

Chapter 2

Bone Aging

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Abstract The aging musculoskeletal system has a profound effect on the health of an individual. In this chapter, the author outlines some of the key changes in bone physiology during aging and explains how they contribute to osteoporosis and the increased fracture risk in the elderly.

Keywords Anatomy • Osteoporosis • Fracture • Osteomalacia • Elderly

Anatomy and Physiology of Bone

Bone is a unique structure made up of cells and extracellular matrix (ECM). This ECM is composed of collagen and non-collagen proteins. The collagen fibers are arranged in bundles, which, in turn, are arranged in specific orientations. These fibers are further mineralized with calcium phosphate and hydroxyapatite. The skeleton serves as the stores for 99% of the total body calcium and 80% of the total body phosphate. The bone organic matrix is predominantly composed of type I collagen (95%) along with sulfated proteoglycans, acidic glycoproteins, and osteocalcin.

The cell types found in bone include osteoblasts, osteoclasts, osteocytes, and stromal cells. Bone continuously undergoes a remodeling process throughout life, where resorption and formation are continuously occurring. This process is known as bone turnover, and it occurs at discrete sites all throughout the skeleton. As a result, 5–10% of the total adult skeleton is replaced each year [1]. This process is closely regulated by the actions of osteoblasts (which are responsible for bone formation) and osteoclasts (which are responsible for bone resorption). The osteoblasts and osteoclasts build basic multicellular units (BMUs), which are under the control of various systemic hormones and local growth factors. As a result, these factors regulate the activity

and number of osteoclasts and osteoblasts through controlling the replication rate of undifferentiated cells and the differentiation of these cells [2]. This balance between formation and resorption determines the total body bone mass.

In the skeleton, two types of bone can be observed. Cortical or (compact) bones make up about 80% of the total skeleton and are present in the shafts of long bones. Trabecular (or cancellous) bone accounts for the remaining 20% of the total skeleton and is present in the end of long bones, vertebrae, and ribs.

In the adolescence, there is net bone formation, as bone formation exceeds the rate of resorption, thus leading to an increase in total bone mass. However, this rate of growth ceases when linear growth stops, and at this point, the person's peak bone mass is achieved. This usually occurs by age 15–25 [3]. The total bone mass usually remains constant for about 10 years, as the rates of bone formation and resorption are balanced during this time. By the third to fourth decade of life, total bone mass will begin to decrease. By age 80, it is estimated that the body's total bone mass will be about 50% of its peak value [3]. This process is known as senile osteoporosis, which describes a process of age-related bone loss. Furthermore, women have an accelerated period of bone loss shortly postmenopause. This phenomenon will be discussed in subsequent chapters in this book.

Senile Osteoporosis

Osteoporosis is a disease leading to progressive decreases in bone mineral density (BMD), decreased bone strength, and increased risk of skeletal fractures [4]. Approximately 30% of women will have sustained at least one vertebral fracture by the age of 75 [5]. There are over 1,500,000 total fractures each year in the USA related to osteoporosis, and 700,000 of these were incident vertebral [5] (see Chap. 19).

Although the process of bone turnover is normally in equilibrium, the aging process has involuntary changes on the process of bone formation and resorption [3]. Two types of osteoporosis have been described. Type I which is seen in women

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and is believed to be estrogen-dependent accelerated bone loss shortly after menopause. In a state of estrogen deficiency, a high bone turnover state results from increased numbers of osteoblasts and osteoclasts. In type I osteoporosis, resorption exceeds the rate of bone formation, thus leading to an accelerated bone loss state. The exact cellular mechanism by which estrogen deficiency exerts its effects on bone turnover is not entirely understood. However, increased cytokine production clearly plays an essential role in promoting osteoclast production and activity in the estrogen-deficient state (*vide infra*).

Type II, also known as senile osteoporosis, affects both men and women and is associated with aging. Unlike in type I, this form of osteoporosis has a decreased rate of bone turnover. The pathophysiology is due to a decrease in osteoblast numbers and activity, thus leading to a decrease rate of bone formation with subsequent net decrease in total bone mass. The mechanism by which this occurs will be discussed later on.

Age-Related Changes in Bone

Cytokines

Chronic inflammation secondary to the aging process plays a significant role in the bone remodeling process through the actions of proinflammatory cytokines. The immunosenescence process involves a chronic inflammatory state with subsequent hyperproduction of proinflammatory cytokines [6] (see Chap. 1). Numerous studies have shown that interleukin (IL)-6, tumor necrosis factor alpha (TNF- α), IL-1, among other cytokines are elevated during the aging process [7, 8]. As previously mentioned, many of these cytokines and growth factors have a role in the regulation of bone metabolism and subsequent rate of bone turnover. IL-6 is a prominent example, as it increases steadily with aging. IL-6 is also a potent promoter of osteoclast differentiation and activation, thus favoring net bone resorption. IL-1 is another potent stimulator of osteoclast differentiation and activation, and its levels also rise steadily with aging. Parathyroid hormone (PTH) levels also increase with aging, and PTH has downstream effects of inducing IL-6 production. TNF- α has the effects of stimulating bone resorption and inhibits new bone formation [9]. Furthermore, the inducible nitric oxide synthesis pathway (iNOS) is activated through the effects of TNF- α and IL-1. *In vitro* studies have shown that iNOS pathway activation inhibits the production of new osteoblasts and can induce osteoblast apoptosis.

GH-IGF Axis

In addition to changes in circulating cytokine levels with aging, the growth hormone (GH) and insulin-like factor

(IGF) axis is also altered. GH plays a role in regulating somatic growth, while IGFs serve as mediators of GH's actions and also serve as regulators of connective tissue cell function [10]. As humans age, there is a progressive, yet gradual fall in GH secretion, and this is correlated with a concurrent drop in circulating IGF-1 levels [11]. Furthermore, the serum levels of IGF-binding proteins have been found to increase in the elderly population. This compounds the problem, since IGF-binding proteins decrease the bioavailable level of IGFs and antagonize the actions of IGF [12]. The GH-IGF axis plays a pivotal role in regulating bone metabolism and subsequent BMD. IGF-1 is a potent bone anabolic factor through directly stimulating osteoblast activity [13]. IGFs also increase the number of active osteoblasts through its effects on stimulating the rate of bone marrow stem cell proliferation, and differentiation of mesenchymal cells into osteoblasts [13]. Through these actions, the activation of the GH-IGF axis promotes bone formation and has a net anabolic effect when stimulated. Studies have shown a correlation between the age-dependent decline in circulating GH/IGF levels with an increased risk of osteoporosis and increased incidence of fragility fractures [14]. Studies which investigated the therapeutic use of GH in osteoporotic patients revealed a clear correlation between GH dosage and serum IGF-1 levels, with increases in BMD [15]. Furthermore, pulsatile injections of PTH (teriparatide/Forteo®) also increase the circulating levels of IGF-1 which accounts for teriparatide's therapeutic use as an anabolic bone agent [16]. Although chronically high levels of PTH will lead to significant reductions in BMD, it has anabolic effects when given in a pulsatile manner. The reason for this paradoxical effect is due to different signaling mechanisms activated under the different two conditions. The exact mechanism is still uncertain, but it is believed that when PTH is given in a pulsatile fashion, the Wnt- β catenin pathway is activated, which has subsequent effects on increasing IGF-1 levels.

Therefore, the age-dependent reduction in circulating GH and IGF-1 levels may play a significant role in the development and progression of senile osteoporosis.

Fracture Healing in the Elderly

Aging is a complex physiological process with multiple involvements on the molecular, cellular, and systemic levels. The aging process and osteoporosis are intimately intertwined. Osteoporosis has a serious impact on the morbidity and mortality of elderly, if they sustain an osteoporotic fracture. Approximately 30% of women will have sustained at least one vertebral fracture by the age of 75 [5]. The lifetime risk for sustaining a hip fracture is 17% in Caucasian women and 6% in men above age 50. There are over 1,500,000 total fractures each year in the USA related to osteoporosis, and

700,000 of these were incident vertebral [5]. Patients who have suffered an osteoporotic fracture, especially a vertebral or hip fracture has significant impacts on their mortality and morbidity [17]. Both clinical and radiographic fractures are associated with an increase mortality rate. One study identified a 16% reduction in expected 5-year survivability. Approximately 75% of patients who present with a clinical vertebral fracture will experience chronic pain [5]. The number and severity of vertebral fractures also increases the risk of developing chronic back pain. Aside from the physical limitations suffered by these patients, chronic back pain has a significant impact on the patient's quality of life. Patients suffering from vertebral fractures often have impaired physical functioning, limited activities of daily living, limited leisure and recreational activities, and significant emotional distress.

There is a significant difference in the fracture healing process when comparing the elderly to younger patients. The elderly with osteoporosis most likely sustain fractures in the femoral neck, vertebrae, and distal radius secondary to falls and low-energy trauma [18]. The femoral neck and vertebral bodies are at greater risk of an osteoporotic fracture because these sites contain a high percentage composition of trabecular bone, and it is more affected by the age-related shift on bone remodeling, which favors a net bone resorption. A decrease in BMD certainly has significant contributions to increasing the risk of fractures, as a drop in one standard deviation in BMD (T-scores) increases the relative risk for a fracture by two- to threefolds [19]. However, there are other factors to consider aside from BMD values alone when assessing for fracture risks. Irrespective of BMD value, increasing age alone significantly increases the risk of sustaining a fracture [20]. The repair mechanism is compromised with increasing age, and this also increases the risk of suffering a fracture in the elderly [21]. A disruption in the regulation of osteogenic differentiation, which subsequently disrupts angiogenesis, likely plays an important role in compromising the fracture healing mechanism [22].

In the normal physiology of fracture repair, angiogenesis plays a pivotal role. When a fracture occurs, platelets accumulate, which in turn form a fibrin-rich extracellular matrix. Chemoattractants are released to recruit neutrophils, macrophages, and lymphocytes. Granulation tissue is then formed as blood vessels begin to sprout into the clot along with undifferentiated mesenchymal cells. In stable conditions, intramembranous ossification is able to occur as the mesenchymal progenitor cells differentiate into osteoblasts, which in turn begin to form woven bone. The woven bone spans the fracture site and forms a hard callus. If the fracture is unstable, where angiogenesis is impaired or limited, another mechanism is activated. In this scenario, endochondrial ossification occurs with concurrent penetration of blood vessels and mesenchymal progenitor cells into the newly formed chondrogenic tissue. In either scenario of intramembranous or endochondrial

ossification, the newly formed matrix is remodeled into lamellar bone to conclude the fracture repair process. In this complex sequential repair process, the role of angiogenesis and the action of mesenchymal cells are critical.

The aging process has profound effects on angiogenesis [23]. This results from a decrease in endothelial cells, activity of the hemostatic pathway, growth factors, and neurochemical mediators that are required for angiogenesis [23]. Aging also has an effect on mesenchymal progenitor cell's numbers and activity. The mitotic rate of these progenitor cells decline with aging, and there are fewer the number of progenitor cells in the bone marrow show an age-related decrease [24]. However, it is unclear if the decrease is significant enough to affect fracture healing [25]. Furthermore, in vitro experiments utilizing rat mesenchymal precursor cells showed samples from elderly rats had a significantly lower responsiveness to 1,25 dihydroxyvitamin D3 and TGF- β , when compared with cells from non-elderly rats [26]. Although there are numerous age-related changes to normal physiology which contribute to impaired fracture healing, there is no yet enough evidence to conclude how great an impact these changes at the cellular and molecular level have on clinical disease development.

Pathophysiology of Osteoporosis in Males and Females

Based on comparisons with male database of BMD measurements, the World Health Organization estimates that 1–2 million men in the USA have osteoporosis (defined as T-scores <2.5), and there are 8–13 million men with osteopenia (defined as BMD between 1.0 and 2.5). Like in women, there is an exponential increase in the risk of hip fractures with advancing age, yet this increase begins 5–10 years later than in women [27]. It is estimated that one in five men over the age of 50 will incur an osteoporosis-related fracture in their lifetime. Therefore, although it is often overlooked, there is little doubt that osteoporosis is a very real and significant medical problem in the elderly male population. Although BMD measurements are not as well standardized for men as they are for women, there are a few prospective studies investigating BMD values with fracture risks in men. The Rotterdam Study in 2004 reported that men older than 55 showed a relationship between their absolute BMD value and risk of hip and other non-vertebral fractures. This study also showed that the rates of non-vertebral fractures occurred at a rate that was comparable with women of the same age group [28]. In a prospective study done by the Osteoporotic Fractures in Men (MrOS) Study research group, a cohort of 5,000 men were followed, and this study showed a stronger relationship between hip BMD values and hip fracture risk in men, when compared with women

(relative risk of 3.2-fold in men vs. 2.1-fold in women for each SD decrease in hip BMD) [29]. Aside from hip fractures, osteoporotic men are also at risk of suffering from vertebral fractures. The European vertebral osteoporosis study (EVOS) was a large multinational survey which aimed to determine the prevalence of vertebral involvement in osteoporosis. They found the prevalence of vertebral deformities in males (15.1%) was similar to that seen in females (17.2%) [30]. The implications of the increase in fracture risk is very significant, since the mortality rate associated with hip fractures and vertebral fractures is higher in men than in women [31].

In men, their BMD values increase significantly during puberty in response to sex steroid production, and peak spinal bone density is reached by about age 20, and the peak density in long bones are reached several years later. After reaching their peak bone mass, men lose about 30% of their trabecular bone and 20% of their cortical bone mass during their lifetimes; loss begins shortly after peak bone mass is achieved [32]. In men after the age of 30, it is estimated that the BMD in their proximal and distal radius declines by about 1% per year [33]. At certain sites, including the femoral neck, the rate of decline in BMD may increase with advancing age [34].

During the years where females typically incur a rapid decline in BMD, males have several factors which protect them, which help account for the difference in incidence rates between men and women. Men do not suffer from a loss in sex steroid production during midlife, as seen in women. During menopause, there is an abrupt drop in serum estrogen levels, and this has significant implications on bone metabolism. Estrogen inhibits bone resorption and when estrogen production declines after menopause, there is a marked increase in the rate of bone resorption. The exact mechanism by which estrogen regulates the rate of bone turnover is not entirely clear. However, in states of estrogen deficiency, there is an upregulation of selected cytokines [especially IL-6 and macrophage colony-stimulating factor (M-CSF)]. These cytokines have an essential role in regulating osteoclast genesis and also regulate osteoclast function. IL-6 is a cytokine produced by many different cell types including the osteoblasts, and its production increases during states of estrogen deficiency [35]. IL-6 acts as a mediator to stimulate osteoclastogenesis and bone resorption through a prostaglandin-dependent mechanism. Monocyte colony-stimulating factor (M-CSF) levels also increase markedly in estrogen-deficient states, and it is essential for the activation of osteoclasts through a cytokine-mediated mechanism. In addition to IL-6 and M-CSF, a number of other cytokines and growth factors are involved in a very complex process by which estrogen deficiency leads to a marked rise in the rate of bone resorption and overall net bone loss. This rate then slows with time after menopause, but still progresses at a steady rate.

About 50% of osteoporotic men are diagnosed with a form of secondary osteoporosis, where there is a specific underlying cause. This leaves the other 50% of men with a primary form of osteoporosis, which encompasses idiopathic osteoporosis and senile osteoporosis. As in females, genetic factors play an essential role, as the rates of bone loss are correlated within twin pairs [36]. Serum concentrations of testosterone decreases with advancing age and this factor has been proposed to have effects on increasing bone resorption or decreasing the rate of bone formation. However, most cross-sectional studies investigating the relationship between serum testosterone concentrations and bone density have failed to find a correlation, especially when adjusting for age body weight and serum estrogen levels [37].

However, low estrogen levels may also be an important factor leading to male osteoporosis. In older men, serum estrogen concentrations are correlated with their BMD, independent of serum testosterone levels [38]. It is still unclear whether estrogen levels have their beneficial effects primarily by maximizing peak bone mass in adolescent men or have a major effect on determining the rate of bone loss in elderly men. In men, low serum estradiol levels are also associated with an increase risk of hip fractures. In addition, men with concurrently low levels of estradiol and testosterone have the greatest risk for future hip fractures.

Other Age-Related Factors

Vitamin D is an essential factor in the regulation of calcium metabolism. 1,25-Dihydroxy vitamin D3, the active form of vitamin D has effects on increasing intestinal calcium absorption, decreasing serum PTH levels through both a direct inhibition of PTH secretion, and also indirectly, through inhibiting PTH secretion through increased serum calcium levels. Therefore, vitamin D has overall effects of decreasing PTH-mediated bone resorption. Vitamin D deficiencies often occur with advanced aging, and this may be another contributor to the pathogenesis of senile osteoporosis. Although severe vitamin D deficiency will result in the development in osteomalacia in an adult person, a mild deficiency could lead to a state of secondary hyperparathyroidism, with resultant development of osteoporosis. Both primary (due to deficiency of vitamin D) and secondary vitamin D deficiency (reduced level of 1,25-dihydroxy vitamin D3 resulting from renal impairment or a lack of target tissue responsiveness) could occur with aging. Serum levels of 1,25-dihydroxy vitamin D3 are seen at lower levels in those above the age of 65, and it is believed that the aging kidney's inability to synthesize 1,25-dihydroxy vitamin D3 at an optimal level contributes to this observation [39].

In addition to the vitamin D deficiency, there is also an age-dependent decline in intestinal calcium absorption efficiency, which may correspond with a Vitamin D deficient state. Furthermore, there is also an age-related rise in serum biologically active PTH levels, which also would correspond to a vitamin D deficient state [40]. Finally, there is a correlation between urine NTx levels (a marker for bone resorption) and serum PTH levels in postmenopausal women, thus a vitamin D deficient state leading to an elevated serum PTH concentration may be a contributor senile osteoporosis.

There are also a number of factors in the elderly population which may predispose them to falls, resulting in subsequent osteoporotic fractures. These factors include lack of physical activity, muscle weakness/atrophy, neuromuscular disease, impairment in gait, balance, and proprioception among other risk factors for falls. As a result, many of these low velocity falls may result in osteoporotic fractures in the elderly which will have a significant impact on the patient's quality of life and mortality rates, if a vertebral or hip fracture is sustained.

Osteomalacia

Osteomalacia is a relatively common metabolic bone disease leading to a reduced bone density. It is a disorder seen in the adult population, where there is defective mineralization of newly formed bone matrix. Rickets shares the same pathogenesis as osteomalacia, but by definition, it occurs in children with still open growth plates.

Normal bone turnover occurs continually on trabecular and Haversian bone surfaces. This process begins as osteoclasts secrete protons, proteases, and proteoglycan-digesting enzymes onto the bone surface, thus producing a tunnel in cortical bone. Osteoblasts then lay down a new bone matrix (osteoid), which serves as a scaffolding onto which mineral crystal hydroxyapatite can form. Bone mineral, in the form of amorphous calcium phosphate is deposited, which in turn undergoes conversion into hydroxyapatite. Given this normal physiological process necessary for bone turnover, the failure of mineralization seen in osteomalacia can occur due to a number of etiologies.

Firstly, a normal concentration of minerals (calcium and phosphate) must be available in the extracellular matrix to form hydroxyapatite crystals in the osteoid. Phosphate deficiency is the most common cause of osteomalacia. Causes of hypophosphatemia include decreased intake, antacid use, vitamin D deficiency, secondary hyperparathyroidism, and phosphate wasting through renal tubular defects. Vitamin D deficiency is another common cause of osteomalacia. Common etiologies of vitamin D deficiency include deficient intake, impaired gastrointestinal absorption, lack of sun exposure,

cirrhosis leading to defective 25-hydroxylation, vitamin D loss through nephritic syndrome, and defective 1- α 25-hydroxylation seen in chronic renal failure and hypoparathyroidism. Calcium deficiency may also lead to osteomalacia, but it is an extremely rare cause.

Osteomalacia can still occur in the setting of adequate mineral availability in the extracellular fluid. This can occur in the setting of impaired matrix formation, as there is not a proper scaffolding onto which hydroxyapatite is deposited. Abnormal matrix formation is seen in conditions such as osteogenesis imperfecta, fibrogenesis imperfecta, chronic renal failure, and hypophosphatasia.

Finally, there are a number of drugs and toxins which interfere with the mineralization of the osteoid. Bisphosphonates inhibit both bone resorption and formation and lead to impaired mineralization. Aluminum is another inhibitor of mineralization, especially in the setting of total parenteral nutrition use. Fluoride can also inhibit matrix mineralization, and osteomalacia is commonly found in the setting of endemic fluorosis and in chronic fluoride toxicity.

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