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Diagnosis and treatment of osteopenia

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Abstract Osteopenia is a term to define bone density that is not normal but also not as low as osteoporosis. By definition from the World Health Organization osteopenia is defined by bone densitometry as a T score −1 to −2.5. There are many causes for osteopenia including calcium and vitamin D deficiency and inactivity. Genetics plays an important role in a person's bone mineral density and often Caucasian women with a thin body habitus who are premenopausal are found to have osteopenia. Correction of calcium and vitamin D deficiency and walking 3 to 5 miles a week can often improve bone density in the hip and spine. There are a variety of pharmaceutical agents that have been recommended for the treatment of osteopenia and osteoporosis including hormone replacement therapy, selective estrogen receptor modulator therapy, anti-resorptive therapy. In addition patients with osteoporosis who have failed anti-resorptive therapy can have a significant improvement in their bone density with anabolic therapy.

Keywords Osteopenia · Osteoporosis · Vitamin D · Anti-resorptive · Calcium · Bone health

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1 Introduction

A gradual loss of bone mass causes osteopenia and osteoporosis with aging. The terms "low bone density" or "decreased bone density" can be used instead of osteopenia, but "osteopenia" is accepted in the medical literature and describes reduced bone mass. The diagnostic difference between osteopenia and osteoporosis is based on the measure of bone mineral density (BMD). Worsening of osteopenia and osteoporosis markedly increases the risk of skeletal fractures that increase the risk for fracture. Both sexes are effected but the main burden of disease is in menopausal women. The cumulative lifetime fracture risk for a 50-year old women with osteoporosis is as high as 60% [1–6]. The main goal of screening and treating for osteopenia is to prevent the development of osteoporosis and osteoporotic fractures. Effective fracture prevention would have a major impact on women's morbidity and an important impact on mortality.

2 Definition

The World Health Organisation (WHO) has established the definition based on BMD measurement at the spine, hip, or forearm by dual-energy x-ray absorptiomery (DXA) devices [1]. According to WHO criteria, osteopenia defined as a BMD between 1.0 and 2.5 SD below that of a "young normal" adult (T-score between −1.0 and −2.5, whereas osteoporosis as a T score at −2.5 or lower).

Osteopenia associates with osteoporosis and other metabolic diseases such as hyperparathyroidism and vitamin D deficiency. It has been compared with prehypertension, impared fasting glucose, and borderline high colesterol in defining an intermediate risk group with somewhat uncertain limits [7–9].

Some people may have naturally have a lower bone density. Childhood and adolescence are important for optimal bone formation and for prevention of osteoporosis in older age. An estimated 50% of the calcium in adult skeleton is deposited during the formative ages of 13 to 17 years. After age of 30, a gradual natural bone mass reduction ensues [2]. Although heritable factors account for 60 to 80% of optimal bone mineralization, modifiable factors that contribute to the development of osteopenia and osteeoporosis in adulthood (weight-bearing exercise, nutrition, body mass, hormonal milieu) have their genesis in utero, infancy, childhood, and adolescence [5].

3 Prevalence and risk factors

It is estimated that 18 million Americans have low bone mass and another10 million are currently affected with osteoporosis, placing them at future risk. Osteopenia prevalence is estimated that will be over 47 million by 2020 [10]. In the US, the lifetime risk of hip fracture that is the most disabling fracture is at least 17.5% in white women and 6.0% in men, clinically evident vertebral fractures and distal forearm fractures after the age of 50 years for women is 15.6% and 16.0%, and men 5.0% and 2.5%, respectively [11]. In the UK the lifetime risk of hip fracture for a women aged 50 years is estimated at 11.4%, and for men aged 50 years 3.1% [12].

Vertabral fractures are the most common osteoporotic fractures and account for 70% of all fractures. One in five woman with an asymptomatic or symptomatic vertebral fracture will experience another vertebral fracture within one year. It is also known that presence of a vertebral fracture increases risk of nonvertebral fractures. Other typical osteoporotic fractures include the hip, proximal upper arm, and distal arm. Osteoporotic fractures not only cause high health care cost but also are associated with a decreased quality of life and an increased risk of mortality [13, 14].

The Fracture Risk Assessment Tool (FRAX tool) has been developed by WHO to evaluate fracture risk of patients [15]. The FRAX algoritm (quiestionaire includes 12 questions regarding age, sex, weight, height, previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol 3 or more units per day, femoral neck BMD) gives the risk of having a fracture within the next ten years. The fracture risk can be calculated based on induvidual patients model that integrate the risks associated with clinical risk factors as well as BMD at the femoral neck. Table 1 shows risk factors for osteopenia and osteoporosis.

4 Diagnosis, clinical and laboratory evaluation and monitoring

Since many fractures among postmenopausal women occcur in those with T scores better than in the osteoporotic range [16–18], early diagnosis of osteopenia is important. The gold standart for determining the presence of osteopenia or osteoporosis is measuring BMD. A DXA has a single x-ray beam that can determine with 1% to 2% precision the mineral content of various skeletal sites, including the lumbar spine, hip region, and wrist [2]. Despite its limitations (provision of areal rather than volumetric BMD data failure to distinguish between trabecular and cortical bone), DXA is the most widely employed bone densitometric method [5]. The T-score helps interpret bone densitometry readings from different instruments and across gender, age, and race; it is the standart deviation (SD) from the peak bone mass of a person of the same race and gender. The WHO has defined a T-score of −1.0 to −2.5 as osteopenia or decreased BMD [2].

Women approaching menopause should know their bone density. A follow-up measurement in one to two years can identify women losing 2% to 3% of their bone mass a year and at increased risk of osteoporosis. Bone density also documents the effectiveness of therapy and therefore can increase patients compliance [2].

Physical examination should include height and weight for body mass index (BMI) and determining any loss of height. An increased in skin elasticity or a doughy skin texture and increased flexibility of finger joints are evidence of Ehlers-Danlos syndrome, a collagen-cross-linking genetic disease. Other pathological findings such as dowager's hump, exophthalmos, brisk reflexes or tachycardia, blue sklera, centripedal obesity, proximal muscle wasting etc. should be checked regarding causes of secondary osteopenia or osteoporosis [2] (Table 2).

The blood tests to evaluate a patient identified as having osteopenia or osteoporosis include calcium, phosphorus, albumin, alkaline phosphatase, liver function tests, creatinine, 25(OH)D, and TSH. For males, free testosterone should be measured if hypogonadism is suspected. An intact PTH is worthwhile to obtain only when the serum calcium is elevated. Measurements of a bone turnover markers (BTM) also helps to determine if increased bone remodeling is resulting in bone loss [2].

Repeated BMD measurement is the most widely used for monitoring treatment. BTM are also measured in the course of the treatment.

5 Prevention

Early diagnosis and treatment of osteopenia/osteoporosis has been demonstrated to reduce fracture rates and improve

Table 1 Risk factors for development of osteopenia/ osteoporosis

Caucacian or Asian heritage
Family history
Thin body habitus
Early menopause
Amenorrhea or oligoamenorrhea in 2nd and 3rd decades
Hypogonadism
Inadequate lifelong calcium intake
Chronic vitamin D deficiency
Cigarette smoking
Excessive drinking alcohol
Excessive drinking cola
Low physical activity
Immobilization
Premature graying (50% of hairs gray before age 40)
Steroid and other medications (heparin, valproic acid, proton pump inhibitors, methotrexate,etc.)
Excessive thyroid hormone replacement

life quality. In addition to primacy of genetic and hormonal factors, the most important considerations for accrual and maintanance of bone mass are those that relate to diet (sufficient intake of calcium and protein), sustained normal vitamin D stores by exposure to sunlight or ingestion of supplements, and consistent weight-bearing exercise. Therapeutically, when trying to prevent bone loss or restore lost bone initial efforts are directed to the assurance that these basic approaches are being utilized to the fullest extent possible for the specific patient [5].

5.1 Exercise

Ocarino et al [19] determined that daily physical exercise, on a motor-driven treadmill in ovariectomized female rats, increased the quantity of trabecular and cortical bone, the trabecular bone tissue in the long bones, osteocyte connection, and restored bone mass. Their results provided evidence through bone hystomorphometry that exercise had important protective and therapeuetic effects on osteopenia on rat bones. It is known that physical exercise triggers a series of physiological responces involving stimulating the release of growth hormone which has direct or indirect anabolic effect or mediated by insulin-like growth factor [19–22]. Additionally, there are some studies showing an increased plazma levels of thyroid hormones during physical activity [23].

Asikainen et al [24] suggested that early postmenopausal women could benefit from 30 min of daily moderate walking in one to three bouts combined with a resistance training programme twice a week regarding bone density. Bonaiuti et al [25] showed walking significantly increase BMD at both the spine and the hip from meta-analysis of randomized clinical trials in postmenopausal women. Additionally they founded that aerobics, weight-bearing and resistance exercises were all effective on BMD of the spine in postmenopausal women. Conversely, Martyn-St James et al [26] reported that regular walking had no significant effect on preservation of BMD at the spine in postmenopausal women, whilst significant positive effects at femoral neck were evident in their meta-analysis. Furthermore, they concluded that the effects of walking on BMD might be too small clinically in relation to reduction of fractures and interventions that combined walking with other forms of exercise that provided adequate skeletal loading and were more directly targeted at specific skeletal regions might be required. However, they pointed out that diverse methodological and reporting discrepancies were apparent in the published trials on which those conclusions were based.

It has been suggested in a recent meta-analysis that recommendations regarding optimum exercise for augmenting BMD in premenopausal women should included and clearly described combinations of impact and resistance exercises that provided adequate skeletal loading and that were directly targeted at specific skeletal regions [27].

National Osteoporosis Foundation (NOF) also endorses lifelong physical activity at all ages, both for osteoporosis prevention and overall health, as benefits are lost when the person stops exercising [28]. Weight-bearing exercise helps to maintain and increase BMD, as well as muscle mass and muscle tone, thereby decreasing their risk of falling and fracture. Weight-bearing exercise includes walking, jogging, Tai-Chi, stair climbing, dancing, and tennis [28]. Once the exercise has stopped, however, any bone gain is lost. Osteoporosis can not be adressed simply with exercise; every muscle cannot be exercised to influence the BMD of every bone in the body [2].

The best recommendation for adults is to walk 3 to 5 miles a week. This helps to maintain and possibly increase BMD of the lumbar and sacral spine and hip regions.

Table 2 Common causes of secondary osteopenia/osteoporosis

Endocrine diseases
Hyperthyroidism
Hyperparathyroidism
Hypercorticolism
Diabetes mellitus
Hypogonadism
Premature menopause
Growth hormon deficiency
Connective tissue diseases
Osteogenesis imperfecta
Ehlers Danlos syndrome
Marfan syndrome
Homocystinuria
Rheumatological diseases
Rheumatoid arthritis
Systemic lupus erythematosus
Ankylosing spondylitis
Gastrointestinal disorders
Celiac disease
Inflammatory bowel disease
Malabsorption syndromes
Liver cirrhosis
Primary biliary cirrhosis
Gastrectomy
Hematologic diseases
Leukemia and lymphoma
Thalasemia and sickle cell anemia
Multipl myeloma
Disseminated carcinoma
Monoclonal gammopathy
Others
Drugs
Prematurity
HIV infection
Anorexia nervosa
Cystic fibrosis
Hypophosphatasia

5.2 Life style changes

Avoiding excessive use of alcohol and cola and quitting smoking should be encouraged. Excessive intake of cola drinks with high phosphoric acid content lower body calcium content because of the sequestration of dietary calcium in the intestinal tract and the needed dissolution of bone mineral to neutralize acid-with consequent development of mild secondary hyperparathyroidism [5, 29, 30]. Administration of drugs that are known to be harmful to bone health, such as glucocorticoids and anticonvulsants, should be avoided or minimized in dose and duration.

5.3 Diet

Proper nutrition is one of the important preventive methods of osteopenia/osteoporosis, and dietary risk factors are modifiable. Adequate intake of calcium and vitamin D are the most important nutritional factors in prevention of osteopenia/osteoporosis.

Calcium and vitamin D

It is crucial to document lifetime intake of **calcium** for both women and men. A low intake of calcium during the formative teenage and young adult years results in a decrease in attainable peak bone mass, which occurs between ages 20 and 30. After men and women have reached their peak bone mass, they can lose 0.25% to 0.5% of their bone mass a year if they are not receiving adequate calcium in adults up to age 50. Thus 20 years of inadequate calcium intake can lead to as much as a 5% to 15% reduction in BMD before age 50. The easiest method to obtain an adequate intake of calcium is by drinking skim milk; since 8 ounces of skim milk has 300 mg of calcium, drinking one glass with each meal approaches the recommended adequate intake for calcium in adults up to age 50 [2]. Switching orance juice to calcium and vitamin D fortified orange juice is an another good choice. Plant-based sources of calcium are broccoli, kale, and other green leafy vegetables that contain readly absorbable calcium.

Although considerable uncertainity exists regarding optimal intakes of calcium and vitamin D, recommended adequate intakes for calcium and vitamin D are shown in Table 3 [2, 5].

Vitamin D plays a critical role in maintaining both serum calcium and phosphate concentrations and it is essential for the development and maintenance of bone health from birth until death. Vitamin D deficiency is very common in patients with osteoporosis. Vitamin D deficiency will not only precipitate and exacerbate osteopenia and osteoporosis in both women and men, it will also cause a mineralisation defect of the skeleton and muscle weakness, all of which increase the risk of fracture [2].

Very few foods naturally contain vitamin D. These include oily fish such as salmon and mackerel (400–500 IU/3.5 oz), cod liver oil (400 IU/5 mL), irradiated mushrooms (100–1000 IU/3.5 oz) and egg yolk (20 IU). In the US, milk and orange juice are fortified with 100 IU/8 oz. In addition, some yogurts, cheeses, cereals and breads are fortified with vitamin D (Table 4). In Europe, most countries forbid fortification of milk with vitamin D, the exceptions being Sweden and Finland. The major dietary sources of vitamin D in Europe are margarine and some cereals [4].

Table 3 Adequate Intake (AI) Tolerable Upper Limit (UL) recommendations by Institute of Medicine [80] and Recommended Daily Allowance and Upper Level (RUL) for Vitamin D based on the committee's recommendations

	IOM Recommendations		Suggested	
	RDA (IU/d)	UL (IU/d)	Daily Allowance (IU/d)	RUL [IU]
0–12 mo	400	1,000	400–1,000	2,000
1–18 yr	600	1,500–4,000	600–2,000	4,000
19–50 yr	600	4,000	1,500–2,000	10,000
51–70 yr	600	4,000	1,500–2,000	10,000
71+ yr	800	4,000	1,500–2,000	10,000
Pregnancy	600	4,000	1,500–2,000	10,000
Lactation	600	4,000	1,500–2,000	$10{,}000_{\text{(mother's requirement)}}$

4,000–6,000 (mother's intake for infant's requirement if infant is not receiving 400 IU/d)

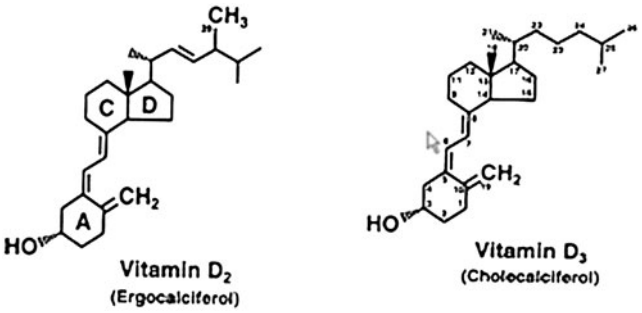
The major source of vitamin D for most humans is exposure to sunlight. When the skin is exposed to sunlight, UVB photons with wavelengths between 290 and 315 nm are absorbed by epidermal 7-dehydrocholosterol (provitamin D_3). This energy transform 7-dehydrocholosterol into previtamin D_3, which rapidly converts by a temperature-dependent process to vitamin D_3 (cholecalciferol). Once formed, it is ejected out of the epidermal cell into the extracellular space, and by diffusion, enters the circulation bound to the vitamin D binding protein (DBP) [31]. Vitamin D_3 and vitamin D_2 (D represents D_2 or D_3) in the diet are ingested and the fat soluble vitamins are incorporated into chylomicrons and absorbed into the lymphatics. Vitamin D_2 and vitamin D_3 are equally absorbable and are able to maintain both children and adults vitamin D requirement. The lymphatic drainage into the thoracic venous system permits the entrance of vitamin D into the circulation where it is bound to the DBP and lipoproteins [31, 32].

Vitamin D is converted in the liver by a vitamin D-25-hydroxylase (25-OHase) to form the major circulating form of vitamin D (D reperesents D_2 or D_3), 25-hydroxyvitamin D, [25(OH)D]. 25(OH)D is, however, biologically inert and requires hydroxylation in the kidneys on carbon 1 by the 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) by the CYP27B mitrochrondial enzyme. This results in the formation of 1α,25-dihydroxyvitamin D [$1,25(OH)_2D$] which is the biologically active form of vitamin D responsible for regulating calcium and phosphorus homeostasis [31, 33]. $1,25(OH)_2D$ enters the circulation and is bound to the DBP and travels to its target tissues (Fig. 1). $1,25(OH)_2D$ increases the efficiency of intestinal calcium absorption. In a vitamin D deficient state, the small intestine is able to passively absorb about 10–15% of dietary calcium. Vitamin D sufficiency enhances the absorption of calcium in the small intestine to about 30–40% [33].

Patients with vitamin D deficiency usually have a normal serum calcium and often have a low normal serum phosphorus because of the phosphaturic action of PTH in the kidney. PTH interacts with its receptor on the osteoblast and increases the expression of RANKL to induce osteoclastogenesis [31, 34, 35]. The osteoclasts release hydrochloric acid and enzymes to dissolve the matrix and release calcium, which results in a decrease in bone mineral density. Vitamin D deficiency causes a mineralization defect of the skeleton and therefore results in a decrease in BMD that can further exacereble both osteopenia and osteoporosis. Osteopenia and osteoporosis are over to increased osteoclastic activity resulting in loss of matrix and mineral appears the same on x-ray and BMD as osteomalacia. Thus, vitamin D deficiency causes osteopenia and osteoporosis and can exacerbate both conditions [4]. It is important to diagnose vitamin D deficiency in people with risk of osteopenia since vitamin D may affect both bone density and risk for falls. Recent studies have shown that there is an association between vitamin D deficiency and falls or postural instability [13].

Data from the Third National Health and Nutrition Examination Survey (NHANES III) has revealed that the prevalence of vitamin D deficiency and insufficiency is >50% among children and young middle-aged, and older adults [36, 37]. The vitamin D deficiency/insufficiency epidemic is caused by the fact that few foods naturally contain or are fortified with vitamin D. For adults, 100 IU of vitamin D increases the blood 25-(OH)D concentration by approximately 1 ng/ml (2.5 nmol/L). In the winter, the mean 25(OH)D concentration is approximately 18–22 μg/L in Caucasian adults and approximately 15–18 μg/L in African American adults [33, 36, 38]. Thus, to raise blood concentration into a sufficient range requires between 1,500 and 2,000 IU of vitamin D supplementation per day. Studies of children have suggested that 400 IU of vitamin D per day is inadequate to raise blood concentration into the sufficient range [36]. Young girls 10–17 years of age who received the equivalent of 2,000 IU vitamin D per day for 1 year raised their blood concentrations into the sufficient range. In the US, both vitamin D_2 and vitamin D_3 supplements are available as 50,000 IU dosage forms. Holick et al [38] and Gordon et al [39] demonstrated that

Table 4 Sources of Vitamin D_2 and Vitamin D_3 (with permission, copyright Holick 2007)

Source	Vitamin D content (IU=25 ng)
Natural Sources	
Cod liver oil	~400–1,000 IU/tsp vitamin D_3
Salmon, fresh wild caught	~600–1,000 IU/3.5 oz vitamin D_3
Salmon, fresh farmed	~100–250 IU/3.5 oz vitamin D_3, vitamin D_2
Salmon, canned	~300–600 IU/3.5 oz vitamin D_3
Sardines, canned	~300 IU/3.5 oz vitamin D_3
Mackerel, canned	~250 IU/3.5 oz vitamin D_3
Tuna, canned	236 IU/3.5 oz vitamin D_3
Shiitake mushrooms, fresh	~100 IU/3.5 oz vitamin D_2
Shiitake mushrooms, sun dried	~1,600 IU/3.5 oz vitamin D_2
Egg yolk	~20 IU/yolk vitamin D_3 or D_2
Sunlight/UVB radiation	~20,000 IU equivalent to exposure to 1 minimal erythemal dose (MED) in a bathing suit. Thus, exposure of arms and legs to 0.5 MED is equivalent to ingesting ~3,000 IU vitamin D_3
Fortified Foods	
Fortified milk	100 IU/8 oz usually vitamin D_3
Fortified orange juice	100 IU/8 oz vitamin D_3
Infant formulas	100 IU/8 oz vitamin D_3
Fortified yogurts	100 IU/8 oz usually vitamin D_3
Fortified butter	56 IU/3.5 oz usually vitamin D_3
Fortified margarine	429/3.5 oz usually vitamin D_3
Fortified cheeses	100 IU/3 oz usually vitamin D_3
Fortified breakfast cereals	~100 IU/serving usually vitamin D_3
Pharmaceutical Sources in the U.S.	
Vitamin D_2 (Ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid	8000 IU/cc
Supplemental Sources	
Multivitamin	400, 500, 1000 IU vitamin D_3 or vitamin D_2
Vitamin D_3	400, 800, 1000, 2,000, 5,000, 10,000, and 50,000 IU

*Designated calciferol which usually means vitamin D_2

vitamin D_2 is as effective as vitamin D_3 in maintaining circulating concentrations of 25(OH)D in adults and children respectively.

It is known that there is a decline circulating 25(OH)D levels in people living at high latitudes in winter, when little if any vitamin D can be produced in the skin. People of color, especially African Americans, are at very high risk, owing to their avoidance of sun exposure and their decreased production of vitamin D due to their skin pigmentation. Obesity, which is also epidemic in children and adults, increases the risk of deficiency/insufficiency, partly because of the sequestration of the fat-soluble vitamin in body fat. All of these high-risk groups, along with all children and adults, can maintain adequate serum

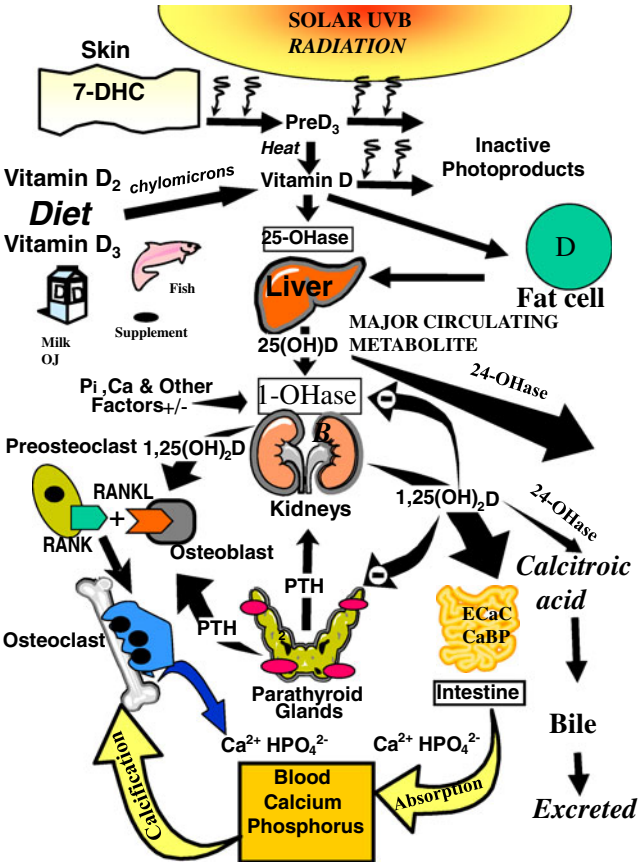


Fig. 1 Schematic representation of the synthesis and metabolism of vitamin D for regulating calcium, phosphorus and bone metabolism. During exposure to sunlight 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin D_3 ($preD_3$). $PreD_3$ immediately converts by a heat dependent process to vitamin D_3. Excessive exposure to sunlight degrades previtamin D_3 and vitamin D_3 into inactive photoproducts. Vitamin D_2 and vitamin D_3 from dietary sources are incorporated into chylomicrons, transported by the lymphatic system into the venous circulation. Vitamin D (D represents D_2 or D_3) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D binding protein which transports it to the liver where vitamin D is converted by the vitamin D-25-hydroxylase (25-OHase) to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to measure vitamin D status (although most reference laboratories report the normal range to be 20–100 ng/ml, the preferred healthful range is 30–60 ng/ml). 25(OH)D is biologically inactive and must be converted in the kidneys by the 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to its biologically active form 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. Serum phosphorus, calcium, fibroblast growth factor (FGF-23) and other factors can either increase (+) or decrease (−) the renal production of $1,25(OH)_2D$. $1,25(OH)_2D$ feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. $1,25(OH)_2D$ increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize $1,25(OH)_2D$ and 25(OH)D to the water soluble biologically inactive calcitroic acid which is excreted in the bile. $1,25(OH)_2D$ enhances intestinal calcium absorption in the small intestine by stimulating the expression of the epithelial calcium channel (ECaC; also known as transient receptor potential cation channel sub family V member 6; TRPV6)) and the calbindin 9 K (calcium binding protein; CaBP). $1,25(OH)_2D$ is recognized by its receptor in osteoblasts causing an increase in the expression of receptor activator of NFκB ligand (RANKL). Its receptor RANK on the preosteoclast binds RANKL which induces the preosteoclast to become a mature osteoclast. The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. Adequate calcium and phosphorus levels promote the mineralization of the skeleton and maintain neuromuscular function. Holick copyright 2007. Reproduced with permission

25-(OH)D concentrations through vitamin D supplementation, ingestion of foods fortified with vitamin D, and sensible sun exposure [33, 36–38].

In addition to calcium and vitamin D, adequate intake of magnesium, phosphorus, copper, zinc, fluoride, vitamin K, vitamin C, several B vitamins, carotenoids, sodium, and potassium has been related to bone health [40–42].

The major food sources of **magnesium**, which are whole-grain bread, milk, breakfast cereal, banana, and orange-juice, are similar to **potassium**. Basic sources of potassium are milk, potatoes, orange-juice, banana and tomato. Important sources of calcium also overlap with these [42]. Tucker et al [42] reported that there were significant association between intakes of potassium and magnesiun and BMD. They suggested that long-term diet high in potassium and magnesium or both may protect BMD [42]. Potassium administration promotes renal calcium retention, whereas low potassium intake increases daily and fasting urinary calcium excretion rates [43]. In another study, tabecular bone was improved with magnesium given orally to postmenopausal osteoporotic women [44].

Protein is also essential to bone, but calcium-wasting effect of a high protein intake is still an important point of the debate. High-protein diet creates a higher acid load and to compensate this acid load the body pulls calcium from the skeleton to balance the pH at the expense of the bone stracture, and calcium excreted in the urine [45]. However, protein is an substantial component of the skeleton and adequate protein intake maintains IGF-1 levels which over is important for stimulating osteoblasts and therefore maintaining bone remodeling activity.

Dietary **soy isoflavone** supplements have been studied for their effect on ameliorating bone loss associated with menopause and it has been suggested that soy isoflavone consumption for six months could be enough to exert beneficial effects on bone in menopausel women [46]. Furthermore, **equol** that is the end product of intestinal metabolism of daizedin is chemically similar to estrogen and has 80 times more estrogen receptor-beta binding affinity than its parent precursor [47]. Compared with other phytoestrogens (genistein and daidzein), equal was more bioavailable and rapidly absorbed [48]. Although evidence suggests that equol may attenuate estrogen deficiency-related bone loss, further research are needed.

6 Treatment

6.1 Preventive treatment

NOF [28] recommends to initiate treatment in postmenopausal women and men age 50 and older with osteopenia (T-score between −1.0 and −2.5) at the femoral neck or spine and 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on the US-adapted WHO absolute fracture risk model [15].

Calcium

Calcium supplementation is often recommended for the prevention of osteopenia/osteoporosis and fractures. However, it was reported that calcium alone might not prevent hip fractures in women and suggested an increased risk with calcium supplementation among men and women. Calcium carbonate and calcium citrate supplements can reduce phosphate absorption because a balanced ratio of calcium to phosphate is needed for bone mineralization. A calcium supplement of 1000 mg may shift an elderly person with a relatively low phosphorus intake into phosphate deficiency. This change could augment bone resorption and increase fracture risk [49]. However, it was shown that vitamin D plus calcium supplementation had beneficial effect on hip fracture risk in frail elderly women [50].

There is no evidence of a statistically significant difference between vitamin D alone or vitamin D and calcium in the prevention of hip fracture [4, 51–53]. NOF recommends that women older than age 50 consume at least 1,200 mg per day of elemental calcium. Intakes in excess of 1,200 to 1,500 mg per day have limited potential for benefit and may increase the risk of developing kidney stones or cardiovascular disease [28]. Deciding which calcium supplement to recommend, cost and bioavailability are important. When taken with a meal, calcium carbonate is bioavailable even in patients with achlorhydria. Calcium citrate is recommended for patients with a history kidney stones.

Vitamin D

NOF recommends an intake of 800 to 1,000 IU of vitamin D per day for adults age 50 and older [28]. The results of randomized clinical trials investigating the effects of vitamin D supplementation on falls and fractures have been inconsistent [50, 51, 53–56]. Bischoff-Ferrari et al [56] reported that supplemental vitamin D_3 in a dose of 700–1,000 IU a day reduced the risk of falling among older individuals by 19% and to a similar degree as active forms of vitamin D. They suggested that doses of supplemental vitamin D of less than 700 IU or serum 25(OH) D concentrations of less than 24 ng/ml may not reduce the risk of falling among older individuals. Sanders et al [55] studied the effect of a single unnual dose of 500,000 IU of vitamin D_3 administred orally to older women (≥70-year ages) in autumn or winter on the risk of falls and fractures. They established an increased risk of falls and fractures. However, it is not possible that those elderly who received the vitamin D felt better and were more active and thus were at higher risk for fracture. Also administration of vitamin D alone, whether by annual injection, periodic bolus oral dosage, or daily oral dosage, are unlikely to be effective in fracture prevention in doses below 1,100 IU daily [51].

We recommend 400–1,000 IU/day for infants, 1,000–1,500 IU/day for children 1–10 years of age, 1,500–2,000 IU/day for teenagers, and 1,500–2,000 IU/day for adults (Table 3). Although the medical community has been greatly concerned about vitamin D intoxication, it is one of the rarest reported medical conditions and is usually not observed until >10,000 IU of vitamin D are ingested per day for >5 months [33, 36]. However, some patients with granulomatuos disorders such as sarcoid are at risk for hypercalciuria and hypercalcemia need to have their 25(OH)D concentration monitored more frequently [36].

Richy et al [57] reported that vitamin D analogs, α-calcidiol and calcitriol, compared to native vitamin D might exibit better efficacy in preventing spinal bone loss and spinal and/or nonspinal fractures in primary osteoporosis. Additionally, they suggested that vitamin D analogs were found to be active in preventing hip and spinal bone loss in cortocosteroid osteoporosis, whereas native vitamin D provided similar efficacy but was restricted to the hip. However, the use of calcitriol is associated with a statistically significantly increase in risk of hypercalcemia [51].

6.2 Pharmacologic treatment

A number of therapeutic agents, that increase bone mass act by inhibiting resorption (antiresorptive drugs) or by stimulation bone formation (anabolic medications), have demonstrated increased BMD and decreased risk of skeletal fractures [5]. Treatment of osteopenia/osteoporosis is primarily based on antiresorptive drugs (bisphosphanates, estrogens, selective estrogen receptor modulator raloxifene, calcitonin, and the recently approved denosumab).

6.2.1 Bisphosphonates

Bisphosphonates began to be used for treatment of metabolic bone diseases including Paget's disease in the late 1960s. Their binding affinity and antiresorptive potency differ among the compounds. The biphosphonates are prescribed most often and structurally resemble pyrophosphate (Fig. 2). The oxygen between the two phosphorus has been replaced with a carbon, however, making the compound essentially indestructible. The various attachments of this carbon give rise to a variety of biphosphonates. The rank order for binding affinity is zolendronate greater than alendronate greater than ibandronate greater than risedronate. Higher affinity biphosphonates will bind avidly to the bone surface but will spread through bone more slowly and have less access to the osteocyte network. Lower affinity agents with be distributed more widely through the bone and also have a shorter residence time in bone if treatment is stopped [2, 58]. They act by inhibiting a key enzyme necessary for osteoclasts to function and survive. Thus, this class of drugs induces apoptosis of osteoclasts reducing their number on bone remodeling surfaces. Bisphosphonates has been found to be cost-effective in postmenopausal women with low bone mineral density and /or prevalent vertebral fractures to prevention and treatment for osteoporosis [16, 59, 60].

Alendronate (Fosamax®, for prevention 5 mg daily or 35 mg weekly tablets and for treatment 10 mg daily and 70 mg weekly tablet and 70 mg weekly tablet with 2.800 IU or 5.600 IU of vitamin D_3), one of the most popular bisphosphonates, prescribed worldwide for the treatment and prevention of osteoporosis, is alendronate. Alendronate may increase BMD of both hip and spine by 1–2% and 2–4% a year respectively [2, 28] and may decrease risk of fractures of the hip and the spine by 51% and 63%, respectively [2, 28]. It reduces the incidence of spine and hip fractures by about 50 percent over three years in patients with a prior vertebral fracture. Alendronate reduces the incidence of vertebral fractures by about 48 percent over three years in patients without a prior vertebral fracture [28].

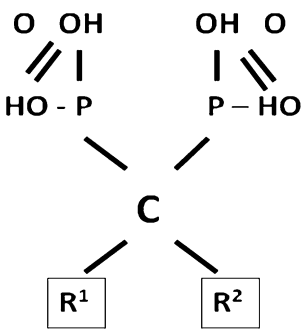


Fig. 2 Structure of pyrophosphate and geminal bisphosphonates. R^1 side chain and R^2 side chain determines influence of binding capasity and antiresorptive potency, respectively

Schousboe et al [16] had used a Markov cost-utility model that contained 8 health states and compared five years of treatment with alendronate with no drug therapy for women 55 to 75 years of age with varying levels of BMD T-scores (−1.5 to −2.4) and they reported that alendronate therapy was not cost-effective for white postmenopausal women who had not had a fracture and did not have additional risks strongly predictive of fracture independent of BMD.

Risedronate (Actonel®, for prevetion and treatment, 5 mg daily tablet; 35 mg weekly tablet; 35 mg weekly tablet packaged with 6 tablets of 500 mg calcium carbonate; 75 mg tablets on two consecutive days every month; and 150 mg monthly tablet). Risedronate reduces the incidence of vertebral fractures by about 41–49 percent and non-vertebral fractures by about 36 percent over three years, with significant risk reduction occurring after one year of treatment, in patients with a prior vertebral fracture [28].

Ibandronate (Boniva®, for treatment 2.5 mg daily tablet, 150 mg monthly tablet, and 3 mg every three months i.v.). Ibandronate reduces the incidence of vertebral fractures by about 50 percent over three years [28]. It does not have the efficiacy indication for reducing of non-vertebral fractures.

Zoledronate (Reclast®, 5 mg by intravenous infusion over at least 15 min once yearly for treatment and once every two years for prevention), a third-generation bisphosphonate, is used once-yearly i.v. In contrast to other nitrogen-containing bisphosphonates, zoledronate has two nitrogen atoms, contained in a heterocyclic imidazole ring. Zoledronate is also indicated for the prevention of new clinical fractures in patients who have recently had a low-trauma hip fracture. Zoledronic acid reduces the incidence of vertebral fractures by about 70 percent (with significant reduction at one year), hip fractures by about 41 percent and non-vertebral fractures by about 25 percent over three years [28, 61].

In a 2-year, double-blind study, McChung et al [62] randomized 581 postmenopausal women with osteopenia (lumbar spine T-score between −1.5 and −2.5 and femoral neck T-score greater than −2.5) to receive zoledronic acid at baseline and 1 year, zoledronic acid at baseline and placebo at 1 year, or placebo at baseline and 1 year. They established that both once-yearly dosing and a single dose of zolendronic acid regimens produced significantly greater increases in mean lumbar spine BMD from baseline than placebo at 24 months (5.18% and 4.2%, respectively, versus placebo −1.32%). Maricic [61] suggested that with the approvel of once-yearly zolendronic acid 5 mg was an option that could circumvent the problems of frequent and complicated dosing regimens, poor absorption, and upper GI intolerance and that ensured adherence and persistence

for a full 12 months; that should translate into improved fracture reduction in clinical practice.

Adverse effects When taken orally, bisphosphonates are poorly absorbed (~0.7%) and can cause esophageal irritation/gastrointestinal (GI) symptoms. Therefore, patients must fast overnight prior to ingestion, avoiding eating, drinking, and taking other medications for 30 to 60 min afterward to ensure adequate absorption, and maintain an upright position for 30 to 60 min after ingestion to avoid upper GI symptoms [28, 58].

The only route of elimination for bisphosphonates is renal excretion, but little information is avaliable on dosing in patients who have impaired renal function. Renal toxicity may accour with rapid iv administration [58].

Recent reports suggested that there is a link between bisphosphonate usage and the development of atypical insufficiency fractures. It is thought to be due to long-term oversuppression of bone turnover leading to impared bone remodeling, accumulation of microdamage in bone and increased fragility [58]. There are a number of case reports which have described unusual low-energy subtrocanteric femoral fractures and pelvic insufficiency fractures in patients on long-term bisphosphonate therapy. Bone biopsies in such patients often show severely suppressed bone turnover. However, Abrahamsen et al [63] reported that these atypical fractures were more likely due to osteoporosis rather than the bisphosphonate therapy itself [58]. Another recent report from American Society for Bone and Mineral Research (ASBMR) suggested that based on published and unpublished data and the widespread use of bisphosphonates, the incidence of atypical femoral fractures associated with bisphosphonates therapy for osteoporosis appeared to be very low, particularly compared to the number of vertebral, hip and other fractures that were prevented by bisphosphonates [64]. ASBMR also reported that there was evidence of relationship between long-term bisphosphonates use (usually more than 3 years, median treatment 7 years) and a specific type of subthrochanteric and femoral shaft fracture and the apparent increased risk for atypical femoral fractures in patients receiving glucocorticoids was a concern, as bisphosphonates were the mainstay for prevention of glucocorticoid-induced osteoporotic fractures [64].

It is still a considerable discussion about how long to treat with bisphosphonates, because biphosphonates accumulate in the skeleton, leading to reservoir that continues to be released for months or years after treatment is stopped. This makes it possible to consider drug holidays and then resuming therapy [58]. More definitive data would be critical because this may influence decisions regarding duration of therapy in selected individuals. Furthermore, biphosphonates offer a safe and effective treatment to reduce fracture risk, with evidence for broad spectrum fracture risk reduction not shown for other available agents. Questions have been raised about their assocoation with other possible side effects such as osteonecrosis of the jaw occurs in cancer patients receiving frequent bisphosphonates therapy by the intra venous route, muskuloskeletal pain, atrial fibrilation (not well founded), esophageal cancer, that appear to be rare and may not be causally related [58].

6.2.2 Estrogen/Hormone Therapy (ET/HT)

Estrogen/hormone therapy is approved by the FDA for the prevention of osteoporosis. Endogenous estrogen helps with maintaining bone mass and its deficiency with transition to menopause has been associated with rapid bone loss. There is convincing evidence that estrogen stimulates osteoclast apoptosis acting via estrogen receptor-α and supresses osteoblast and osteocyte apoptosis. Additionally, estrogen deficiency leads to increases in RANKL production [65]. Writing group for the Woman's Health Initiative (WHI) reported that five years of HT reduced the risk of clinical vertebral fractures and hip fractures, and increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein phlebitis during five years of treatment with conjugated equine estrogen (0.625 mg) and medroxyprogesterone (2,5 mg) (Prempro®) [28, 66]. In the estrogen only arm of WHI, no increase in breast cancer incidence was noted over 7.1 years of treatment. Furthermore, further analysis revealed no increase risk for cardiovascular disease if none was present when the HT was initiative. Because of the risks, ET/HT should be used in the lowest effective doses for the shortest duration to meet treatment goals. When ET/HT use is considered solely for prevention of osteoporosis, the FDA recommends that approved non-estrogen treatments should first be carefully considered [28].

In healthy postmenopausal women, Prestwood et al [67] studied low-dose estrogen (0.25 mg/d of 17β-estradiol, eqivalent to 0.156 mg/d conjugated equine estrogen) therapy; all women who had not had a hysterectomy received 100 mg/d oral micronized progesterone for 2-week periods, over 3 years of follow-up, they established sigmificant increases in BMD of the hip, spine, and total body and decrease N-telopeptide in the estrogen group compared with placebo group, They observed similar adverse events in the estrogen and placebo groups. However, the optimal low dose of estrogen still remains to be defined. Whereas low-dose estrogen/progestin (Prempro®; 3,0/1,5) therapy appears to be a promising approach for some postmenopausal women, it remains to be seen whether large-scale studies examining fracture and

safety endpoints (breast cancer, cardiovascular events, and others) [65].

6.2.3 Selective Estrogen Receptor Modulators—SERMs (estrogen agonist/antagonist)

Raloxifene (Evista®) is the only SERM approved by the FDA for both prevention and treatment of osteoporosis in postmenopausal women. Arzoxifene, lasofoxifene, and basedoxifene are more recent SERMs [65]. SERMs are nonsteroidal compounds with tissue-specific actions that are believed to be due to the fact that these drugs induce a a different conformation of the ER than estradiol [68] and enhance osteoclast apoptosis [69]. Raloxifene reduces the risk of vertebral fractures by about 30–55 percent in postmenopausal women over three years, although it did not protect against nonvertebral or hip fractures [28, 65]. Raloxifene is indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. It increases the risk of deep vein thrombosis to a degree similar to that observed with estrogen and does not reduce the risk of coronary heart disease. It also increases hot flashes [28].

In the Multiple Outcomes of Raloxifene Evaluation (MORE) study, a multicenter, randomized, blinded, placebo-controlled trial, Ettinger B et al [70] investigated the effect of raloxifene therapy on risk of vertebral and nonvertebral fracture in a total of 7705 women with osteoporosis who had been postmenopausal for at least 2 years. They determined that the risk of vertebral fracture was reduced in both study groups receiving raloxifene (for 60 mg/d group and for 120 mg/d group), but the risk of nonvertebral fracture for raloxifene vs placebo was not found significantly different, and compared with placebo, raloxifene increased BMD in the femoral neck by 2.1% (60 mg) and 2.4% (120 mg) and in the spine by 2.6% (60 mg) and 2.7% (120 mg) ($P<0.001$ for all comparisons). Additionally, they reported that women receiving raloxifene had increased risk of venous thromboembolus vs placebo (RR, 3.1; 95% CI, 1.5–6.2) and raloxifene was associated with a lower incidence of breast cancer. Kanis et al [71] reanalyzed of the MORE study and they concluded that treatment with 60 mg/day raloxifene significantly decreased the risk of new vertebral fractures (47%) and new clinical vertebral fractures (75%) in postmenopausal women with osteopenia at the total hip, but without vertebral fracture.

Bouxsein et al [72] conducted a secondary analysis of data from two randomized controlled trials in postmenopausal women with osteoporosis and they published that compared with placebo, raloxifene treatment reduced the risk of any new, new adjacent, and new nonadjacent vertebral fractures by 54%, 54%, and 53%, respectively. Similarly, compared with placebo, teriparatide treatment had reduced the risk of any new, new adjacent, and new nonadjacent vertebral fractures by 72%, 75%, 70%, respectively.

Another approach is the combination of SERM with estrogen therapy of postmenopausal women, but clearly larger scale studies with fracture and other safety endpoints are needed to fully evaluate this approach [65].

6.2.4 Parathyroid Hormone (PTH) peptide; teriparatide

Teriparatide (Forteo®) is a fragment of full-length PTH (1–34). It is approved by the FDA for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture. Teriparatide is also approved for treatment in men and women at high risk of fracture with osteoporosis associated with sustained systemic glucocorticoid therapy and in men with primary or hypogonadal osteoporosis who are at high risk of fracture. It is an anabolic agent administered by daily subcutaneous injection. Teriparatide in a dose of 20 μg daily was shown to decrease the risk of vertebral fractures by 65 percent and non-vertebral fractures by 53 percent in patients with osteoporosis, after an average of 18 months of therapy. In Europe, the full-lenght PTH (1–84) molecule also is approved for therapy [28, 73].

PTH releases calcium and phosphorus by stimulation of osteoclastic activity in the bone and continuous secretion of excess PTH causes bone resorption. However, when PTH is given at a low dosage and intermitently, its anabolic proporties are much more clearly seen [74]. Misof et al [75] showed by paired iliac crest bone biopsies that the bone mineralization density after PTH treatment was shifted toward a lower mineralization density and bone mineralization density distributions peak got broader, indicating increased heterogeneity in mineralization and new bone formation compared to that before PTH treatment.

Body et al [76] studied the effects of a high dose of teriparatide (40 μg/day) and alendronate (10 mg) on BMD in 146 postmenopausal women with osteoporosis and they established that lumbar spine BMD increased by 12.2% in the teriparatide group and 5.6% in the alendronate group at 3 months, and teriparatide increased femoral neck BMD significantly than alendronate. However, the 40 μg of teriparatide had been failed to demonstrate a benefit over the 20 μg dose, only the 20 μg dose was ultimately approved [74].

Teriparatide is well tolerated, although some patients experience leg cramps and dizziness. Because it caused an increase in the incidence of osteosarcoma in rats, patients with an increased risk of osteosarcoma (e.g., patients with Paget's disease of bone) and those having prior radiation therapy of the skeleton, bone metastases, hypercalcemia or a history of skeletal malignancy should not receive

teriparatide therapy. The safety and efficacy of teriparatide has not been demonstrated beyond two years of treatment. Teriparatide is used for a maximum of two years. It is common practice to follow teriparatide treatment with an antiresorptive agent, usually a bisphosphonate, to maintain or further increase BMD. Together with the lack of effect on hip fractures, the need for daily self-injection of both PTH analogues, and the cost of PTH therapy inevitably impose some limitations on their use [28, 74].

6.2.5 Denosumab

Denosumab (AMG-162, Prolia®), a fully human monoclonal antibody (mAb), directly inhibits the receptor activator of NF-kappaB (RANK)/RANK ligand (RANKL) signaling pathway, which is known to be vital for osteoclast activation, function and survival. Denosumab has been approved for the treatment of postmenopausal osteoporosis and bone loss due to hormone ablation therapy for prostate and breast cancer [77]. Brown et al [78] reported the results of phase 3, international, multicenter, double-blind, 12 month study aimed at comparing the efficacy and safety of denosumab with alendronate in 1.189 postmenopausal women with low bone mass (T-score ≤ -2.0 at the lumbar spine or total hip). The patients were randomized equally into two research arms that either received sc denosumab injections (60 mg every six months) along with an oral placebo weekly, or oral alendronate weekly along with sc placebo injections. At month 12, denosumab treatment significantly increased BMD from baseline measurements compared with alendronate (3.5% denosumab vs 2.6% alendronate), and the overall safety profile and the frequency of adverse events were found similar for both treatments. They concluded that denosumab treatment led to a significantly increase in BMD and a reduction of bone turnover markers compared with alendronate therapy. In the FREEDOM trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 months), Cummings et al [79] studied the effectes of 60 mg of denosumab or placebo s.c. every 6 months for 36 months in 7868 women between the ages of 60 and 90 years who had a bone mineral density T-score between −2.5 and −4.0 at the lumbar spine or total hip. They established that denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group, versus 7.2% in the placebo group (risk ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.41; $P<0.001$). Denosumab also reduced the risk of hip fracture and the risk of nonvertebral fracture as compared with placebo. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of denosumab [79].

6.2.6 Calcitonin (Miacalcin® or Fortical®)

Salmon calcitonin is FDA-approved for the treatment of osteoporosis in women who are at least five years postmenopausal. A single daily intranasal spray (200 IU) and subcutaneous administration are available [28].

Stevenson et al [51] evaluated 90 RCTs related to the five interventions (alendronate, etidronate, risedronate, raloxifene and teriparatide) and to five comparators (calcium, calcium plus vitamin D, calcitriol, hormone replacement therapy and exercise), as well as placebo or no treatment. They had been reported that all five interventions had been shown to reduce the risk of vertebral fracture in women with severe osteoporosis with adequate calcium intakes. Alendronate and raloxifene had also been demonstrated to reduce the risk of vertebral fracture in women with adequate calcium or vitamin D who had osteoporosis without fracture. However, only risedronate and teriparatide had also been demonsrated to reduce risk of non-vertebral fracture in women with severe osteoporosis and adequate calcium intakes. Alendronate had been shown to do so in women with osteoporosis with or without fracture and with adequate calcium or vitamin D intakes. However, none of those drugs had been demonstrated, by direct comparison, to be significantly more effective than either each other or the other active interventions reviewed in their report. Although, of the five interventions, only raloxifene had appeared to reduce the risk of vertebral fracture in postmenopausal women unselected for low bone density, there was some uncertainty regarding this resullt. None of the five interventions had been shown to reduce the risk of non-vertebral fracture in women unselected for low BMD [51].

7 Conclusion

Supplementation with adequate doses of calcium and vitamin D in combination with exercise i.e., walking 3–5 miles/week is one of the most important cornerstones of the prevention of osteopenia/osteoporosis and are necessary during treatment with pharmacologic agents. Osteoporotic medications are effective only if the patient is vitamin D sufficient and receiving adequate calcium. BMD and BTM changes with treatment might provide a better prediction of the antifracture efficacy of a therapeutic agent.

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