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REVIEW

# A comprehensive overview on osteoporosis and its risk factors

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Farkhondeh Pouresmaeili[1,2]
Behnam Kamalidehghan[2,3]
Maryam Kamarehei[4]
Yong Meng Goh[5]

[1]Infertility and Reproductive Health Research Center (IRHRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Medical Genetics Department, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [3]Medical Genetics Center, National Institute of Genetics Engineering and Biotechnology (NIGEB), Tehran, Iran; [4]Department of Biochemistry and Biophysics (IBB), University of Tehran, Tehran, Iran; [5]Department of Veterinary Preclinical Sciences, Faculty of Veterinary Medicine, Universiti Putra Malaysia (UPM), Serdang, Malaysia

Correspondence: Behnam Kamalidehghan
Medical Genetics Department, School of Medicine, Shahid Beheshti University of Medical Sciences, Daneshjou Boulevard, PO Box 19839-63113, Tehran, Iran
Email kamalidehghan.behnam@gmail.com

Maryam Kamarehei
Department of Biochemistry and Biophysics (IBB), University of Tehran, Qods street, PO Box 13145-1384, Tehran, Iran
Email maryamka67@gmail.com

**Abstract:** Osteoporosis is a bone disorder with remarkable changes in bone biologic material and consequent bone structural distraction, affecting millions of people around the world from different ethnic groups. Bone fragility is the worse outcome of the disease, which needs long term therapy and medical management, especially in the elderly. Many involved genes including environmental factors have been introduced as the disease risk factors so far, of which genes should be considered as effective early diagnosis biomarkers, especially for the individuals from high-risk families. In this review, a number of important criteria involved in osteoporosis are addressed and discussed.

**Keywords:** atherosclerosis, hyperparathyroidism, HPT, bone and hip fractures, bone mineral density, BMD

## Introduction

Osteoporosis is a skeletal characterized by decreased bone mass and microarchitectural deterioration of bone tissue resulting in less bone tension and strength and increased risk of fragility fracture.[1,2] Osteoporosis is a major threat to elderly people, a fast-growing population of the world, in whom the risk of fracture increases with continued aging of the population.[3]

### Impact of bone density and bone quality on the fracture risk

Bone geometry, microarchitecture and size are the factors influencing the ability of bone to withstand trauma. However, 75%–90% of variance in bone strength is related to bone mineral density (BMD).[4] Indeed, bone strength arises from the integration of bone density and bone quality. The World Health Organization has defined the criteria including T-score and *z* score for evaluating bone status. T-score is explained as the number of SDs which fall below the young adult mean value in osteoporosis (the World Health Organization defines osteoporosis as a T-score of $<-2.5$), and *z* score is the expected BMD for the individual's age and sex. BMD is expressed as a correlation of the T-score and the *z* score.[5] Dual-energy X-ray absorptiometry is the most widely utilized quantitative method for measuring BMD and appraisement of fracture risk.[6]

### Prevalence of fractures

Worldwide, osteoporosis causes >8.9 million fractures annually, with the greatest number of osteoporotic fractures occurring in Europe (34.8%).[7] The most serious clinical consequence of osteoporosis is osteoporotic fracture. Fractures of the hip, vertebrae and distal forearm are considered as osteoporotic fractures with common epidemiologic

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characteristics: the fracture incidences are higher in women compared to men, and they increase steeply with advancing age and occur at body positions with a large proportion of trabecular bone. Besides, osteoporosis can lead to fractures at other sites. These include fractures of the humerus, ribs, tibia (in women), pelvis femoral fractures.[4]

Ethnicity and race are important factors influencing the prevalence of osteoporosis. Older Asian men are reported to have 50% lesser risk of sustaining a hip fracture over their lifetime than Caucasian men. Similar to men, Asian women also have lower fracture risk than Caucasian women. Moreover, there are differences in drug treatment response for osteoporosis based on ethnicity and race.[9] A study conducted on different populations support the fact that BMD is higher in African American women than in white women at every level of body weight and is consistent with their lower fracture rates.[10] The prevalence of both lifestyle-related metabolic disorders and osteoporosis is increasing in Asia. Metabolic syndrome may be associated with bone loss in Asian men, and atherosclerosis is associated with increased fractures.[11]

## Bone fractures of hip

Hip fracture is one of the seriously occurring osteoporotic fractures resulting in drastic morbidity, disability, diminished quality of life and mortality events.[12] Proximal femur (hip) fractures which demonstrate about 20% of all osteoporotic fractures are the most destructive ones and responsible for the most payments related to health care resources.[13] Hip fractures are associated with an 8%–36% excess mortality within 1 year, with a higher mortality in men than in women.[14] Since 1990, the number of fractures has continued to increase as the population ages. It is estimated that the annual worldwide hip fracture occurrence will increase up to >6 times by 2050, compared to the 1990 hip fracture rate in Europe and North America.[14] As the number of elderly people is increasing most rapidly in Asia, Latin America, the Middle East and Africa, it is expected that over 70% of the 6.26 million hip fractures will occur in these regions by year 2050 and Asian countries will contribute more to the pool of hip fractures in coming years.[15] A total of 72 studies from 63 countries by Kanis et al[250] showed a remarkable heterogeneity in hip fracture risk between the populations. The highest annual incidences were observed in countries from North Western Europe (Denmark [574/100,000 individuals], Norway [563/100,000 individuals] and Sweden [539/100,000 individuals]). But the hip fracture rate in men was approximately half of that was reported in women.[16] This low prevalence in men has been attributed to 12%–13% greater bone mass in men.[12] However, mortality rate following hip fracture is substantially higher in men than in women.[17,18] These findings showed that the variation in hip fracture incidence between countries was much greater than the differences between genders within a country.[16]

## Bone fractures of vertebral bodies

Osteoporosis-related vertebral fractures as a hallmark of osteoporosis are common problems for the aged people.[19,20] However, it has been estimated that only about one-third of them seek clinical attention due to the absence of recognizable symptoms.[20] Older white women with clinically recognized incident vertebral fracture experience substantial increases in back pain associated with decreased quality of life and functional limitation due to back pain.[21,22] In Europe, the incidence of new vertebral fracture was 10.7/1,000 per year in women and 5.7/1,000 per year in men aged 50–79 years. The prevalence of vertebral fracture was greater in Scandinavia compared with other European regions, while the geographic heterogeneity of vertebral fracture rate was less than that observed for hip fracture.[23] Vertebral fracture rate increases exponentially with age in the same way as for hip fracture, and the risk of death is associated with the number of vertebral fractures. This raises the possibility that prevention of further vertebral fractures might decrease the mortality rate.[24] Vertebral fracture cascade is a term referring to the occurrence of subsequent vertebral fracture after sustaining an initial vertebral fracture, and the risk of second vertebral fracture within a year following the first incident vertebral fracture in women is reported to be ~20%.[25] Women with vertebral osteoporotic fractures have reduced vertebral BMD and vertebral dimensions compared with controls with no history of fracture.[26] Similar findings exist for men.[27] Intravertebral distribution of bone mass, bone quality parameters, vertebral macroarchitecture, amount of intervertebral disc degeneration and balance control are factors varying significantly between individuals with and without vertebral fractures.[28]

## Bone fractures of the distal forearm

Fracture of the distal forearm is a common osteoporotic fracture accounting for up to 18% of all fractures in the above 65 years age group[29] and 75% of fractures of the forearm.[30] Recent data show an increase in incidence of distal radius (wrist) fractures for the pediatric, adult and elderly populations in recent years.[29] Brogren et al documented

comparable differences between men and women in the age group of 49–65, wherein they found that women had almost double the rate of fracture compared with men, likely due to the early onset of osteoporosis in women.[31] A research by O'Neill et al identified that the incidence of forearm fractures in 3,161 adult British men and women aged 35 years and over was 36.8/10,000 person-years in women and 9.0/10,000 person-years in men.[32] The age distribution of the wrist fractures is typically bimodal, with peaks found in the age groups 5–14 years and above 60 years.[30] The prevalence of distal radius fractures in the adult population is significantly lower than in elderly groups.[31] However, it has been suggested that this fracture is the most common injury in adult population and is more predominant than hip fractures. The rate of forearm fractures in Denmark was somewhat higher in both genders than that recently imputed from hip fracture rates and was close to the rates previously reported in studies from Norway and Sweden.[33] Urban/rural differences in BMD are a risk factor contributing to the fracture rate difference. A study showed that women residing in urban areas have a higher BMD than those in rural areas, which is entirely consistent with a 30% increased risk of sustaining a forearm fracture.[34] The occurrence of a distal forearm fracture convincingly predicts future fracture risk.[35] Overall, a 1.5-fold increase in the risk of a subsequent hip fracture among 2,252 Swedish women ≥40 years of age with a forearm fracture in 1968–1972[36] and also a 1.8-fold increase among 1,162 Danish women ≥20 years of age with a forearm fracture in 1976–1984 support the present hypothesis.[37] Fractures are also common among children, which result from mild or moderate trauma, endocrine dysfunction, chronic illnesses, genetic disorders, lack of weight-bearing physical activity and obesity.[38]

## Risk factors for osteoporosis and osteoporotic fractures

Osteoporosis is initiated by an imbalance between bone resorption and formation.[39,40] Research studies point to a number of risk factors for osteoporosis that are modifiable, including diet and lifestyle factors, while some factors are non-modifiable (Box 1).

**Box 1** Risk factors involved in osteoporosis

1. Major modifiable risk factors:
   - Inadequate nutritional absorption
   - Lack of physical activity or fall risk
   - Weight loss
   - Cigarette smoking
   - Alcohol consumption
   - Air pollution
   - Stress
2. Major non-modifiable risk factors:
   - History of falls
   - Older age
   - Gender
   - White ethnic background
   - Prior fracture
   - Reproductive factors (family history of osteoporosis)
3. Secondary causes of osteoporosis
   - Chronic use of certain medications (prolonged corticosteroid use, and so on)
   - Hypogonadism
   - Hyperparathyroidism
   - Chronic liver disease
   - Inflammatory diseases (rheumatoid arthritis, and so on)
   - Vitamin D deficiency
   - Renal disease (history of kidney stones)
   - Cardiovascular disease
   - Diabetes mellitus
   - Dementia

### Nutritional deficiency (especially consumption of junk food) and sedentary lifestyle

Health-promoting behaviors, such as consuming a healthy diet, could lessen the impact of chronic diseases such as osteoporosis and cardiovascular diseases.[41] It was previously recognized that maternal diet can influence bone mass in the offspring and a good general nutritional status with adequate dietary protein, calcium, vitamin D, fruits and vegetables has a positive influence on bone health, while a high-caloric diet and heavy alcohol consumption have been associated with lower bone mass and higher rates of fracture.[42] It is now proven that a dietary pattern with high intake of dairy products, fruits and whole grains may contribute positively to bone health and dietary pattern-based strategies could have potential in promoting bone health.[43] Confirming this evidence and similar investigations, a study on Chinese older women in Hong Kong showed that higher "vegetables–fruits" and "snacks–drinks–milk products" pattern scores were associated with reduced risk of cognitive impairment.[44]

Moreover, absence of vitamin K, particularly as vitamin K2, in junk food results in impairment of the calcium removal process and increases the risk of calcification of the blood vessels. An increased intake of vitamin K2 could be a means of lowering calcium-associated health risks.[45] In addition, the recent trends in avoiding sunbathing and eating fewer fish products have resulted in a high prevalence of vitamin D deficiency in the general Japanese population.[46]

## Use of alcohol and its relation to BMD

In 2013, Sommer et al demonstrated the results from Osteoporosis Risk Factor and Prevention-Fracture Prevention Study (OSTPRE-FPS) which suggested that low-to-moderate alcohol intake may exert protective effects on bone health in elderly women.[47] Nevertheless, osteoporotic patients should be counseled regularly about cigarette cessation, alcohol intake, and estrogen status.[48] Recently, a meta-analysis identified a nonlinear association between alcohol consumption and the risk of hip fracture. Light alcohol consumption was inversely significantly associated with hip fracture risk, whereas heavy alcohol consumption was associated with an elevated hip fracture risk.[49] Alcohol consumption (low and moderate/high) may have a detrimental impact on bone health in both the cortical and trabecular compartments at the distal radius in men, and similar results were found in the trabecular and distal tibia compartments of women with minimal alcohol and low alcohol consumptions, respectively, suggesting that avoidance of alcohol may be beneficial for bone health.[50]

## Smoking

Cigarette smoking is considered as a risk factor for osteoporosis and is related to a loss of bone mass and increased risk of osteoporotic fractures.[51,52] Krall and Dawson-Hughes[53,54] reported decreased BMD at the radius, femoral neck and whole in smokers than in nonsmokers. However, other investigators found no link between smoking and fracture risk in women.[55,56] Parathyroid hormone (PTH) and vitamin D metabolites play a vital role in the regulation of calcium homeostasis and bone metabolism.[57,58] Notably, serum PTH showed an increasing level in heavy smokers, which is consistent with the result of a similar study by Ortego-Centeno et al in young male smokers.[51] Smokers had about 10% decrease of circulating levels of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D).[59] Smoking is associated with increased follicle stimulating hormone and luteinizing hormone, which directs the estrogen levels to decrease and results in rapid bone loss.[52] The influence of some of the osteoporosis risk factors and their role in the bone formation pathway regulation and bone diseases is illustrated in Figure 1.

There is no clear evidence to show the direct causal relationship between passive cigarette smoking and osteoporosis. Furthermore, the underlying mechanism is unknown. The bone turnover biochemical markers in urine and serum and also the bone microarchitecture by micro-computed tomography were compared with the control group exposed to normal ambient air. In the cell culture experiments, MC3T3-E1 and RAW264.7 mouse cell lines used as osteoblast and

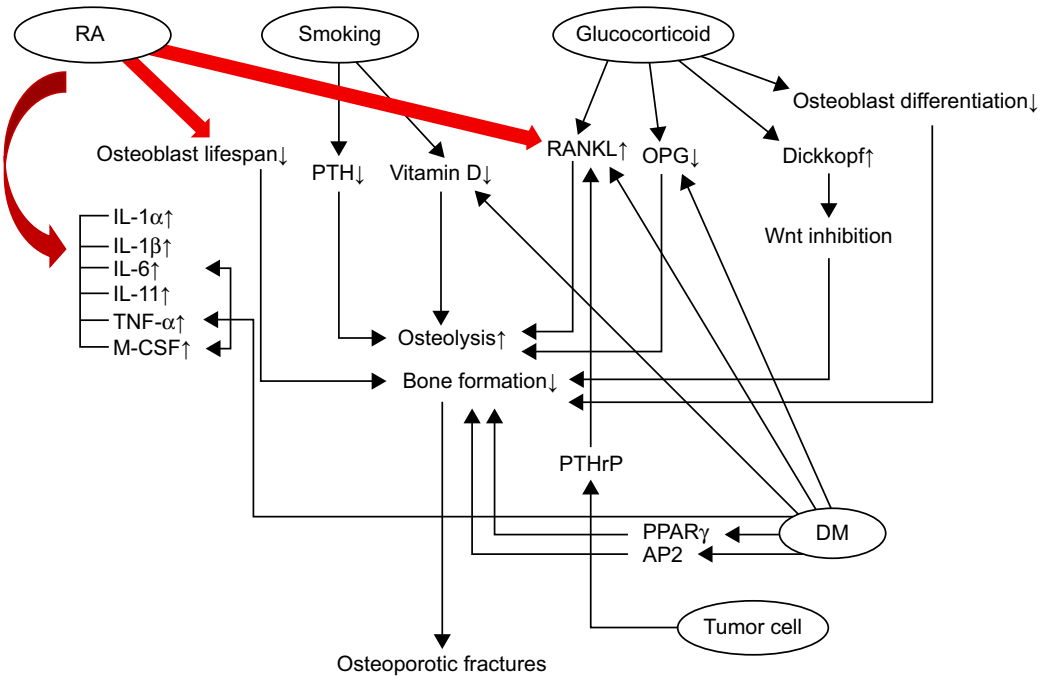


**Figure 1** Common osteoporosis risk factors involved in pathways associated with bone formation and osteoporotic fractures.

**Note:** RA, smoking, glucocorticoids, diabetes mellitus and tumors, the most common risk factors, negatively control the bone organization pathway, resulting in osteoporotic fractures.

**Abbreviations:** IL, interleukin; M-CSF, macrophage colony stimulating factor; OPG, osteoprotegerin; PPARγ, peroxisome proliferator-activated receptor-γ; PTH, parathyroid hormone; RA, rheumatoid arthritis; RANKL, RANK with its ligand; TNF, tumor necrosis factor; DM, diabetes mellitus; AP2, adipocyte fatty acid binding protein 2; RANK, receptor activator of nuclear factor κ.

osteoclast, respectively, were treated with the sera obtained from BALB/c mice exposed to 4% cigarette smoke during 14 weeks. Their actions on cell viability, differentiation and function on these bone cells were assessed. The urinary mineral and deoxypyridinoline levels and also serum alkaline phosphatase (ALP) activity were significantly higher in the 4% smoking group when compared with the control group, indicating an elevated bone metabolism after cigarette smoking. In addition, femoral osteopenia was observed in the 4% smoking group, as shown by a decrease in relative bone volume and trabecular thickness. In isolated cell studies, osteoblast differentiation and bone formation were inhibited, while osteoclast differentiation was increased. The current mouse smoking model and the isolated cell studies demonstrate that passive cigarette smoke could induce osteopenia by exerting a direct detrimental effect on bone cells differentiation and further on bone remodeling process.[60]

## Genetic factors

The genetics of osteoporosis represents one of the greatest challenges and the most active area of research in bone biology. It is well established that the variation in BMD is determined by our genes. Several candidate gene polymorphisms in relation to osteoporosis have been implicated as determinants of BMD. The vitamin D receptor (*VDR*) gene, the collagen type I α1 (COLIA1) gene and the estrogen receptor-α (ERα) gene are among those most intensively studied. VDR modulates the transcription of target genes involved in calcium uptake or bone formation, including calcium-binding proteins[61–63] and osteocalcin (OC).[64] The VDR gene maps to chromosome 12q13-14 and possesses at least 11 exons.[65] Allelic variants of the gene encoding VDR are recognized by ApaI (allele A/a), BsmI (allele B/b), FokI (allele F/f) and TaqI (allele T/t) restriction endonucleases.[66–69] All these polymorphisms are restriction fragment length polymorphisms.[70] VDR BsmI polymorphism, genotype bb showed the maximum influence on BMD in combination with other alleles and has been associated with higher rate of calcium absorption compared to that in women with the BB genotype.[71] Furthermore, BMD levels were consistently higher in women with the VDR bb genotype.[72] The BB genotype had a greater set point for the feedback inhibition of PTH initiated by an increase in 1,25-$(OH)_2D$, more active bone resorption and breakdown of type I collagen, and greater concentrations of $1,25(OH)_2D$, compared with the bb genotype.[71] The assessment of BsmI polymorphism in a group of normal and osteoporotic Iranian women confirmed that BsmI polymorphism of VDR gene is significantly associated with BMD in the lumbar spine and may have a minor effect on the proximal femur BMD.[73] BsmI polymorphism could influence expression of the *VDR* gene and alter BMD through different mechanisms, including disruption of a splice site for VDR mRNA transcription and changes in mRNA stability or in the intronic regulation element.[74,75] BMD was also associated with polymorphisms at other marker loci of the *VDR* gene, including the TaqI[76] and FokI.[77] Genotype TT for the TaqI polymorphism had lower rate of bone loss than those with other genotypes. Given the tight linkage disequilibrium of the b allele with the T allele, the bb individuals had lesser bone loss.[78] FokI is an independent polymorphism, and FF genotype is associated with higher BMD at the femoral neck,[79] spine and hip.[80] The FF individuals had greater calcium absorption and BMD values than Ff and ff genotypes. This leads to the conclusion that the VDR alleles act differentially on intestinal calcium absorption.[71] Another polymorphism, the start codon polymorphism (SCP), is identified by the FokI polymorphism and is located at the translation initiation site in exon II of VDR. Unlike the above polymorphisms, which do not result in amino acid changes, the SCP changes the VDR structure. SCP makes the F allele VDR three amino acids shorter than the f allele, leading to altered receptor function.[78] Recently, a novel polymorphism in the Cdx-2–binding site of the VDR gene promoter region was identified. Polymorphic region function, which is also called the human VDR-sucrose-isomaltase footprint 1 sequence, was analyzed using an intestinal cell line as a model system.[81,82] Cdx-2 was able to activate VDR gene transcription by binding to the human VDR-sucrase-isomaltase footprint 1 sequence. Mutations of the sequence suppressed transactivation activity.[81] VDR also regulates OC which plays a role in bone mineralization and calcium ion homeostasis. Higher OC levels have been reported in premenopausal Japanese women with the BB genotype.[83,84] However, Willing et al found no such association between the BB genotype and either OC levels or their change over a 3-year period.[72]

In addition to VDR, estrogen receptors (ERs) also play an important role in controlling skeletal growth and maintenance of bone mass. Two functional ERs, ERα and ERβ, are encoded by different genes and have similar structure and considerable homology in the DNA-binding and ligand-binding domain. The human ERα gene (ESR1) is located on chromosome 6q25, and consists of eight exons and spans >140 kb. The ERβ gene (ESR2) is located on chromosome 14q23-24.1.[85] Decreased BMD in mice lacking functional ERα supports the hypothesis that ERα is probably a candidate gene for osteoporosis.[86–89] Several polymorphisms of this gene have been studied, including the T→C and the

A→G in intron 1 and the TA repeat in the promoter region, codon 325 (CCC→CCG),[90] T262C of exon 1,[91] G2014A of exon 8[92] and G261C of exon 1.[93] Furthermore, the TA repeat polymorphism is located within the promoter region 1,174 bp upstream from exon 1, which affects BMD by changing the production or stability of mRNA leading to changes in ER number. Linkage of two intronic PvuII and XbaI polymorphisms with BMD has been extensively studied. In general, the XX and pp genotypes (or the X and p alleles) were associated with greater BMD, as compared with the xx and PP genotypes (or the x and P alleles).[72,94–97] Pouresmaeili et al[98] observed a majority of PX haplotypes among 200 pre- and/or postmenopausal Iranian women, which is in contrast with the frequencies for Caucasians with a reduced PX haplotype.[99]

Potentially, there is a physiologic functional relationship between the ER and VDR.[100] We observed that BMD levels were consistently higher in women with the VDR bb genotype and the (–/–) PvuII and Xba I ER genotypes.[17] However, a significant gene-by-gene interaction effect indicated that women who were homozygous (–/–) at the PvuII or Xba I loci had significantly different BMD levels according to their VDR status.[72]

Osteoporosis may also be caused by mutations in the Collagen I alpha 1 (COL1A1) gene that has been consistently associated with fracture risk.[101] The Sp1 polymorphism stems from a G→T substitution at the first base of a consensus site in the first intron in the COLIA1 gene for the transcriptional factor, Sp1.[102,103] BMD was greater for the G/G (SS) genotype than for the G/T (Ss) and T/T (ss) genotypes. The s allele had greater affinity than the S allele for Sp1 protein. Brown et al[104] found that lumbar spine bone loss was greater in the ss and Ss genotypes than in the SS genotype.

Most genetic polymorphisms are associated with the genes encoding the important pathways of bone metabolism, including transforming growth factor-β1 (TGF-β1), interleukin-6 (IL-6), insulin-like growth factor (IGF)-I, calcitonin (CT), calcitonin receptor (CTR) and interleukin-1 receptor antagonist (IL-1ra). The TGF-β1 gene has seven exons, of which exons 5–7 encode the active TGF-β1. Keen et al[105] reported that the T→C polymorphism of intron 5 was associated with femoral neck BMD. Yamada et al[106] studied the 509 C→T polymorphism in postmenopausal Japanese women and found a link with lumbar spine and total body BMD. Activation of cytokine expression in bone is a feature of postmenopausal women, leading to bone loss. IL-6, a pleiotropic cytokine, mediates estrogen deficiency-related bone loss in patients.[107] Several studies have demonstrated the relationship of polymorphisms of the IL-6 gene with BMD, including the variable number tandem repeat (VNTR) polymorphism in the 3′ flank region of the gene,[108] the CA repeat polymorphism[109] and the −174 G→C polymorphism.[110] IGF-I is produced by osteoblasts and is involved in bone metabolism.[111] Serum IGF-I concentrations were correlated with BMD in humans.[112,113]

CT is a polypeptide hormone secreted by the thyroid gland and inhibits osteoclastic bone resorption. The human CTR belongs to a family of G-protein-coupled receptors. In a study in 663 postmenopausal and 52 premenopausal Italian women, the AluI restriction enzyme polymorphism of the CTR gene was associated with spine BMD.[114] The TaqI polymorphism and the T→C polymorphism are two polymorphisms of the CTR gene which are related to lumbar and femoral neck BMD.[115,116]

IL-1 acts as a powerful stimulant of bone resorption by inhibiting osteoclast apoptosis. IL-1ra competes with both IL-1α and IL-1β, the two isoforms of IL-1, for binding with IL-1 receptors. Postmenopausal increase in IL-1 and IL-1ra production results in bone loss.[117]

The human IL-1ra gene consists of four exons.[118] The VNTR is due to an 86 bp repeat within intron 2 of the gene. VNTR polymorphism is associated with spinal bone loss.[117]

Wong et al's [119] study assessed the correlation between BMD and allele E4 of apolipoprotein E (ApoE4) in the Chinese population. One hundred and ninety women aged 55–59, 267 women aged 70–79 and 235 men aged 70–79 were studied. High frequency of ApoE4 and a higher incidence of femoral neck fractures in Caucasians were shown in other studies.[120,121] Table 1 presents some of the genes known to be involved in the etiology of bone disorders.

## Medication

Synthetic glucocorticoids are administered to treat disorders caused by autoimmune, pulmonary and gastrointestinal diseases, as well as in patients receiving organ transplantation and with malignancies.[122] Glucocorticoids cause profound effects on the skeleton, and glucocorticoid-induced osteoporosis is the most common secondary cause of osteoporosis.[122,123] Glucocorticoids induce a biphasic bone loss with a rapid initial phase showing 10%–20% bone loss in as little as 3 months of therapy and a slower phase of 2%–5% bone loss annually.[124] They increase the expression of receptor activator for nuclear factor κ-B ligand (RANKL) and decrease the expression of its soluble decoy receptor, osteoprotegerin (OPG), in stromal and osteoblastic cells, leading to elevated bone resorption.[123] Glucocorticoids inhibit osteoblast cell differentiation by increasing the expression of dickkopf, an inhibitor of Wnt signaling, and opposing Wnt signaling.[125] Glucocorticoids suppress IGF-I gene

**Table 1** Candidate genes associated with osteoporosis

| Candidate gene | Protein | Chromosome | Function | Reference |
|---|---|---|---|---|
| *VDR* | Vitamin D receptor | 12q12-14 | The nuclear hormone receptor for vitamin D3 | Ferrari et al,[62] Durrin et al,[252] Remes et al,[253] Lambrinoudaki et al,[254] Wang et al,[255] Pouresmaeili et al,[73] |
| *ER-α* | Estrogen receptor-α | 6q25 | An estrogen receptor | Ioannidis et al,[256] Yamada et al,[257] van Meurs et al,[99] Tang et al,[258] |
| *ER-β* | Estrogen receptor-β | 14q22-24 | A member of the family of estrogen receptors and the superfamily of nuclear receptor transcription factors | Ogawa et al,[259] Lau et al,[260] Scariano et al,[261] Kung et al,[262] |
| *CT* | Calcitonin | 11p15 | A peptide hormone that causes reduction in serum calcium | Miyao et al,[263] Magaña et al,[264] |
| *CTR* | Calcitonin receptor | 7q21 | A high-affinity receptor for the peptide hormone calcitonin | Tural et al,[265] |
| *PTH* | Parathyroid hormone | 11p15 | This hormone elevates blood $Ca^{2+}$ level by dissolving the salts in bone and preventing their renal excretion | Hosoi et al,[266] |
| *PTHR* | Parathyroid hormone receptor 1 | 3p22-21 | A receptor for PTH and for PTHLH | Minagawa et al,[267] |
| *CYP19* | Aromatase (cytochrome P450) | 15q21 | A member of the cytochrome P450 superfamily of enzymes and catalyzes the last steps of estrogen biosynthesis | Napoli et al,[268] |
| *CYP17* | Steroid 17-alpha-hydroxylase/17,20 lyase | 10q24 | A member of the cytochrome P450 superfamily of enzymes and a key enzyme in the steroidogenic pathway | Zmuda et al,[269] Sharp et al,[270] |
| *GCR* | GC receptor | 5q31 | Receptor for GCs that affects inflammatory responses, cellular proliferation and differentiation in target tissues | Huizenga et al,[271] |
| *CaSR* | Calcium-sensing receptor | 3q13-21 | It senses changes in the extracellular concentration of calcium ions and maintains ion homeostasis | Tsukamoto et al,[272] |
| *AR* | Androgen receptor | Xq11-12 | A nuclear receptor that affects IGF-1 and genes involved in the development of primary and secondary male sexual characteristics expression | Langdah et al,[273] |
| *TGF-β1* | Transforming growth factor-β1 | 19q13 | Potent stimulator of osteoblastic bone formation | Langdahl et al,[274] |
| *IL-6* | Interleukin-6 | 7p21 | A cytokine that functions in inflammation and also as a bone-resorbing cytokine | Murray et al,[108] Tsukamoto et al,[109] |
| *IGF-1* | Insulin-like growth factor 1 | 12q22-24 | A physiologic regulator of [1-14C]-2-deoxy-D-glucose transport and glycogen synthesis in osteoblasts | Rivadeneira et al,[275] |
| *IL-1ra* | Interleukin-1 receptor antagonist | 2q14 | A member of the IL-1 cytokine family which inhibits the activities of IL-1 | Langdahl et al,[93] |
| *OPG* | Osteoprotegerin | 8q24 | As a potent inducer of DKK-1 can inhibit the Wnt signaling pathway | Arko et al,[276] García-Unzueta et al,[277] Jurado et al,[278] |
| *TNF-αcω* | Tumor necrosis factor-α | 6p21 | A multifunctional bone-resorbing cytokine | Mencej et al,[279] |

(*Continued*)

**Table 1** (*Continued*)

| Candidate gene | Protein | Chromosome | Function | Reference |
|---|---|---|---|---|
| *TNFR2* | Tumor necrosis factor receptor 2 | 1p36 | A member of the TNF-receptor superfamily | Hoshino et al,[280] |
| *COL1A1* | Collagen type Iα1 | 17q21-22 | A fibril-forming collagen found in most connective tissues and bone | Grant et al,[281] Tural et al,[265] |
| *COL1A2* | Collagen type Iα2 | 7q22 | A fibril-forming collagen found in most connective tissues and bone | Lau et al,[282] |
| *BGLAP* | Osteocalcin | 1q22 | Constitutes 1%–2% of the total bone protein and binds strongly to apatite and calcium | Chen et al,[283] McGuigan et al,[284] |
| *MGP* | Matrix Gla protein | 12p12 | An inhibitor of bone formation | Zebboudj et al,[285] |
| *AHSG* | α-2-HS-glycoprotein | 3q27 | Influences the mineral phase of bone | Eichner et al,[286] |
| *ApoE* | Apolipoprotein E | 19q13 | Mediates the binding, internalization and catabolism of lipoprotein particles | Johnston et al,[287] Cauley et al,[288] |
| *MTHFR* | Methylenetetrahydrofolate reductase | 1p36 | Catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, which is used for homocysteine methylation to methionine | Villadsen et al,[289] |
| *P57 (KIP2)* | Cyclin-dependent kinase inhibitor 1c | 11p15 | Regulates osteoblast proliferation and differentiation | Urano and Inoue,[290] |
| *HLA-DR15* | Major histocompatibility complex, class II, DR | 6p21 | Interacts with another gene related to bone metabolism such as TNF-α | Douroudis et al,[291] |
| *PPARγ* | Peroxisome proliferator-activated receptor-γ | 3p25 | Key regulator of adipocyte differentiation and glucose homeostasis | Altshuler et al,[292] |
| *FRA-1* | Fos-related antigen-1 | 11q13 | Leucine zipper proteins that act as regulators of cell proliferation, differentiation and transformation | Albagha et al,[293] |
| *RUNX-2* | Runt-related transcription factor-2 | 6p21 | Essential for osteoblastic differentiation and skeletal morphogenesis | Vaughan et al,[294] Doecke et al,[295] |
| *Klatho gene* | Klotho protein | 13q12 | Involved in the regulation of calcium and phosphorus homeostasis by inhibiting the synthesis of active vitamin D | Kawano et al,[296] |
| *WRN (Werner syndrome gene)* | Werner helicase | 8p12 | A DNA helicase involved in many aspects of DNA metabolism | Ogata et al,[297] |
| *LRP5* | Receptor related protein 5 | 11q12-13 | A coreceptor with frizzled protein family members for transducing signals by Wnt proteins | Babij et al,[298] Ai et al,[299] |
| *CTSK* | Cathepsin K | 1q21 | A lysosomal cysteine proteinase involved in bone remodeling and resorption | Giraudeau et al,[300] |
| *BMP4* | Bone morphogenetic protein 4 | 14q22 | It plays an important role in the onset of endochondral bone formation in humans | Babu et al,[301] |
| *CLCN7* | Chloride channel 7 | 16p13 | Slow voltage-gated channel mediating the exchange of chloride ions against protons | Pettersson et al,[302] Kornak et al,[303] |
| *TCIRG1* | T cell immune regulator | 11q13.4-q13.5 | Part of the proton channel of V-ATPases | Lee et al,[304] |
| *FDPS* | Farnesyl pyrophosphate synthase | 1q22 | Key enzyme in isoprenoid biosynthesis | Marini et al,[305] |

(*Continued*)

**Table 1** (*Continued*)

| Candidate gene | Protein | Chromosome | Function | Reference |
|---|---|---|---|---|
| *P2X7* | Purinergic receptor P2X, ligand-gated ion channel, 7 | 12q24 | Found in the central and peripheral nervous systems and increases the release of proinflammatory molecules such as IL-1β, IL-6 and TNF-α | Gartland et al,[306] |

**Abbreviations:** GC, glucocorticoid; IGF, insulin-like growth factor; IL, interleukin; PTH, parathyroid hormone; PTHLH, parathyroid hormone-like hormone; TNF, tumor necrosis factor.

transcription[123] which is responsible for bone formation and the synthesis of type I collagen.[126]

## Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a calcium metabolic disorder with the highest incidence in postmenopausal women.[127] Several studies have shown decreased BMD in patients with PHPT.[128] Vestergaard et al[129] reported high fracture risk of the forearms and the vertebrae in a group of 674 patients with PHPT. PTH is normally the major regulator of calcium homeostasis and functions mainly on kidney and bone.[130] It acts on kidney cells by increasing the renal tubular reabsorption of calcium and as well as the conversion of 25-hydroxy vitamin D (25-(OH)D) to 1,25$(OH)_2$D through activation of 1α-hydroxylase.[131,132] In vitro and in vivo studies confirm that PTH directly activates survival signaling in osteoblasts and increases osteoblast number.[133] Indeed, the preosteoblastic precursors and preosteoblasts possess receptors for PTH, which induces differentiation from the precursor to osteoblast.[134] The fibroblast growth factor-2, which primarily produced by osteocytes in bone, regulating phosphate metabolism through its inhibitory effects on the renal sodium-phosphate contransporter.[135] However, increased secretion of PTH in PHPT leads to elevated serum calcium levels due to release from the bone stores. This has been shown to increase the risk of osteoporosis by increasing the rate of bone turnover.[130]

## Rheumatoid arthritis (RA)

RA is the most common form of inflammatory disease in adults characterized by progressive and systemic inflammation.[136] RA is associated with osteoporosis due to active systemic inflammation, immobilization and the use of glucocorticoids.[137] Osteoporosis occurs in two forms in RA: 1) generalized bone loss with axial distribution including the spine, pelvis, hips, ribs and humerus and 2) periarticular or localized bone loss in the proximity of the inflamed joints.[138] Several studies reported that the rate of spine or hip fractures is higher in patients with RA compared with primary osteoporotic patients.[139–142] Histomorphometric and biochemical markers analysis indicates that generalized bone loss in RA is related to a decrease in bone formation and increase in bone resorption.[143] Rheumatoid synovial tissues are enriched with bone-resorbing cytokines including IL-1α and IL-1β, tumor necrosis factor (TNF)-α, macrophage colony-stimulating factor, IL-6, IL-11, PTH-related peptide and the newly described T-cell–derived cytokine IL-17.[144–150] The interaction of RANK with its ligand (RANKL) has been identified as a common pathway to control the differentiation, proliferation and survival of osteoclasts.[151] Expression of RANKL is upregulated by inflammatory cytokines. RANKL, also known as TRANCE (TNF-related activation induced cytokine), is a membrane-bound TNF receptor. RANKL is expressed on osteoblast precursor cells that interact with RANK on the osteoclast surface. OPG, a soluble decoy receptor protein, is produced by osteoblast/stromal cells that bind to RANKL and prevent its binding to RANK on the preosteoclast cells.[152–154] OPG protects against TNF-induced bone loss.[155] TNF, as a potent inducer of dickkopf-related protein 1 (DKK-1), can inhibit the wingless (Wnt) signaling pathway and expression of OPG, leading to bone formation limitation.[156] TNF-α promotes the production of proinflammatory cytokines (eg, IL-1, IL-6 and IL-8) in RA. TNF-α also prolongs osteoclasts' lifespan or it may promote osteoclast formation by directly stimulating its precursors.[157,158]

## Diabetes mellitus

Diabetes mellitus is a debilitating metabolic disease with substantial morbidity characterized by hyperglycemia resulting from defects in insulin secretion and/or insulin action.[159] In the USA, about 8% of youth have diabetes[160] and it has been predicted that the number of Americans with diabetes will rise from 11 million in 2000 to 29 million in 2050.[161]

Reports about the prevalence of diabetes mellitus in Saudi Arabia estimate the current prevalence to be around 17%, with expectations that it will peak to >20% by the year 2030. Advanced age, oral hypoglycemic agents and vitamin D deficiency are determinants of decreased BMD in Saudi women with type 2 diabetes.[162] Skeletal disorders in diabetes may be caused by multiple mechanisms including changes in insulin and IGF levels, hypercalciuria associated with glycosuria, reduced renal function, obesity, higher concentrations of advanced glycation end products (AGEs) in collagen, angiopathies, neuropathies and inflammation.[163–166] Comparison of BMD values in type 1 and type 2 diabetic patients of similar age showed that type 1 diabetes mellitus (T1DM) is associated with reduction in BMD. However, type 2 diabetes mellitus (T2DM) can be related to increased BMD.[167] It can be speculated that T1DM and T2DM are associated with higher fracture risk.[168] Schwartz et al in a study of osteoporotic fractures, confirmed that women with T2DM experience higher fracture rates in hip, humerus and foot than nondiabetic women.[169] A previous research by Nicodemus and Folsom[170] evaluated the incidence of hip fracture (1.6 per 1,000 person-years). A statistically significant positive association between T2DM and hip fracture incidence was found. Women with T1DM had 12.25 (95% CI 5.05–29.73) times higher risk of hip fracture compared with nondiabetic women. Women with T2DM were 1.70-fold more likely than women without diabetes to sustain a hip fracture.[170,171] This rate is consistent with that reported in a similar survey by the National Hospital Discharge.[172] Women with T2DM who were treated with insulin and nondiabetic women had similarly lower risk for hip fracture.[173] Diabetic patients usually have an elevated risk of falling because of vision-related risk factors including diabetic retinopathy, advanced cataracts, laser therapy for retinopathy, hypoglycemia and also balance-related risk factors such as peripheral neuropathy, foot ulcers, polyuria, nocturia and decreased reflexes.[169,174] Hip fracture risk increases in both T1DM and T2DM due to increased risk of falling and not decreased BMD.[174] Insulin has been proposed to be an anabolic agent in bone, capable of stimulating osteoblast proliferation and differentiation. It has been reported that insulin stimulates increase of human osteoblastic cell line MG-6 in a time- and dose-dependent manner, and blockade of both MAPK and PI3K pathways could inhibit cell proliferation.[175] Data obtained in this study suggested that insulin promoted ALP activity, which is a bone formation enzyme secreted by osteoblasts,[176] the secretion of type I collagen, OC gene expression and mineralized nodule formation. Insulin also upregulates osterix (Osx) and IGF-1 expression through ERK and significantly downregulates runt-related transcription factor 2 (Runx2) expression through MAPK pathway.[175,177] High glucose inhibits cell growth, mineralization and expression of osteogenic markers including Runx2, collagen I, OC and osteonectin.[177] Adipogenesis or lipogenesis is still active in diabetic type I bone, and the number of lipid-dense adipocytes and the expression of adipogenic markers (peroxisome proliferator-activated receptor-γ [PPARγ2], resistin, adipocyte fatty acid binding protein [aP2] and adipsin) are increased.[178] PPARγ levels lead to increased adipogenesis in mice with a dominant suppressive influence on osteogenesis.[178,179] It is recognized that fatty acids can activate PPARγ2 and suppress ALP expression in osteoblastic cells.[180] In addition to hyperglycemia, impaired leptin function may indirectly be related to osteoporosis in DM, since leptin receptor knockout mice showed an increase in bone mass compared to normal mice.[181,182] Some BMP and TGF-β signaling pathway inhibitors including DKK-1,[183,184] sclerostin,[185] gremlin,[186] PTH,[187] angiotensin II (Ang-II),[188] IL-6[189] and TNFs[190] are overexpressed in DM. DM also sequesters the overexpression of vitamin D required for the normal growth of osteoblasts.[191] Vitamin D increases the uptake of calcium and phosphorus and improves calcium reabsorption by the kidney, thus resulting in maintenance of mineral homeostasis and regulation of bone remodeling.[192] DM decreases the expression of endothelial progenitor cells derived from bone and, consequently, the rate of angiogenesis required for bone healing.[193] Pancreatic β cells also produce amylin and preptin. It is known that amylin causes bone formation and blocks bone resorption. Preptin induces osteoblast differentiation and mineralization and also decreases osteoblast apoptosis. DM reduces the production of OC that regulates osteogenesis positively.[194] It can be speculated that formation of AGEs plays a crucial role in the pathogenesis of diabetic neuropathy.[195] Under hyperglycemic conditions, levels of methylglyoxal, 3-deoxyglucosone and glyceraldehyde increase, leading to the formation of AGEs which signal through the receptor for advanced glycation end product expressed on the nerve cells, resulting in different types of cytokine production, which may have roles in nerve damage as well as deleterious effect on nerve cells because they modify neuronal proteins including tubulin, neurofilament, laminin and actin through glycation, and thereby sequester the nerve function.[196] In a recent study, Catalano et al have shown that lower bone formation and increased bone resorption, although not statistically significant, were observed in patients with poor metabolic control in comparison to patients with good metabolic control. Therefore, poor metabolic

control may worsen the quality of bone in T1DM. Phalangeal quantitative ultrasound could be considered as a tool to screen T1DM women for osteoporosis in premenopausal age.[197] However, Neumann et al showed that trabecular bone score was lower in T1DM patients with prevalent fractures in comparison to healthy controls, suggesting an alteration of bone strength in this subgroup of patients.[198]

Walsh and Vilaca believe that BMI is positively associated with BMD, and the mechanisms of this association in vivo may include increased loading, adipokines such as leptin and higher aromatase activity. However, some fat depots could have negative effects on bone; T2DM is also associated with higher BMD, but increased overall and hip fracture risk. There are some similarities between bone in obesity and T2DM, but T2DM seems to have additional harmful effects where glycation of collagen may be an important factor. Higher BMD but higher fracture risk presents challenges in fracture prediction in obesity and T2DM. It seems that osteoporosis treatment does reduce the fracture risk in obesity and T2DM with generally similar efficacy to that in other patients.[199] A very recent meta-analysis strongly supported the association between T2DM and increased risk of overall fracture. These findings emphasize the need for fracture prevention strategies in patients with diabetes.[200]

## Dementia

Osteoporosis and Alzheimer's disease (AD) are common chronic degenerative disorders prevalent in elderly people. The large majority of AD cases occur sporadically by genetic mutation, aging and environmental factors as pathogenic mechanisms. Osteoporosis is a multifactorial, mostly polygenetic disease, and no single factor can completely account for their occurrence as well. Common risk factors in both diseases include body mass loss, vitamin D deficiencies, less exposure to sunlight and less physical activity.[201] Evatt et al[251] showed a substantial incidence of vitamin D deficiency among Parkinson's disease cohort patients compared with the AD patients and control cohorts. It can be speculated that Parkinson's disease may cause patients to have decreased activity levels and lower sunlight exposure. In 2003, Weller and Schatzker from Canada observed that femoral neck fractures were more prevalent in patients with AD compared to those without the disease.[202] The incidence of hip fracture, the most common type of fracture, among patients with AD (17.4 per 1,000 person-years) was consistently higher than in patients without AD (6.6 per 1,000 person-years). In both men and women with AD, the incidence rate of sustaining a hip fracture was the same. Among the patients who experienced a hip fracture, approximately one-third (32.4%) of AD patients and 18.8% of non-AD patients did not survive >1 year after a hip fracture,[203] which is consistent with another study in which Haasum et al[204] confirmed that hip fractures occurred in 16% of the people with dementia and 3% of the people without dementia. AD also could increase the incidence rate of osteoporosis through the neurotoxic effects of amyloid beta (Aβ), a 40–42 aminoacid peptide considered to play a role in the development of AD.[205] Aβ leads to increased levels of $H_2O_2$, one of the main reactive oxygen species (ROS), resulting in free radical damage.[206] $H_2O_2$ and peroxides are potent inducers of osteoclastogenesis.[207] Osteoclasts are cells that are derived from the monocyte–macrophage cell lineage and strongly participate in bone resorption. It is known that different types of mediators including nuclear factor κB (NF-κβ), RANKL, osteopontin, PTH, macrophage colony stimulating factor and angiotensin-II play outstanding roles to induce osteoclastogenesis.[208] RANKL is a key element derived from osteoblasts and stromal cells and stimulates the differentiation of preosteoclast to osteoclast through activating NF-κβ, as well as induces nuclear factor of activated T cells (NFAT) by ROS-mediated pathway.[207,209] Park et al[210] found that RANKL stimulation induces a novel signaling pathway that leads to generation of ROS and calcium oscillations and is essential for osteoclastogenesis. The constant RANKL-induced calcium oscillations result in activation of NFATc1 and osteoclast differentiation to mediate bone remodeling.[211] Hence, it is seen that OC, a marker of bone matrix synthesis, increases in osteoporosis (63%) and substantially in AD (76%) versus controls, while there is no change visible in cases with mild cognitive impairment.[212]

## Cancer

Cancer-induced bone disease can originate from the primary disease itself or from therapies administered to treat the cancer. Bone metastases are a common consequence of cancer, leading to pathologic fractures. Bone is the most common site for metastasis in cancer and is of particular clinical importance in breast and prostate cancers because of the prevalence of these diseases. At postmortem examination, ~70% of patients dying of these cancers have evidence of metastatic bone disease.[213] It has estimated that ~350,000 people in the USA die annually of bone metastases.[214] Bone metastases predominantly includes osteolytic or osteoblastic metastases. Osteolysis might be caused by parathyroid-hormone-related peptide (PTHrP) released by tumor cells in the bone microenvironment that stimulate the production of

the cytokine RANKL leading to osteoclast activation.[214,215] Osteoblastic metastases are caused by osteoblast proliferation, differentiation and bone formation.[216] On the other hand, treatment-induced osteoporosis may occur as a result of androgen deprivation therapy (ADT), glucocorticoid therapy, chemotherapy-induced ovarian failure and estrogen deprivation therapy.[217]

ADT as a treatment for metastatic prostate cancer increases the risk of osteoporosis in men with prostate cancer associated with a gradual decline in BMD at the hip.[218] ADT administration by orchiectomy (surgical removal of the testes) or by luteinizing hormone releasing hormone injections suppresses the production of testosterone which is necessary to maintain bone mineralization.[219,220] Radiation treatment for prostate cancer also leads to bone injury through a fall in blood flow and bone tissue oxygenation as well as reduction of bone-forming cells and bone atrophy.[221] Dickman et al showed that the risk of hip fracture from diagnosis until death was 1.6 in men exposed to ADT within 6 months of diagnosis, compared to control men in a Swedish population.[221] Breast and prostate cancer treatments that cause hypogonadism disrupt the normal bone remodeling process because estrogen and testosterone have been shown to play a key role in bone health in both men and women.[223]

## Pharmacologic treatment

Most of the studies have focused on the effects of anabolic therapies and antiresorptive therapies on generalized bone loss.

### Anabolic therapy

This type of osteoporosis therapy refers to the usage of drug components, that is, recombinant hormones such as rhPTH (1–34); hPTH (1–84) for strengthening, stimulating bone synthesis and treating the disease;[224] calcium supplements to prevent bone resorption and to increase BMD;[223] short-term treatment with calcimimetics[225] and PTH to increase trabecular bone mass and cortical bone mass.[225]

### Antiresorptive therapy

This kind of therapy is applied for osteoporosis treatment due to its effect on strengthening the bone. The therapy consists of five types of chemical components, that is, bisphosphonate, a class of antiresorptive drugs which can affect osteoclast activity,[226,227] hormone replacement therapy for the treatment of osteoporosis and particularly for relief of menopausal symptoms,[228] tibolone, a synthetic steroid used for early post menopausal women, leading to increase BMD due to extend of estrogen replacement therapy therapy,[229] selective ER modulators such as raloxifene used for the treatment of postmenopausal osteoporosis increase BMD and reduce the risk of vertebral fracture,[230] bazedoxifene inhibits estrogen-induced responses in mammary glands in animal models[231] and in conjugation with estrogen is used for the treatment of menopausal osteoporosis,[227] and anti-RANKL antibody[226] and cathepsin K inhibitors, inducing bone mineral density (BMD) gain in a phase II study in postmenopausal osteoporosis patients.[232]

## Influence of lifestyle on osteoporosis risk

Different societies have different information and awareness about health. In a report about knowledge and health beliefs on osteoporosis in a sample of 262 men aged 36–55 years, it was revealed that level of osteoporosis knowledge and perceived susceptibility were low. Given the increased prevalence of osteoporosis-related fracture in men, there is a need to develop methods to increase knowledge and awareness.[233] Observational findings suggest weight-bearing physical activity may influence bone strength due to favorable geometric adaptation, independent of changes in BMD. Overall, young healthy individuals with "average" baseline bone mass are unlikely to display notable changes in parameters of bone strength. While exercise interventions in pediatric cohorts have been primarily jump-based programs, exercise protocols in older adult trials have varied by mode, intensity, frequency and duration.[234] Among physical activities, walking is not effective in osteoporosis prevention, as it only provides a modest increase in the loads on the skeleton above gravity.[235] The menopausal women may improve the muscle strength and physical activities levels by exercise intervention for reducing the osteoporotic and sarcopenic risk.[236]

# Discussion

Osteoporosis originates from loss of bone mass along with microarchitectural deterioration of the skeleton. Bone mass starts decreasing among men and women in their 40s, leading to increased risk of fragility fractures. However, women lose bone more rapidly, particularly during the first 5–10 years after menopause due to estrogen deficiency, while men experience a slow loss of bone.[237] Multiple risk factors are associated with low bone density-related fractures. Significant associations include advancing age, white race, history of prior fractures and genetic factors. Modifiable factors such as increased alcohol consumption and smoking are also prominent. Furthermore, chronic glucocorticoid use, hypogonadism, diabetes, dementia and RA were discussed as secondary causes of osteoporosis in the current review.

Since osteoporosis is asymptomatic, early diagnosis can help in deciding treatment strategies and preventing disease progress. On the other hand, many metabolic bone diseases including hyperparathyroidism and osteomalacia also are associated with low BMD. Thus, a conclusive test is essential to diagnose osteoporosis and future fracture risk prediction. Several methods of imaging have been developed to measure bone density and decide treatment strategies.[238] Fracture Risk Assessment Tool is an algorithm used to evaluate the 10-year probability of hip fracture and major osteoporotic fracture (spine, proximal humerus and forearm) risk in either men or women that integrates clinical risk factors (individual's age, sex, weight, height, prior fracture, parental history of hip fracture, smoking, long-term use of glucocorticoids, RA and alcohol consumption) and BMD at the femoral neck in its calculations.[239] With regard to the clinical consequenses and heavy economic burden of fractures in the aging population, significant efforts to decrease fracture risk are needed. Our study updates reviews on available treatments for osteoporosis.

The two key elements in treating osteoporosis are increasing the bone mass by using anabolic therapies and decreasing bone resorption through antiresorptive therapies.

First and foremost, regular physical activity is recommended in all age groups to maximize peak bone mass and maintain bone strength.[240] Physical activity has been suggested as a nonpharmacologic intervention for increasing bone density in youth and preventing bone loss in the elderly.[241] Both aerobic exercise and resistance training, the best forms of weight-bearing exercise, increase the rate of bone remodeling in postmenopausal women. However, resistance exercise training induces more effective favorable changes in BMD status than aerobic exercise training in postmenopausal women.[242] These findings are consistent with a previous study which showed that resistance exercise had a significant protective influence on several changes associated with loss of BMD, unfavorable changes in serum and urinary bone markers and hypercalciuria.[243] A 10% increase in peak bone mass was predicted to delay the development of osteoporosis by 13 years[244] and reduce the risk of fragility fractures after menopause by 50%.[245] Adequate daily calcium and vitamin D is required to maximize bone mass and for the subsequent maintenance of bone health.[246] The National Osteoporosis Foundation recommends that postmenopausal women should consume at least 1,200 mg per day of calcium and 800–1,000 international units of vitamin D per day.[247] With an unhealthy diet, calcium and vitamin D supplementations may be needed. Dietary supplementation with calcium and vitamin D reduced bone loss and the rate of nonvertebral fractures in both 65-year-old men and women during a 3-year study.[248] Other active osteoporosis therapies should be considered for adjunctive treatment with calcium and vitamin D.[249] Osteoporosis is a challenging human disease. In spite of using various therapeutic approaches for the prevention or treatment of osteoporosis, their side effects are undeniable. Increasing our knowledge about the signaling pathways involved in bone remodeling will help us to design new therapeutic options for osteoporosis.

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The authors report no conflicts of interest in this work.

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