The Pathophysiology and Treatment of Osteoporosis

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ABSTRACT

Purpose: The objectives of this article are to review the pathophysiology of bone loss associated with aging and to review current pharmacologic approaches for the treatment of osteoporosis.

Methods: A literature search with PubMed was performed with the terms *osteoporosis and pathophysiology* and *osteoporosis and treatment* and limited to studies written in English that were published within the preceding 10 years. Given the large number of studies identified, we selectively reviewed those studies that contained primary data related to osteoporosis pathophysiology or osteoporosis pharmacologic treatments and references included within selected studies identified from abstract review.

Findings: Published studies have consistently reported that osteoporosis in older adults is caused by an imbalance of bone resorption in excess of bone formation. The dominant factor leading to bone loss in older adults appears to be gonadal sex steroid deficiency, with multiple genetic and biochemical factors, such as vitamin D deficiency or hyperparathyroidism, that may accelerate bone loss. Conditions that adversely affect growth and development may limit development of peak bone mass and accelerate subsequent bone loss. Studies of bone microarchitecture have shown that trabecular bone loss begins in the third decade of life, before gonadal sex steroid deficiency develops, whereas cortical loss typically begins in the sixth decade, about the time of menopause in women and about the same age in men. Antiresorptive agents for the treatment of osteoporosis act primarily by limiting osteoclast activity, whereas osteoanabolic agents, such as teriparatide, act primarily by stimulating osteoblastic bone formation. Clinical investigation of new compounds for the treatment of osteoporosis is mainly directed to those that stimulate bone formation or differentially decrease bone resorption more than bone formation. Therapies for osteoporosis are associated with adverse effects, but in patients at high risk of fracture, the benefits generally far outweigh the risks.

Implications: Current osteoporosis therapies mitigate or reverse the loss of bone associated with age-related decreases of gonadal sex steroids, increase bone strength, and reduce fracture risk. With improved knowledge of the pathophysiology of osteoporosis, new targets for therapeutic intervention have been identified. Clinical investigations of potential new treatments for osteoporosis are primarily directed to stimulating osteoblastic bone formation or to modulating the balance of bone resorption and formation in ways that improve bone strength. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: aging, bisphosphonate, bone, bone mineral density, menopause, osteoporosis.

INTRODUCTION

As described in the National Institutes of Health Consensus Development Conference Statement,[1] osteoporosis is a skeletal disorder characterized by diminished bone strength that results in increased fracture risk, with bone strength a function of both bone mineral density (BMD) and bone quality. BMD is commonly assessed clinically by dual-energy x-ray absorptiometry (DXA), a technology that measures integrated cortical and trabecular areal (2-dimensional) BMD at several skeletal sites. Bone quality refers to the non-BMD determinants of bone strength

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that are less easily measured, including bone microarchitecture, degree of mineralization, remodeling activity, and microdamage accumulation.[1]

Epidemiologic data have convincingly indicated that bone loss, as assessed with BMD testing by DXA, occurs in both women and men as part of the natural aging process.[2] Associated with this bone loss is an increased fracture risk. Current estimates are that ~40% of white women aged >50 years will experience an osteoporosis-related fracture, with this risk rising to nearly 50% if vertebral fractures identified by imaging, rather than clinical history, are included.[3] Similarly, it is estimated that ~13% of men will experience an osteoporosis-related fracture.[4] Accordingly, osteoporosis and osteoporosis-related fractures are a major public health concern and impose enormous health care costs. In 2005, annual costs for osteoporosis-related fractures were US$13.7 to US$20.3 billion, an amount expected to rise to US$25.3 billion annually by 2025 due to a projected 48% increase in fractures.[5] Therefore, identifying and treating persons at greatest fracture risk is of critical importance. Evidence supports the cost-effectiveness of pharmacologic intervention for the treatment of patients with prior fragility fractures, low bone mass (osteopenia) and additional clinical risk factors, or osteoporosis as defined by the World Health Organization (DXA T-score ≤ -2.5).[6]

As our understanding of human bone biology has evolved over the past several decades, so too has our ability to provide increasingly targeted therapies for the treatment of osteoporosis. Central to this has been development of an ever-growing pharmacologic armamentarium of medications proven in clinical trials to reduce fracture risk by limiting ongoing bone loss and/or augmenting existing bone mass. The objectives of this article are to review the pathophysiology of bone loss associated with aging and to review current pharmacologic approaches for the treatment of osteoporosis.

METHODS

A literature search through PubMed was performed with the terms *osteoporosis and pathophysiology* and *osteoporosis and treatment* and limited to studies written in English that were published within the preceding 10 years. Given the large number of studies identified, we selectively reviewed those studies that contained primary data related to osteoporosis pathophysiology or osteoporosis pharmacologic treatments and references included within selected studies identified from abstract review.

AGE-ASSOCIATED CHANGES IN BONE MASS AND MICROARCHITECTURE

Until recently, it was believed that from the end of the pubertal growth spurt (the time point at which peak bone mass is attained) until the onset of middle age, both men and women maintained their skeletons without substantial bone loss or changes in skeletal microarchitecture. This belief was predicated on cross-sectional and longitudinal skeletal measurements performed by DXA. Although it was well recognized that bone remodeling was active during this period of adulthood, it was generally thought that bone resorption was evenly matched by bone formation, resulting in stability of bone mass and maintenance of skeletal integrity.

More recent work that used quantitative computed tomography (QCT), however, has found that, contrary to previous beliefs, large decreases in volumetric BMD begin as early as the third decade in both sexes, ultimately resulting in lifetime losses at the spine, a skeletal site consisting primarily of trabecular bone, of ~45% in men and 55% in women.[7] In women, both DXA and QCT imaging found that bone loss at the spine accelerates at the time of the menopausal transition, with loss of ~20% to 30% of trabecular bone mass over the ~6- to 10-year perimenopausal time period.[7,8] By comparison, ~5% to 10% of cortical bone is lost during the female menopausal transition. A subsequent phase of slower but continuous bone loss predominates after menopause. In this second phase, which lasts throughout the remaining life span unless pharmacologic intervention is undertaken, cortical and trabecular bone loss occur at slower, more similar rates.[8] By comparison, because men do not undergo a menopausal equivalent, they do not sustain the early accelerated trabecular bone loss that occurs in women and so lose comparatively less bone than women.

Although trabecular bone loss begins early in both men and women, evidence is good that relatively little cortical bone is lost in either sex until middle age. Thus, epidemiologic analysis of a cross-sectional cohort of men and women in whom QCT imaging was performed at the distal radius, a site composed primarily of cortical bone, found that from approximately