

Causes, consequences, and treatment of osteoporosis in men

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Abstract: Men undergo gradual bone loss with aging, resulting in fragile bones. It is estimated that one in five men will suffer an osteoporotic fracture during their lifetime. The prognosis for men after a hip fracture is very grim. A major cause is reduction of free testosterone. Many other factors result in secondary osteoporosis, including treatment for other diseases such as cancer and diabetes. Patients should be screened not only for bone density but also assessed for their nutritional status, physical activity, and drug intake. Therapy should be chosen based on the type of osteoporosis. Available therapies include testosterone replacement, bisphosphonates, and nutritional supplementation with calcium, vitamin D, fatty acids, and isoflavones, as well as certain specific antibodies, like denosumab and odanacatib, and inhibitors of certain proteins.

Keywords: risk factors, hormones, bisphosphonates, nutritional supplements, antibodies, protein inhibitors, male osteoporosis

Introduction

Aging is associated with gradual bone loss in men, leading to fragile bones and increased fracture risk. Since bone loss in males was recognized as a serious medical condition a couple of decades ago, studies have focused on several aspects of the disease, including assessment, diagnosis, prevention, and treatment options. It is established that aging men lose bone mineral density (BMD) at a rate of 1% per year,¹ and that one in five men will suffer an osteoporotic fracture during their lifetime.^{2,3} It is also believed that the incidence of osteoporosis-related fracture is similar to that of myocardial infarction and exceeds that of lung and prostate carcinoma combined.⁴ The disturbing fact is that when men have fractures, their chances of survival are considerably decreased. Moreover, awareness about osteoporosis in males is lacking in certain societies.⁵⁻⁷

Although it is recognized that osteoporosis in men is an important medical condition and will remain important as longevity increases around the globe, there are very poor tools for managing male osteoporosis.^{8,9} The diagnostic standards are dependent on the scales for women or young men, but there is a 10-year difference in age before men show signs of an age-related decrease in bone mass.¹⁰ Moreover, many elderly men treated for fractures are not put on any medication regimen to treat osteoporosis.¹¹ It is recommended that men should be evaluated for their bone status after 50 years of age,¹² and the clinical practice guidelines recommend screening in men over 70 years.^{11,13}

Patients older than 80 years are currently excluded, but the changes in physiology at this age usually put them at a different level of risk.¹⁴ Although screening patients

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for BMD is the best measure to know the status of bone, it is very important to collect information about the probable reasons for bone loss, because 75% of patients have been found to have secondary osteoporosis.¹⁵ There may be ethnicity-related differences among men as well. Roughly 7% of white men and 3% of black men have osteoporosis, with an additional 35% of white men and 19% of black men having low bone mass. This requires formulation of treatment and management strategies specific to ethnic groups.¹⁶ In addition to this, men with a combination of low bone mass and low muscle mass are at higher risk of losing bone. In this review, available data on the causes, consequences, and treatment options are discussed.

Causes and consequences

Several factors are believed to cause age-related bone loss in men, including decreased levels of sex hormones and insulin-like growth factor-1, drug side effects, and nutrition lacking minerals. Moreover, secondary osteoporosis may be due to several acquired habits and inherited conditions (Figure 1).

Decrease in hormones

With age, there is certainly a decrease in hormone levels. Androgens may play an important role in the regulation of bone formation in men.¹⁷ Total testosterone levels decrease at a rate of 0.8% per year, of which free and bound testosterone levels decrease at 2% per year (cross-sectional studies) and between 1.6% per year and 2%–3% per year (longitudinal studies).¹⁸ On the other hand, levels of sex hormone binding globulin (SHBG) increase with age.^{19–23} This protein binds to testosterone and decreases free or bioavailable testosterone.^{19,21,24–26} Men are also affected by changes in estrogen due to aging, because testosterone is the precursor to estrogen and it is well established that estrogen plays a greater role in increasing bone resorption.²⁵ Therefore, in men, both hormones are important to maintain bone and are inversely related to fracture risk in older men contributed by decreased BMD.^{27,28} The action of androgen on bones in males may be explained by activation of the androgen receptor or the estrogen receptor (α and β).²⁸ Therefore, low serum estrogen and testosterone with high SHBG increases the risk of osteoporotic vertebral, nonvertebral, and hip fractures.^{28,29}

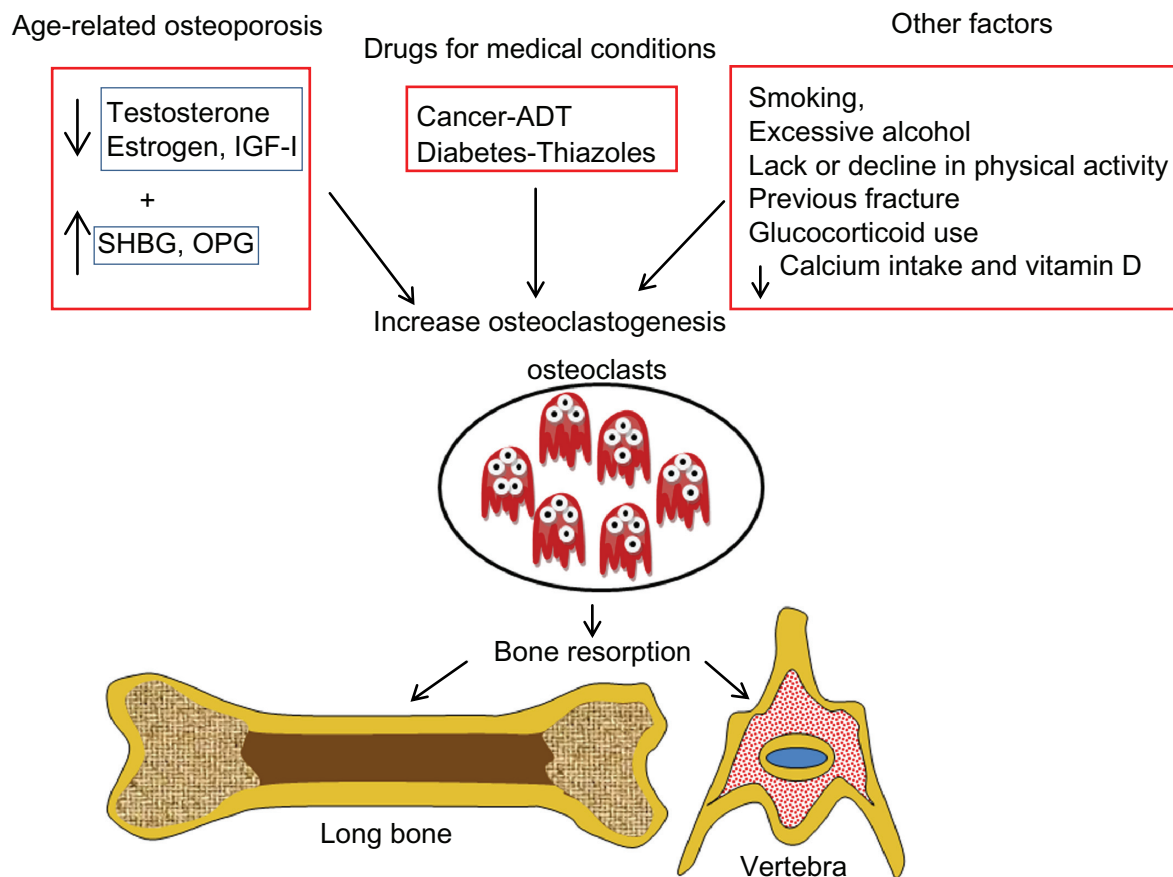


Figure 1 Factors that cause bone loss in men.

Abbreviations: IGF-1, insulin-like growth factor-1; SHBG, sex hormone binding globulin; OPG, osteoprotegerin; ADT, androgen deprivation therapy; ↑, increase; ↓, decrease.

Apart from alterations in sex hormones, decreased insulin-like growth factor-1 levels are found in men with vertebral fractures.³⁰ In addition, men with a low body mass index and a small body frame have decreased estrogen levels, and the offspring of these men also have low BMD.³¹

Bone turnover and bone maintenance is a balance between proteins like osteoprotegerin and receptor activated nuclear factor kappa B ligand (RANKL). Osteoprotegerin levels in serum have been shown to increase with age,³² which in turn may increase bone loss.

Side effects of drugs

Patients with prostate cancer undergoing androgen deprivation and cyclophosphamide therapy have an increased fracture risk.^{33–36} BMD measurements in men with prostate cancer and under an androgen deprivation regimen show 6.5%–17.3% bone loss. Moreover, this effect is site-specific and is also dependent on duration of treatment.^{37–39}

Antidiabetic drugs like thiazides also cause bone loss.⁴⁰ Many studies in humans as well as in animals have shown that bone loss is accelerated by thiazoles.^{41–43} Rosiglitazone decreases bone quality by increasing porosity.⁴⁰ In women and men, decreased bone mass in long bones, but not in the vertebrae, has been attributed to thiazides.^{44,45} There are a few studies that explain the mechanism by which these antidiabetic drugs cause bone loss. In males, glitazones reduce the biosynthesis of androgens, increase their binding to SHBG, and attenuate androgen receptor activation, thus reducing the physiologic actions of testosterone, causing relative and absolute androgen deficiency.⁴⁶ In addition to this, activation of peroxisome proliferator activated receptor gamma initiates an imbalance in the bone resorption and bone formation process, resulting in high bone loss.⁴⁷ Moreover, rosiglitazone induces apoptosis of osteoblasts which reduces bone formation.⁴⁸

Changes in bone turnover markers

Bone turnover is assessed by measuring biomarkers such as cross linking C-terminal telopeptide of type I collagen and procollagen type 1 N-terminal propeptide. Cross linking C-terminal telopeptide of type I collagen, in addition to being a bone resorption marker, is also used to assess adherence with bisphosphonates, while procollagen type 1 N-terminal propeptide is a measure of bone formation. Higher bone turnover is not always related to decreased BMD in men.⁴⁹ However, in the Dubbo study, only cross linking C-terminal telopeptide of type I collagen could predict fractures.⁵⁰ Increased bone turnover reduces bone strength

because faster bone loss increases bone formation. This sudden increase in bone formation impairs bone connectivity because a higher fraction of protein matrix undergoes partial post transcriptional modification, resulting in a malformed matrix. It is commonly observed that bone turnover markers are increased in institutionalized patients⁵¹ to a greater extent than in community-dwelling individuals. In older men, increased bone turnover markers are associated with lower areal BMD.⁴⁹

Secondary osteoporosis

Most men who sustain fractures do so because of multiple other factors, including age, smoking, alcohol consumption, low weight, physical/functional limitations, previous fracture, weight loss, prolonged corticosteroid use, androgen deprivation therapy, dietary calcium intake, chronic lung disease, and prostate cancer. Accumulation of kidney stones is negatively correlated with BMD.^{52–54} Recent research shows that low levels of free 25(OH) vitamin D result in bone loss.⁵⁵ The major mineral lost in bone loss is calcium, and calcium absorption is influenced by vitamin D. Therefore, individuals who consume calcium in low amounts and who are diagnosed with vitamin D deficiency also have an increased fracture risk.^{56–58}

Osteoporosis affects men over 70 years of age. When BMD in both the trabecular and cortical bones is reduced, there is an increased risk of fractures of the hip and vertebrae, which are often fatal in men. Some patients have hypogonadism due to testicular failure or pituitary disorders, leading to bone loss.⁵⁹ Medications for other medical conditions, including those for cancer, diabetes, and seizures, also cause osteoporosis.⁶⁰ Apart from these, drugs that raise serum prolactin levels and chronic opioid use for pain control are also implicated in bone loss. Men who have fractures of the distal forearm and those who have symptomatic vertebral and hip fractures show lower BMD as well.⁶¹

Nevertheless, men have the advantage of accruing a higher peak bone mass (8%–10%) compared with women.^{62,63} In addition, microarchitectural changes in the radius have been found to include higher trabecular thickness and bone volume/total volume in men compared with women.^{64,65} In the tibia, significantly higher bone volume/total volume, trabecular number, and cortical thickness⁶⁵ were reported. Although trabecular thickness was also increased, this was not statistically significant. However, these data are from younger individuals aged 19 years and 20–29 years. Longitudinal studies in older men showed an age-related decrease in trabecular thickness of the radius. However, there was decreased trabecular thickness,

number, and separation in the distal tibia.⁶⁶ Cortical porosity is increased with age in men.⁶⁷ Moreover, men undergo periosteal bone accretion compensating the endosteal bone loss and maintaining strength for almost a decade after women show bone fragility.^{66–70} However, men do lose bone gradually and are susceptible to fractures after the sixth decade of life.

The action of androgen on male bone may be explained by activation of the androgen receptor or estrogen receptor (α and β).²⁸ Serum estrogen and testosterone are inversely related to fracture risk in older men, while SHBG shows a positive relationship; low serum estrogen and testosterone levels coupled with high SHBG predict clinical vertebral and nonvertebral osteoporosis and hip fractures.¹⁷ SHBG has been reported to increase with age and is associated with bone loss.²⁹

Orchidectomized rodents have been shown to have an increase in bone resorption markers and periosteal bone formation, and decreased bone strength, implicating the role of decreased testosterone.⁷¹ Because androgens play an important role in regulation of bone formation in males, their receptors, ie, the androgen receptor and estrogen receptor, should be activated for maintenance of bone in male mice. Estrogen receptor- α and the androgen receptor were found to increase cortical radial bone growth and mediate protection of cancellous bone in males.⁷¹ Moreover, androgen receptor activation is solely responsible for the development and maintenance of trabecular bone in males, and the androgen receptor and estrogen receptor- α are responsible for cortical bone mass and muscle mass.^{72,73} It is reported that estrogen receptor- α may act indirectly via the growth hormone-insulin-like growth factor-1 axis.⁷⁴ Therefore, there is ample evidence that an age-related reduction of hormone secretion, especially sex hormones, affects bone maintenance in men.

Osteoporosis in men is a gradual disease that progresses with age.¹⁴ In the US, two million men are diagnosed with osteoporosis and another 12 million have low bone mass and are at the risk of developing the disease.⁷⁵ The outcome for male patients after hip fracture (30% of hip fractures occur in men) is grim. One third (32%) die within the first year of hip fracture.^{76–78} Only 21% are able to live independently in the community a year after the fracture, with 26% receiving home care and 53% living in an institution for the rest of their lives.⁷⁹ Unfortunately, men with osteoporosis have higher mortality rates than women, and the fracture burden also increases the problems of osteoporosis in men. In one study, men with subsequent fractures were found to have an increased mortality rate and more men were immobilized at 120 days after their fracture.¹¹

Treatment options

Available treatment options for men with osteoporosis are those that were developed for and are currently used in women. Many of these drugs/supplements have been very beneficial in males as well, and include hormones, bisphosphonates, antibodies, protein inhibitors, and nutritional supplements (Figure 2). Pharmacologic options for treating osteoporosis in men are listed in Table 1.

Hormones

Hormone therapy, especially estrogen, has been widely used to treat osteoporosis in women. Testosterone supplementation is also used in men, because a decrease in testosterone is linked to decreased bone mass. With such therapy, site-specific improvement has been reported in some cases, with benefits only at the spine and not at the hip.^{80,81} Moreover, treatment with testosterone not only increased BMD⁸² but also increased prostate gland size and prostate specific antigen (PSA) levels. However, the prostate size is not affected when testosterone was given with finasteride (inhibitor of 5 α reductase), therefore in these patients androgen replacement therapy was effective.⁵² It is important to note that testosterone treatment should be given only to those who have low levels of testosterone and need agents that will prevent fractures.^{80,83}

The only anabolic bone agent approved by the US Food and Drug Administration for prevention and treatment of osteoporosis is teriparatide, a truncated parathyroid hormone. It may be one option for treating osteoporosis in men because it is associated with major gains in BMD at the lumbar spine, but less at the hip.^{4,14,80,84–86} Bone formation markers also increased with this treatment, and the risk of fracture reduced by 51%.⁸⁷ In patients with existing vertebral fractures, the risk went down to 13:1. However, continuous treatment with teriparatide is not recommended because of several side effects. Combination therapy using bisphosphonates and teriparatide did not increase BMD, however, patients on teriparatide therapy alone showed significantly increased BMD, in the lumbar and femur neck, although the BMD were similar in both groups (combined and teriparatide groups).⁸⁸ At this point in time, the Food and Drug Administration has approved the use of teriparatide only for 24 months. After cessation of teriparatide, patients show a gradual decrease in BMD unless they are put on other medications.⁸⁷ Although combination treatment with alendronate was not encouraging, administration of alendronate after teriparatide treatment maintained BMD, so sequential treatment is recommended.^{86,89,90} Whenever treatment with teriparatide was restarted, there was an increase in BMD.⁹¹

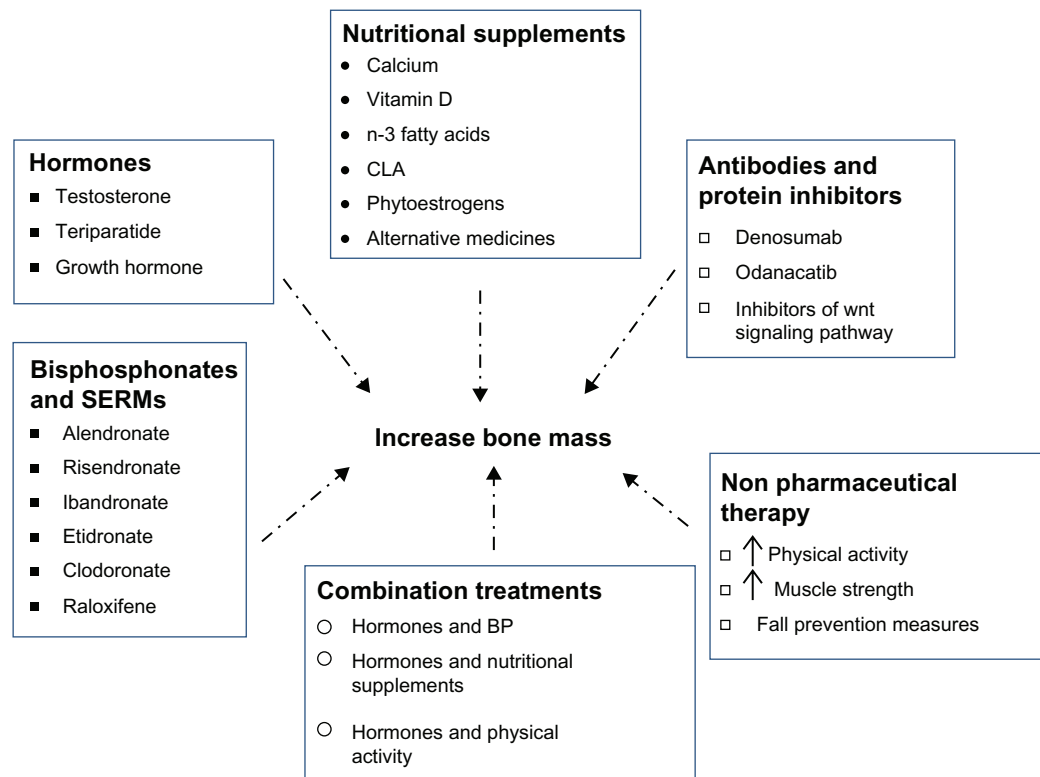


Figure 2 Treatment options for osteoporosis in men.

Abbreviations: BP, bisphosphonates; CLA, conjugated linoleic acid; SERMs, selective estrogen receptor modulators; ↑, increase.

Table 1 Pharmacological options available for treating osteoporosis in men

Drug	Dosage/Frequency	Advantages	Side effects	References
Hormones				
Testosterone		↑ Hypogonadal men, BMD at lumbar vertebrae	Fluid retention, increased blood pressure	59,81,84
Intramuscular	200 mg/every 2 weeks			
Skin patch	5 mg daily			
Gel	50 mg/5 g daily			
Parathyroid hormone		↑ BMD, bone formation markers	Dizziness, nausea, palpitations, hypercalcemia	85–88
Calcitonin		↑ BMD of lumbar and femoral neck	Dizziness, nausea, pain	92,93,109
Selective estrogen receptor modulator				
Raloxifene		↑ Bone mass		94,95
Bisphosphonates				
Alendronate	10 mg daily or 70 mg weekly	↑ BMD in vertebrae, femoral neck	GI tract intolerance	88,91
Risendronate	5 mg daily or 35 mg weekly or 75 mg monthly (2 consecutive days) or 150 mg monthly	↑ Bone mass	GI tract intolerance	14
Etidronate	400 mg daily	↑ BMD in lumbar vertebrae	GI tract intolerance, joint, bone, and muscle pain, severe diarrhea, jaw pain, numbness or swelling, hives, swelling of mouth and throat	98
Ibandronate	2.5 mg daily or 150 mg monthly or 3 mg every 3 months (IV)	↑ BMD spine, trochanter, femur neck	GI tract intolerance, flu-like symptoms, osteonecrosis of jaw	99,102
Zoledronate	5 mg yearly (IV)	↑ Bone mass	Flu-like symptoms, osteonecrosis of jaw	101,103,104,118

Abbreviations: IV, intravenously; GI, gastrointestinal; BMD, bone mineral density; ↑, increase.

Another hormone that regulates circulating calcium is calcitonin. This hormone is a powerful inhibitor of osteoclasts. Administration of this agent is nasal, and it is reported to increase BMD at the lumbar spine and femoral neck but not at the proximal femur.^{4,14,82,86,92,93} During the last decade, calcitonin has been tested as a treatment option for osteoporosis in men.^{92,93} Growth hormone would also be beneficial to patients who are growth hormone-deficient.

Administration of hormones like testosterone, parathyroid hormone, and calcitonin may be useful for preventing bone loss and increasing bone mass. However, such treatment options should be used on an individual basis. Outcomes are dependent on the initial hormone status in some cases, while sequential treatment may be important in others.

Selective estrogen receptor modulators

Selective estrogen receptor modulators bind to estrogen receptors and have estrogen-like activity in bone. Raloxifene has been shown to increase bone mass and decrease urinary and circulating bone resorption markers.^{94,95} However, use of these agents may be limited to men with prostate cancer.

Bisphosphonates

Bisphosphonates are recommended for treating osteoporosis in men.^{4,80,86} Alendronate (Fosamax[®], Merck, Whitehouse Station, NJ, USA) improves BMD at the vertebrae and femoral neck in both eugonadal and hypogonadal men, with significant reductions in the incidence of vertebral fractures and less height loss.^{14,82,96,97} Other bisphosphonates like risendronate (Actonel[®], Warner Chilcott, Dublin, Ireland) and ibandronate (Boniva[®], Genentech Inc, South San Francisco, CA, USA) are also options for treating osteoporosis in men.¹⁴ Intermittent etidronate (Didronel[®], Warner Chilcott, Dublin, Ireland) therapy increases BMD at the lumbar spine by 3%, with

smaller increases at the hip (0.7%) in patients with secondary osteoporosis.^{82,98} Ibandronate, another bisphosphonate, when given intravenously in combination with calcium and vitamin D supplementation increased BMD at the spine, femoral neck, and trochanter in a small study of 14 individuals.⁹⁹ In yet another study, administration of ibandronate increased BMD at the lumbar vertebrae and hip in men and significantly reduced the risk of vertebral fractures.¹⁰⁰ Zoledronate (Zometa[®], Zomera[®], Aclasta[®], Reclast[®], Novartis, Basel, Switzerland) may be an alternative (administered intravenously, which may be better than the oral route for bisphosphonates) and is shown to be as effective as other bisphosphonates.^{14,101–104} Bisphosphonates have been shown to be effective therapeutic agents for patients with osteoporosis, but there are certain limitations in using them. Many patients show tolerance, and each of the oral bisphosphonates has very strict and specific guidelines for dosage. However, great strides have been made in developing drugs that can be taken daily, weekly, monthly, or even yearly.

Antibodies and protein inhibitors

A recent trend in drug development has focused on targeting important proteins involved in development of osteoporosis. Specific antibodies and inhibitors of these proteins have been developed, and are listed in Table 2. RANKL stimulates osteoclastogenesis and increases bone resorption. Denosumab, a monoclonal antibody against RANKL, is one of the newer medications that is available as a therapeutic option.^{14,94,105,106} It decreases bone resorption, thereby decreasing bone loss. This antibody should be taken with caution because it can affect the immune system, leading to infections.

Another protein, cathepsin K, which is expressed in osteoclasts and is capable of releasing minerals from bone, has

Table 2 Biological therapy possibilities for treating osteoporosis in men

Antibodies	Target	Advantages	Disadvantages	References
Denosumab	RANKL	↓ Bone resorption	Reduces immunity, skin rashes, high cholesterol	14,94,105,106
Odanacatib	Cathepsin K	↓ Bone resorption markers, ↑ BMD spine and hip	Not known	94,107,108
Inhibitors				
AMG 785	Sclerostin	↑ Bone formation markers, BMD	Oncogenic, calcium homeostasis,	105,109–112
Specific to DKK1	DKK1	↑ Bone formation	uncontrolled bone formation	
Specific to Frp	Frp	May ↓ bone loss	leading to complications	
Lithium	GSK-3	↑ BMD		
603281-31-8	GSK-3	↑ Bone formation markers, bone strength		
6-bromindirubin-3'-oxime	GSK-3	↓ Glucocorticoid-induced bone loss		
AR28	GSK-3	↑ Bone mass		

Abbreviations: BMD, bone mineral density; DKK1, Dickkopf 1; Frp, frizzled-related proteins; RANKL, receptor activated nuclear factor kappa B ligand; ↑, increase; ↓, decrease; GSK-3, glycogen synthase kinase 3.

also been targeted. Odanacatib, an inhibitor of cathepsin K, decreased bone resorption markers and increased BMD at the spine and hip over two years.^{94,107} This therapy is recommended in men because it increases BMD and decreases the fracture rate in patients with prostate cancer, delays the time to the first skeletal-related event, and increases bone metastasis-free survival.¹⁰⁸

The wingless-type and integrase 1 (Wnt) signaling pathway regulates osteoblastogenesis, and inhibitors of some of these proteins can be considered as potential drug targets.¹⁰⁹ When sclerostin (a natural antagonist of the Wnt signaling pathway) is inhibited, the anabolic properties of bone are increased in animal models.¹¹⁰ In healthy men, inhibition of sclerostin using AMG 785 significantly increased bone formation markers and BMD, while significantly decreasing bone resorption markers.¹¹¹ A polymorphism of the gene coding for sclerostin showed site-specific association with BMD of the femoral neck.¹⁰⁵ Dickkopf 1, another endogenous inhibitor of the Wnt signaling pathway, has also been investigated, and a Dickkopf 1 antagonist was found to increase bone formation.¹⁰⁹ Another possible target is the frizzled-related proteins, which are also inhibitors of the Wnt signaling pathway. Studies in mice have shown that overexpression of serum frizzled-related proteins decreases bone mass and inhibits osteoblast function as well as the anabolic effects of parathyroid hormone.^{109,112} Other possible targets that have been reported include glycogen synthase kinase 3 (GSK-3), another endogenous inhibitor of the Wnt signaling pathway.¹⁰⁹ Further, several inhibitors of GSK-3, including lithium, 603281-31-8, 6-bromoindirubin-3'-oxime, and AR28, have been tested.¹⁰⁹ However, a major concern in using Wnt signaling pathway antagonists is the oncogenic effects resulting from inhibition of this pathway.¹⁰⁹ Targeting specific proteins in the metabolic pathway related to bone metabolism is a novel approach, but extreme caution is needed because many of these proteins are not just part of bone metabolism but also play a key role in other important pathways. Therefore, when these drugs are used, a balanced approach that increases the benefits but decreases other health complications and side effects must be taken into consideration. This approach is very important in treating osteoporosis, mainly because a majority of the patients are elderly, moreover, with increase in life expectancy the quality of life should also be improved.

Nutritional supplementation

Several nutritional supplements are also implicated in maintaining bone health. These include minerals like

calcium, vitamins, fatty acids, and herbal products (Table 3). Nutritional supplementation with calcium and vitamin D to increase calcium absorption is commonly prescribed to patients with osteoporosis, including men.^{4,97,113–117} Calcium and vitamin D monotherapy has been reported to reduce hip fractures.^{14,80,118,119} It is reported that community-dwelling elders are likely to have sufficient intake of calcium and vitamin D, but institutionalized elders showed calcium and vitamin D deficiency. Intermittent monofluorophosphate and calcium increased bone density and decreased the risk of vertebral fractures in upper middle aged men (mean age 53).¹²⁰ Irrespective of ethnic background, vitamin D supplementation is recommended.¹⁶ Supplementation with calcium and vitamin D, in addition to helping bone, decreases hyperthyroidism and improves muscle strength, function, and balance.^{56–58}

Other nutritional supplements that have shown promise in reducing bone loss are n-3 fatty acids, conjugated linoleic acid, soy isoflavones, and some herbal compounds. Several studies of n-3 fatty acids have reported benefits on bones in male animal models by decreasing prostaglandin 2^{121,122} and bone resorption as well as increasing BMD at the lumbar vertebrae¹²³ and tibia.¹²⁴ n-3 fatty acids benefit bone mainly by reducing bone turnover.¹²⁵ In men, a positive correlation has been found between consumption of docosahexaenoic acid and peak BMD.¹²⁶ Another fatty acid, known as conjugated linoleic acid and commonly found in milk and dairy products, increased bone mass in male

Table 3 Possible nutritional supplements for the prevention and treatment of osteoporosis in men

Supplements	Evidence	References
Calcium	Men, postmenopausal women	4,14,80,97,113–120
Vitamins		
Vitamin D	Men, postmenopausal women	16,56–58,113–120
Fatty acids		
n-3 fatty acids	Preclinical	121,122,125
Conjugated linoleic acid	Preclinical (males, females)	126,127
Herbal products		
Soy isoflavones	Preclinical, postmenopausal women	116,128
Black cohosh		116,129
<i>Fructus lingustris lucidi</i>	Preclinical	
<i>Cissus quadrangularis</i>	Preclinical	
Prunes	Preclinical, postmenopausal women	130,131

Table 4 Nonpharmacologic therapies available for men

Therapies	Benefits	References
Exercise	↑ Muscle and bone mass	80
Muscle strengthening	↑ Muscle strength, ↓ frailty, ↑ bone mass	80
Fall prevention		
Vision	↓ Visibility, ↑ falls	132,133
Hearing	Improved hearing ability ↓ accidents	
Neurologic factors	Treatment for depression improves health condition and ↓ falls and accidents	
Safety features	Installing hand rails ↓ falls	
Healthy lifestyle		
Diet	Balanced nutrition ↓ bone loss	132,133
Tobacco	↓ Bone mineral density	
Alcohol	↓ Bone mass	

Abbreviations: ↑, increase; ↓, decrease.

mice.¹²⁷ Phytoestrogens like soy isoflavones increased bone mass in orchidectomized rats, primarily by increasing bone turnover markers and the microarchitecture of trabecular bone.¹²⁸ Ipriflavone, a synthetic isoflavone, is also beneficial in maintaining bone mass.¹¹⁶

Herbal supplements and alternative medicines, including vitamin E, black cohosh, red clover, *Fructus linguistri lucidi*, *Cissus quadrangularis*, and prunes, have shown to have bone-protective properties in preclinical studies.^{116,129–131} Although many of these studies have been conducted in females, there is a high probability that these will also be beneficial to men. More systematic studies using these promising compounds may be worth pursuing to develop safer and more cost-effective treatment options.

Apart from drug interventions, nonpharmacologic therapies (Table 4) including exercise and muscle-strengthening strategies are also recommended, eg, increasing physical activity in patients with osteoporosis.⁸⁰ Fall prevention measures such as checking vision and hearing, neurologic assessment, and installing safety features in the home should be part of the treatment regimen.^{132,133} In addition, leading a healthy lifestyle, including eating healthy foods, avoiding tobacco, and limiting alcohol consumption is also recommended.¹³³

Conclusion

Traditionally, osteoporosis was considered a disease that affects only women. However, a little over two decades ago, osteoporosis came to be recognized as a disease that is also prevalent in elderly men and with bleak survival outcomes following fracture. As the population is moving toward an increased life span, it is logical to predict that the number

of patients with osteoporosis will increase. In individuals suffering from osteoporosis, living conditions are highly compromised, apart from the financial burden on society.

Although we have learned a lot about osteoporosis from studies in women, there are basic differences between women and men which need to be addressed, hence a need for more studies in men. In particular, assessment must include standards determined for men followed by treatment options. Evidence from existing studies shows most men do not get treated for osteoporosis after a hip fracture. Patients should be screened during initial evaluation for serum calcium, phosphorus, creatine, alkaline phosphatase, vitamin D, liver transaminases, thyroid-stimulating hormone, total testosterone, 25-hydroxyvitamin D, parathyroid hormone, prostate-specific antigen, bone turnover markers (ie, terminal telopeptide and procollagen type 1 amino-terminal propeptide), glucocorticoid use, and family history in order to decide on the correct treatment options.^{4,88,106} Currently there are very few clinical studies on osteoporosis in men, limiting the understanding and development of the disease as well as the therapeutic options.¹³⁴ Dual X-ray absorptiometry, high resolution quantitated computed tomography with finite element analysis, and magnetic resonance imaging are common methods for detection of the disease.^{62,94} Use of these diagnostic tools in men after a certain age will help in identifying those at risk so that preventive measures to avoid fractures can be implemented. Moreover, the focus in identifying new drugs for preventing and treating osteoporosis should also include reducing or eliminating harmful side effects and be more cost-effective.

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