Pathophysiology of Osteoporosis
New Mechanistic Insights

Laura A.G. Armas, MD, MS[a,*], Robert R. Recker, MD, MACP, FACE[b]

KEYWORDS

• Osteoporosis • Remodeling • Bone quality • Mechanical loading • Microdamage

KEY POINTS

- The definition of osteoporosis includes bone strength and fragility.
- Factors other than bone mineral density contribute to bone strength and resistance to fracture:
  - Defects in the microarchitecture of bone
  - Poor intrinsic material properties of bone
  - Defective repair of microdamage to bone
  - Excessive bone remodeling.

EPIDEMIOLOGY OF OSTEOPOROSIS

Osteoporosis, defined by the World Health Organization (WHO) as a bone mineral density (BMD) T-score less than -2.5 as measured by dual-emission x-ray absorptiometry (DXA) is a common condition affecting 30% of women and 12% of men at some point in their lifetimes. The risk of fracture increases with age, and is increasingly common in the elderly. In the United States, the lifetime risk in white women more than 50 years old is 50%.[1,2] A white man has a 6% risk of hip fracture and 16% to 25% risk of any low-trauma fracture.[3] Fractures lead to significant health care costs ($19 billion in 2005, $25.3 billion by 2025), and impairment of physical function. Hip fractures are particularly risky and are associated with high rates of disability and mortality.

OSTEOPOROSIS DEFINITION

Changing ideas regarding the pathophysiology of osteoporosis are reflected in the changing definitions of osteoporosis as noted in National Institutes of Health

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[a] Osteoporosis Research Center, Endocrine Division, Department of Internal Medicine, Creighton University Medical Center, 601 North 30th Street, Suite 4820, Omaha, NE 68131, USA; [b] Osteoporosis Research Center, Endocrine Division, Department of Internal Medicine, Creighton University Medical Center, 601 North 30th Street, Suite 5766, Omaha, NE 68131, USA
* Corresponding author.
E-mail address: larmas@creighton.edu

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consensus conferences held in 1984 and again in 2001. In 1984, it was defined as follows: "Primary osteoporosis is an age-related disorder characterized by decreased bone mass and by increased susceptibility to fractures in the absence of other recognizable causes of bone loss."[4] In 2001 it was changed to, "Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality."[5] The change in 2001 came from review of literature published between 1995 and 1999 (2449 references). Extensive research conducted since then has further emphasized that, although bone mass or density, however measured, remains an important element in the risk of fracture, it reveals only a portion of that risk in postmenopausal osteoporosis or other syndromes of excess skeletal fragility. Thus, the clinical diagnosis of osteoporosis (ie, the definition) now seems to depend on the presence of low-trauma fracture, defined as fracture resulting from trauma equal to, or less than, a fall from a standing height, excluding fractures of face, skull, or digits. In addition, although risk of fracture is inversely related to bone density, and positively related to age, most low-trauma fractures occur in patients in whom bone density is greater than the WHO threshold for a densitometric diagnosis of osteoporosis (ie, a T-score <-2.5 by DXA).[6,7]

For the purposes of this discussion, osteoporosis is defined as the presence of low-trauma fractures in women after menopause or in men of similar age in the absence of a primary diagnosis or condition that weakens the skeleton. These primary diagnoses or conditions include osteomalacia from any cause; disuse; treatment with corticosteroids or other bone-active medications; gastrointestinal diseases that cause nutritional defects or systemic inflammation; chronic kidney, lung, or liver disease; and a host of conditions/diagnoses that damage the skeleton. Although bone loss, changes in bone quality, and resultant propensity to fracture are usually referred to as osteoporosis when occurring in patients with these diagnoses, the osteoporosis occurring with them is regarded as secondary, and is not included in the definition of postmenopausal or idiopathic osteoporosis as discussed herein. This article addresses the clinical effects of increased bone remodeling rates and defects in bone quality that contribute to the development of osteoporosis. To reiterate, features of bone quality that contribute to skeletal fragility and risk of low-trauma fracture, separately or in combination, are defects in microarchitecture of trabeculae, defective intrinsic material properties of bone tissue, and defective repair of microdamage. Defective repair of microdamage results from physiologic loading occurring in normal daily life. These features occur in the context of age-related bone loss, and bone remodeling rates greater than those found in normal premenopausal women.[8–10]

CLINICAL OBSERVATIONS PERTINENT TO THE PATHOPHYSIOLOGY OF OSTEOPOROSIS

Menopause: The Effect of Estrogen Deprivation on Bone

Menopause is the cessation of menstruation, which is preceded by 1 to 2 years of gradual decline in ovarian estrogen production. It occurs in most women at approximately age 51 years.[11] Estrogen inhibits osteoclast activity and estrogen deprivation removes this inhibition and contributes to loss of bone mass. Estrogen deprivation is also associated with decreased intestinal calcium absorption and increasing urinary calcium loss, likely secondary to infusion of calcium into the plasma from the estrogen-deprived bone, and resultant reduction in parathyroid hormone levels.[12] The rapid bone loss associated with menopause is impressive. In the 5 to 7 years surrounding menopause, women lose approximately 12% of their bone mass[13]; the equivalent of 1 T-score measured by DXA. The trabecular bone is especially affected

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