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Osteoporosis in males and females: Is there really a difference?

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Abstract

The prevalence of osteoporosis increases with advancing age. Fractures are more common in women than in men and, apart from the menopause, the reasons for this difference remain poorly understood. The growth period is crucial to skeletal development and results in larger bones in males than in females. The sudden drop in estrogen levels that characterizes the menopause contrasts with the gradual decline in sex hormones seen in aging men, and the proportion of individuals with hypogonadism is considerably lower among older men than among older women. Although estrogens play a crucial role in bone homeostasis in both men and women, via direct and indirect mechanisms, differences exist between the sexes in hormonal physiopathology and its consequences on bone tissue. Many genetic and environmental factors influence the fracture risk. Although women are more prone to fractures, the mortality rate associated with fractures is higher in men. Most of the osteoporosis medications were developed for the treatment of postmenopausal osteoporosis and some are licensed for use only in women. Overall, the diagnosis of osteoporosis is somewhat less neglected than previously, but the treatment of high-risk individuals (those with a history of fracture) remains inadequate, most notably among males.

Keywords: Osteoporosis; Fractures; Sex; Genetics; Absorptiometry; Dual energy X-ray; Bone architecture

Osteoporosis is typically a disease of females, and most osteoporotic fractures occur among postmenopausal women. Nevertheless, in recent years awareness of osteoporotic fractures in males has increased in the medical community. The sudden drop in estrogen production that characterizes the menopause is an obvious risk factor in females, but males experience a gradual decline in the levels of estrogen, a hormone whose influence on bone metabolism at least matches that of testosterone. In addition, in older individuals changes related to bone aging tend to erase the effects of the initial hormonal difference. Therefore, the reason for the higher fracture rate among women is unclear. Whether the pathophysiology of osteoporosis differs between men and women deserves discussion. Here, rather than an exhaustive review, we supply clarifications about male and female osteoporosis based on the many review articles published in the medical literature.

1. Epidemiology

1.1. Fracture rate

The lifetime fracture risk in 50-year-olds is estimated at about 50% in women and 20% in men [1]. Thus, the risk is about 2.5 times higher in women. However, these global statistics mask a number of differences.

In children and adolescents, the annual fracture incidence increases over time but, in contrast to older age groups, fractures are more common among boys than among girls. Although one third of boys and girls experience at least one fracture before 17 years of age, the fracture rate is 60% higher in boys. The most common fracture site is the distal forearm (30%). The age at the fracture incidence peak is 11 years in girls and 14 years in boys. Between 25 and 40 years of age, the fracture incidence is low in both males and females [2].

After 40 years of age, the fracture risk increases in both males and females. The overall 10-year fracture risk at 50 years of age is 9.8% in women and 7.1% in men; corresponding figures at 80 years of age are 21.7 and 8%. In women aged 50 years, the fracture risk is 3.2% at the wrist, 0.3% at the hip, and 0.3% at the spine; corresponding figures at 80 years of age are 5.5,

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8.7, and 1.6%, respectively. In men, the 10-year fracture risk at 50 years of age is 1.1% at the wrist, 0.2% at the hip, and 0.2% at the spine; corresponding figures at 80 years of age are 0.9, 2.9, and 0.7%, respectively [3]. In 2000, the worldwide prevalence of osteoporotic fractures was estimated at over 56 million, with a female-to-male ratio of 1.6. This ratio varies across regions and fracture sites, being highest in Europe and North America, with values of 4 at the wrist, 3 at the humerus, 2.3 at the hip, and 1.6 at the spine [4]. The prevalence of osteoporosis increases from 5% at 50 years of age to 50% at 85 years of age in women; the corresponding increase in men is from 2.4 to 20% [5].

The frequency of vertebral fractures is more difficult to estimate. Although the female-to-male ratio was 3 in several studies from the US, more recent data from Canada and Europe indicate a ratio of 1 for radiographic vertebral deformities, with an increase in prevalence with advancing age, at a faster pace in women than in men [6]. In the 50- to 59-year age group, the prevalence of vertebral deformities is higher in men, suggesting traumatic lesions or Scheuermann's disease, in keeping with the clinical impression. After 70 years of age, however, vertebral deformities are more prevalent in females than in males, strongly suggesting a role for osteoporosis [7].

1.2. Impact of fractures

Pain is the initial consequence of appendicular or vertebral fractures. Among vertebral fractures, only one third cause symptoms (or at least prompt a physician visit) and only 10% require hospital admission [8]. Overall, admissions for fractures are 2.7 times more common among women than among men [9].

The severity of osteoporosis resides in the excess mortality associated with osteoporotic fractures. After a vertebral or hip fracture, the excess mortality persists for up to five years. Mortality differs between men and women: during admission for a hip fracture after 50 years of age, mortality is 8% in men and 3% in women. Mortality is increased within the first few months after hospital admission; one-year mortality is 36% in men and 21% in women. After two years, mortality tends to decrease except in the oldest patients, particularly older men. In patients with vertebral fractures, five-year survival is lower in men (72%) than in women (84%) [8]. In a cohort from Australia followed for 18 years, the standardized mortality ratio (SMR) after a fracture at any site compared to the general population was 1.76 (95%CI, 1.59–1.95) in women and 1.96 (95%CI, 1.69–2.28) in men; corresponding figures for hip fractures were 2.43 (95%CI, 2.02–2.93) and 3.51 (95%CI, 2.65–4.66). Comorbidities significantly associated with mortality in both sexes were a previous history of fracture, age, quadriceps muscle weakness, balance disorders, and smoking. Independent risk factors for mortality were quadriceps muscle weakness and a low level of physical activity in men and a low bone mineral density (BMD) value in women. The fracture itself contributed significantly to mortality in men but not in women. Other comorbidities were cardiovascular, respiratory, and infectious diseases [10].

2. Pathophysiology: similarities and differences

2.1. Bone mass changes over time

In adults, the prevalence of fractures is higher in females than in males in all age groups. The menopause cannot fully explain this difference.

The amount and organization of bone in the body are already determined in utero. A highly significant association has been found between body weight at one year of age and bone surface area or bone mineral content (BMC) at the spine and hip in adulthood. This association persists after adjustment for factors known to influence bone mass including genetic factors (e.g., vitamin D receptor polymorphism) and adulthood lifestyle factors (physical activity, nutrition, calcium intake, smoking, and alcohol use). The association between birth weight (a reflection of growth in utero) and bone mass in adulthood has been replicated in twins, indicating a role for environmental factors on a shared genetic background. The season also influences bone mass: compared to babies born in summer, babies born in winter have lower BMC values and lower cord blood vitamin D concentrations. Maternal factors (smoking, alcohol use, coffee use, and diabetes) are among the environmental factors that may influence bone mass in utero [11].

Morphological differences in skeletal growth exist between males and females. The contributions made by the axial skeleton and appendicular skeleton differ. Before puberty, bone length is the same in both sexes but bone width is greater in males in most studies. This difference in width is probably determined in utero and may be related to sex hormone exposure. The greatest differences in bone length, width, mass, and strength between males and females develop after puberty. Between one year of age and puberty, the growth rate of appendicular bones is twice that of axial bones so that most of the growth recorded in prepubertal children reflects limb lengthening. The prepubertal period is two years longer in boys, who therefore have longer appendicular bones compared to girls. At puberty, differences exist between males and females in the remodelling process that affects the bone layers (periosteum, cortex, and endosteum). In boys, intensified periosteal apposition increases bone width, while a simultaneous increase in endosteal resorption widens the medullary cavity. Cortical thickness increases because the addition of external layers outweighs the inner resorption. In females, in contrast, there is an early decrease in periosteal apposition, and the medullary cavity remains unchanged at some sites and narrows at others. The bones are consequently smaller and narrower with no difference in cortical thickness compared to boys. At the metaphysis of long bones, the trabecular compartment remains unchanged from the age of five years to puberty. At puberty, males have thicker trabeculae and a higher trabecular bone volume. Volumetric BMD (vBMD) does not increase at the spine, because the increase in vertebral size is commensurate with the increase in bone mass. After puberty, vBMD increases in both sexes as a result of an increase in the thickness, but not the number, of trabeculae. Vertebral cross-section width in males is 15% greater before puberty and 25% greater in adulthood, compared to females, whereas trabecular number and thickness are