalamus. As soon as hypothalamus is stimulated, it sends signal that initiate sympathetic nervous system (SNS) and production of cortisol in the adrenal gland. Cortisol is a life sustaining adrenal hormone essential to maintenance of

homeostasis. Cortisol regulates or modulates many of changes that occur in the body in response to physiologic and mental stress (Lewis, 2013). Studies report that smoking is associated with increased cortisol secretion (Badrick, Kirschbaum, & Kumari, 2007). Cortisol has a diurnal profile, which represents a substantial increase in cortisol secretion after awakening, peaking at 30 minutes, and a subsequent decline over the day. According to the article, there is evidence that the cortisol awakening response is greater in smokers, compared with non-smokers, and smokers have greater cortisol production level in assessment of samples over the rest of the day (Field, Coldditz, Willett, & MCKinlay, 1994). Other research also refers that small increases in cortisol are associated with reduced bone mineral density; this is a potential link between smoking and development of osteoporosis (Badrick, Kirschbaum, & Kumari, 2007). Based on evidence mentioned above, it clearly indicates that increased serum cortisol level influences on the body same as glucocorticoid drugs. It depletes the pool of osteoblasts and enhances apoptosis of osteoblasts and osteocytes in bones. On the other hand, in case of osteoclasts, high serum level of cortisol augments production of osteoclasts and decreases apoptosis of osteoclasts. Therefore, smoking and cortisol level are linked as resulting in increased serum level of cortisol which causes the occurrence of osteoporosis and low bone mass.

Diabetes-related Osteoporosis

Diabetes also may increase a risk of osteoporosis in men. Diabetes occurs when the pancreas is no longer able to produce the hormone insulin called type 1 diabetes. With type 2 diabetes, the body either resists the effects of insulin or does not produce enough insulin to maintain a normal glucose level. The relationship between diabetes and osteoporosis is not completely clear (Thrailkill et al., 2005). Although

more research is needed to clarify the complex relationship between two diseases, researchers have found that the hormone osteocalcin, which derives from bone, regulates insulin secretion by the pancreas. The relationship between bone and insulin is a key link between osteoporosis and diabetes (Thrailkill et al., 2005). Type 1 diabetes is related to several disorders of skeletal health, including decreased bone density, an increased risk for osteoporosis and poor bone healing and regeneration. Type 1 diabetes results in detrimental effects on bone formation. Diabetic patients show decreased expression of transcription factors that regulate osteoblast differentiation in type 1 diabetes. They also demonstrate decreased osteoblast number, osteoid volume, and mineral apposition rates. Plasma osteocalcin concentrations, a marker of osteoblast activity, are lower in type 1 diabetes, which means remodeling of bone formation does not function well (Thrailkill et al., 2005).

Body Weight

Increased body weight can reduce patient's risk of developing osteoporosis. Since excessive weight is common in patients with type 2 diabetes, affected people were regarded as being safe from osteoporosis. But, although bone density is increased in people with type 2 diabetes, fractures are increased. The reason of this is that type 2 diabetes causes vision problems and nerve damages as with type 1 diabetes, which increases a risk of falls. In addition, the sedentary lifestyle in patients with type 2 diabetes accentuates bad effects on bone health (National Institutes of Health, n.d.). Decreased body weight has an increased incidence of osteoporosis. Low body weight is defined as that body mass index is below than 18.5 kg/m^2 (CDC, 2015). According to National Osteoporosis Society in the United Kingdom (2014), relatively less amounts of estrogen compared to are produced in fatty tissue which contributes to protection of bones. Low level of fat padding may have more risk of fracture in men.

Increase body weight may also be correlated with increased pressure on bone structure, causing an increased incidence of osteoporosis. Above body mass index of 25.0 kg/m^2 is thought as overweight range (CDC, 2015). According to Nielson, Srikanth, and Orwoll (2012), there was an increased risk of osteoporotic fracture in patients with greater percent body fat and for patients with higher waist circumference.

Vitamin D Intake

Vitamin D is such an important nutrition for absorption of calcium. Vitamin D is required for the regulation of the minerals calcium and phosphorus found in the body, which also regulates the bone health. Vitamin D helps to absorb calcium from the intestines. In vitamin D deficiency, absorption of calcium is decreased from the intestines, causing increased osteoclast production to compensate deficiency of calcium in the intestines (Sunyecz, 2008). It eventually enhances the mobilization of calcium from the bone to the intestines. During periods of either decreased exposure to sunlight or decreased dietary intake, osteoclasts are produced. The mature osteoclast releases enzymes which break down bone matrix, releasing calcium and other minerals into the circulation (Sunyecz, 2008). If the serum calcium level remains low due to deficiency of vitamin D, PTH hormones are produced from the parathyroid gland. Release of PTH increases reabsorption of calcium in the kidneys and stimulates osteoclast production, resulting in breaking down calcium from bones and increasing serum calcium level. If vitamin D deficiency is not fixed, calcium keeps being dragged from the bone, and osteoporosis can occur in men (Sunyecz, 2008).

Diagnostic Testing

The goals of testing are to determine bone mass density in a specific patient, whether patient has osteoporosis, is hormone-deficient, has an increased risk of

developing osteoporosis, and has other conditions that may be causing or exacerbating bone loss. Testing is used to monitor for bone density loss or to evaluate bone status and may be used for monitoring osteoporosis therapy for effectiveness. Several different diagnostic testing can be done to detect symptoms of osteoporosis. But diagnostic imaging is used in the Bone Mineral Density test, the first screening and diagnostic test for osteoporosis (American Association for Clinical Chemistry, 2012).

DEXA Scan

According to Winzenberg and Graeme (2011), the goal of densitometric techniques is the measurement of parameters to determine bone strength to predict fractures, and assess effects of aging and treatment on these parameters. A dual energy X-ray absorptiometry (DEXA) scan, also called a bone density scan, is the most common technique used to measure bone density. An x-ray is a noninvasive medical test that helps physicians determine whether a patient has osteoporosis and low bone mass. Imaging with x-rays involves exposing a part of the body to a small dose of ionizing radiation to provide pictures of the inside of the body (Winzenberg & Graeme, 2011). A DEXA scan is most often performed on the lower spine and hips to diagnose osteoporosis and asses an individual's risk for developing fractures. There are two types of DEXA scans: central DEXA and peripheral DEXA. In case of central DEXA, it measures bone density in the center of the skeleton such as the hip and spine. In peripheral DEXA, wrist, heel, or finger is used to measure bone density on the periphery of the skeleton (Winzenberg & Graeme, 2011).

After examination, a radiologist, a physician specifically trained to supervise and interpret radiology examinations, analyzes the images to determine whether a patient has osteoporosis or not. Test results are in the form of two scores: T score and Z score. Numbers in T score show the amount of bone a patient has compared with a

young adult of the same gender with peak bone mass. A score above -1 is considered normal. A score between -1 and -2.5 is considered as low bone mass, also called osteopenia. A score below -2.5 is defined as osteoporosis (Winzenberg & Graeme, 2011). The T score is used to measure a patient's risk of developing a fracture and osteoporosis. Numbers in Z score represent the amount of bone a patient has compared with other people in a patient's age group and of the same size and gender. The Z score is in units of standard deviations and shows whether a patient's bone is denser or less dense than what might be expected. If the Z score is abnormally high or low, it may indicate a need for further medical tests to figure out whether a patient is in condition of osteoporosis or in a risk of fracture (Winzenberg & Graeme, 2011).

Quantitative Computed Tomography

Quantitative computed tomography (QCT) bone densitometry is also an accurate method of measuring bone density in the spine, proximal femur, and distal forearm. In case of DEXA, Bone Mineral Density (BMD) estimates may be changed and biased by severe degenerative changes of the hip or spine, vascular calcifications, oral contrast agents, and foods or dietary supplements containing significant quantities of calcium or other heavier minerals (Johnston, Masri, & Wilson, 2009). However, QCT is more accurate in patients with extreme obesity or low body mass index. QCT uses a standard X-ray computed tomography (CT) scanner with a calibration standard to convert Hounsfield Units (HU) of the CT image to bone mineral density values. BMD is the most important single parameter acquired for densitometric techniques (Johnston, Masri, & Wilson, 2009). However, BMD does not fully explain bone strength. Fracture prediction or diagnosing testing of osteoporosis can be improved by measuring additional parameters, which is a 3D technique. In contrast to DEXA, QCT is well suited to understand bone strength in

patients because QCT is a 3D technique to separate analysis of BMD of the trabecular and cortical compartments, which allow physicians to look into bones more specifically and accurately. Using 3D imaging substantially also reduce image acquisition time (Johnston, Masri, & Wilson, 2009).

Average bone mineral density in patients is calculated and is compared with patients of the same age or sex. For example, when compared bone mineral density of the spine to others, a volumetric BMD measurement is made using QCT. As following guideline thresholds from the American College of Radiology, BMD below 80 mg/cm^3 indicates osteoporosis. BMD between 80 and 120 mg/cm^3 is considered as osteopenia. Number of BMD above 120 mg/cm^3 is considered normal (D'Elia, Caracchini, Cavalli, & Innocenti, 2009). Like the way to interpret results of DEXA, QCT also uses T score. A score above -1 is considered normal. A score between -1 and -2.5 is considered as low bone mass, also called osteopenia. A score below -2.5 is defined as osteoporosis. This T score may also be used for fracture risk probability calculation in the Fracture Assessment Tool (FRAX) (Osteogenesis Imperfecta Foundation, 2007).

Fracture Assessment Tool

FRAX is an assessment tool to measure a patient's risk of fracture in order to provide general clinical guidance for screening risks of osteoporosis and treatment decisions. According to International Osteoporosis Foundation (n.d.), FRAX is a scientifically validated risk assessment tool, endorsed by the World Health Organization (WHO). It is a major milestone in helping healthcare providers to improve identification of patients at high risk of osteoporosis and fracture. The FRAX assessment tool includes questions about age, smoking, family history of hip fracture, glucocorticoid use, arthritis, femoral neck bone mineral density, smoking, alcohol use,

previous fracture, weight, and height (Siris, Baim, & Nattiv, 2010). After putting information based on questions in the FRAX assessment tool, the FRAX calculator assesses the ten-year risk of osteoporosis fracture based on individual risk factors, with or without BMD values. Also the current National Osteoporosis Foundation Guide recommends treating patients with FRAX to reduce their fracture risk. The FRAX assessment tool has a function to clarify fracture risk assessment in patients with osteoporosis or low bone mass and gives information to make fracture prevention strategies (Siris, Baim, & Nattiv, 2010).

Blood and Urine Tests

Other than testing regarding bone mass, there are several laboratory tests to rule out or diagnose osteoporosis. Blood and urine tests can be used to identify possible causes of bone loss. Some of these tests include blood calcium levels, 24-hour urine calcium measurement, thyroid function tests, parathyroid hormone levels, testosterone levels in men, 25-hydroxyvitamin D test to find whether the body has enough vitamin D, and biochemical marker tests such as N-terminal telopeptide (NTx) and C-terminal telopeptide (CTx) indicating increased bone resorption. Most likely, these tests are performed due to secondary osteoporosis (Seibel, 2005). Depending on an individual's symptoms and other risk factors, the healthcare provider may test patients for other conditions that can cause bone loss. Laboratory tests for osteoporosis are not diagnostic testing. These tests help to find causes of osteoporosis and low bone mass in patients. Therefore, laboratory tests are performed in most situations as tools of finding causes of osteoporosis (American Association for Clinical Chemistry, 2012).

Prevention

No guidelines exist for managing osteoporosis in men, but maintaining healthy levels of dietary calcium and vitamin D, smoking reduction/cessation, tapering alcohol consumption off, and engaging in regular physical activity all have benefits for males at risk of osteoporosis (Furlow, 2006). According to Mayo Clinic (2014), essential factors to keep bones healthy throughout life are three: adequate amounts of calcium, adequate amount of vitamin D, and regular exercise. Low calcium intake and vitamin D deficiency have been repeatedly observed in men population. Continuous supplement of calcium and vitamin D is required in men to keep bones strong when they age (Srivastava & Deal, 2002). The skeleton contains 99% of the body's calcium supply, which is mobilized when serum calcium level is low. Adequate calcium levels are so important for bone health. Meeting the daily dietary requirement of calcium is the first step to prevent osteoporosis because calcium is directly related to the incidence of osteoporosis. The best way to meet the daily dietary requirement of calcium is taking high calcium in foods. Dairy products are the good sources due to high elemental calcium content and high absorptive rate of calcium in gastrointestinal tract. Dietary sources of calcium include dairy products such as milk, cheese, and yogurt and some green vegetables. Each daily dairy serving consumed contains 300 milligrams of calcium. A serving size of dairy equals one cup of milk, eight ounces, one cup of yogurt or one to 1.5 ounces of cheese (Sunyecz, 2008). According to National Institutes of Health (2012), the recommended amount of calcium in males at the age of 51-70 years old is 1,000 mg a day, and males over 70 years old need to take at least 1,200 mg of calcium a day to keep their bones healthy. Therefore, each daily dairy serving multiplied by 300 mg would provide estimated

total calcium consumption. Mineral waters with high calcium are another source of dietary calcium (Heaney et al., 2001).

Calcium Supplements

In order to assure calcium intake, a variety of calcium supplements are available in the market. Calcium supplements commonly used are calcium carbonate and calcium citrate. Calcium carbonate supplements dissolve better in an acid environment so they should be taken with a meal. A case study reported that proton pump inhibitor therapy in a long-term care with the intake of calcium carbonate caused an increased risk of hip fracture. This study shows that calcium carbonate dissolves better in an acidic environment, and calcium absorption can be ensured by ingestion with food (Yang, et al., 2006). Calcium citrate supplements can be taken any time because they do not require an acid environment to dissolve. Because of this reason, an individual who has problems with absorption could use calcium citrate instead of calcium carbonate (Cleveland Clinic, 2012). Patients should have a consultation, receiving advice form a healthcare provider, to have optimal absorption of calcium by calcium supplement in divided doses. Because the gastrointestinal tract can absorb calcium less than 500 mg at one time, calcium supplements should be taken at least four to five hours apart to absorb the recommended intake of calcium (Sunyecz, 2008). Even though the intake of calcium supplements is needed in patients, an excessively high intake of calcium can cause side effects. Side effects can be constipation, renal insufficiency, vascular and soft tissue calcification, and kidney stones. Some researchers also link high calcium intake, particularly from supplements, with increased risk of cardiovascular disease (National Institutes of Health, 2013). However, in a recent study at the University of Auckland in New Zealand (2015), it found that increasing calcium intake through either diet or supplements does not

prevent or treat osteoporosis. They analyzed two studies about men over 50 who increased calcium intake. In the first study, it showed that increasing calcium intake from dietary sources or taking supplements produces small increase in bone mineral density, which does not lead to a clinically meaningful reduction of fracture. In the second study, dietary calcium intake is not related to risk of fracture, and there is no clinical evidence that increasing calcium intake prevents fracture. On the other hand, they were concerned about adverse effects of high calcium intake such as gastrointestinal side effects (University of Auckland, 2015). Until now, calcium intake was one of the most essential methods to prevent and treat osteoporosis. However, it is now controversial whether calcium intake is effective to prevent or treat osteoporosis in men.

Vitamin D Supplements

Vitamin D is an important source to ease calcium to be absorbed in GI tract. Because intakes of vitamin can reduce bone resorption, it is recommended to take vitamin D. Sunlight is the most common source of vitamin D. Vitamin D is made in the skin when it is exposed to sunlight. To get adequate vitamin D from sunlight is five to 15 minutes of sun exposure from 10 am to 3 pm at least two times per week. This is enough for males to maintain adequate vitamin D levels (Holick, 2004). If sufficient sunlight is not obtained, dietary sources of vitamin D can be taken as an alternative to sunlight. According to National Institutes of Health (2012), a daily intake of 600 IU (International Units) of vitamin D up to age 70 is recommended. Men over age 70 should increase intake amounts of vitamin D up to 800 IU daily, which can be also obtained from supplements or foods enriched with vitamin D such as egg yolks, saltwater fish, liver, and fortified milk. In case of osteoporosis and low bone mass, calcium should be taken with vitamin D. some studies suggest that

calcium, along with vitamin D, may have benefits on bone health because vitamin D facilitates the absorption of calcium in GI tract (National Institutes of Health, 2014).

Use of Corticosteroid

Since osteoporosis can be derived from the use of glucocorticoid, current and prospective users of long-term corticosteroid drugs should be educated regarding the potential risk of osteoporosis. For patients who are already taking corticosteroids the therapeutic regimen should be constantly reviewed by healthcare providers, and dosage should be reduced where possible. The safe dosage of glucocorticoid is still controversial, and depending on how patients react on glucocorticoids, the range of dosage could be broad. However, according to Pereira and other researchers (2012), patients are recommended to initiate glucocorticoid at a minimum of 5 mg/day for three months, which prevents the incidence of osteoporosis. On the other hand, other guidelines have recommended that the minimum glucocorticoid dose that indicates risk of fracture is 7.5 mg/day (Devogelaer et al., 2006). Minimizing the dosage of glucocorticoid is optimal. If glucocorticoid should be used in higher doses, patients should begin with adequate calcium intake of 1,000-1,200 mg/day, intake of vitamin D, stopping smoking, avoiding excessive alcohol consumption, and doing regular weight-bearing exercise (Roy & O'neill, 2005).

Exercise

Exercise has a twofold contribution to reducing fracture risk: it may enhance bone strength by optimizing BMD and improving bone quality, and it has the potential to reduce the risk of falling. Weight-bearing exercise is an exercise to prevent osteoporosis in men. Multiple studies demonstrate the health benefits of exercise including reduced risk of osteoporosis and fractures. Weight-bearing and muscle-strengthening exercise is recommended to prevent osteoporosis because it

improves balance, strength, and posture of bones. However, exercise increases some patients' risk of fracture and osteoporosis, so that healthcare providers must keep it in mind, making recommendations for type and degree of activity based on individual risk (Kling, Clarke, & Sandhu, 2002). A recent Cochrane review included 43 randomized controlled trials which investigate whether exercise could prevent bone loss and fractures in men. A small, but significant effect of exercise on BMD was observed. The study goes on to say there are two different weight-bearing exercises: high-impact weight-bearing exercises and low-impact weight-bearing exercises. High-impact weight-bearing exercises help build bones and keep them strong. Examples of high-impact weight-bearing exercises are dancing, doing high-impact aerobics, hiking, jogging and running, jumping rope, stair climbing, and tennis. If individuals have broken a bone due to osteoporosis or are at risk of low bone mass, they may need to avoid high-impact exercises. In case of an individual who cannot do high-impact exercises, low-impact weight-bearing exercises can be applied. It also helps keep strengthening bones and are a safe alternative if one cannot do high-impact exercises. Examples of low-impact weight-bearing exercises are doing low-impact aerobics using elliptical training machines, doing fast walking on treadmill or outside, and using stair-step machines (Mishra & Mishra, 2011).

Cessation of Smoking and Intake of Alcohol

Smoking may cause less calcium intake from their diets, damage the function of osteoblasts and osteocytes, and enhances the activity of osteoclasts; thus, it decreases bone mineral density. However, smoking cessation has the reversible effect on bone health. Two cross-sectional studies have shown that bone density of formal smokers improves as early as less than 10 years and approaches bone density of non-smokers with over 30 years of smoking cessation. Studies dealing with the effects of

smoking cessation have shown an improvement in markers of bone formation and bone resorption and sex hormone abnormalities in 6 weeks after smoking reduction/cessation and one year with improvement in bone density (Yoon, Maalouf, & Sakhaee, 2012). Above information clearly presents that smoking reduction/cessation can help to keep bone healthy.

Heavy drinking has a negative effect on bone health by interfering with the ability of osteoblasts, decreasing the amount of osteoblast cells, and interfering with the ability of absorption in the gastrointestinal tract. Regular consumption of more than two alcohol drinks a day increases a risk of osteoporosis (Mayo Clinic, 2014). Individuals with osteoporosis and low bone mass must avoid excessive use of alcohol. Education can be used to cut down excessive amount of alcohol. Healthcare providers can educate patients to limit alcohol consumption to less than two drinks per day, which hardly affects bone health. Patients should be educated to taper alcohol intake amount off because quitting the use of alcohol at one time could cause alcohol withdrawal which is a life-threatening condition (Rao, Budhwar, & Ashfaque, 2010).

Treatment

The primary goal of treatment is to reduce the risk of fracture. Research on drug therapy for males with low BMD is incomplete; however, despite a lack of scientific consensus, pharmaceutical interventions are considered appropriate for men at high risk for fracture. At the same time, continuous non-pharmacologic therapy is important adjunct to pharmacologic management of osteoporosis by reducing the potential modifiable risk factors along with exercise and calcium and vitamin D supplementation. Several medications and therapy can be used to manage osteoporosis in men: Alendronate, risedronate, zoledronic acid, the use of PTH, and testosterone therapy (Rosen, Rosen, & Mulder, 2014).

Bisphosphonate

Bisphosphonates which strengthen bone by inhibiting bone resorption by osteoclasts currently approved for treating osteoporosis in men, and bisphosphonates are used to treat bone loss from secondary causes, such as corticosteroid use, androgen deprivation therapy, and hypogonadism. Alendronate, one of bisphosphonate drugs, is considered as a first-line drug therapy for osteoporosis. The clinical trial resulted in the approval of alendronate to treat osteoporosis in men older than 60 with no active secondary causes of osteoporosis (Furlow, 2006). According to studies (Orwoll, et al., 2000), 241 men having osteoporosis treated with alendronate showed increased BMD in the femoral neck and spine, and diminished occurrence of vertebral fracture. Another study shows that alendronate is demonstrated efficacy for enhancing bone mineral density in men with idiopathic or secondary osteoporosis and has proven an ability to prevent vertebral fractures in men with low bone mass (Olszynski, & Davison, 2008). University of Washington (2009) ended up with the positive effects of alendronate on osteoporosis as well. The subjects were men with mean T-score of -2.0 or less, which means men with low bone mass or osteoporosis were randomized to receive alendronate 10 mg daily or placebo for two years. The statistics resulted in significant increase in BMD at the lumbar spine versus placebo, 7.1% versus 1.8%, and significant increase in BMD at the femoral neck versus placebo, 2.5% versus 0.1%. Similarly, another study of 280 men who are 65 years and older received risedronate involved in bisphosphonate or placebo. Men in the risedronate group had a 2.5% increase in BMD compared with the placebo group ending up with a 3.5% decrease of BMD; treatment with risedronate also was associated with a decrease in hip fractures (Rao, Budhwar, & Ashfaque, 2010).

Another type of Bisphosphonates is Zoledronic acid which is administered intravenously (IV). Zoledronic acid was approved by the U.S. Food and Drug Administration in 2008 for the treatment of osteoporosis in men. It is a potent inhibitor of bone resorption. It decreases osteoclast proliferation and differentiation and induces apoptosis of osteoclastic cells. Its high affinity results in increasing mineralized bone, especially for sites of high bone turnover (Lambrinoudaki, Vlachou, Galapi, Papadimitriou, & Papadias, 2008). One study concluded that five regimens of IV zoledronic acid from one to four mg administered as one to four doses over one year showed that lumbar spine BMD increased similarly in all five groups between 4.3 to 5.1% (Reid, et al., 2000). At a dose of 5 mg once a year, it has positive effects on bone mineral density in men. The University of Washington (2009) had an experiment by randomizing men to take either zoledronic acid 5 mg IV or a weekly oral bisphosphonate. The increase in BMD of the spine was similar in both groups, 6.2% in oral bisphosphonate versus 6.1% in the zoledronic acid. It refers that zoledronic acid has effects on men with osteoporosis and low bone mass as same as using alendronate and risedronate. Zoledronic acid could be useful drug for men who are experiencing or have experienced a fracture or osteoporosis to prevent further risk of a fracture and treat current concern of a fracture.

Interestingly, long-term intake of bisphosphonates may cause jaw necrosis. The risk of medication-related osteonecrosis of the jaw (BRONJ) development has been shown to be higher in patients with high doses of bisphosphonates treatment intravenously. Components of bisphosphonates are stayed in the bone for more than 10 years, and administration over a long period of time might cause high-dose accumulation in the jawbones, the risk of BRONJ is increased. However, this risk is dose and time dependent. So appropriate dose of drug should be drug-specific and

continuous monitoring of bisphosphonates are recommended to prevent BRONJ (Ayora et al., 2015).

Parathyroid Hormone

Another way to treat osteoporosis is the use of Parathyroid Hormone (PTH). PTH is a key regulator of calcium metabolism that is produced as an 84-amino acid protein in response to changes of extracellular calcium concentration. In the process of bone formation, bone resorption should occur to renew the setting of bones. PTH temporarily separates bone formation from bone resorption and induces the activity of osteoblastic cells without requiring prior resorption. Although the exact mechanisms are not still clear, researchers have observed that daily intermittent PTH injections increase levels of the bone density above normal (American Academy of Orthopaedic Surgeons, 2007). Teriparatide involved in drug class of PTH analog is the only FDA-approved osteoporosis drug, which is a synthetic form of the natural human PTH. Teriparatide is useful to men who cannot take bisphosphonates and are with severe osteoporosis or multiple risk factors for fracture (Rao, Budhwar, & Ashfaque, 2010). In the study of taking daily teriparatide treatment, men were administered with teriparatide at 20 μg/day for 12 months. When researchers observed the change in lumbar spine and femoral neck, the percent lumbar spine BMD in men significantly increased by 11.3 ± 9.9% (mean ± standard deviation) and femoral neck BMD was increased by 0.4 ± 6.4% without a significant difference over 12 months (Niimi, 2015). Another study refers that men treated by teriparatide medication for one month has been shown not only to increase the thickness of trabecular bone and trabecular connectivity, but also to increase the bone formation rate in the periosteal surface of iliac cortical bone in patients (Anthony et al., 2005). These studies showed that daily teriparitide treatment has positive and effective influence to treat osteoporosis in men.

Testosterone Therapy

Testosterone therapy increases BMD and is only used in men who have low levels of testosterone. According to Rao, Budhwar, and Ashfaque (2010) a meta-analysis of eight trials enrolling 365 men displayed that men injected with testosterone intramuscularly had eight percent gain in lumbar BMD compared with placebo. In a study, intramuscular injections of 250 mg testosterone ester augmented lumbar spine bone density by 5% over six months. Measurement of the biochemical markers of bone turnover in this study also brings a point of that treatment increases bone density by decreasing bone resorption. After injection of testosterone, there was the increase in serum estradiol level, which promotes bone density. Testosterone therapy is also effective in men with corticosteroids. A randomized controlled cross-over study in a group of men receiving oral corticosteroids presented that monthly intramuscular injections of 250 mg testosterone esters increased lumbar spine bone density up to 5% over 12 months (Francis, 1999). Testosterone therapy may offer a wide range of benefits for men with hypogonadism and osteoporosis. However, so far, the benefits of testosterone therapy only have been seen with intramuscular injections, there is no evidence that testosterone therapy improved bone density in men with normal levels of testosterone (Bassil, Alkaade, & Morley, 2009).

Conclusion

The incidence of osteoporosis in men has been increasing rapidly. Presently, one in four men over age 50 has an osteoporosis-related fracture in his lifetime in the Unites States (National Osteoporosis Foundation, 2011). It is becoming a common disease and also has become a major public health problem in men as the number of elderly population has increased. As aging, men are more likely to experience osteoporosis, but compared to osteoporosis in women the peak incidence of

osteoporotic fracture occurs 10 years later in men. The prevalence of osteoporosis in men could be different depending on patients' ethnicity as well.

A number of risk factors can help to broadly recognize patients at risk for osteoporosis and fracture. Risk factors should be identified to prevent and treat men with osteoporosis and low bone mass. Patients with glucocorticoid drugs may have the incidence of osteoporosis and fracture due to the activity of components of glucocorticoid such as decreasing the number and the function of osteoblasts, apoptosis of osteocytes, and enhancing the activation of osteoclasts. Alcohol consumption is one of risk factors which disrupt the absorption of calcium in GI tract and impairs the ability of parathyroid glands. Other risk factor, smoking, causes oxidative stress through NO, which damage bone cells; enhances apoptosis of osteoblasts and osteocytes; augments production of osteoclasts and decreases apoptosis of osteoclasts. Diabetes increases risk for osteoporosis because it causes poor bone healing and regeneration as decreasing osteoblast number, osteoid volume, and mineral apposition rates. If vitamin D is deficient, it could decrease calcium absorption in the intestines, causing production of osteoclasts to move calcium from the bone to bloodstream. In men, male hypogonadism, which presents with low serum testosterone level, is one of factors causing osteoporosis. It acts directly on osteoblast as influencing growth, proliferation, and differentiation of osteoblastic cells. It also inhibits osteoclastic activity. Since estrogen can be overlooked because there is a stereotype that estrogen is only influencing on women. However, in men, estrogen-deficiency causes osteoporosis by enhancing osteoclast differentiation and activation frequency of it; studies also found that men with lower levels of estrogen metabolites tended to have lower bone density.

Preventive measures and the various treatments can be strategically used to minimize the incidence of osteoporosis and low bone mass. For prevention, patients need to take calcium and vitamin D. The first step to prevent osteoporosis is to meet the daily dietary requirement of calcium and vitamin D. Males between 51-70 years old should take at least 1,000 mg/day of calcium, and males above 70 years old need to take at a minimum of 1,200 mg/day of calcium to prevent and treat osteoporosis. At the same time taking calcium, males also need to take in vitamin D 600 IU for males up to age 70 and 800 IU for males over age 70 daily, but no more than 4,000 IU a day. Patients with glucocorticoid treatment should be reviewed by healthcare provider and be educated about safe dosage to prevent osteoporosis. The safe dosage of glucocorticoid is still controversial between 5 mg/day and 7.5 mg/day. However, the best way to prevent osteoporosis is to minimize the dosage of glucocorticoid as much as possible. Exercise is another method to prevent osteoporosis as doing weight-bearing exercise classified by high-impact weight-bearing exercise and low impact exercise. Smoking cessation and quitting drinking alcohol are big parts to prevent osteoporosis as well. Studies showed that after smoking reduction/cessation bone density improved. Since alcohol interferes with the ability of osteoblasts and absorption in GI tract, patients should taper the use of alcohol off.

If patients are at the risk of fracture by osteoporosis and have low bone mass, treatments can be used. Bisphosphonate drugs are the first-line drug therapy for osteoporosis. Males who had treatments of alendronate, risedronate and zoledronic acid, inhibiting bone resorption, demonstrated the increase in BMD compared with the placebo group and the decrease in hip, lumbar, and vertebral fracture. The use of PTH, another way to treat osteoporosis, displayed that daily intermittent PTH injects increased levels of the bone density above normal. Teriparatide treatment involved in

PTH increased lumbar spine and femoral neck BMD in men over 12 months after taking this medication. Lastly, testosterone therapy is useful to males with hypogonadism. Males injected with testosterone intramuscularly not only had an increase of lumbar spine BMD by 5%, but also showed that this therapy is effective in men with corticosteroids.

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