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### **BONE DISEASE IN WOMEN (osteoporosis)**

**Osteoporosis** is a disease of bone leading to an increased risk of fracture. In osteoporosis the bone mineral density (BMD) is reduced, bone microarchitecture is disrupted, and the amount and variety of non-collagenous proteins in bone is altered. Osteoporosis is defined by the World Health Organization (WHO) in women as a bone mineral density 2.5 standard deviations below peak bone mass (20-year-old sex-matched healthy person average) as measured by DXA; the term "established osteoporosis" includes the presence of a fragility fracture.<sup>[1]</sup> Osteoporosis is most common in women after the menopause, when it is called **postmenopausal osteoporosis**, but may develop in men and premenopausal women in the presence of particular hormonal disorders and other chronic diseases or as a result of smoking and medications, specifically glucocorticoids, when the disease is called **steroid- or glucocorticoid-induced osteoporosis** (SIOP or GIOP).

Osteoporosis can be prevented with lifestyle advice and medication, and preventing falls in people with known or suspected osteoporosis is an established way to prevent fractures. Osteoporosis can be treated with bisphosphonates and various other medical treatments.

### **Signs and symptoms**

Osteoporosis itself has no specific symptoms; its main consequence is the increased risk of bone fractures. Osteoporotic fractures are those that occur in situations where healthy people would not normally break a bone; they are therefore regarded as *fragility fractures*. Typical fragility fractures occur in the vertebral column, hip and wrist.

The symptoms of a vertebral collapse ("compression fracture") are acute back pain, often with radiculopathic pain (shooting pain due to compression of a nerve) and rarely with spinal cord compression or cauda equina syndrome. Multiple vertebral fractures lead to a stooped posture, loss of height, and chronic pain with resultant reduction in mobility.<sup>[2]</sup>

Fractures of the long bones acutely impair mobility and may require surgery. Hip fracture, in particular, usually requires prompt surgery, as there are serious risks associated with a hip fracture, such as deep vein thrombosis and a pulmonary embolism, and increased mortality.

The increased risk of falling associated with aging leads to fractures of the wrist, spine and hip. The risk of falling, in turn, is increased by impaired eyesight due to any cause (e.g. glaucoma, macular degeneration), balance disorder, movement disorders (e.g. Parkinson's disease), dementia, and sarcopenia (age-related loss of skeletal

muscle). Collapse (transient loss of postural tone with or without loss of consciousness) leads to a significant risk of falls; causes of syncope are manifold but may include cardiac arrhythmias, vasovagal syncope, orthostatic hypotension and seizures. Removal of obstacles and loose carpets in the living environment may substantially reduce falls. Those with previous falls, as well as those with a gait or balance disorder, are most at risk.<sup>[3]</sup>

## **[] Risk factors**

Risk factors for osteoporotic fracture can be split between non-modifiable and (potentially) modifiable. In addition, there are specific diseases and disorders in which osteoporosis is a recognized complication. Medication use is theoretically modifiable, although in many cases the use of medication that increases osteoporosis risk is unavoidable.

### **Nonmodifiable**

The most important risk factors for osteoporosis are advanced age (in both men and women) and female sex; estrogen deficiency following menopause is correlated with a rapid reduction in BMD, while in men a decrease in testosterone levels has a comparable (but less pronounced) effect. While osteoporosis occurs in people from all ethnic groups, European or Asian ancestry predisposes for osteoporosis.<sup>[4]</sup> Those with a family history of fracture or osteoporosis are at an increased risk; the heritability of the fracture as well as low bone mineral density are relatively high, ranging from 25 to 80 percent. There are at least 30 genes associated with the development of osteoporosis.<sup>[5]</sup> Those who have already had a fracture are at least twice as likely to have another fracture compared to someone of the same age and sex.<sup>[6]</sup>

### **Potentially modifiable**

- Tobacco smoking - tobacco smoking inhibits the activity of osteoblasts, and is an independent risk factor for osteoporosis.<sup>[7]</sup>
- Low body mass index - being overweight protects against osteoporosis, either by increasing load or through the hormone leptin.<sup>[8]</sup>
- Malnutrition
- Alcoholism
- Insufficient physical activity - bone performs remodeling in response to physical stress. People who remain physically active throughout life have a lower risk of osteoporosis. The kind of physical activity that have most effects on bone are weight bearing exercises. The bony prominences and attachments in runners are different in shape and size than those in weightlifters. Physical activity has its greatest impact during adolescence, affecting peak bone mass most. In adults, physical activity helps maintain bone mass, and can increase it by 1 or 2%. Physical fitness in later life is associated more with a decreased risk of falling than with an increased bone mineral density. Conversely, people who are bedridden are at a significantly increased risk.
- Excess physical activity - excessive exercise can lead to constant damages to the bones which can cause exhaustion of the structures as described above. There are numerous examples of marathon runners who developed severe

osteoporosis later in life. In females, heavy exercise leads to amenorrhea (suppression of the menstrual cycle), which is associated with decreased estrogen levels.

- Heavy metals - a strong association between cadmium, lead and bone disease has been established. Low level exposure to cadmium is associated with an increased loss of bone mineral density readily in both genders, leading to pain and increased risk of fractures, especially in elderly and in females. Higher cadmium exposure results in osteomalacia (softening of the bone).<sup>[9]</sup>
- Soft drinks - some studies indicate that soft drinks (many of which contain phosphoric acid) may increase risk of osteoporosis;<sup>[10]</sup> others suggest soft drinks may displace calcium-containing drinks from the diet rather than directly causing osteoporosis.<sup>[11]</sup>

## Diseases and disorders

There are many disorders associated with osteoporosis:<sup>[citation needed]</sup>

- Hypogonadal states - Turner syndrome, Klinefelter syndrome, Kallmann syndrome, anorexia nervosa, hypothalamic amenorrhea, hyperprolactinemia. In females, the effect of hypogonadism is mediated by estrogen deficiency. It can appear as early menopause (<45 years) or from prolonged premenopausal amenorrhea (>1 year). A bilateral oophorectomy (surgical removal of the ovaries) or a premature ovarian failure cause deficient estrogen production. In males, testosterone deficiency is the cause.
- Other endocrine disorders - Cushing's syndrome, hyperparathyroidism, thyrotoxicosis, hypothyroidism, insulin-dependent diabetes mellitus, acromegaly, adrenal insufficiency
- Nutritional and gastrointestinal disorders - malnutrition, parenteral nutrition, malabsorption syndromes (e.g. coeliac disease, Crohn's disease), gastrectomy, severe liver disease (especially primary biliary cirrhosis) - those with an otherwise adequate calcium intake can develop osteoporosis due to the inability to absorb calcium.
- Rheumatologic disorders - rheumatoid arthritis, ankylosing spondylitis
- Hematologic disorders/malignancy - multiple myeloma, lymphoma and leukemia, mastocytosis, hemophilia, thalassemia.
- Inherited disorders of the bone - osteogenesis imperfecta, Marfan syndrome, hemochromatosis, hypophosphatasia, glycogen storage diseases, homocystinuria, Ehlers-Danlos syndrome, porphyria, Menkes' syndrome, epidermolysis bullosa, Gaucher's disease.
- Other disorders - immobilization, scoliosis

## Medication

Medication - for medication potentially causing osteoporosis, the positive effects of them needs to be compared with the degenerative effects on bone.

- Steroid-induced osteoporosis (SIOP) arises due to use of glucocorticoids - analogous to Cushing's syndrome and involving mainly the axial skeleton. The synthetic glucocorticoid prescription drug prednisone is a main candidate after prolonged intake. Some professional guidelines recommend prophylaxis in

patients who take the equivalent of more than 30 mg hydrocortisone (7.5 mg of prednisolone), especially when this is in excess of three months.<sup>[12]</sup>

- Barbiturates and some other enzyme-inducing antiepileptics - these probably accelerate the metabolism of vitamin D.<sup>[13]</sup>
- Proton pump inhibitors - these drugs inhibit the production of stomach acid; it is thought that this interferes with calcium absorption.<sup>[14]</sup>
- Anticoagulants - long-term use of heparin is associated with a decrease in bone density,<sup>[15]</sup> and warfarin (and related coumarins) have been linked with an increased risk in osteoporotic fracture in long-term use.<sup>[16]</sup>
- Thiazolidinediones (used for diabetes) - rosiglitazone and possibly pioglitazone, inhibitors of PPAR $\gamma$ , have been linked with an increased risk of osteoporosis and fracture.<sup>[17]</sup>

## Diagnosis

The diagnosis of osteoporosis is made on measuring the bone mineral density (BMD). The most popular method is dual energy X-ray absorptiometry (DXA or DEXA). In addition to the detection of abnormal BMD, the diagnosis of osteoporosis requires investigations into potentially modifiable underlying causes; this may be done with blood tests and X-rays. Depending on the likelihood of an underlying problem, investigations for cancer with metastasis to the bone, multiple myeloma, Cushing's disease and other above mentioned causes may be performed.

### Dual energy X-ray absorptiometry

Dual energy X-ray absorptiometry (DXA, formerly DEXA) is considered the gold standard for the diagnosis of osteoporosis. Osteoporosis is diagnosed when the bone mineral density is less than or equal to 2.5 standard deviations below that of a young adult reference population. This is translated as a T-score. The World Health Organization has established the following diagnostic guidelines:<sup>[1][18]</sup>

- T-score  $\geq -1.0$  is "normal"
- T-score between  $-1.0$  and  $-2.5$  is "low bone mass" (or "osteopenia")
- T-score  $\leq -2.5$  is osteoporosis

When there has also been an osteoporotic fracture (also termed "low trauma-fracture" or "fragility fracture"), defined as one that occurs as a result of a fall from a standing height, the term "severe or established" osteoporosis is used.<sup>[1]</sup>

## Screening

The US Preventive Services Task Force (USPSTF) recommends that all women 65 years of age or older should be screened with bone densitometry.<sup>[19]</sup> The Task Force recommends screening women 60 to 64 years of age who are at increased risk. The best risk factor for indicating increased risk is lower body weight (weight  $< 70$  kg).

Clinical prediction rules are available to guide selection of women for screening. The Osteoporosis Risk Assessment Instrument (ORAI) may be the most sensitive strategy.<sup>[20]</sup> The ORAI is available online at <http://osteod.org/tools.php?type=orai>.

Regarding the screening of men, a cost-analysis study suggests that screening may be "cost-effective for men with a self-reported prior fracture beginning at age 65 years and for men 80 years and older with no prior fracture".<sup>[21]</sup>

## Pathogenesis

The underlying mechanism in all cases of osteoporosis is an imbalance between bone resorption and bone formation. In normal bone, there is constant matrix remodeling of bone; up to 10% of all bone mass may be undergoing remodeling at any point in time. The process takes place in bone multicellular units (BMUs) as first described by Frost in 1963.<sup>[22]</sup> Bone is resorbed by osteoclast cells (which derive from the bone marrow), after which new bone is deposited by osteoblast cells.<sup>[5]</sup>

The three main mechanisms by which osteoporosis develops are an inadequate *peak bone mass* (the skeleton develops insufficient mass and strength during growth), excessive bone resorption and inadequate formation of new bone during remodeling. An interplay of these three mechanisms underlies the development of fragile bone tissue.<sup>[5]</sup> Hormonal factors strongly determine the rate of bone resorption; lack of estrogen (e.g. as a result of menopause) increases bone resorption as well as decreasing the deposition of new bone that normally takes place in weight-bearing bones. The amount of estrogen needed to suppress this process is lower than that normally needed to stimulate the uterus and breast gland. The  $\alpha$ -form of the estrogen receptor appears to be the most important in regulating bone turnover.<sup>[5]</sup> In addition to estrogen, calcium metabolism plays a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition; in addition, the parathyroid glands react to low calcium levels by secreting parathyroid hormone (parathormone, PTH), which increases bone resorption to ensure sufficient calcium in the blood. The role of calcitonin, a hormone generated by the thyroid that increases bone deposition, is less clear and probably less significant.<sup>[5]</sup>

The activation of osteoclasts is regulated by various molecular signals, of which RANKL (receptor activator for nuclear factor  $\kappa$ B ligand) is one of best studied. This molecule is produced by osteoblasts and other cells (e.g. lymphocytes), and stimulates RANK (receptor activator of nuclear factor  $\kappa$ B). Osteoprotegerin (OPG) binds RANKL before it has an opportunity to bind to RANK, and hence suppresses its ability to increase bone resorption. RANKL, RANK and OPG are closely related to tumor necrosis factor and its receptors. The role of the *wnt* signalling pathway is recognized but less well understood. Local production of eicosanoids and interleukins is thought to participate in the regulation of bone turnover, and excess or reduced production of these mediators may underlie the development of osteoporosis.<sup>[5]</sup>

Trabecular bone is the sponge-like bone in the ends of long bones and vertebrae. Cortical bone is the hard outer shell of bones and the middle of long bones. Because osteoblasts and osteoclasts inhabit the surface of bones, trabecular bone is more active, more subject to bone turnover, to remodeling. Not only is bone density decreased, but the microarchitecture of bone is disrupted. The weaker spicules of trabecular bone break ("microcracks"), and are replaced by weaker bone. Common osteoporotic fracture sites, the wrist, the hip and the spine, have a relatively high trabecular bone to cortical bone ratio. These areas rely on trabecular bone for strength,

and therefore the intense remodeling causes these areas to degenerate most when the remodeling is imbalanced.<sup>[citation needed]</sup>

## Treatment

There are several alternatives of medication to treat osteoporosis. However, lifestyle changes are also emphasised.

### Medication

Bisphosphonates are the main pharmacological measures for treatment. However, newer drugs have appeared in the 1990s, such as teriparatide and strontium ranelate.

#### Bisphosphonates

In osteoporosis, bisphosphonate drugs are prescribed. The most often prescribed bisphosphonates are presently sodium alendronate (Fosamax) 10 mg a day or 70 mg once a week, risedronate (Actonel) 5 mg a day or 35 mg once a week and or ibandronate (Boniva) once a month.

A 2007 manufacturer-supported study suggested that in patients who had suffered a low-impact hip fracture, annual infusion of 5 mg zoledronic acid reduced risk of any fracture by 35% (from 13.9 to 8.6%), vertebral fracture risk from 3.8% to 1.7% and non-vertebral fracture risk from 10.7% to 7.6%. This study also found a mortality benefit: after 1.9 years, 9.6% of the study group (as opposed to 13.3% of the control group) had died of any cause, indicating a mortality benefit of 28%.<sup>[23]</sup>

#### Teriparatide

Recently, teriparatide (Forteo, recombinant parathyroid hormone residues 1–34) has been shown to be effective in osteoporosis. It is used mostly for patients with established osteoporosis (who have already fractured), have particularly low BMD or several risk factors for fracture or cannot tolerate the oral bisphosphonates. It is given as a daily injection with the use of a pen-type injection device. Teriparatide is only licensed for treatment if bisphosphonates have failed or are contraindicated (however, this differs by country and is not required by the FDA in the USA. However, patients with previous radiation therapy, or Paget's disease, or young patients should avoid this medication).

#### Strontium ranelate

Oral strontium ranelate is an alternative oral treatment, belonging to a class of drugs called "dual action bone agents" (DABAs) by its manufacturer. It has proven efficacy, especially in the prevention of vertebral fracture.<sup>[24]</sup> In laboratory experiments, strontium ranelate was noted to stimulate the proliferation of osteoblasts, as well as inhibiting the proliferation of osteoclasts.

Strontium ranelate is taken as a 2 g oral suspension daily, and is licenced for the treatment of osteoporosis to prevent vertebral and hip fracture. Strontium ranelate has

side effect benefits over the bisphosphonates, as it does not cause any form of upper GI side effect, which is the most common cause for medication withdrawal in osteoporosis. In studies a small increase in the risk of venous thromboembolism was noted,<sup>[25]</sup> suggesting it may be less suitable in patients at risk for thrombosis for different reasons.

## Nutrition

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### Calcium

The patient should include 1200 to 1500 mg of calcium daily either via dietary means or via supplementation. The body absorbs only about 500 mg of calcium at one time and so intake should be spread throughout the day.

However, the benefit of supplementation of calcium alone remains, to a degree, controversial since several nations with high calcium intakes through milk-products (e.g. the USA, Sweden) have some of the highest rates of osteoporosis worldwide, though this may be linked to such countries' excess consumption of protein. A few studies even suggested an adverse effect of calcium excess on bone density and blamed the milk industry for misleading customers. Some nutritionists assert that excess consumption of dairy products causes acidification, which leaches calcium from the system, and argue that vegetables and nuts are a better source of calcium and that in fact milk products should be avoided. This theory has no proof from scientific clinical studies. Similarly, nutritionists believe that excess caffeine consumption can also contribute to leaching calcium from the bones.<sup>[citation needed]</sup>

A meta-analysis of randomized controlled trials concluded "Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 years or older. For best therapeutic effect, we recommend minimum doses of 1200 mg of calcium, and 800 IU of vitamin D (for combined calcium plus vitamin D supplementation)."<sup>[26]</sup> A study that examined the relationship between calcium supplementation and clinical fracture risk in an elderly population, there was a significant decrease in fracture risk in patients that received calcium supplements versus those that received placebo. However, this benefit only applied to patients who were compliant with their treatment regimen.<sup>[27]</sup>

### Vitamin D

Increasing vitamin D intake has been shown to reduce fractures up to twenty-five percent in older people, according to recent studies.<sup>[28][26]</sup> The very large Women's Health Initiative study, however, did not find any fracture benefit from calcium and vitamin D supplementation, but these women were already taking (on average) 1200 mg/day of calcium . Muscle weakness can contribute to falls so it is beneficial for people living with osteoporosis to improve muscle function. Vitamin D deficiency causes muscle weakness.<sup>[29]</sup> A meta-analysis of five clinical trials showed 800 IU of

vitamin D per day (plus calcium) reduced the risk of falls by 22%.<sup>[30]</sup> A different randomized, controlled study showed nursing home residents who took 800 IU of vitamin D per day (plus calcium) having a 72% reduction in the risk of falls.<sup>[31]</sup> New vitamin D intake recommendations (National Osteoporosis Foundation, July 2007)<sup>[citation needed]</sup> are adults up to age 50, 400-800 IU daily and those over 50, 800 - 1,000 IU daily.

### Excess protein

There are three elements relating to a person's levels of calcium: consumption, absorption, and excretion. High protein intake is known to encourage urinary calcium losses and has been shown to increase risk of fracture in research studies.<sup>[32][33]</sup>

### Others

There is some evidence to suggest bone density benefits from taking the following supplements (in addition to calcium and vitamin D): boron, magnesium, zinc, copper, manganese, silicon, strontium, folic acid, and vitamins B6, C, and K.<sup>[34][35]</sup> This is weak evidence and quite controversial.

## [] Exercise

Multiple studies have shown that aerobics, weight bearing, and resistance exercises can all maintain or increase BMD in postmenopausal women.<sup>[36]</sup> Many researchers have attempted to pinpoint which types of exercise are most effective at improving BMD and other metrics of bone quality, however results have varied. One year of regular jumping exercises appears to increase the BMD and moment of inertia of the proximal tibia<sup>[37]</sup> in normal postmenopausal women. Treadmill walking, gymnastic training, stepping, jumping, endurance, and strength exercises all resulted in significant increases of L2-L4 BMD in osteopenic postmenopausal women.<sup>[38][39][40]</sup> Strength training elicited improvements specifically in distal radius and hip BMD.<sup>[41]</sup>

## Prognosis

Although osteoporosis patients have an increased mortality rate due to the complications of fracture, most patients die *with* the disease rather than *of* it.

Hip fractures can lead to decreased mobility and an additional risk of numerous complications (such as deep venous thrombosis and/or pulmonary embolism, pneumonia). The 6-month mortality rate following hip fracture is approximately 13.5%, and a substantial proportion (almost 13%) of people who have suffered a hip fracture need total assistance to mobilize after a hip fracture.<sup>[43]</sup>

Vertebral fractures, while having a smaller impact on mortality, can lead to severe chronic pain of neurogenic origin, which can be hard to control, as well as deformity. Though rare, multiple vertebral fractures can lead to such severe hunch back (kyphosis) that the resulting pressure on internal organs can impair one's ability to breathe.

Apart from risk of death and other complications, osteoporotic fractures are associated with a reduced health-related quality of life.<sup>[44]</sup>

## Epidemiology

It is estimated<sup>[citation needed]</sup> that 1 in 3 women and 1 in 12 men over the age of 50 worldwide have osteoporosis. It is responsible for millions of fractures annually, mostly involving the lumbar vertebrae, hip, and wrist. Fragility fractures of ribs are also common in men.

### Hip fractures

Hip fractures are responsible for the most serious consequences of osteoporosis. In the United States, osteoporosis causes a predisposition to hip fractures -- more than 250,000 occur annually. It is estimated that a 50-year-old white woman has a 17.5% lifetime risk of fracture of the proximal femur. The incidence of hip fractures increases each decade from the sixth through the ninth for both women and men for all populations. The highest incidence is found among those men and women ages 80 or older.

### Vertebral fractures

Between 35-50% of all women over 50 had at least one vertebral fracture. In the United States, 700,000 vertebral fractures occur annually, but only about a third are recognized. In a series of 9704 of women aged 68.8 on average studied for 15 years, 324 had already suffered a vertebral fracture at entry into the study; 18.2% developed a vertebral fracture, but that risk rose to 41.4% in women who had a previous vertebral fracture.<sup>[45]</sup>

### Distal radius fractures

Distal radius fractures, usually of the Colles type, are the third most common type of osteoporotic fractures. In the United States, the total annual number of Colles' fractures is about 250,000. The lifetime risk of sustaining a Colles' fracture is about 16% for white women. By the time women reach age 70, about 20% have had at least one wrist fracture.<sup>[citation needed]</sup>

## Prevention

Methods to prevent osteoporosis include changes of lifestyle. However, there are medications that can be used for prevention as well.

### Lifestyle

Lifestyle prevention of osteoporosis is in many aspects inversions from potentially modifiable risk factors.

- Exercise - achieving a higher peak bone mass through exercise and proper nutrition during adolescence is important for the prevention of osteoporosis. Exercise and nutrition throughout the rest of the life delays bone degeneration. Jogging, walking, or stair climbing at 70-90% of maximum effort three times per week, along with 1,500 mg of calcium per day, increased bone density of the lumbar (lower) spine by 5% over 9 months. Individuals already diagnosed with osteopenia or osteoporosis should discuss their exercise program with their physician to avoid fractures.<sup>[46]</sup>
- Nutrition - a proper nutrition is a diet sufficient in calcium and vitamin D. Patients at risk for osteoporosis (e.g. steroid use) are generally treated with vitamin D and calcium supplements. In renal disease, more active forms of Vitamin D such as paracalcitol or (1,25-dihydroxycholecalciferol or calcitriol which is the main biologically active form of vitamin D) is used, as the kidney cannot adequately generate calcitriol from calcidiol (25-hydroxycholecalciferol) which is the storage form of vitamin D.
- Quitting tobacco smoking
- Drinking alcohol in moderation

## ] Medication

Just as for treatment, bisphosphonate can be used in cases of very high risk. Other medicines prescribed for prevention of osteoporosis include raloxifene (Evista), a selective estrogen receptor modulator (SERM).

Estrogen replacement remains a good treatment for prevention of osteoporosis but, at this time, is not recommended unless there are other indications for its use as well. There is uncertainty and controversy about whether estrogen should be recommended in women in the first decade after the menopause; hopefully new research will provide guidance. In men, testosterone replacement therapy is also an effective treatment.

## History

The link between age-related reductions in bone density and fracture risk goes back at least to Astley Cooper, and the term "osteoporosis" and recognition of its pathological appearance is generally attributed to the French pathologist Jean Lobstein.<sup>[47]</sup> The American endocrinologist Fuller Albright linked osteoporosis with the postmenopausal state.<sup>[48]</sup> Bisphosphonates, which revolutionized the treatment of osteoporosis, were discovered in the 1960s.<sup>[49]</sup>

## References

1. <sup>a b c</sup> WHO (1994). "Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group". *World Health Organization technical report series* **843**: 1–129. PMID 7941614