Osteoporosis: Epidemiology, Histology, Bone Remodeling, and Classification

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Abstract: Osteoporosis and decreased bone mineral density affect a large proportion of Americans of both sexes. Physical therapists play a role in screening for undiagnosed osteoporosis, and in prevention and treatment of osteoporosis. Bone mineral density is determined by the activity of the cells contained in bone. These cells react to demands on calcium and phosphate metabolism, hormonal influences, and mechanical loading. Osteoporosis can be classified as primary or secondary.

Key Words: Osteoporosis, Epidemiology, Histology, Remodeling, Classification

Decreased bone density or *osteopenia* is pathognomonic for *osteoporosis*[1,2]. Despite the decreased density, the osteopenic bone in osteoporosis is normally mineralized[1-3]. This distinguishes osteoporosis from *osteomalacia*, a condition with which it is commonly confused; in osteomalacia, the bone matrix is insufficiently mineralized[1,4]. One way to assess bone mineral density (BMD) is by dual-energy X-ray absorptiometry (DEXA). According to Glase and Kaplan[1], the World Health Organization (WHO) has used this diagnostic test to establish criteria for the classification of osteoporosis (Table 1). The physical therapist has three distinct roles with regards to patients at risk for or diagnosed with osteoporosis or osteopenia.

Our first role pertains to screening patients for osteoporosis and osteopenia. The fracture threshold is a hypothetical concept representing a BMD below which fracture as a result of unspecified external forces becomes more likely. Some physical therapy interventions may generate mechanical forces that exceed the fracture threshold in a patient with decreased BMD. In this era of direct access to physical therapy services and limited patient contact time with the primary-care physician due to managed care constraints, the physical therapist, therefore, needs to be able to screen patients for a low BMD. Being able to identify patients at risk for low BMD will not only allow the therapist to appropriately choose intervention parameters but also enable a timely referral to medical colleagues.

Our other two roles deal with prevention and treatment. The *Guide for Physical Therapist Practice*[5] contains a preferred practice pattern for primary prevention and risk-factor reduction for skeletal demineralization. It describes two treatment goals. One is having the patient who is at risk for low BMD maintain a density above the fracture threshold. The other goal is having the patient with identified low BMD reverse the demineralization process and achieve BMD above the fracture threshold.

This article is Part I of a two-part series. The goal of this part is to increase the physical therapist's knowl-

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Table 1. World Health Organization diagnostic criteria for osteoporosis. BMD- bone mineral density; SD- standard deviation. Modified from Glase and Kaplan (1997)[1]

Group	Diagnostic criteria
Normal	BMD within 1 SD of the mean of a young adult reference population
Osteopenia	BMD between 1.0 and 2.5 SD below the mean of a young adult reference population
Osteoporosis	BMD greater or equal to 2.5 SD below the mean of a young adult reference population
Severe osteoporosis	Osteoporosis with one or more fragility fractures

edge of the epidemiology of osteoporosis, the histology of bone, the influences on bone remodeling, and the classification of osteoporosis. This knowledge will serve as a basis for the follow-up article, which deals with the more practical aspects of diagnosis and treatment. Together these two articles will enable the physical therapist to effectively screen patients for undiagnosed osteoporosis and to develop appropriate treatment programs for those patients at risk for or diagnosed with osteoporosis.

Epidemiology

Following the WHO classification mentioned above approximately 0.6% of young women may be diagnosed with osteoporosis; 16% are osteopenic. By age 75, some 38% of white women are estimated to be osteoporotic, while 94% can be diagnosed with osteopenia[1]. Osteoporosis affects between 20 and 25 million people in the United States[3,6,7]. This number has been estimated to increase to 35 million by the year 2015[6].

Reduced BMD decreases the mechanical strength of bone and increases fracture risk[1]. Yearly 1.5 million fractures are associated with osteoporosis: 700,000 vertebral fractures, 300,000 hip fractures, 250,000 distal forearm fractures, and another 250,000 fractures in other sites[6]. In 1995, the direct medical costs alone for treatment of osteoporotic fractures in the United States were estimated at 13.8 billion dollars[8]. Thirty percent of all white postmenopausal women eventually have osteoporotic fractures[3]. Forty percent of women in their eighties have fractured one or both hips[9]. Vertebral fractures occur in approximately 25% of postmenopausal women[8]. As cited by Kosmahl[10], the National Osteoporosis Foundation estimated that 90% of these hip and vertebral fractures in older white women are to be attributed to osteoporosis.

Osteoporosis is not limited to women: it affects an estimated 5 million men over the age of 50 in the United States. Approximately 5% of white, Asian, Hispanic, and Native American males aged 50-79 have osteoporosis; 3.5% of black men in this age group are osteoporotic. These numbers increase to approximately 24% of white men, 17% of black men, and 5% of Asian, Hispanic, and Native American men age group 80 and older. The lifetime risk of having an osteoporosis-related fracture for men over 50 is estimated at 13%[11]. This may even be an underestimation: Kelley et al[11] quoted an Australian study that found a 29% residual lifetime risk for osteoporotic fractures in 60-year-old men of an average life expectancy.

Histology

Bone tissue is the primary storage depot in the body for calcium (Ca^{2+}), phosphate (PO_4^{3-}), sodium, and magnesium[7]. Bones contain the red (hematopoietic) marrow, where the blood cells are formed[12]. Bone protects components of the nervous system and visceral structures, provides a rigid internal support to the trunk and extremities, and provides attachment sites for soft tissue, such as capsule, ligaments, and tendons[3,12]. It is a specialized connective tissue composed of a cellular component, the organic bone matrix, and inorganic calcified intracellular material[12]. Internal and external surfaces of bone are lined with the *endosteum* and *periosteum*, respectively[12].

The three main cell types in bone are *osteoblasts*, *osteocytes*, and *osteoclasts*[12]. Osteoblasts have an abundant endoplasmatic reticulum, characteristic of cells manufacturing proteins for export out of the cell[13]. They are formed by mitosis and differentiation of *osteoprogenitor* cells in the inner, more cellular layer of the periosteum, and in the endosteum which lines the internal surface of bone cavities[12]. Osteoblasts are, therefore, only found at the inner and outer surfaces of bone tissue. Due to their location, resting osteoblasts are known as *bone lining cells*[13]. More metabolically active osteoblasts synthesize the organic components of the bone matrix[12]. Deposition of the inorganic components of the bone matrix also depends on the presence of viable osteoblasts, presumably because of the ability of the osteoblasts to concentrate these components in intracytoplasmic vesicles which are re-

leased into the extracellular matrix when needed[12].

The osteoblasts produce a layer of initially uncalcified matrix, called *osteoid*[12]. As this matrix is calcified, the osteoblasts, now called osteocytes, become contained within the matrix in *lacunae*[12]. There is one osteocyte per lacuna. Osteocytes have a higher nucleus-to-cytoplasm ratio than osteoblasts and contain less cell organelles[13]. Metabolites cannot diffuse through the calcified matrix: osteocytes extend cytoplasmic processes through thin cylindrical spaces perforating the matrix, called *canaliculi*[12]. This way they form junctions with the cytoplasmic processes of the osteocytes in adjacent lacunae, and eventually with blood vessels in order to perform their function of maintaining the surrounding bone matrix[12]. The osteocytes are also in contact via these canaliculi with the osteoblasts on the bone surface[13]. This fits into the hypothesis that osteoblasts receive the majority of local and systemic signals and then transmit these to the other cells contained in bone[13]. Conversely, signals generated due to mechanical deformation of the bone might be perceived in the local osteocytes, which could pass on regulatory information to the osteoblasts by way of the canaliculi[13].

Osteoclasts are large motile, multinucleated cells[12,13]. Junqueira et al[12] reported that they are formed by the fusion of blood-derived monocytes. Other authors have noted that they are derived from the pluripotent cells of bone marrow; these hematopoietic precursors also give rise to macrophages and monocytes[13,14]. Osteoclasts may move from the bone marrow to the bone either by direct migration from the marrow, or by migration through the circulation[14], possibly explaining the controversy regarding their origin. Osteoclasts secrete hydrogen ions to facilitate dissolution of calcium phosphate from the bone matrix as well as collagenase and other proteolytic enzymes to break down the organic bone matrix[12]. Osteoclasts do not have receptors for a majority of the locally and systemically released substances that affect bone cell function[13] (we will discuss this later). For the osteoclast to resorb bone, the activated osteoblast must first contract somewhat in order for the osteoclast to gain access to the bone surface. The osteoblast must also produce and deposit neutral proteases to degrade the thin layer of unmineralized osteoid covering the bone. Osteoclasts may have to be exposed to a mineralized bone surface as well as certain matrix components to become active[13].

Approximately 50-60% of the dry weight of the bone matrix is inorganic matter[9,12]. The main components are calcium and phosporus, laid down alongside collagen fibers, both in the form of hydroxy-apatite crystals with the composition $Ca_{10}(PO_4)_6(OH)_2$, and as non-crystalline, amorphous calcium phosphate[9,12]. The surface ions of the hydroxy-apatite crystals are hydrated. This layer of water around the crystal, known as the *hydration shell*, facilitates rapid exchanges of ions between the crystal and the extracellular fluid[12]. The organic component of the matrix consists of type I-collagen, proteoglycans, phosphoproteins, phospholipids, hyaluronic acid, and glycoproteins[9]. Several glycoproteins unique to bone tissue such as bone sialoprotein and osteocalcin have been identified; these proteins have a high affinity for calcium and may play a role in calcification of the bone matrix[12]. Also present in very small amounts in the bone matrix are growth factors and cytokines, such as transforming growth factor beta (TGF-beta), insulin-like growth factor (IGF), interleukin (IL)-1 and IL-6, and bone morphogenic proteins (BMP) 1 through 6[13]. These substances are capable of influencing bone cells; released from the matrix as a result of osteoclastic bone resorption, they may play a role in a feedback mechanism that regulates bone remodeling[13].

The two most common types of bone are *compact* bone and *cancellous* bone[9,12]. Visual observation of cross-sections of bone shows dense areas without any cavities, corresponding with compact bone, and areas with multiple interconnecting cavities, corresponding with cancellous bone. Because of its structure, cancellous bone is also known as *spongy* or *trabecular* bone[9,12]. Compact bone is located in the cortex of bones and in the shaft (*diaphysis*) of the long bones: it is, therefore, also known as *cortical* bone[9]. Cancellous bone is found in the bulbous ends or *epiphyses* of the long bones, covered by a thin layer of compact bone; in a thin layer underneath thicker compact bone lining the marrow cavity of the long bones; and in the core of the short bones[12]. The microscopic structure of compact bone and of the bone in the *trabeculae* separating the cavities in cancellous bone is similar despite the distinctly different appearance on gross observation[12]. Compact and cancellous bone involvement is used to differentiate between the different types of osteoporosis[3,9].

Bone Remodeling

During life, bone is constantly being resorbed and newly formed: the turnover rate of calcium in bone is 100% per year in infants and 18% per year in adults[15]. Bone turnover is a surface event; because cancellous bone has a greater surface area than compact bone, its turnover is more rapid[13]. The renewal rate is about 4% per year for compact bone versus 20% for cancellous bone[15]. The three primary influences on the bone remodeling process[7] are discussed next:

- Calcium and phosphate levels in the extracellular fluid
- Levels of certain hormones with an effect on bone metabolism
- Mechanical stress on bone

Calcium and Phosphate Metabolism

The skeletal bones contain 99% of all the calcium in

the body[13,15]. Calcium is physiologically very important. Calcium salts provide structural integrity to the skeleton[14]. Calcium also plays an important role in blood coagulation[15]: calcium ions act a co-factor for the clotting factors VII, IX, and X[14]. Calcium ions link the processes of excitation and contraction in skeletal and cardiac muscle. In secretory cells, cytosolic calcium connects the secretory vesicles to the plasma membrane allowing for exocystosis of cell products. The intracellular ionized calcium levels also control the activity of key regulatory metabolic enzymes. Calcium activates phosphoenolpyruvate-carboxykinase and inhibits pyruvate-kinase, resulting in increased gluconeogenesis in the kidney. In skeletal muscle, calcium enhances glucogenolysis by acting upon phosphorylase-b-kinase[14]. Calcium also has an important role in maintaining the membrane potential of excitable tissues, such as nerves and muscles[9]. Low intracellular ionized calcium concentrations increase nervous system excitability by increased permeability of the neuronal membrane to sodium. Hyperexcitable nerve fibers spontaneously depolarize, eliciting tetanic contractions in the skeletal muscles that they innervate. Increased central nervous system excitability may even lead to seizures[14]. Hypocalcemic tetany is a situation in which low calcium blood levels cause extensive spasms of the skeletal muscles, especially in the extremities; the laryngeal muscle spasms induced by hypocalcemia can be fatal[15]. Increased serum levels of ionized calcium depress central and peripheral neural excitability, resulting in mental sluggishness and hyporeflexia[14]. Forty percent of the serum calcium is bound to proteins: 90% to albumin and 10% to globulins. The binding to albumin is pH-dependent. Acidosis decreases this binding and leads to increased ionized serum calcium levels. Respiratory alkalosis as a result of hyperventilation causes increased binding: the resultant hypocalcemia explains complaints of perioral paraesthesiae, carpal muscle spasms, and even seizures[14].

Phosphates and phosphorus are found in many proteins, ATP, cAMP, and other compounds vital to cell function; (de)phosphorylation of proteins plays a role in the regulation of multiple cell functions[15]. The skeleton contains 85-90% of all the phosphorus in the body[15].

Calcium is absorbed from food in the intestine[15]. Sufficient nutritional intake of calcium is critical to bone maintenance[13]. Even a chronic mild dietary calcium deficiency will cause a negative calcium balance and gradual loss of bone mass. In young individuals, approximately 15-25% of the ingested calcium is absorbed; in the elderly, this percentage declines. Augmented dietary calcium may be necessary during the adolescent growth spurt and early adulthood when a peak bone mass is achieved, and during pregnancy and especially lactation[13]. If during pregnancy the mother's diet is deficient, the developing fetus tends to have priority at the mother's expense[16]. Insufficient calcium intake is common: only 15% of girls and 53% of boys actually meet the recommended minimal daily allowance (RDA) of 1200 mg for people between ages 11 and 24[16]. As we will discuss later, vitamin D_3 plays an important role in the active transport of calcium across the intestinal wall. Other nutrients may affect calcium absorption. Substances such as phosphates or oxalates, which form insoluble salts with the Ca^{2+}-ions, will decrease intestinal absorption[15]. Alkalis in food favor the formation of insoluble calcium soaps, again decreasing absorption[15]. Overconsumption of fatty acids produces oxalates and phytates; these substances will decrease the action of anti-oxidants, increasing the oxydative binding of free radicals to calcium, thereby preventing its absorption[9]. High quantities of dietary fiber will also decrease calcium absorption[9,17]. A high protein diet increases calcium absorption in adults[15].

Phosphorus is absorbed from dietary sources in the duodenum and the small intestine. Vitamin D_3 also plays a role in increasing absorption. Unlike in the case of calcium, the amount of phosphorus absorbed increases linearly with dietary intake[15].

After crossing the intestinal wall, most of the calcium is deposited in the skeletal bones. From here, it is continually released to maintain appropriate blood levels[7,12,15]. Approximately 500 mmol per day is released into the bloodstream from the interstitial fluid by diffusion of calcium ions into the hydration shell of the hydroxyapatite crystals[12,15]. A small amount of calcium (7.5 mmol per day) is released into the bloodstream as a result of continuous bone remodeling[15]. Small amounts of calcium are excreted through the kidneys, but most of the calcium is re-absorbed (98-99%), mainly in the proximal tubules of the kidney (60%), and to a lesser extent in the ascending limb of the loop of Henle and in the distal tubule (40%). Some nutrients affect renal calcium re-absorption. Excessive protein intake increases urinary excretion[4,14,18]. Excessive intake of refined sugar increases urinary calcium excretion by altering renal tubular calcium reabsorption[14]. Caffeine and alcohol can increase excretion by their diuretic action, flushing the system of calcium and other important nutrients[9]. Excessive sodium intake may also impair calcium re-absorption[14]. Plasma phosphorus is filtered in the glomeruli with an 85-90% reabsorption fraction[15].

Hormonal Influences

As we discussed earlier, 99% of the total body calcium is sequestered in the skeleton; this leaves 1% to circulate in the extracellular and intracellular fluid[13]. Similarly, 85 to 90% of all phosphorus is contained in the skeleton[15]. The biochemical roles of calcium require that its extracellular and intracellular concentrations be maintained within a relatively narrow range[14]. The serum calcium and phosphate concentrations are maintained by a flux of these two substances between the blood and three organs: bone, kidney, and intestine[14]. Three hor-

mones are primarily responsible for regulating calcium and phosphate metabolism: *1,25-dihydroxy-cholecalciferol*, *parathyroid hormone*, and *calcitonin*[3,7,9,13-15]. We will discuss these and other hormones and cytokines with an effect on calcium and phosphate metabolism.

A healthy diet contains *vitamin D_3* or *cholecalciferol*[9,12,15]. Vitamin D_3, however, is not a vitamin in the strictest sense; i.e., it is not an essential dietary requirement as it is photochemically produced in the high dermis and lower epidermis[12,14,15]. Exposure to mid-ultraviolet radiation (250-310 nm) turns *7-dehydrocholesterol* or *provitamin D_3*, an inert precursor available in the skin, into *previtamin D_3*; over days, previtamin D_3 undergoes a temperature-dependent isomerization into vitamin D_3[14]. Vitamin D_3 is then hydroxylated twice before it becomes the active metabolite 1,25-dihydroxy-calciferol or *calcitriol*: first in the liver by the enzyme *25-hydroxylase* to *25-hydroxycalciferol* or *calcidiol*, and then in the kidneys by the enzyme *1-alpha-hydroxylase* to calcitriol or 1,25-$(OH)_2D_3$[15]. Calcitriol increases the active transport of calcium from the intestine by forming *calbindin-D* proteins, calcium-binding proteins that have been correlated with increased transport of calcium across the intestinal epithelium[15]. It also increases the number of *Ca^{2+}-H^+-ATPase* molecules in the intestinal cells, molecules needed to pump calcium into the interstitium[15]. Calcitriol also increases the active transport of phosphate ions from the small intestine and facilitates calcium and phosphate reabsorption in the kidneys[13-15]. Osteoprogenitor cells and osteoblasts, but not osteoclasts, have been shown to have receptors for calcitriol[14]. Osteoblast-mediated activation of osteoclasts as discussed earlier stimulates overall bone cell function resulting in higher serum calcium and phosphate levels[15]. There is also some evidence that circulating monocytes as a result of interaction with calcitriol may fuse into multinucleated macrophages resembling osteoclasts[14]. Calcitriol also stimulates the production of osteocalcin and alkaline phosphatase, which may play a role in the mineralization of osteoid[14]. High blood phosphate and calcitriol levels decrease the activity of 1-alpha-hydroxylase and, therefore, the production of additional calcitriol[15]. Hyperthyroidism is associated with decreased calcitriol production[15]. Anticonvulsants stimulate the production of hepatic microsomal mixed oxidase enzymes, which convert vitamin D metabolites into hydroxylated, biologically inactive substances; this may explain decreased mineralization in patients receiving prolonged high-doses of anticonvulsant medication[14]. Calcitonin and growth hormone increase calcitriol production. Prolactin, a hormone produced during lactation, increases the activity of calcitriol, thus maintaining high calcium reabsorption rates during this time of increased calcium demand[15].

Parathyroid hormone or *PTH* is produced in the *chief cells*, the principal parenchymal cells of the parathyroid gland, cleaved into biologically inactive fragments in the liver, and then excreted through the kidneys[9,14,15]. PTH acts on the lacunar osteocytes: stimulation results in *osteocytic osteolysis*, a rapid mobilization (within minutes) of bone mineral by these osteocytes in response to PTH[14]. PTH also results in osteoclastic resorption, which is more delayed; it may take hours to days[14]. Osteoclasts have no PTH cell membrane receptors: PTH stimulates receptors on osteoblasts, which in turn mediate osteoclastic activity[13]. PTH also stimulates osteoclastic precursor cells to differentiate into the multinucleated osteoclasts[14]. The overall result of this bone cell stimulation is increased calcium and phosphate mobilization from the bone[9,15]. PTH is believed to influence bone cell activity by stimulating membrane *adenylyl-cyclase* to form cAMP and by promoting calcium influx into the bone cells[14]. PTH also decreases phosphate re-absorption, increases renal calcium re-absorption, and increases calcitriol production[7,14,15]. PTH production is self-regulatory through two negative feedback loops. The parathyroid glands have cell membrane receptors for calcium ions: high blood calcium levels will decrease PTH production[14,15]. High calcitriol levels, partly the result of high PTH levels, will also decrease PTH production by decreasing the production of a precursor to PTH[14,15]. Epinephrine and glucocorticosteroids stimulate PTH secretion; hypomagnesia decreases production of PTH[14]. Intermittent PTH secretion increases osteoblastic activity and stimulates remodeling resulting in increased bone growth. However, a chronic increase in circulating PTH results in a net bone resorption and the formation of large osteoclast-filled cavities in the bone, a condition known as *classic osteitis fibrosa cystica*[14].

Calcitonin is excreted by the parafollicular or C[clear]-cells of the thyroid gland in response to high serum calcium levels[9,14,15]. Osteoclasts have cell membrane receptors for calcitonin[14]. Calcitonin decreases calcium and phosphate concentrations by directly inhibiting osteoclast activity and by increasing calcium excretion in the urine[9,14,15]. Increased calcitonin levels during pregnancy and lactation protect the mother's bone density, as the growing skeleton of the baby and calcium loss with lactation can be major drains on the calcium blood levels of the mother[15].

Other hormones and substances may also have an effect on bone remodeling. Estrogen has a bone-sparing effect. Cell membrane receptors for estrogen have been found on osteoblasts[3,14,15]. Estrogen inhibits secretion of IL-1 and tumor necrosis factor-alpha (TNF-alpha). These cytokines play a role in the development of osteoclasts[3,9,15]. Estrogen decreases IL action by affecting their receptor on the osteoclastic cell membrane[9]. It increases TGF-beta production: this substance increases apoptosis or genetically programmed cell death of osteoclasts[15]. TGF-beta also stimulates differentiation and replication of osteoblastic progenitors and inhibits osteoclastogenesis[14]. Estrogen reduces prostaglandin E_2 (PGE_2) levels[14]. Estrogen and testosterone decrease the sensitivity of bone cells to PTH[9].

Estrogen also stimulates the parathyroid glands to increase production of calcitonin and facilitates PTH action in the kidneys[4,9,14,15].

Glucocorticoids lower serum calcium levels by inhibiting osteoclastic activity. However, long-term elevated glucocorticoid levels, as occur with Cushing's syndrome or may occur iatrogenically as a result of overmedication, will cause decreased BMD by inhibition of protein synthesis in osteoblasts, impaired maturation of osteoprogenitor cells into osteoblasts, increased osteoclastic activity, decreased vitamin D-dependent intestinal calcium absorption, and increased renal excretion of calcium and phosphate ions[7,15]. Glucocorticoids also suppress gonadal estrogen and testosterone production and directly stimulate PTH production[14,16]. PTH production is also increased as a result of the secondary hyperparathyroidism associated with chronically decreased serum calcium levels[13,14,16]. Corticosteroids may also directly decrease bone formation by their inhibitory effect on collagen synthesis[13].

In hyperthyroidism both *thyroxine* and *triiodothyronine* may cause increased bone resorption, hypercalcemia, decreased PTH-levels, decreased calcitriol levels, and decreased intestinal calcium absorption[14]. Thyroid hormones also favor increased urinary excretion of calcium[15]. The net result of hyperthyroidism is increased bone remodeling with a loss of bone mass[4,16]. Of course, excessive thyroid hormone levels may also be the result of overreplacement for hypothyroidism[14].

Growth hormone increases both urinary excretion and intestinal absorption of calcium: the net result is increased calcium absorption[15]. *Somatomedin C*, or IGF-I, is a growth hormone-dependent peptide produced in the liver and in bone[14]. It is mitogenic for chondrocytes and osteoblasts, stimulates osteoblast activity, and increases protein synthesis in bone[9,14,15]. Administration of growth hormone to deficient children stimulates bone growth via somatomedin C production. It also increases intestinal calcium absorption by way of a vitamin D-independent mechanism and it increases renal tubular phosphate re-absorption[14].

Insulin increases bone formation, but untreated diabetes may result in bone loss[15]. This may be related to the diuresis of calcium in untreated and poorly controlled diabetes with secondary hyperparathyroidism as a result of the resultant hypocalcemia[13]. Heparin, released by mast calls or administered therapeutically, enhances collagenase activity and may have a resorptive effect on the bone matrix[13]. We discussed earlier how the bone matrix contains small quantities of TGF-beta, IGF, IL-1, IL-6, and BMP 1-6[13]. These cytokines may also be produced and released by local monocytes and lymphocytes[13]. We already discussed the role of TGF-beta. IL-6 is produced by osteoblasts in response to PTH, calcitriol, IL-1, and TNF-alpha. The latter two substances may be released from the matrix during bone resorption. IL-6 stimulates the early stages of osteoclastogenesis; its production is inhibited by estrogen and testosterone. IL-1 is also osteoclastogenic but, unlike IL-1, its production is not regulated by sex hormones[13]. BMP 1-6 modulate bone remodeling with their mitogenic, differentiating, and chemoattracting properties[13]. Osteoblasts have receptors for PGE_2: stimulation allows osteoclasts access to the bone as a result of osteoblast contraction and osteoblastic osteoid degradation as discussed earlier[13].

Mechanical Loading

Gravity and muscular contraction both cause mechanical deformation of bone[9]. Cellular function normally generates bio-electric effects independent of mechanical stress, but mechanical deformation results in stress-generated electrical potentials, superimposed on this normal bio-electric activity. There are two types of stress-generated potentials: piezo-electric and streaming potentials[13]. In piezo-electric materials, potentials are produced by strain in the organic components of the material, i.e., collagen and proteoglycans. Streaming potentials are the result of electrolyte fluid flow produced by deformation of the tissue[13]. Compression causes an increase in negative charges and increased osteoblastic function; tension results in increased positive charges with increased osteoclastic function[9]. The role stress-generated potentials play in bone remodeling remains uncertain[13].

The response to mechanical load is specific to the bone being loaded[19]. Mechanical load stimulates bone cells to increase synthesis of *prostacyclin* (PGI_2), PGE_2, *glucose-6-phosphate-dehydrogenase*, and RNA within minutes of loading[9,19,20]. PGE_2 and PGI_2 mediate the resorptive response to cytokines and growth hormone in bone: thus, intermittent mechanical force through the increased production of these substances will stimulate bone formation[20].

As discussed earlier, IL-1 and IL-6 stimulate bone resorption. Strenuous exercise increases the IL-1 production. This effect, however, is less pronounced in trained versus untrained individuals. Furthermore, trained individuals have lower average levels of cytokines than untrained people. Regular exercise may result in lower average cytokine levels, which in turn could result in a reduced stimulation of osteoclasts[20]. The relative importance of all these mechanisms is unclear at present[20]. Mechanical loading through exercise has the potential to be a safe and effective way to avert or delay the onset of osteoporosis. The use of exercise as an intervention is discussed in the second article in this series.

Classification

Osteoporosis can be classified as primary or secondary. Included in the primary category are idiopathic,

postmenopausal, and senile osteoporosis. Senile osteoporosis is also known as involutional osteoporosis. Secondary osteoporosis is osteoporosis caused by other disorders[3,7].

Primary Osteoporosis

Idiopathic osteoporosis is osteoporosis of an unknown etiology that occurs in pre-menopausal women and young to middle-aged men with normal gonadal function[4,7]. Juvenile idiopathic osteoporosis is a usually self-limiting disease affecting previously healthy, prepubertal children between ages 8 to 14. It usually runs an acute course over a period of two to four years, during which time skeletal growth stops. Multiple fractures may occur in both the appendicular and axial skeleton. The disease may be mild, affecting only one to two vertebrae, or it can be severe, resulting in deformity of virtually all the lumbar and thoracic vertebrae and multiple extremity fractures. Remission is spontaneous with resumed linear and radial growth. A main goal of treatment is to protect the spine until such remission occurs[16].

The two most important factors in the development (and prevention) of osteoporosis are the peak bone mass (PBM) and the rate of bone loss after attaining PBM[9,13]. PBM is the maximal bone mass that an individual experiences during his or her lifetime[9]. Bone mass peaks after skeletal maturity, somewhere in the third decade[13]. Boissonnault[7] placed PBM between the ages of 25 and 35 years old. However, nearly maximal BMD may already be achieved in both the lumbar spine and the femoral neck before the end of the second decade. Gains during a person's 20s are small when compared to the dramatic gains during adolescence. In girls, the rate of gain in the lumbar spine and femoral neck already starts to decline two years after menarche. By age twelve, girls have already achieved 50% of their adult bone mineral content and 80% of their adult BMD[16]. This prompted Gleeson[16] to view osteoporosis as a pediatric disease rather than as a disease of middle to old age. (The implications of this for prevention of osteoporosis are discussed in the second article.)

After attaining PBM, bone formation rates remain constant, but bone resorption rates increase: in the decade after age 40 men lose 0.5-0.75% of their bone mass every year, while women lose 1.5-2% per year[13]. The rate of bone loss increases dramatically after menopause. Boissonault[7] reported a bone loss of 11% in the first 5 years after menopause and an additional loss of 5% in the next 20 years. Kaplan et al[13] reported bone loss of up to 3% per year. McCloy[17] reported a postmenopausal bone loss of 3 to 5% per year for a period of 10 to 15 years. Typical for postmenopausal or type I osteoporosis is selective loss of cancellous bone[9]. The metabolically less active compact bone is less affected[3]. Cancellous bone loss may be as high as 7% per year in the first 5 years after menopause[9]. Postmenopausal osteoporosis is thought linked primarily to a decreased production of estrogen[7]. We discussed earlier the bone-sparing effects of estrogen. Postmenopausal women still produce estrogen, but their levels are below those of age-matched men and premenopausal women[13]. However, the estrogen levels of osteoporotic and non-osteoporotic post-menopausal women are similar[9]. Bottomley[9] hypothesized an interaction with other factors, suggesting a role for dietary calcium intake and absorption and activity and exercise levels.

Type-II or senile osteoporosis occurs in both men and women over the age of 70. It is characterized by a proportionate loss of cancellous and compact bone. This is in contrast to the mainly cancellous bone loss in type-I osteoporosis[9]. With aging, the number of osteoblasts decreases. This may be related to decreased levels of growth hormone. Growth hormone stimulates the production of IGF-I in the liver and locally in the osteoblasts. As we discussed, IGF-I plays a role in mitogenesis and activity of osteoblasts[14,21]. Aging also results in decreased levels of TGF-beta and testosterone[9,14]. Type-II osteoporosis is also associated with a primary defect in the kidney's ability to produce calcitriol. This may be related to a primary impairment in renal 1-alpha-hydroxylase function[21]. Decreased calcitriol levels result in decreased intestinal calcium absorption and a secondary hyperparathyroidism and hyperthyroidism[3,9].

Secondary Osteoporosis

In the sections on calcium and phosphate metabolism and on hormonal influences above, we discussed a number of causes for secondary osteoporosis. Osteoporosis can be caused by nutritional deficiencies, endocrinopathies, gastrointestinal diseases, bone marrow disorders, connective tissue diseases, medications, and a number of other problems[3,7].

Nutritional deficiencies of calcium and vitamin D can cause secondary hyperparathyroidism, resulting in increased bone loss, especially in the elderly[22]. In 1994, the National Institutes of Health's Consensus Development Panel on optimal calcium intake as cited by Lane[22] made recommendations regarding calcium RDA (Table 2). We discussed earlier the calcium-deficient diet among adolescent boys and especially girls. Even though this will not cause osteoporosis, it may decrease peak bone mass, an important determinant of osteoporosis risk later in life. Dairy is the most important dietary source of calcium; however, up to 65% of the elderly are lactose-intolerant[22]. Calcium supplementation is especially important in the elderly: supplementation does not prevent perimenopausal bone loss, but it may stabilize bone mineral content in people over 65, presumably by preventing secondary hyperparathyroidism[22]. It is important to know when educating patients regarding calcium supplementation that calcium is best absorbed when the doses are spread throughout the day: doses over 500 mg may be

Table 2. National Institutes of Health recommendations for optimal daily calcium intake
Modified from Lane (1997)[22]

Target population	Optimal daily calcium intake (mg)
Women	
• 25 to 50 years old	1000
• 50 to 65 years old (postmenopausal)	
Taking estrogens	1000
No estrogens	1500
• Over 65 years old	1500
• Pregnant and nursing	1200-1500
Men	
• 25 to 65 years old	1000
• Over 65 years old	1500
Adolescents to young adults (11 to 24)	1200-1500
Children	
• 1 to 5 years old	800
• 6 to 10 years old	800-1200
Infants	
• Birth to 6 months old	400
• 6 months to 1 year old	600

wasted by the gastrointestinal tract[22]. We already discussed the negative effect that diets high in phosphates, oxalates, alkalis, fatty acids, and dietary fibers have on intestinal calcium absorption. Excessive dietary intakes of protein, refined sugar, caffeine, alcohol, and sodium may increase urinary calcium excretion. Vitamin D deficiency is common in the housebound elderly. Especially during the winter months, photochemical production in the skin may be insufficient. RDA is 400 IU per day, but this may need to be increased to 800 IU in the debilitated, homebound elderly[22]. Vitamin D at supra-physiologic levels, however, can stimulate bone resorption and cause hypercalcemia[4,22].

Many endocrine diseases have the potential to cause osteoporosis. We already discussed the effects of diabetes, hyperthyroidism, hyperparathyroidism, and hypercortisolism (Cushing's disease). Hypogonadism and decreased testosterone production may affect bone mass in men[3]. Cystic fibrosis is often associated with delayed puberty and hypogonadism in boys[16]. Estrogen deficiency in women may occur as a result of menopause, but it can also occur with premature ovarian failure or as a result of oophorectomy[3]. Anorexia nervosa can cause decreased bone mass as a result of estrogen deficiency, but also due to the associated overproduction of endogenous glucocortocoids, generalized malnutrition, and calcium deficiency[16]. Hypothalamic amenorrhea can produce estrogen deficiency among female athletes and especially runners[4]. Periods of amenorrhea or oligomenorrhea during adolescence and early adulthood have been shown to result in bone loss of up to 2% per year; return to a normal menstrual cycle stops further bone loss[22].

Gastrointestinal disorders can interfere with the absorption of calcium, phosphate, and other important nutrients. They may also interfere with the metabolism of hormones important for maintaining calcium and phosphate homeostasis. Bone marrow disorders may affect the formation of the cellular component of bone and connective tissue disease may affect production of the organic matrix of bone. We already discussed a number of medications that may affect bone metabolism. Excessive alcohol intake not only has a diuretic effect resulting in increased calcium excretion; it may also directly inhibit osteoblastic activity and increase serum glucocorticoid levels. It is often associated with malnutrition. Alcoholism is the most common cause of osteoporosis in men[17]. Cigarette smoking has been associated with a 5 to 10% reduction of bone mass in women[7]. This may be the result of inactivation of estrogen in the liver, increased resistance to calcitonin, interference with osteoblastic function, a smoking-related weight reduction, and inadequate intake of nutrients[7,17]. Women who smoke appear to enter menopause earlier; smoking also seems to negate some of the positive effects of hormone replacement therapy in postmenopausal women[17]. Chemotherapeutic agents generally may negatively affect bone metabolism; the exception is tamoxifen. Tamoxifen is an estrogen-antagonist used in the treatment of patients with breast cancer. It is a selective estrogen receptor modulator (SERM) and as such it is recognized by the bone cells as estrogen[22,23]. It has been shown to be 70% as effective as estrogen in preventing osteoporosis[22]. Other SERMs being developed for the treatment of osteoporosis are discussed in the second article.

Conclusion

Osteoporosis and osteopenia affect a large portion of the population. Both sexes are affected, but women are more prone to decreased BMD than men. Bone remodeling is the result of activity of the cellular component of bone. This activity is regulated by a complex interaction of extracellular calcium and phosphate levels, hormonal influences, and mechanical stress to the bone. There are three types of primary osteoporosis: idiopathic, postmenopausal, and senile osteoporosis. Secondary osteoporosis can be the result of a variety of nutritional deficiencies, endocrinopathies, gastrointestinal diseases, bone marrow disorders, connective tissue diseases, medications, and other problems. The information presented in this article will allow for better understanding of diagnosis and treatment as discussed in the second article in this two-part series.

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