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REVIEW

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Overview of osteoporosis: pathophysiology and determinants of bone strength

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Abstract Recent advances in both the pharmacological and surgical treatment of osteoporosis and vertebral compression fractures offer exciting new options for elderly patients. However, these treatments should be considered only with an indepth knowledge of osteoporosis as a metabolic disorder with complex effects on bone, its homeostatic regulation, and vertebral strength. Bone homeostasis is under the influence of both endogenous hormonal changes and external mechanical loads resulting from physical activity. These impart their effects through regulation of the relative activities of bone cells, in particular osteoblasts and osteoclasts, which control bone deposition and resorption, respectively. The strength of a vertebra is directly influenced by the amount and relative proportions of its components, with bone mineral density a useful measure of fracture risk. The purpose of this article is to discuss these issues, among others, in order to offer the reader a better understanding of the pathophysiology of osteoporosis and the determinants of bone strength as they relate to the aging skeleton.

Keywords Osteoporosis · Aging · Mechanical effects · Pathophysiology

Introduction

Decreases in bone mass are inevitable with age. The condition when bone mass drops to a critical level below which fracture risk is substantially higher is termed osteoporosis [17]. Most simply, osteoporosis arises from an imbalance of bone formation and bone resorption. However, understanding the unique characteristics of osteoporosis compared to other metabolic bone disorders requires more indepth knowledge of bone biology and specific pathophysiological mechanisms.

Bone homeostasis is under the influence of both endogenous hormonal changes and external mechanical loads resulting from physical activity [6, 12]. These impart their effects through regulation of the relative activities of bone cells, in particular osteoblasts and osteoclasts. These cells control bone deposition and resorption, respectively. The strength of bone is directly influenced by the amount and relative proportions of its components, with bone mineral density a useful measure of fracture risk [2]. This article will discuss these issues in order to offer the reader a better understanding of the pathophysiology of osteoporosis as well as the determinants of bone strength as they relate to the aging skeleton.

Architectural composition: cortical versus cancellous bone

To understand a pathological process, one must first comprehend relevant normal physiology and microanatomy. There are two contrasting types of bone in the adult human skeleton. Cortical bone is compact and dense. It is found encasing all parts of the skeleton but is most prominent in the diaphyses of long bones such as the femur. The femoral cortex is thick, forming an elliptical tube that surrounds a medullary canal containing sparse trabecular bone. In this example, the mechanical function of cortical

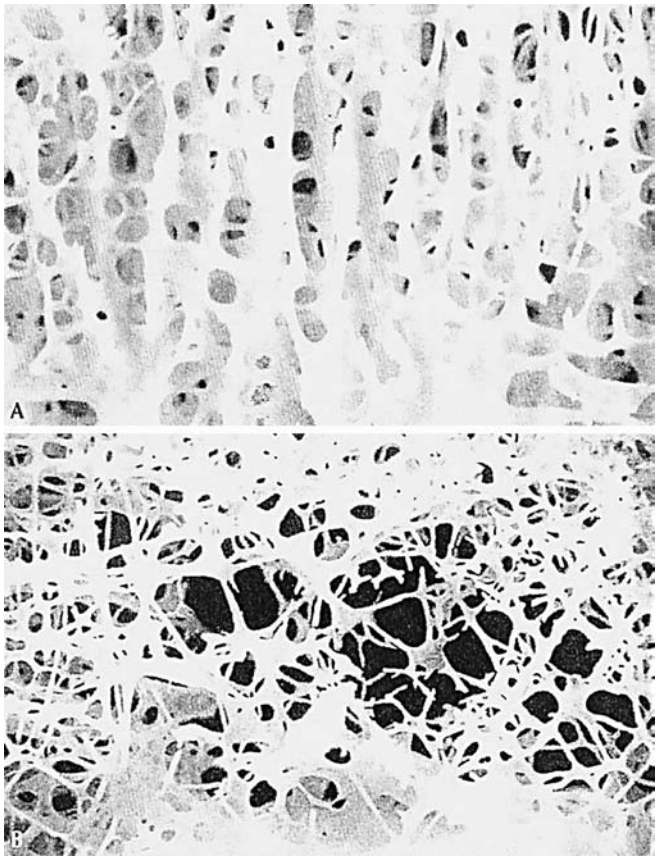

Fig. 1a, b Comparing close-up of views of normal and osteoporotic bone demonstrates a key pathological feature. Note the greater quantity of normal bone (**a**), as well as its greater interconnectivity, compared to osteoporotic bone (**b**)

bone can be best understood. The femur, a major weight-bearing bone, sustains large bending and torsional forces arising during movement. Imagine the forces while ascending a staircase. With extension of the hip and femur, vector forces in opposite directions place huge bending moments along the longitudinal axis of the femoral shaft.

The other type of bone, more abundant in the spine, is trabecular bone. Also known as cancellous bone, it can be considered as a porous interlocking scaffold of vertical and horizontal columns of bone (Fig. 1). Thus, trabecular bone is best at resisting compressive loads. The vertebral body is made up of mostly trabecular bone. In terms of the biomechanics of the spine, this is well suited to the demands of the anterior spinal column. The vertebral body and intervertebral disc sustain approximately 80% of the load during axial compression, with the remaining 20% sustained by the facet joints [21].

The structural differences between cancellous and cortical bone also have metabolic significance. In the densely packed cortical bone, nutrition is supplied by low-pressure vessels within the haversian canalicular system. Considering the amount of bone in relation to the amount of vascularity, the ratio is relatively low. In contrast, cancellous bone is much more richly vascularized by osseous vascular complexes that pass between the less densely packed trabeculae. This arrangement produces a much higher surface-to-volume ratio of bone to extracellular fluids. Therefore, cancellous bone responds more quickly to metabolic alterations and, for this reason, the vertebral bodies are more susceptible to processes that increase bone resorption, such as osteoporosis [9].

Molecular composition: mineralized versus nonmineralized components

While cortical and cancellous bone are architecturally different, they are similar at the molecular and biochemical level. Bone is composed of cells and extracellular matrix (ECM). The cells produce and control the production and removal of bone. The mechanical properties of bone are derived from the composition of the ECM as well as the geometric and architectural characteristics resulting from the way this tissue is distributed in space.

The ECM has mineralized and nonmineralized components. The nonmineralized component is known as osteoid. It is produced and secreted by osteoblasts. The mineralized component is made up of a crystalline material known as calcium hydroxyapatite. The important elements of this material are calcium and phosphate ions. The serum levels of these ions are tightly controlled by various mechanisms that influence bone metabolism and, in turn, bone mass.

Osteoid is made up of both collagenous and noncollagenous proteins. The predominant protein is type I collagen. In general, the collagenous portion of bone is responsible for its tensile strength. The greater the collagen concentration, the higher tensile and shear strength will be. Other noncollagenous proteins include osteonectin, osteopontin, and other various compounds. These noncollagenous proteins affect many of the cellular activities in bone such as the ability of bone cells to attach to the ECM.

The mineralized portion of bone determines its compressive strength. With greater concentrations of calcium, compressive strength increases. Processes that diminish the levels of either bone mineral or collagen substantially decrease the ability of bone to withstand respective loads.

Bones fail and fractures occur when ultimate stress levels are exceeded. Stress is a property defined as an internal resistance to an externally applied load. Tensile and compressive stresses are the result of loads/forces acting along the same line (Fig. 2). Tensile forces act away from each other, while compressive forces act towards each other. Shear forces act towards each other in different, but parallel, planes. Bone can fail under tension, compression, or shear. The relative amounts of mineralized and nonmineralized bone influence its behavior under various loading patterns. Bone fails more easily under shear and ten-

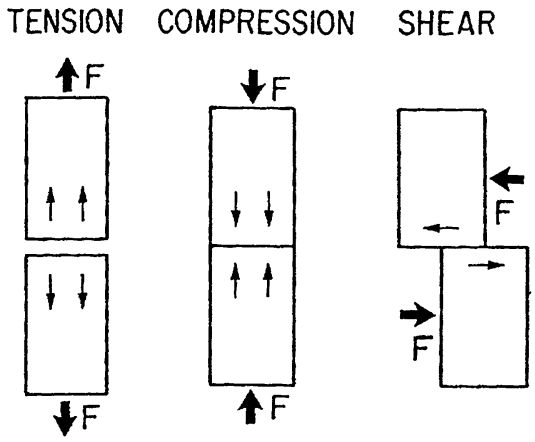

Fig. 2 The three basic types of stress that bone must endure are tension, compression, and shear. *Tension* is produced by forces acting in the same plane but away from each other. *Compression* is produced by forces acting in the same plane but towards each other. *Shear* is produced by two forces acting towards each other but in two different planes

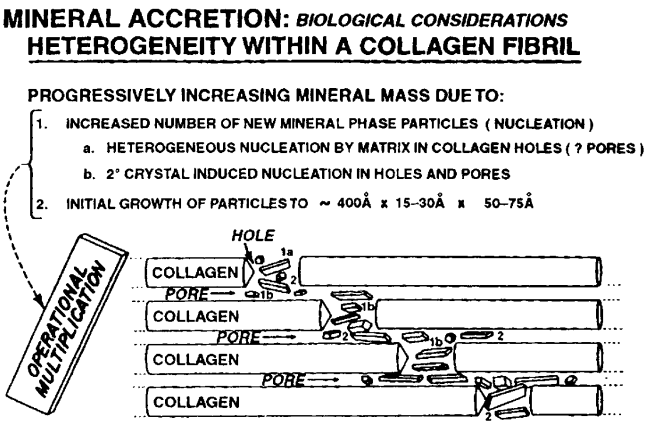

Fig. 3 Bone mineralization is initiated at sites known as *holes* and *pores*. Holes are located between the ends of juxtaposed collagen molecules. Pores are formed longitudinally between collagen molecules

sile forces, while it is strongest in compression. This is true for both cortical and trabecular bone.

These concepts can be illustrated with a simple analogy. Take, for example, a column of bricks stacked one on top of each other, but each connected to its neighbor by a strong rubber band. If one picks up the top brick, while the bottom brick is held fixed to the ground, the bricks will begin to separate, but only as far as the elasticity of the rubber bands will allow it. The rubber bands act like the long fibrils of collagen in bone. Eventually, if the column of bricks is stretched long enough, one of the rubber bands will break. It can be imagined, however, that this would not take an excessive amount of force. Now, consider placing a load on top of the column of bricks. As bricks are used in a similar manner to build a house, they can sustain great loads. One could stand on the column of bricks without fear of the bricks crushing or crumbling. The bricks act like the calcium/mineral component of bone. With this example, it can be understood that (1) the mineral component is responsible for compressive strength, (2) the collagen is responsible for tensile strength, and (3) much greater compressive loads can be endured than tensile loads before failure.

Using the same analogy, shear strength can be illustrated as well. If one were to push the top brick to the right and the bottom brick to the left, the resistance to failure would be from two sources. One would be the elastic tethering effect of the rubber bands. The other would be the friction between the two bricks. Thus shear force would be influenced by both the collagenous and mineral components of bone. In this way, one might also understand why shear strength is dramatically less than compressive strength.

Cellular control of bone mass: osteoblasts and osteoclasts

Osteoblasts are bone-forming cells. They both secrete osteoid and conduct its mineralization. The collagen fibrils within the osteoid are arranged into linear columns, forming pores and holes (Fig. 3). It is at these sites that mineralization is initiated. Osteoblasts have receptors for several factors that are known to control bone metabolism, most notably parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D. Osteoblasts appear to influence the activity of osteoclasts, which suggests that the former may ultimately be in control of both bone formation and resorption.

Recent data have increased the available knowledge of how osteoblasts regulate bone remodeling and resorption. Lacey et al. [13] found that exposing bone marrow cells and osteoblasts to substances like PTH, prostaglandin E_2, and 1,25-dihydroxyvitamin D_3 stimulated osteoclast differentiation and osteoclast activity. This former is effected by expression of an osteoclast differentiation factor known as RANK ligand (receptor activator of NF-κB ligand). RANK ligand binds to a receptor located on the surface of osteoclast precursors. When macrophage colony stimulating factor, a cytokine also produced by bone marrow stromal cells and osteoblasts, binds to its receptor, known as c-fms, the precursor cell then matures into a functioning preosteoclast. This causes an increase in the number of osteoclasts and thus, more bone resorption. To further activate bone resorption, RANK ligand can bind RANK on mature, differentiated osteoclasts. Osteoprotegerin, which is the product of a distinct gene from RANK, inhibits differentiation of osteoclasts by binding RANK as a so-called decoy receptor and preventing its interaction with its ligand [13].

Osteoclasts are bone-resorbing cells. They have several features that make them an ideal vehicle for this func-

tion. They have a ruffled border with extensive membrane folding that increases their metabolically active surface area. The cells effect bone resorption by the release of protons (H^+) via a carbonic anhydrase-dependent proton pump. This lowers the pH of (i.e., acidifies) the region surrounding the cell, which in turn activates specific acid proteases. These proteases then break down the bone within the extracellular matrix. The multinucleated osteoclasts reside within bone resorption cavities or pits known as Howship's lacunae, which can be recognized on microscopic examination. Osteoclasts *do not* have receptors for PTH or 1,25-dihydroxyvitamin D. Therefore, these factors appear to influence osteoclastic activity through mechanisms mediated via the osteoblast binding.

Osteocytes are osteoblasts that have terminally divided. Histologically, they are surrounded by, or trapped within, mineralized bone. Metabolically, they are relatively inactive, with a high nucleus-to-cytoplasm ratio. In view of their radiating processes that extend from the cell border to infiltrate the surrounding canaliculi, it is postulated that osteocytes may transmit signals between the bone cells [9, 19]. However, their role still remains unclear.

Circulating factors that influence bone cell function

A number of circulating substances influence the activity of bone cells. As alluded to above, these are mostly directed towards osteoblasts. PTH is secreted by the parathyroid glands and has direct effects on osteoblasts, as these cells have receptors for this hormone. However, PTH also acts to increase bone resorption in response to low serum levels of calcium. It does this by inducing a rounding of the osteoblast, so that it has less surface area contact with the surrounding bone and allows osteoclasts to have more access to the bony surfaces. In addition, it has recently been shown that PTH binding to osteoblasts induces a secondary messenger system involving RANK and RANK ligand, which activates osteoclast activity as described above.

Vitamin D has known effects on bone metabolism. In its initial form (either ingested or produced with exposure to sun), vitamin D is converted to $25(OH)D_3$ in the liver. It is hydroxylated again to its active form, 1,25-dihydroxyvitamin D, in the kidney. 1,25-Dihydroxyvitamin D stimulates intestinal absorption of calcium [15]. Although the exact mechanism is still not known, it also enhances osteoclastic activity. However, as for PTH, osteoclasts do not have receptors for 1,25-dihydroxyvitamin D, so that these effects are most likely mediated by a secondary messenger mechanism with binding of the vitamin D metabolite to an osteoblast receptor.

Osteoclasts have receptors for calcitonin. Calcitonin is produced in the parafollicular cells of the thyroid gland in response to elevated blood levels of calcium. As calcitonin acts to lower serum calcium, binding of this factor to its receptor has an inhibitory effect on the cell's function. Because of this ability, calcitonin administration has been developed as a potential pharmacological treatment for osteoporosis [10].

More recently, a mechanism of hypothalamic control of bone metabolism has been demonstrated. In contrast to the metabolic pathways of PTH and vitamin D, factors are secreted by bone cells and then themselves in turn affect overall bone metabolism through a centrally mediated mechanism. Leptin, a small polypeptide hormone, is secreted by osteoblasts. Its direct effects are thought to be through control of body weight, while its indirect effects may be through modification of gonadal function via interactions within the hypothalamus [1]. In animal studies, mice with leptin deficiency demonstrated obesity, hypogonadism, and increased bone formation and bone mass. This newly discovered interrelationship between the central nervous system and bone metabolism offers an exciting new frontier in the understanding and possible treatment of metabolic bone disorders such as osteoporosis.

Age-related bone loss and osteoporosis

Primary osteoporosis related to aging has been classified as type II, or senile, osteoporosis. The type I disorder is related to the onset of menopause, and is thus termed postmenopausal osteoporosis. Other causes of osteoporosis can be secondary, such as that caused by long-term corticosteroid use or endocrinopathy.

Peak bone mass is achieved between the ages of 16 to 25 years in most people. After this age, bone mass slowly, but continuously, decreases. The greater the amount of bone achieved during the peak period, the lower the chance that a person will develop osteoporosis later in life. Normal rates of bone loss are different in men and women. In men, bone mass is lost at a rate of 0.3% per year, while for women this rate is 0.5%. In contrast, bone loss after menopause, in particular the first 5 years after its onset, can be as high as 5–6% per year [17]. Because women live longer than men, it is believed that increased longevity places women at higher risk of senile osteoporosis.

Besides the difference in age at onset, types I and II osteoporosis have somewhat different effects on the kinds of bone lost. Type I appears to affect mostly trabecular bone, while type II affects both cortical and trabecular bone [16]. While both types substantially increase the risk of fracture in cancellous bone, such as osteoporotic vertebral compression, distal radius, or intertrochanteric hip fractures, patients with type II disease may be at greater risk of fractures through cortical bone, such as the femoral neck, pelvis, proximal humerus, and proximal tibia.

The cellular mechanism of type II osteoporosis is multifactorial. A major factor is probably progressive dietary calcium deficiency [3]. As patients age, appetite can become suppressed, leading to lower intake of foods rich in

calcium. Financial constraints, as endured by many elderly individuals with low fixed incomes, can be a disincentive to purchasing foods that support a well-balanced diet. This factor, by itself, has been known to contribute to states of malnutrition in elderly people. Moreover, the presence of osteoporotic vertebral compression fractures and the resultant alterations in the dimensions of the trunk can lead to early satiety in affected individuals [14]. This would have a self-perpetuating effect on osteoporosis, as this can lead to further calcium deficiency and more profound loss in bone density.

Another contributing mechanism is progressive inactivity. Bone mass is positively affected by mechanical loads (i.e., exercise and activity). With age, most people become less active, which can potentiate progressive bone loss. While osteoporosis itself is painless, profound inactivity from the pain of an osteoporotic compression fracture can lead to a vicious cycle of further bone loss, more fractures, and more pain and inactivity.

While not the primary mechanism as in type I osteoporosis, decreases in estrogen levels have been demonstrated in both elderly men and women and this is thought to be an important cause of senile osteoporosis as well.

The cumulative effect of normal aging, dietary calcium deficiency, and lower activity is the upregulation of bone resorption and downregulation of bone formation. While it is commonly held that these effects are mediated by stimulation of osteoclasts and inhibition of osteoblasts, the exact mechanisms by which they lead to age-related bone loss is still not well understood.

Geometry: effects of osteoporosis on cancellous bone

Normal cancellous bone, such as that in the vertebral body, is composed of both horizontal and vertical trabeculae. These trabecular struts are interconnected, much like the scaffolding used to surround buildings during construction. While the individual vertical and horizontal members, are, by themselves, important in resisting loads in particular directions (i.e., anisotropic properties), it is their interaction that gives cancellous bone its great compressive strength.

Osteoporosis is a disorder in which total bone mass is reduced yet the quality of the bone is normal. If a microsection of bone were to be biochemically analyzed, it would demonstrate a normal ratio of osteoid to mineral. Though total bone mass is affected, there is a predisposition to loss of the horizontal trabeculae [4]. This leads to decreased interconnectivity of the internal scaffolding of the vertebral body (Fig. 1b). Without the support of crossing horizontal members, unsupported vertical beams of bone easily succumb to minor, normally subcatastrophic, loads. Clinically, this leads to crush of the cancellous bone within the vertebral body, recognizable as an osteoporotic compression fracture, which may occur with low-energy maneuvers such as picking up a bag of groceries.

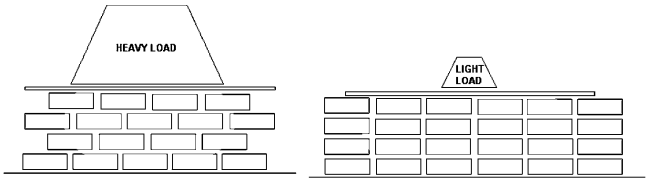

Fig. 4 The importance of interconnectivity of bone is shown by the analogy to a brick wall. Normal bone has interconnectivity, like the overlapping of the brick wall on the *left*. It can sustain heavy loads. Osteoporotic bone has lost its interconnectivity, like the brick wall on the *right*. Its walls can sustain only light loads, as they will collapse and buckle under heavier loads

Using the analogy of the column of bricks detailed above, imagine two different brick buildings. The first is built in the usual manner: the bricks are overlapped with each other in a staggered pattern, representing interconnectivity of the trabeculae. The second building is built with columns of bricks stacked on top of each other with no overlapping, representing loss of interconnectivity (Fig. 4). While both houses might support some weight of objects placed on the roof, the first house would be able to support much greater loads. The walls of the second house would only be able to support much lighter loads. With heavier loads, the walls of the second house will have a tendency to buckle and topple, like an osteoporotic vertebral fracture. Taking the example one step further, consider the first house to be built with bricks made of granite and the second house made of bricks of porous sandstone. The sandstone bricks would have a greater tendency to crumble with loads, as would the osteoporotic vertebral body.

Geometry: effects of osteoporosis on cortical bone

Decreases in bone mass occur throughout the skeleton. As the dense cortices of long bones are designed to withstand bending and torsional loads, decreases in bone mass would potentially diminish loads to failure. Fortunately, long bones exhibit a compensatory mechanism to counteract the mechanical effects of decreased bone mass. In aging individuals, increased endosteal bone resorption and periosteal bone deposition leads to an overall increased diameter of bone. This relationship can be expressed as a formula for the moment of inertia resulting from the loading [4]. Long bones resist failure in bending by their areal moment of inertia and in torsion by their polar moment of inertia properties.

This phenomenon helps explain why mid-shaft long bone fractures do not occur in a proportionately higher frequency in older than younger individuals. Unfortunately, this same adaptive mechanism does not appear to have a role in the vertebral column, as the cortical shell of the vertebral body contributes only about 10% of its overall strength [18].

Geometry: effects on vertebral body strength

The major mechanical role of the vertebral body is to withstand compressive loads. Its broad transverse surface area and primarily trabecular composition are ideal to fulfill these demands. Both bone density and its geometry determine a vertebral body's strength.

The surface area of the vertebral endplates determines the compressive stress concentration imparted to the underlying cancellous bone. In the best case scenario, surface area would be maximized and the compression would be uniform along the entire endplate [20].

In some groups of people, the vertebrae are proportionately smaller. Asians, for example, have a higher rate of vertebral compression fractures than Caucasians. This is thought to be related to the smaller cross-sectional dimensions of the Asian vertebral body. Interestingly, a somewhat opposite relationship is true for osteoporotic hip fractures. Greater hip axis length in Caucasians corresponds to a higher incidence of fracture than the shorter lengths in Asians. This most likely is a result of differences in cantilever bending forces, which would be higher with longer hip axis lengths, as well as with the greater body weights notable in the generally larger Caucasian.

The pattern of loading is another important influence on the amount of weight that can be sustained by the vertebral body. Normal spinal balance dictates that a weight-bearing plumb line dropped from the base of the occiput should fall through the C7 vertebral body, T12–L1 junction, and caudally within or just anterior to the sacral (S2) promontory. This facilitates even distribution of compressive loads to each of the vertebrae in the spinal column. Forward bending of the spine, either fixed or dynamic, leads to a greater percentage of compressive forces along the anterior aspect of the endplates, and thus of the vertebral bodies. Combined with the presence of decreased bone mineral density, this anterior concentration of force can lead to catastrophic failure of the underlying bone. This mode of failure is most common in the thoracic spine, which has a physiologic degree of pre-existing kyphosis [11]. Decreases in cortical bone density with aging within the anterior vertebral body may also predispose to such fracture patterns [7].

The lumbar spine is normally lordotic. Although anterior wedge compression fractures can occur in this region, more commonly fractures demonstrate uniform compression or central (biconcave) types [11]. This may be related to the pattern of loading. One might infer that loads are concentrated within the center of the lumbar endplate if lordosis is maintained at the time of fracture. Ultimately, the pattern of failure, and thus the type of fracture, is most likely influenced by the position of the spine at the time of injury.

Conclusion

As advances in medicine continue to prolong life, an understanding of disorders related to aging becomes increasingly important. Osteoporosis and its complications have important detrimental effects on the quality of life of affected individuals. As with any disorder, a sound understanding of the pathophysiology of the underlying disease process is crucial to effective decision making regarding treatment. Recent advances in both the pharmacological and surgical treatment of osteoporosis and vertebral compression fractures offer exciting new options for elderly patients [5, 8]. However, these treatments should be considered within the context of an indepth knowledge of osteoporosis as a metabolic disorder with complex effects on bone, its homeostatic regulation, and vertebral strength.

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