Chapter 2
Causes and Risk Factors of Osteoporosis

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Bone is a complex matrix of organic collagen upon which inorganic hydroxyapatite, composed of calcium and phosphate, is layered. The internal collagen, often referred to as the scaffolding of bone, has a triple helical, lamellar arrangement that is further cross-linked by a compound of collagen fibers termed pyridinolines. Bone undergoes periodic remodeling—the dual processes of bone formation and resorption—through the action of multicellular units comprised of two types of bone cells—osteoblasts and osteoclasts. Osteoblast cells initially build and continually replace bone throughout the life span; osteoclast cells remove weakened sections of bone. Remodeling leads to thicker and stronger bones until approximately the age of 25; subsequently bone is essentially maintained or slowly lost until age 50 when effects of aging and hormonal changes occur (Fig. 1) [1, 2].

Pathophysiology

Osteoporosis is caused by the excessive breakdown of bone structure, inadequate bone formation, or an imbalance in the activity between the bone cells responsible for bone remodeling. It results from the increased number or activity of osteoclasts, the cells of bone resorption; the decreased number or activity of osteoblasts, the cells of bone formation; or areas of bone that demonstrate both of these abnormal bone cell characteristics [3]. Osteoporosis is evaluated by a bone mineral density (BMD) test which measures the amount of mineral per square centimeter and can be performed by a number of radiological densitometry procedures, most often dual energy x-ray absorptiometry (DXA) [4]. The most common areas evaluated are the lumbar spine or proximal hip and distal radius. With osteoporosis, bone mineral density is decreased due to the breakdown of bone without compensatory, subsequent remodeling [5].

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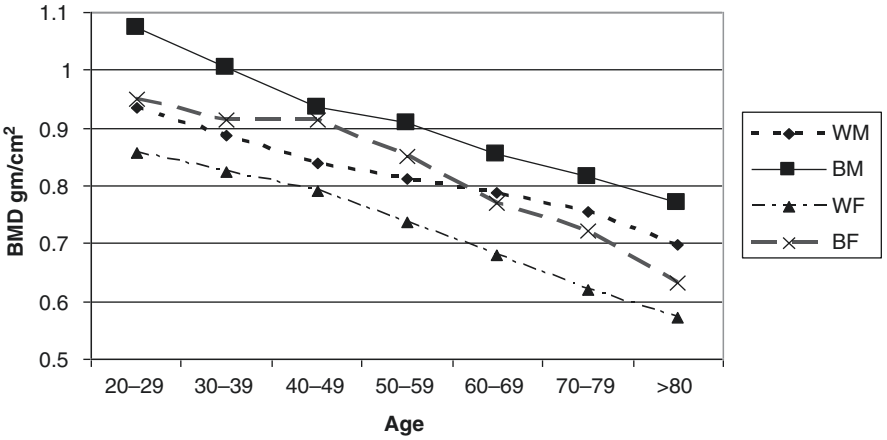

Fig. 1 Mean BMD at the femoral neck by age in the United States, *WM* white males, *WF* white females, *BM* black males, *BF* black females (*Source*: Data from Looker AC)

Compromised bone density results in decreased ability to withstand trauma. Bone loss can accelerate rapidly in certain conditions of high bone turnover such as menopause when estrogen levels fall sharply, neoplasia, metabolic abnormalities, or sudden immobility such as spinal cord injury (SCI) [6]. Bone fractures may occur with minimal external trauma forces such as a mechanical fall or internal trauma resulting from the force of a cough or sneeze. Due to weakened microarchitecture of bone and normal forces of gravity and routine, daily activities can result in spontaneous fractures, particularly in vulnerable populations.

The anatomical characteristics of bone in certain regions of the body can cause increased susceptibility to damage from osteoporosis. Although 80 % of the total skeleton is comprised of densely packed cortical bone, this type of bone is principally found in outer layers of long bones of the appendicular skeleton and is designed for structural support. Cortical bone has low bone turnover rates and is thus less likely to fracture than trabecular bone [7]. Characterized by increased porosity and reduced tensile strength, trabecular bone is heavily concentrated in the axial skeleton of the spine and is constantly being shaped and remodeled. Both the appendicular and axial skeleton are at risk of a fracture after a fall or other sustained trauma [7].

Epidemiology

Osteoporosis has generally been divided into two categories: primary and secondary osteoporosis. Primary osteoporosis is age related, affects 95 % of women and about 80 % of men, and is related to estrogen loss in women and a testosterone deficiency in men; other factors include low calcium and vitamin D intake as well as hyperparathyroidism. In contrast, secondary osteoporosis stems from other conditions including hormonal imbalances, diseases, and medications that predispose to bone

Table 1 Risk factors in the development of osteoporosis

Controllable	Uncontrollable
Inadequate dietary calcium or vitamin D	Age >75 years
Inadequate fruit and vegetable consumption	Female
Excessive protein, sodium, or phosphorous intake	Postmenopausal
Sedentary lifestyle	Family history
Ethyl alcohol (EtOH)	Low body weight/thin build
Smoking	Genetics
Weight loss	Hormonal levels (may be controlled with medications if diagnosed)
Medications	Environment with low sunlight

loss. It may arise at any age and affects both men and women [8]. The risk of osteoporosis and its severity is influenced by a variety of controllable and uncontrollable factors. Controllable factors include dietary deficiencies in vitamin D and calcium and in certain fruits and vegetables that enhance calcium absorption by limiting urinary excretion of calcium; in contrast, diets high in animal protein or sodium favor calciuria or bodily elimination of calcium through urine. Vitamin D is essential for calcium absorption which, if impaired, leads to an increase in parathyroid hormone (PTH) produced by the parathyroid glands. If calcium levels are low, these glands, the most important regulators of calcium levels in the blood, respond by secreting more PTH, resulting in increased calcium levels which, in turn, trigger bone resorption [9]. Other controllable factors range from high caffeine intake and an inactive lifestyle to smoking, alcohol consumption, and intentional weight loss beyond one's ideal body weight or implemented at the expense of overall nutritional status [1, 6]. Uncontrollable risk factors include age greater than 75 years old, female gender, postmenopausal status, family history of osteoporosis, and low body weight, thin build, or sudden unintentional weight loss from illness [1, 6].

Gender differences can affect the prevalence and severity of osteoporosis. Beginning at age 40, both sexes lose axial bone mass at relatively slow rates, but women lose bone mass more rapidly because of the onset of menopause in the late 40s or early 50s, contributing to increased risk of fracture to the axial skeleton. For men, who do not experience the sudden loss of gonadal sex steroid secretion, the reduction of reproductive hormones is more gradual, and bone loss occurs at a slower rate [10] (Table 1).

Medications Leading to Osteoporosis

Several medications have been shown to contribute to the development of osteoporosis. Glucocorticoids (aka corticosteroids), the leading secondary cause of osteoporosis, decrease bone formation by downregulating osteoblasts and prolonging their life span [11]. In addition, an inhibitory effect on sex hormones influences bone formation. When used chronically in high doses, glucocorticoids restrict intestinal

vitamin D-dependent calcium absorption, increase calcium excretion, and can cause osteomalacia, a softening of bone generally caused by vitamin D deficiency.

Thiazolidinediones given to persons with diabetes mellitus can lead to osteoporosis by their direct action on bone cell differentiation. A Diabetes Outcome Progression Trial (ADOPT) found that patients randomized to rosiglitazone have a higher risk of fractures than those receiving metformin or glyburide [12, 13].

Unfractionated heparin given for greater than one year has been associated with decreased bone formation and increased resorption, but the effects are notably less with low molecular weight heparin [14]. Proton pump inhibitors moderately impede the calcium resorption essential to bone formation; some studies show that H2 blockers have a smaller adverse effect, yet others report a neutral effect [11]. Significant doses of thyroxine suppress thyroid-stimulating hormone (TSH) causing bone loss. Vitamin A (greater than10,000 units/day) and vitamin D (greater than 2,000 units/day) have a similar effect.

Immune modulating drugs can also lead to decreases in BMD. Methotrexate decreases osteoblast activity and bone resorption in a dose-dependent manner. Calmodulin–calcineurin phosphatase inhibitors, used for immunosuppression post organ transplants, have been implicated in osteoporosis because they increase bone turnover; however the exact mechanism is unknown. Their effect is further complicated because they are often used concurrently with glucocorticoids [15, 16]. Long-term use of the antiepileptic drugs (AEDs) carbamazepine, phenobarbital, phenytoin, and valproic acid have been associated with decreased BMD due to elevated vitamin D catabolism, elevated parathyroid hormone, or increased osteoclastic activity [17, 18]. Increasing evidence points to a negative association between antidepressant drugs, particularly selective serotonin reuptake inhibitors (SSRIs), and low bone density coupled with fracture risk. A study of 5,008 adults over the age of 50, conducted by the Canadian Multicentre Osteoporosis Research Group, found that patients taking SSRIs on a daily basis experienced an increased risk of fragility fracture, increased chance of falling, and lower BMD at the hip and spine than those not taking the drugs [19].

Fractures

Statistics show that approximately 50% of women and 25% of men will break a bone due to osteoporosis [20]. Worldwide, it is estimated that there are 8.9 million fractures annually, resulting in an osteoporotic fracture every three seconds [21]. A prior fracture is associated with an 86% increased risk of any future fracture [22]. A 10% loss of bone mass in the vertebrae can double the risk of vertebral fractures; similarly, a 10% loss of bone mass in the hip can result in a 2.5 times greater risk of hip fracture [23].

By 2050, the worldwide incidence of hip fracture is projected to increase 310% in men and 240% in women, as a result of longer life spans in the developed and developing world [20]. The number of patients hospitalized due to an osteoporotic complication is comparable to the number hospitalized for hypertensive-related heart disease, and the disease causes greater disability than that caused by cancer.

Vertebral Compression Fractures

Vertical compression fractures occur when trauma causes the vertebra in the spine to compress and eventually collapse. Unlike most spine fractures of a traumatic nature, individuals with vertebral compression fractures may present without complaints of pain; indeed, approximately two-thirds of vertebral compression fractures are painless [24]. Regardless of pain intensity, if a vertebral fracture goes unrecognized, it can result in cumulative damage including further breakdown of bone structure, producing loss of vertebral height, increased curving of the spine leading to a "hunchback" deformity (spinal thoracic kyphosis, Fig. 2), and spinal cord compression. Vertebral fractures most often occur in the lower thoracic and upper lumbar portions of the spine because of the higher proportion of trabecular bone to cortical bone [25].

Clinical consequences of an osteoporotic compression fracture range from mild to severe. Significant kyphoscoliosis, a combination of outward curvature (kyphosis) and lateral curvature (scoliosis) of the spine, can lead to decreased pulmonary function from reduced lung surface area [26] or altered sitting or standing posture, resulting in compromised thoracic expansion. Larger fractures in the spine can progress to spinal instability through angulation of the vertebral column. If such changes compromise the spinal canal, cord compression can be observed, creating an urgent need for surgical decompression to avert devastating neurological consequences, including motor or sensory loss [26].

Hip Fractures

Hip fractures account for increased morbidity and mortality in people with osteoporosis. One in four adults who lived independently before their hip fracture is forced to reside in a nursing home for at least a year after injury. Approximately one in five hip fracture patients dies within a year of injury, and only 60 % of patients with a hip fracture return to their pre-fracture functional level [27].

The hip is a ball-and-socket joint linking two bones, the thighbone or femur and the pelvis; the ball is the head of the femur while the socket is a curved section of the pelvic bone. There are three types of high fractures. *Intracapsular fractures* occur near the neck and head of the femur, generally within the capsule, the soft tissue envelope that contains the lubricating and nourishing fluid of the high joint. By pressing on blood vessels, it may cut off blood circulation to the ball of the hip. *Intertrochanteric fractures* occur about 3–4 inches away from the joint, between the neck of the femur and a lower projection of bone called the lesser trochanter, an "attachment point" for one of the major muscles of the hip (Fig. 3). This type of fracture does not restrict blood flow to the femur. *Subtrochanteric fractures* occur even further down the bone, below the lower trochanter (Fig. 4) [28].

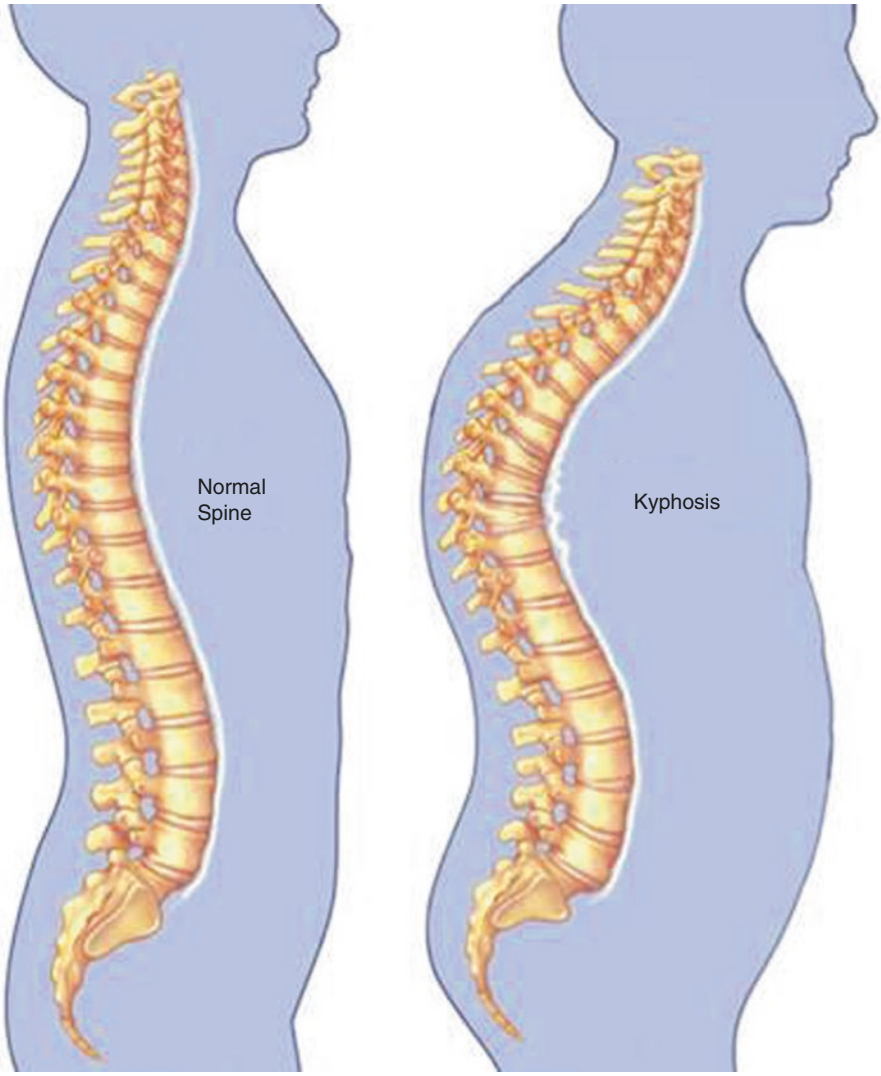

Fig. 2 Image showing a normal and kyphotic spine (*Source*: Used with permission from Mayo Clinic Foundation for Education and Research)

Anatomic Changes

Pain due to osteoporosis can be acute, progressive, or chronic [29]. As bones become increasingly osteoporotic, kyphoscoliosis develops secondary to stress and strain on the posterior ligamentous structures of the spine. With this weakening, eventual collapse of the vertebral body and the formation of an osteoporotic compression fracture occur. This type of fracture can happen even with low-amplitude, low-force

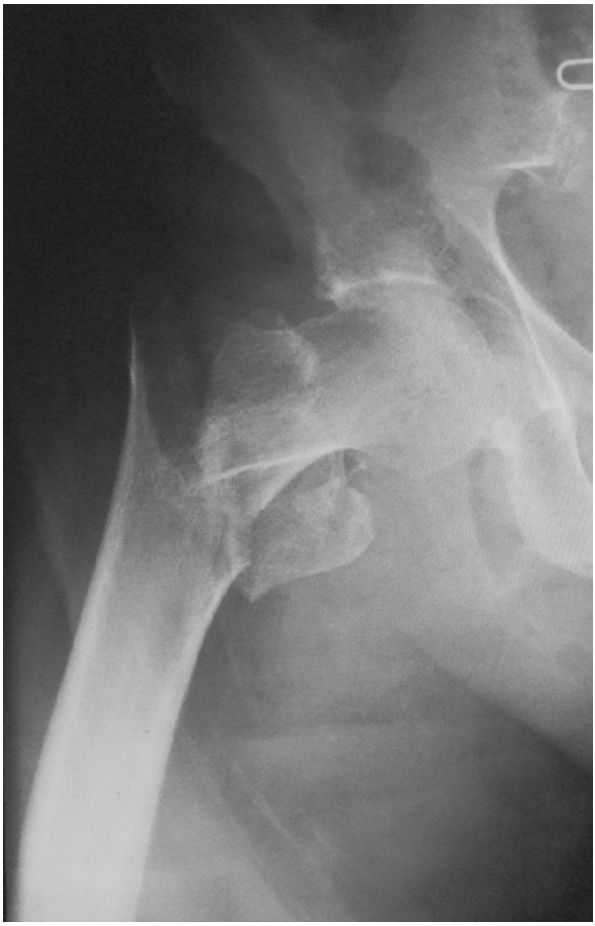

Fig. 3 Radiographic image showing an intertrochanteric fracture (*Source*: Wikipedia public domain [WPD] 1.0)

motions. Coughing, bending over to pick up an object, and other activities of daily living (ADL) can lead to fracture.

Kyphotic posture kinematically places the spine at a disadvantage for proper recruitment of back extensors, resulting in decreased extensor strength and an imbalance in the core musculature [30]. Other pertinent consequences of excessive kyphosis are altered balance and instability of posture in sitting or stance. Balance has been defined as the ability to maintain the body's center of mass over its base of support. Studies have shown that kyphotic subjects have less anteroposterior displacement of the center of mass, resulting in greater mediolateral displacement. This imbalance between center of mass and the base of support (i.e., the greater the displacement, the greater the imbalance) increases an individual's fall risk to one side or the other.

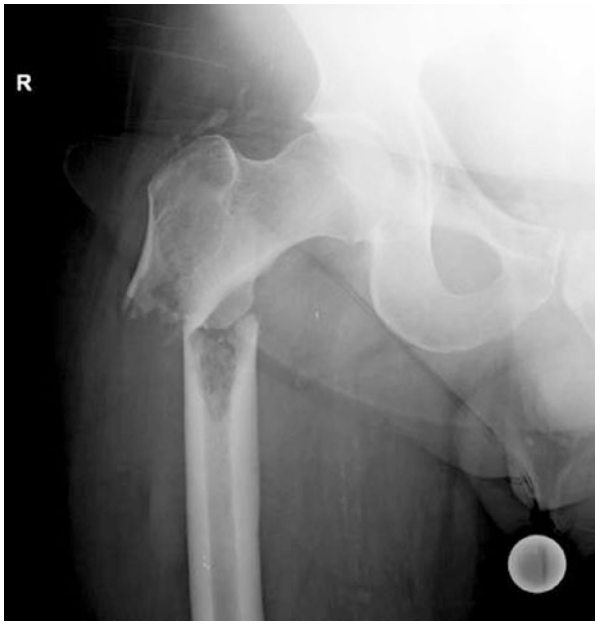

Fig. 4 Radiographic image showing a subtrochanteric fracture (Courtesy of Thomas Jefferson University, Philadelphia, PA)

Falls

As Nevitt et al. point out, the direction of the fall determines the type of fracture. It is likely that women who suffer wrist fractures have fallen to the side or straight down, whereas women who experience hip fractures have fallen, landing on an outstretched hand [31]. Intrinsic age-related changes in vision, strength, cognition, lack of coordination, dizziness posture, and polypharmacy (the use of four or more medications), particularly the use of sedatives, are among the factors contributing to postural instability and increased risk of falls. Regardless of having a diagnosis of osteoporosis, aging patients may exhibit impaired peripheral sensory input, resulting in altered proprioception or decreased muscle strength. Studies reveal that osteoporotic patients with a recent history of falls carry greater risk for fractures than osteoporotic or non-osteoporotic individuals without such history [32–34]. Other than vertebral fractures which can be traumatic or spontaneous, fractures at other body sites are usually the result of a fall [35]. Computerized dynamic posturography has linked thoracic kyphosis to falls [30, 36]. Increased energy expenditure is observed during standing activities in osteoporotic patients with kyphosis, compared to those without kyphosis [37]. Elderly patients may experience fatigue from standing and ambulation for other medical reasons, compounding the risk of falls.

Extrinsic risk factors include safety hazards in the home and community: slippery and uneven surfaces; poor lighting; loose rugs; clutter on floors, walks, and yards; and inappropriate footwear and poorly designed walking aid. Intrinsic factors are

most likely the cause of falls in persons age 80 and over because loss of consciousness (indicating a medical factor) is more common in this population. In persons under 75, falls are most often caused by extrinsic factors [38].

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