Open Access

OBM Geriatrics

LIDSEN Publishing Inc.

Review

Osteoporosis Etiology, Epidemiology, Diagnosis, Diet, and Treatment: A Narrative Review

Behzad Foroutan *

Department of Pharmacology, School of Medicine, Iranshahr University of Medical Sciences Iranshahr, Iran; E-Mail: behzad_foroutan@hotmail.com

* **Correspondence:** Behzad Foroutan; E-Mail: behzad_foroutan@hotmail.com

Academic Editor: Ray Marks

Special Issue: Osteoporosis in the Elderly

OBM Geriatrics
2024, volume 8, issue 2
doi:10.21926/obm.geriatr.2402277

Received: December 26, 2022
Accepted: March 19, 2024
Published: April 09, 2024

Abstract

This narrative review aimed to select, gather, and present inclusive evidence about osteoporosis etiology, epidemiology, diagnosis, diet, and treatment. We searched PubMed and Google using these terms: osteoporosis AND etiology, osteoporosis AND epidemiology, osteoporosis AND diagnosis, osteoporosis AND diet, and osteoporosis AND treatment. Each title of the extracted manuscripts was read first. If deemed suitable, the abstracts of the manuscripts and text were read carefully. Afterward, the details of each term were selected, put together, and summarized. The review attempted to find associated literature up to the beginning of 2022. Limits were used to restrict the search to English language publications. Several 3988 manuscripts relevant to the search objectives were retrieved. The results were analyzed and presented with important evidence to shape this narrative review. Osteoporosis leads to bone fragility, disability, and risk of fracture. These events cause many problems, particularly in the elderly. The publication of narrative review articles can provide helpful information such as timely disease diagnosis, prescribing the most appropriate medicines, correct nutrition methods, and prevention strategies to clinicians and their patients. It is suggested that the results of such studies be included in the agenda of relevant organizations such as the WHO.

Keywords
Osteoporosis; etiology; epidemiology; diagnosis; diet; treatment

1. Introduction

Like other parts of the body, bones are living tissues continuously being renewed. Bone is a compact mineralized connective and dynamic tissue that adapts to load variations with constant change. These adjustments occur through continuous structural remodeling procedures.

This narrative review aimed to select, compile, and present comprehensive and informative evidence on the etiology, epidemiology, diagnosis, diet, and treatment of osteoporosis (OP). Information was searched in PubMed and Google to gather the necessary data for this narrative review.

Table 1 lists the OP titles of this narrative review, along with the contents of each title.

Table 1 lists the OP titles along with the contents of each title.

Osteoporosis (OP)					
Bones	Etiology	Epidemiology	Diagnosis	Diet	Treatment
- Biology - Role of hormones - Pathophysiology	- Hormonal imbalance - Aging skeleton - Calcium imbalance - Medications - Chronic diseases - Immobility life - Menopause - Pregnancy - Breastfeeding - Hereditary factors - Caffeine consumption - Smoking - Drinking alcohol	- Global prevalence - National prevalence	- Characteristics - Clinical sign & symptoms - Common complications	- Calcium & Vit D - Trace minerals - Vit C & Vit K - Omega-3 polyunsaturated fatty acids - Vegetables - Forbidden foods	- Medications - Nanomedicine - Herbs - Natural remedies - Physiotherapy - Exercise - Magnetic therapy

2. Osteoporosis Bones

2.1 Biology of the Normal Bones

Bone is considered a living tissue that can grow, feed, change shape, and even die. Osteoclasts, osteoblasts, bone lining cells, and osteocytes are 4 types of cells in natural bone tissues. Bones are always resorbed by osteoclasts and re-formed by osteoblasts. Osteocytes act as mechanosensors and leaders of bone structural remodeling. The function of lining cells seems to play an important role in coupling bone resorption to bone creation.

Bone remodeling is a lifelong process in which old bone is broken down and replaced with new bone tissue. They also control the bone remodeling or healing process following injuries such as bone fractures or minor injuries that occur during normal daily activities. In humans, the entire body's skeleton is regenerated approximately once every ten years by bone breakdown and formation. Aging disturbs these dynamic processes. Bone resorption, in which osteoclasts remove old and damaged bone, takes about 4-6 weeks, a relatively rapid process. Meanwhile, new bone formation by osteoblasts takes approximately 4-5 months. Osteoclasts and osteoblasts are differentiated from hematopoietic stem cells and mesenchymal cells, respectively. An imbalance between the regulation of the two processes of bone breakdown and formation leads to many bone metabolic diseases such as OP. Bone breakdown by osteoclasts is such that the mineral matrix is decomposed by the release of hydrochloric acid and the release of proteases, especially cysteine protease cathepsin K and matrix metalloproteinase, causing the breakdown of the organic matrix.

2.2 The Role of Hormones in Bones

Hormones help to increase the number of bone-forming cells to fight against osteoclasts; thus, more bones are made instead of destroyed. Here, we summarize the role of hormones in bones.

2.2.1 Parathyroid Hormone

Parathyroid hormone (PTH) directly affects bones and kidneys. It indirectly affects the intestines through the effects of vitamin D. PTH operates within a physiological negative feedback loop regulated by the calcium level in the blood. When it decreases, there is less binding to calcium-sensing receptors (CaSR) in the parathyroid gland. This leads to increased secretion of PTH to increase calcium levels. PTH indirectly affects osteoclasts by increasing the activity of the receptor activator of nuclear factor kappa ligand (RANKL), which regulates the osteoclastic activity of bone resorption and leads to the release of more calcium into the blood. Conversely, high blood calcium levels bind to CaSR in the parathyroid gland and inhibit PTH release. Stimulation of CaSRs causes conformational change of the receptor and stimulation of the phospholipase C pathway. This ultimately leads to an increase in intracellular calcium, thereby inhibiting PTH exocytosis from the chief cells of the parathyroid gland. This explains only one piece of the calcium homeostasis puzzle because PTH also acts in the kidneys and intestines to regulate calcium and phosphate levels.

2.2.2 Estrogen

Estrogen deficiency leads to increased bone remodeling, where bone resorption outpaces bone formation and decreases bone mass. According to animal studies, estrogen may affect local factors

that regulate osteoblast and osteoclast precursors. Estrogen may block interleukin-6 (IL-6) production and action and prevent bone resorption. Moreover, osteoclast survival is believed to be augmented in cases of estrogen deficiency, leading to a higher rate of bone turnover.

2.2.3 Calcitonin

The C cells in the thyroid gland release calcitonin hormone, which helps increase calcium levels in the body. Calcitonin binds to calcitonin receptors on osteoclasts to prevent bone resorption. Calcitonin is not thought to have a prominent role in calcium homeostasis in adults, but it may be more critical in skeletal development in childhood. It may be used clinically as a therapeutic option for treating OP.

2.2.4 Growth Hormone

Growth hormone (GH), a peptide hormone secreted by the pituitary gland, acts through insulin-like growth factors (IGF) to stimulate bone formation and resorption. GH acts directly and indirectly through IGF to stimulate the proliferation and activity of osteoblasts. It also stimulates bone resorption and osteoclastic activity. The cumulative net effect of this dual activity favors bone formation.

2.2.5 Glucocorticoids

Glucocorticoids reduce bone formation by portioning the survival of osteoclasts and causing the death of osteoblast cells. There is an increase in RANKL function and a decrease in osteoprotegerin. Osteoprotegerin is a cytokine receptor that acts as a decoy receptor for RANKL, thus normally inhibiting RANKL-RANK interaction and activity.

2.2.6 Thyroid Hormone

Thyroid stimulating hormones, thyroxine (T4) and triiodothyronine (T3) stimulate osteoblastic activity and origin bone elongation in the epiphyseal plate of long bones through the proliferation of cartilage cells. In cases of hypothyroidism or hyperthyroidism, the amount of bone turnover is low and high, respectively. The rate of bone turnover is due to the effect of T3 and T4 on the number and activity level of osteoblasts and osteoclasts. For example, the increased metabolic state of thyrotoxicosis leads to increased osteoblast function and osteoclastic number and activity, leading to higher bone turnover.

2.3 Pathophysiology of Bones

The understanding of the pathophysiology of bones has increased rapidly. Clinicians have a special interest in bone-related diseases, so bone pathophysiology has become an interest for clinicians [1].

Osteoporosis (OP) is a term used for “porous bone,” meaning insufficient or inadequate bone mass. The disease is common, with an increasing prevalence and bone fractures worldwide. A changed bone microenvironment initiates it, eventually predisposing both genders to low-impact, fragility fractures. These types of bone fractures cause a remarkable upsurge in disability, decreasing

the quality of life of sufferers and resulting in increased morbidity and mortality, particularly among aged populations [2, 3]. More than half of postmenopausal white women develop osteoporotic fractures. Only one-third of aged women with a pelvic fracture will be able to return to their previous condition. For white men who are diagnosed with OP, the risk of fractures is 20%, but the annual mortality rate in men with pelvic fractures is twice as high as in women. Black ethnicity is less likely to develop OP than their white counterparts, but cases with OP have similar fracture possibilities [4].

Assuming bone as a static "skeleton in the closet" has shaped the misguided impression that, once formed, it will remain unchanged [5]. However, remarkably, bone mass is constantly being absorbed, replaced, and changed during its age. When the absorption rate surpasses the replacement rate, which usually occurs with age, the bone frame starts its reduction [6]. The literature does not show a consensus on the age when peak bone mass (PBM) is achieved in men and women [7]. Depending on the skeletal site, PBM arises by the end of the second or early in the third decade of human life [8]. Persons with less bone mass before this period have a higher risk of developing OP [2]. Gender, race, family history (genetic/ancestor), physical activity, diet, nutrition and supplemental plan in particular with low vitamin D and calcium consumption, weight, tobacco and alcohol addiction, socioeconomic status, age at menarche, and other secondary causes like suffering from various diseases and of course using several medicines are important factors and therefore are in charge of the majority of PBM gain during childhood and adolescence [9]. Figure 1 shows the relationship between bone mass and age in males and females. Bone density reaches its peak around 30 years of age in both genders. Males gradually lose bone mass at a slower rate than females. Taken from [10].

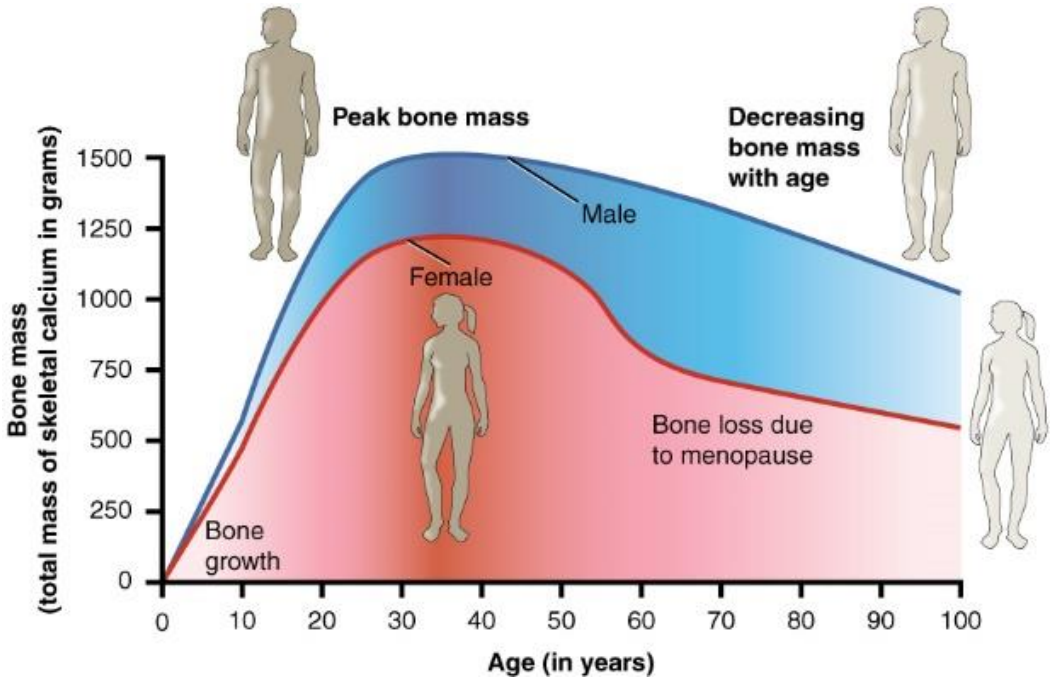

Figure 1 Graph shows PBM and decreasing bone mass in males and females regarding age [10].

3. Osteoporosis Etiology

OP can be classified into primary and secondary categories based on its causes. The most prevalent type of OP is primary, with two subtypes - juvenile and idiopathic. Idiopathic OP is further divided into postmenopausal (type I) and age-associated or senile osteoporosis (type II). Type I is primarily due to estrogen deficiency, but type II is primarily due to an aging skeleton and calcium deficiency. The specific cause of primary OP is unknown; however, there are many contributing factors to the disease, including persistent calcium imbalance, gonadal as well as adrenal dysfunction, estrogen deficiency, or life with little activity. Postmenopausal OP is characterized by increased bone loss due to reduced estrogen production [11-13]. Women usually lose bone 10-11% each year after peak bone mass and up to eight years after menopause [14]. At 70 years of age, the bone mass has decreased by 30-40% [15]. Elderly OP is an age-related form that often occurs with age [16]. Long-term medication use or other complications that affect calcium uptake or bone generation can cause it [17].

Medications such as anticonvulsants [18], antiretroviral [19], aromatase inhibitors [20], chemotherapeutic/transplant drugs such as cyclosporine, and tacrolimus [21], cyclophosphamide [22], ifosfamide [23, 24], high-dose methotrexate [25, 26], furosemide [27-29], glucocorticoids [30-32], prednisone (≥5 mg/day for ≥3 months) [33], heparin [34], gonadotropin-releasing hormone agonists [35], luteinizing hormone-releasing hormone analogs [36], depot medroxyprogesterone [37], excessive thyroxine [38], opioids [39], proton pump inhibitors [40], selective serotonin reuptake inhibitors [24, 41], sodium-glucose cotransporter 2 - inhibitors [42], thiazolidinediones [43], and warfarin [44] have been reported that are able to initiate the secondary OP. No significant association between osteoporosis and all antipsychotics was reported, except for perphenazine [45].

History of common chronic diseases such as Opioid Addiction (OA), Cushing, Diabetes Mellitus (DM), Hypothyroidism, Rheumatoid Arthritis (RA), and Systemic Lupus Erythematosus (SLE) are other causes of secondary OP. For more details, see Table 2.

Table 2 lists the common diseases that can cause osteoporosis.

Category	Disease
Genetic diseases	Cystic fibrosis [46], Ehlers-Danlos [47], Gaucher's disease [48], Glycogen storage diseases [49, 50], Hemochromatosis [51], Homocystinuria [52], Hypophosphatasia [53], Marfan syndrome [54], Menkes steely hair syndrome [55], Osteogenesis imperfecta [56], Parental history of hip fracture [57], Porphyria [58]
Hypogonadal states	Androgen insensitivity syndrome [59], Anorexia nervosa [60], Athletic amenorrhea [61], Hyperprolactinemia [62], Panhypopituitarism [63], Premature menopause (<40 years) [64, 65], Turner's [66-69]and Klinefelter's [70-72] syndromes
Endocrine disorders	Central obesity [73], Cushing's syndrome [74], Diabetes mellitus (types 1 and 2) [75], Hyperparathyroidism [76], Thyrotoxicosis [77, 78]

Gastrointestinal disorders	Celiac disease [79, 80], Gastric bypass [81, 82], Gastrointestinal surgery [83, 84], Inflammatory bowel disease [85], Malabsorption [86], Pancreatic disease [87], Primary biliary cirrhosis [88]
Hematologic disorders	Hemophilia [89], Leukemia [90] and lymphomas [91-93], Monoclonal gammopathies [94], Multiple myeloma [95], Sickle cell disease [96], Systemic mastocytosis [97], Thalassemia [98]
Rheumatologic and autoimmune diseases	Ankylosing spondylitis [99], RA [100], SLE [101]
Neurological and musculoskeletal risk factors	Epilepsy [102, 103], Multiple sclerosis [104], Muscular dystrophy [105], Parkinson's disease [106], Spinal cord injury [107, 108], Stroke [109]
Miscellaneous conditions and diseases	Addiction to narcotics [110], AIDS/HIV [111, 112], Amyloidosis [113], Chronic metabolic acidosis, COPD [114], CHF [115], End-stage renal disease [116], Hypercalciuria [117], Idiopathic scoliosis [118], post-transplant bone disease [119], Socioeconomic status [120], Sarcoidosis [121], Weight loss [122]

Long-term calcium intake is essential in building bone reserves before the PBM level and maintaining bone mass later at age twenty. The risk of secondary OP can be initiated by calcium deficiency [123] or lack of absorption [124]. Also, excessive drinking of alcohol reduces the body's ability to absorb calcium. Vitamin D, protein, and calcium insufficiencies are responsible for the majority of all types of OP [17]. Sedentary or underweight, more than 10% of youth weight, menopause, pregnancy, breastfeeding, hereditary factors, smoking, and drinking alcohol are important modifiable causes of secondary OP. Osteogenesis occurs in reaction to pressure applied to it. Individuals who engage in regular physical activity tend to have stronger bones than those who are less active.

Hormone levels can interfere with the body's ability to produce and stabilize adequate bone mass. OP regularly accompanies dysfunction of the gonads, thyroid, parathyroid, or adrenal glands.

In brief, the most important factors that increase the risk of the disease are age ≥50 years, being white and Asian, female gender, menopause (especially premature or surgical), family history of the disease or bone fracture, the ancestors of Northern Europe, long periods of inactivity or immobility life, caffeine consumption, tobacco intakes, drinking alcohol, slim body structure, and amenorrhea. Other risk factors are poor diet, low testosterone levels in men, anorexia nervosa, and ongoing use of medications such as anticonvulsants, long-acting benzodiazepines, or corticosteroids.

Observational research proposes a link between depression and OP. However, these should be subject to confounding and reverse causalities [125]. A study that evaluated 10 cohort investigations that investigated the association between depression and fracture revealed that in studies that reported fracture outcomes as hazard ratios (six studies [n = 108,157]), depression was statistically linked with a 17% upsurge in fracture risk (HR = 1.17; 95% confidence interval], 1.00-1.36; P = 0.05); in studies that reported risk ratios as fracture outcomes (four studies [n = 33,428]), it was statistically linked with a 52% upsurge in risk (risk ratio, 1.52; 95% confidence interval, 1.26-1.85; P < 0.001) [126].

Antidepressant usages rendered the association between depression and fracture risk non-significant (three studies with no adjustment, n = 14,777; HR 1.30, 95% confidence interval 1.11 to

1.52, p = 0.001 versus three studies with adjustment, n = 93,380; HR 1.05, 95% confidence interval 0.86 to 1.29, p = 0.6). The authors of the published paper suggest that a significant portion of the apparent association between the disease and bone health might be mediated by the medications used to manage the disease. Considerable heterogeneity existed in the patients who participated in terms of age, gender, ethnicity/race, duration or severity of the disease, and other important factors such as effect size and even co-variables. So, there was insufficient evidence to determine whether depression was associated with increased fracture risk independent of the medication's treatments and other confusing factors acting against their expectations.

4. Osteoporosis Epidemiology

Hundreds of millions of persons are affected globally, and OP prevalence is increasing [127-129]. The global prevalence of OP is problematic to ascertain because of contradictory definitions and diagnostic criteria. Generally, one-eighth of men and one-quarter of women aged ≥50 years are facing OP [130]. Statistics show that nearly fifty-three million individuals suffer from the risk of bone loss in the USA [131]. It is estimated that more than 40 million Americans over 50 years of age are at risk of OP fractures, and that is due to demographic changes. This number will at least double until the year 2040. It is also predicted that 25% of men and women over 50 who have experienced osteoporotic hip fractures will die within a year [132].

About 6% of men and 21% of women aged 50-84 years suffer from OP in the European Union, affecting nearly 28 million men and women [129]. Women are at greater risk than men [133]. In persons who are 50 years of age and older, about a quarter of men and half of women will have a fracture as a result of OP. Across the world, more than 200 million women have been affected, and the incidence rises with age. More than 70% of men and women over eighty are affected. In developed countries, 2-8% of men and 9-38% of women are affected [134]. Worldwide, nearly nine million fractures happen each year, and one in three women and one in five men over the age of fifty will develop an OP fracture [3]. Some parts of the world that receive little vitamin D from sunlight have higher fractures than areas closer to the equator and people living in lower latitudes [135, 136]. Every two hundred seconds, a femoral or vertebral fracture happens with a mortality rate between 15% and 25% around the world [137, 138].

An Iranian report estimated that the prevalence of OP in lumbar vertebrae was 13.4% in men and 44.4% in women aged ≥50 years [139]. Consistent with a study based on the speed of sound criterion in 2003, the prevalence of OP in Chinese women was reported to be 10.08% [140], and its prevalence in Vietnamese women, based on the BMD criteria, was reported to be 15.4% [16].

A recent investigation in Chinese patients documented that the hip fracture rate increased from the early 1990s to 2006 among patients aged ≥65 years [141].

In Japan, nearly 28% of the population is older than 65 years, and the predictable prevalence is 15 million individuals, resulting in roughly 200,000 hip fractures annually [142, 143].

In India, the estimated number increased from 26 million in 2003 to 36 million in 2013 [144]. By 2050, half of the global hip fractures will befall Asian residents aged ≥50 years [144].

5. Osteoporosis Diagnosis

5.1 Characteristics

Physical examination seldom shows changes until OP is in the progressive stage [145]. At this stage, the height loss and kyphosis from vertebral fractures are evident [146]. In persons without risk factors, specialists recommend that they begin screening women at age 65 and men at age 70 [147]. Patients with T scores on the OP risk assessment test and high-risk factors should be screened very soon.

5.2 Clinical Signs and Symptoms

Unlike many other chronic diseases that have many clinical and experimental signs and symptoms, OP is a silent, asymptomatic illness until a fracture happens [148]. Pelvic fractures are common in both genders [149, 150]. Back pain, including acute burst pain, severe back pain, pressure fractures in the spine, bone fracture, height reduction, kyphosis, dowager bulge, decreased activity tolerance, and premature satiety are common [151].

The diagnosis of OP typically involves several steps. Clinicians will thoroughly evaluate the risk for OP as well as fracture risk. Steps for diagnosing comprise the following. Taking a medical history is the first step. Questions related to its risk factors, such as a family history of OP, and lifestyle factors, such as diet plan, physical activity, drinking habits, and smoking, which may influence the risk, should be proposed. The clinicians will also review medical conditions that patients have had and medications they may have taken. Symptoms of OP that clinicians will likely ask patients about include any bone fractures that happened, a history of back pain, a loss of height over time, or a stooped posture. Running a physical exam is step two. The clinicians will measure a person's height and compare this to previous amounts. Height loss may be a sign that points to OP. The clinicians may ask if patients have difficulty rising from sitting without using their arms to push themselves up. They may also order blood tests to assess vitamin D levels and determine the bones' overall metabolic activity. Metabolic activity might be increased in the presence of OP. Undergoing a bone density assessment is the next step. The WHO has advised the dual-energy X-ray absorptiometry detection scan for the fundamental skeleton as the finest assessment for evaluating bone mineral density (BMD) [152]. The reported results of this assessment are based on calculating T-scores. The T-score on the bone density report shows how much the bone mass differs from that of an average healthy 30-year-old. The results for the whole population will be distributed around an average score (the mean). How high or low is the bone density of T-scores compared to healthy 30-year-olds? A T-score indicates the difference between BMD and the mean BMD in young adults. It is measured in standard deviation. The WHO defines normal BMD for women as a T-score in a standard deviation from the average young adult. Scores between -1 and -2.5 points to osteopenia (reduced bone density) and a score below -2.5 points to OP [152].

The Fracture Risk Assessment Tool (FRAX®) would become a more accurate way to measure the likelihood of a fracture in the next 10 years [153]. The FRAX® questionnaire considers elements that affect a person's bone quality as well as his/her bone density.

A Z-score compares bone density to the average bone density of people of gender and age. For example, for a female who is 60 years old, a Z-score compares the bone density to the average bone density of 60-year-old females. Any postmenopausal woman should continuously request her T-

score rather than her Z-score only. A Z-score assists in diagnosing secondary OP and is always used for children, young adults, pre-menopausal women, and men <50 years [154].

They were requesting blood and urine tests as the last step. In some circumstances, medical conditions may cause bone loss, such as thyroid and parathyroid malfunctioning. The physician may perform blood and urine tests to rule this out, so they may cover calcium levels, thyroid functions, and testosterone levels in men.

Persons should be diagnosed with OP by giving a laboratory evaluation of thyroid and renal functions, i.e., 25-hydroxy vitamin D and calcium [155].

5.3 Common Complications

In addition to patients being more prone to fractures, the disease may end in other difficulties like limited mobility. These difficulties can cause restriction and, therefore, lead to limited physical activities, which may help to gain weight and increase stress on the bones, typically knees and hips. Gaining weight can also increase the risk of getting cardiovascular complications and DM. In addition, less physical activity may lead to a loss of independence and isolation. Activities that were joyful before may be painful now. This loss, added to the conceivable fear of fractures, could bring on depression. A poor emotional state can further hinder patients' ability to manage health issues. Fractures as a result of OP can be severely painful and debilitating. Fractures of the spine can result in a loss of height, a stooping posture, and persistent back and neck pain. Some people with OP can break a bone and not see it. However, most broken bones need hospital care. Surgery is often needed for broken bones, which may require an extended hospital stay and additional medical costs. Once in the hospital, these patients are also at a high risk of developing thrombosis (27%), urinary tract infections (12-61%), and pneumonia (7%) [156]. A hip fracture will need long-term care in a nursing home. Suppose a patient is bedridden while getting long-term care. In that case, there is a higher likelihood that they may experience cardiovascular problems, more exposure to infectious diseases, and an increased susceptibility to various other difficulties such as constipation.

6. Osteoporosis Diet

Aging may alter several aspects of oral physiology, habits, and behavior. Teeth play an important role in changing eating habits in patients with OP. A well-adjusted diet that includes a variety of foods is vital for maintaining a healthy status. A suitable diet ensures that bones get enough vitamins, minerals, and energy to stay healthy, which helps them avoid facing the disease.

6.1 Calcium and Vitamin D

Assessing diet can help if a person has OP or is at risk of getting it. In particular, the person needs to ensure he is getting adequate calcium and vitamin D. Calcium is a substantial element for building many parts of the human body, especially bones. The human body in a normal adult has about 1.2-1.4 Kg of calcium, and 99% of this is found in bones and teeth. The remainder exists in blood, extracellular fluid, muscles, and other tissues [157]. In bone, calcium exists mainly in Ca5(PO4)3(OH) often written $Ca_{10}(PO_4)_6(OH)_2$, called hydroxyapatite. Bone minerals make up almost 40% of its weight. The recommended daily allowance values are summarized in Table 3.

Table 3 Recommended value for calcium and vitamin D based on age [158].

Age (Year)	Recommended value (Calcium mg/daily)	Recommended value (Vitamin D IU)
1-3	700	Up to age 12 months = 400 IU (100 mcg) 1-70 years = 600 IU (150 mcg) >70 years = 800 IU (200 mcg)
4-8	1000	
9-13	1300	
14-18	1300	
19-30	1000	
31-50	1000	
51-70 (Female)	1200	
51-70 (Male)	1000	
>71	1200	
14-18 Pregnant/Lactating Women	1300	
19-50 Pregnant/Lactating Women	1000	

Most people can get the recommended amount through their diet. However, some calcium supplements might be used. Patients may need 1000-1200 mg daily based on their gender. Ensuring adequate calcium in the diet is an important factor in bone health. Although a person can consume much calcium, consuming more than 2,500 mg of calcium during the day regularly may cause medical problems [159]. It can also affect the absorption of magnesium [160] and iron [161].

The following foods are rich in calcium and are regularly part of the OP diet. Dairy products (milk, yogurt, cheese, top milk, and cream), green leafy vegetables (cabbage, broccoli, okra, fennel, and spinach), enriched orange juice, sesame seed, dried figs, and apricots [162], Tofu, fortified calcium, soy drink with added calcium, soybeans, nuts, bakery products made from fortified flour, calcium-fortified breakfast cereals, and fish that have small edible bones such as sardines and European sardines.

Also, vitamin D is important because it helps the body absorb calcium [163]. Vitamin D states for ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3). Ergocalciferol is produced from irradiated fungi or yeast. Vitamin D_3 is formed in the skin or found naturally in fatty fish such as salmon or mackerel. Vitamin D_2 and D_3 could be used to fortify food; however, only vitamin D_3 could be made endogenously in the skin. Exposure of human skin to UVB radiation in the wavelength range of 290 to 315 nm converts 7-dehydrocholesterol to Previtamin D_3, which subsequently isomerizes to form vitamin D_3. The total amount of vitamin D_3 made in the human skin can be affected by an individual's skin color, age, and use of sunscreen products, along with the time of day, season, and latitude [163]. Short-term exposure to sunlight without sunscreen (approximately 10 minutes, BID) when the sun is shining meets the day's needs. Vitamin D is found in eggs, enriched fat and breakfast cereals, milk powder, and oily fish such as sardines and salmon. The person needs to be able to get all the vitamin D through diet and lifestyle alone. An OP diet plan will seek to provide adequate amounts of vitamin D.

6.2 Trace Minerals

Calcium and vitamin D are essential for bones but are not the only important nutrients for bone health [164]. Trace minerals such as zinc, boron, copper, Strontium (Sr), and manganese are also

essential because they are like rings that hold a chain together [164]. Also, vitamin K is needed to get bone minerals [164]. It is made from green leafy vegetables, for example, broccoli, Brussels sprouts, cabbage, collards, spinach, salad greens, margarine, and plant oils [164]. Functional foods high in antioxidants and calcium should always be scheduled in diet plans for the elderly to reduce the risk and control the disease. The main antioxidant substances are vitamins C and E, polyphenols, and lycopene. Intake and absorption of calcium are also important, and it has been reported that chicken eggshell powder has a rich content of calcium and can be consumed daily through its application in food products such as bread, biscuits, white bread, breaded fried meat, chocolate cakes, chokeberry and cranberry juice, pizza and spaghetti, and muffin. Besides, the quantity of antioxidants applied to food products is a significant concern. So, it would not interrupt the calcium absorption or could be a pro-oxidant, negatively affecting bone health. Adding vitamin D, prebiotics, probiotics, and synbiotics may help increase calcium absorption. The foods mentioned below are excellent sources of vitamin K. Including them in our daily diet can help promote optimal health. The list includes kale (cooked), mustard greens (cooked), Swiss chard, collard greens (cooked), natto, raw spinach, cooked broccoli, cooked Brussels sprouts, beef liver, chicken liver, goose liver, cooked green beans, prunes, kiwi, soybean oil, soft and hard cheeses, cooked green peas, and avocado.

Functional foods in the elderly diet may improve their quality of life and reduce the risk of getting or delaying the onset of the disease. Usually, a dietary suggestion for the elderly is not much different from that for younger adults, but the aging-related physiological changes raise additional difficulties. These changes may affect the ability to eat and digest the food. Reduction possibly happens in saliva secretion, stomach and pancreatic juices, insulin, and bile. These difficulties may lead to insufficient absorption of nutrients. Merely adding the serving sizes or meal frequency more usually does not work effectively in the elderly due to these physiological problems with eating and with a reduced desire to eat. Therefore, several studies suggested many types of functional foods that can help the elderly improve their nutritional status and prevent deficiencies.

Protein consumption is also needed for bone health. Approximately half of bone volume and one-third of bone mass are proteins. A dietary protein consumption of 1.0-1.2 g/kg body weight daily, with at least 20-25 g of high-quality protein at each main meal, has been recommended by The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis [165]. The main sources are eggs, fish, meat, poultry, and dairy products. In addition, proteins are beneficial in reducing age-related bone loss and hip fracture risk in geriatrics [166]. Dairy product intake is presumably very supportive because they are a source of calcium and proteins since one liter of milk has 1200 mg of calcium and 32 g of proteins. In some parts of the world, yogurts are supplemented with milk powder, resulting in a 50% increased content of these nutrients compared with yogurt made from milk alone. The combination of protein and calcium in dairy products positively affects calciotropic hormones. A reduction in circulating PTH, an increase in IGF-I, and, consequently, a decrease in bone resorption markers and an improving BMD may happen [15]. Regarding the nutrients required for strong bones, fruits and vegetables contain carotenoids, folate, magnesium, potassium, vitamin C, and vitamin K.

Table 4 shows the effects of different diets on BMD and fracture risk.

Table 4 Dietary patterns and bone status.

Dietary Pattern	Study name [Ref. No.]	No. Participants (Gender), Mean age/Age range	Effect on BMD	Effect on Fracture Risk
Asian	Singapore Chinese Health Study [167]; vegetables, fruit, soy	63,257 (27,913 males & 35,241 females) 45-74 years		34% reduced risk of hip fracture
	OP Korean Health and Nutrition Examination Survey 2008-10 [168]	3735 (Postmenopausal Women) 64 ± 9 years	Dairy and fruit patterns reduced the risk of OP of the lumbar spine (53%); white rice, kimchi, and seaweed dietary patterns were negatively related to bone health	
Mediterranean	EPIC Study [169]	188,795 (139,981 Women and 48,814 Men) 48.6 years (±10.8)		7% decrease in hip fracture incidence
	CHANCES Project [170]	140,775 (116,176 Women, 24,599 Men) 60 years and older		The risk of hip fracture reduced to 4%
	Malmir meta-analysis [171]	358,746 13-80 years	Positive relation with lumbar spine, femoral neck, and total hip BMD	The risk of hip fracture reduced to 21%
Vegetarian	Bayesian meta-analysis [172]	2749 (1880 Women and 869 Men) 20-79 years	4% lower BMD (95% CI: 2%, 7%) at femoral neck & lumbar spine	
	EPIC-Oxford investigation [173]	34,696 (7947 Men & 26,749 Women) 20-89 years		Fracture incidence rate ratios: 1.00 (0.89-1.13) for vegetarians and 1.30 (1.02-1.66) for vegans
Western	Co-twin controlled trial, UK [174]	4928 (Postmenopausal Women) 56 ± 12 years	In reverse related to BMD in the femoral neck	

Framingham Offspring Investigation, USA [175]	2740 (1206 Men & 1534 Women) 29-86 years	Higher consumptions of processed food and red meat were inversely associated with femoral neck BMD

6.3 Vitamin C and Vitamin K

Vitamin C, with antioxidant properties, suppresses osteoclast activity [176], performs as a cofactor for osteoblast differentiation, and participates in collagen construction. It is a marker of a well dietary design rich in fruits and vegetables. According to a systematic review and meta-analysis outcomes that compiled observational studies, a greater dietary vitamin C intake showed a direct relation with BMD at the femoral neck and lumbar spine. However, the authors concluded that remarkable between-study heterogeneity existed at the femoral neck. Differences in study design, gender, and age caused this heterogeneity. A higher dietary vitamin C consumption was interrelated with a lower risk of hip fracture and OP, as well as higher BMD, at both the femoral neck and lumbar spine sites [177]; a more recent meta-analysis supports the hypothesis that increasing dietary vitamin C intake could reduce the risk of hip fractures in both genders [178]. Although these benefits are significant, there is little information in clinical practice guidelines regarding vitamin C consumption recommendations, so the amount of vitamin C should be appropriately included in clinical guidelines.

Vitamin K_2 is a fat-soluble vitamin, generally produced in the intestine by bacteria and is less commonly found in food. Vitamin K is important in maintaining bone strength and preventing bone breakdown. Vitamin K_2 deficiency is associated with an increased risk of bone fractures and decreased bone density. New studies have shown that calcium supplements alone without vitamin K_2 cause calcium deposition in soft tissues and veins. Vitamin K_2 activates the bone-forming protein (osteocalcin) and causes the absorption and placement of calcium in bone tissues. In addition, with the activation of osteocalcin by vitamin K_2, bone destruction is prevented by bone-resorbing cells (osteoclasts). In the case of a lack of vitamin K_2, this protein is not activated, and the bones do not absorb calcium, so it remains in the blood. In addition, vitamin K_2 can activate proteins that remove calcium from soft tissues such as arteries, and as a result, it can reduce the risk of cardiovascular diseases and stroke.

6.4 Omega-3 Polyunsaturated Fatty Acids

The effects of omega-3 polyunsaturated fatty acids (PUFAs) on bone metabolism have been reported with inconsistent evidence. The consumption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may affect bone growth and remodeling in humans through the inhibition of bone resorption and also by stimulating bone creation [179]. The mechanism by which PUFAs may affect bone turnover is not known precisely. However, it is assumed that both may exert their aids by regulating osteoprotegerin receptor activator of nuclear factor kB (RANK), with a sense of balance towards bone creation [180]. Fish and seafood are rich in PUFAs. They are identified to have anti-inflammatory effects that progress bone quality [181]. A meta-analysis revealed that omega-3 fatty acids reduced osteocalcin serum levels in postmenopausal women, but no significant reduction in bone-specific alkaline phosphatase was reported [182]. A study performed with a dairy

product enriched in PUFAs, calcium, oleic acid, and vitamins to assess their effects on bone metabolism in postmenopausal women displayed promising changes in bone metabolism markers, for instance an increase in vitamin D levels and a decrease in both PTH and Receptor Activator for Nuclear Factor κB Ligand (RANKL), but did not show the other changes in serum osteoprotegerin or bone turnover markers [183]. The other investigation concluded that the dietary consumption of PUFAs was positively related to BMD in osteopenic and healthy Spanish ladies at both the hips and lumbar spine [184]. A recent systematic review revealed a considerable protective effect between the dietary intake of omega-3 PUFAs through fish eating and the risk of hip fracture [185].

6.5 Folate and Vitamin B_{12}

Folate and vitamin B_{12} might also influence bone status by reducing homocysteine concentrations; homocysteine is linked to lower BMD and a higher fracture risk [186]. A meta-analysis of 4 prospective investigations concluded a 4% lower fracture risk for each 50 pmol/L increase in vitamin B_{12} concentration [187].

Zinc is in beans, nuts, and whole grains, but the phytate in these nourishments makes it less bioavailable than zinc from animal-based sources. Lower serum and bone zinc concentrations have been considered in OP patients [188].

6.6 Fruits

Moreover, to trace minerals, fruits contain magnesium, vitamin K, and calcium which are important for good bone health.

6.6.1 *Prunus domestica L*

Dried plum (*Prunus domestica L.*) effectively prevents and reverses bone mass and structural loss in osteopenic postmenopausal women. A three-month RCT investigated dried plums versus dried apples (control) and measured biomarkers of bone formation. Research has demonstrated that 100 g/day dried plums significantly increased the serum markers of bone formation in postmenopausal women [189]. Another one-year RCT compared the effects of daily consumption of 100 g dried plum versus 75 g dried apple on BMD and biomarkers of bone turnover in 160 osteopenic postmenopausal women. The study concluded that dried plums enhanced ulnar and lumbar BMD compared to the control group [190]. Similarly, an inconsistent outcome was found in a non-randomized six-month intervention trial assessing the effects of resistance training with and without dried plum at a dose of 90 g in 23 postmenopausal breast cancer survivors. Both groups showed improved upper and lower body strength, with no observed changes in body composition or BMD [191]. However, results from a six-month clinical trial assessing the efficacy of 50 g vs. 100 g of dried plum in 48 older postmenopausal females stated that dried plums prevented the loss of total body BMD and reduced the serum concentration of tartrate-resistant acid phosphatase. Also, the investigators concluded that both doses were equally efficacious [192]. The beneficial effect was also observed in a trial involving 35 men aged between 55 and 80 with moderate bone loss. After three months, decreased serum concentration of osteocalcin and an elevation of Osteoprotegerin/Receptor Activator for Nuclear Factor κB Ligand were observed. So, it seems that regular consumption of 50-100 g dried plum for three months should make some contributions to

bone formation and turnover activity and a minimal contribution to decreasing inflammation and improving bone density and quality [193].

6.7 Vegetables

Vegetables are edible herbaceous plants, often consumed as part of a meal. The original meaning is still generally used and is applied to plants collectively to refer to all edible plant matter, including the fruits, leaves, roots, seeds, and stems.

6.8 Forbidden Foods

It seems high sodium chloride consumption may be a facilitator parameter that makes calciuria which weakens bones over the time, causing cardiovascular diseases, and even generating DM. However, the effects of salt on calcium metabolism and the possible impact on bone health in postmenopausal women have not been fully characterized. Authorities recommend that people intake only 6 grams of salt per day. Consuming herbs and spices instead of salt to flavor foods might be caring. However, avoid high-salt, processed foods, ready meals, and soups/canned sauces.

Carbonated drinks containing phosphoric acid may increase calcium excretion during urination, which can be a problem if the daily calcium intake is low. Try to limit the consumption of carbonated beverages and use water and fruit juices instead.

Although caffeine is not as harmful as salt, it has a detrimental effect on bone density. Caffeine intake should be limited to 300 mg daily to ensure the body gets enough calcium from the diet. Patients should try to drink green tea instead of coffee and drink plenty of water and milk.

While beans have some healthy attributes for women with OP, they are also high in phytates. They affect the body's ability to absorb calcium. Not only does wheat bran contain high levels of phytate, which can block calcium absorption, but 100 percent wheat bran is the only nourishment that appears to reduce calcium absorption in other nourishments eaten all at once. Therefore, if calcium supplements have been taken, do not take them within 2 to 3 hours of eating 100 percent wheat bran.

Vitamin A is important for bone health, but too much of it is associated with adverse effects on the bones. This is not likely to happen through diet alone. However, persons who take both a fish liver oil supplement and multivitamins with considerable amounts of vitamin A may face more risk for adverse health effects from excess vitamin A consumption.

Liver has vitamin A, which is very important for skin, teeth and eyes. However, consuming too much of it is unsafe for bone health. The UK's National Health Service advises people who eat liver regularly not to eat liver more than once a week. In addition, it is better to avoid cod liver oil and food containing retinol because it may increase the amount of vitamin A in the body.

7. Osteoporosis Treatment

Osteoporosis is a public health concern worldwide, causing significant disability. Despite its notable occurrence, exploring an effective treatment strategy is still challenging. Osteoporosis medications are capable of increasing bone density. Although the increase may seem slight, it positively reduces the rate of fractures [194]. In bone-targeted pharmacological therapy, anti-resorption agents, such as 1) bisphosphonates, 2) selective estrogen receptor modulators (SERMs),

receptor activators of nuclear factor-kB (RANK) ligand (RANKL) inhibitors, 4) anabolic medications, such as type 1 parathyroid hormone receptor (PTH1R) ligands, and 5) sclerostin inhibitors, have emerged with demonstrated efficacy in treating diseases characterized by abnormal bone remodeling.

7.1 Medications

In this review, the medications are classified according to their active ingredient.

7.1.1 Bisphosphonates

Bisphosphonates, available in tablets, should be taken daily, weekly, or monthly. They include alendronate and risedronate. In this category, one annual intravenous injection is zoledronic acid.

7.1.2 Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) such as raloxifene, which is administrated daily, similarly act on the bones to estrogen, reducing the rate of bone loss and reducing the risk of spinal fractures in postmenopausal women.

7.1.3 Monoclonal Antibodies

Monoclonal antibodies such as denosumab are administrated monthly by injection. Denosumab acts in a different mechanism than bisphosphonates but has a similar effect in slowing down bone fractures and reducing the risk of fractures.

7.1.4 Hormone Replacement Therapy

Hormone replacement therapy (HRT) uses drugs that have estrogen. Some of them also contain progestogen, called combined HRT. Even at low doses, HRT helps reduce the rate of bone loss, reducing the risk of OP and fractures in postmenopausal women. HRT is harmless and operative for most ladies under 60 years who have OP and need HRT to relieve menopausal symptoms. It might also be prescribed for women under 60 years of age who are incapable of taking other OP medications. It is beneficial for women who have experienced menopause before the age of 45. This therapy is more suitable for women over 60 years of age than other medications because of a slightly increased risk of cardiovascular diseases such as stroke and breast cancer.

7.1.5 Testosterone

Testosterone is resourceful for men at high risk for fracture with testosterone levels less than 200 ng/dl (6.9 nmol/l). This should be measured even for patients who lack standard indications for testosterone therapy but who have contraindications to other osteoporosis therapies [195]. Its side effects are cardiovascular and metabolic and rise in prostate-specific antigen.

7.1.6 Teriparatide

Teriparatide is a medication that is given through injection daily for 18 months. The injections can be self-administered by the patient. It stimulates osteoblasts, thereby improving bone structure and strength. It is only prescribed for people with severe conditions if other medications have not operated, and the risk of additional fractures is still very high. A specialist must prescribe it, which can only be used for eighteen months. At the end of the tri-parathyroid cycle, another medication should be on course to ensure the new bone is preserved and healed [31, 196-199]. Abaloparatide is also in this category.

7.1.7 Strontium Ranelate

Strontium ranelate (SrRan) is another drug. Strontium (Sr) is a trace element chemically close to calcium. The human body takes 4 mg Sr daily from leafy vegetables, grains, and dairy products. The body poorly absorbed it [4]. Most absorbed St is found in the skeleton, but its content is only 0.035% of the calcium content [5]. In the organism, Sr is possibly built into the crystals of biological apatite. It can produce carbonate, citrate, and lactate salts and bind with calcium-transporting proteins. Dissimilar with other medications, SrRan has several direct effects on bone cells, intensifying osteoblastogenesis while inhibiting osteoclastogenesis. Strontium ranelate administration shows amplification expression of key osteoblastogenesis genes by activating manifold signaling paths. These pathways promote the differentiation and proliferation of pre-osteoblasts and osteoblasts, which increases the bone formation rate and the synthesis of collagen and non-collagen proteins in the bone matrix [5]. At the same time, the mechanisms that prevent osteoblast apoptosis increase their survival, positively affecting bone formation. The resemblance of Sr and calcium proposes that particular processes occurred chiefly through the calcium-sensing receptor [200].

7.1.8 Salmon Calcitonin

Salmon calcitonin (after this, referred to as “calcitonin”) is an analog of human calcitonin used in the treatment of hypercalcemia, postmenopausal OP, and Paget’s disease of bone. Calcitonin directly inhibits the breakdown of calcium from bone. This effect is exerted by increasing the amount of cAMP in bone cells and, consequently, by disrupting the transport of calcium and phosphate through the plasma membrane of osteoclasts. It directly blocks the reabsorption of calcium, phosphate, and sodium into the renal tubules and, as a result, increases their excretion.

7.1.9 Beta Blockers

Beta adrenolytic medications are accompanied by reduced fracture risk [201] and higher BMD. Pharmacological β1- adrenolytic may deliver a small but significant increase in bone mass and thus support fracture prevention. Given the small effect size, β1- adrenolytic may be an insufficient treatment for OP, per se, but could represent a cost-effective and safe treatment for patients with osteopenia, particularly in light of recent evidence that increased SNS signaling contributes to a spectrum of bone-loss phenotypes. For many patients already using beta blockers, the comparatively small effect size may deliver considerable assistance over the long term on the population level. Careful assessment of β1- adrenolytic for age-related bone loss and other illnesses will answer the question of what is best for bone health and beyond in the elderly. Pharmacotherapy

is not the only choice for treating OP. Daily exercise, an appropriate diet plan that contains adequate calcium and vitamin D, quitting smoking, and warning related to drinking beverages containing ethanol are also important.

The bone-targeted medications can increase bone density in the buttocks and the spine by around 1-3% and 4-8% during the first 3-4 years of treatment, respectively. They can reduce spinal and pelvic fractures by nearly 30-70% and 30-50%, respectively.

7.2 Nanomedicine

One of the new strategies to improve the treatment of osteoporosis is the development of drug delivery systems based on nanomaterials. These nano pharmaceutical systems reduce toxicity and increase medicines' therapeutic efficacy and pharmacokinetic profile. So far, several nanoplatforms have been introduced for the treatment of osteoporosis. For example, double-layer hydroxides and silicate and graphene nanomaterials are emerging as significant candidates. Recently, a new nano-method based on nano-bubbles for the treatment of osteoporosis using cathepsin K has been introduced. Cathepsin K plays a vital role in the process of bone resorption. The nano-bubbles target osteoclast cells (bone cells that harbor the CTSK gene) and protect the siRNA from contacting the surrounding environment. In this method, the delivery system helps prolong the effectiveness of the process by reducing the speed of medicine distribution. The advantage of ultrasonically responsive nano-bubbles is that they act as a dual technology where ultrasound disrupts the bubbles, transfers genes, and even aids in bone growth.

From the point of view of commercialization of nanotechnologies related to osteoporosis, it should be said that many companies active in the field of nanosciences are developing diagnostic and treatment platforms for osteoporosis, including Nanox. The company develops artificial intelligence-based medical imaging tools to screen for early indicators of the disease. Nanox received FDA approval for its HealthOST device in 2022. This artificial intelligence tool measures low bone density and osteoporosis-related fractures. Reports indicate that this method is 90% accurate. Advances in nanoscience have led to the emergence of new techniques to improve the therapeutic properties of osteoporosis. The development of nano-carriers promises clinical applications to deliver medicines to bone tissues. These nanomedicines help to expand therapeutic opportunities, improve local medicine concentration, and reduce off-target negative effects. In this regard, research focused on the release, stability, and safety of the medicine, focusing on optimizing nano-carriers, is currently being carried out and supported.

7.3 Herbs

Some studies revealed that botanical agents or herbs effectively treat the disease [202]. While further related investigations are needed on the usefulness of herbs in treating OP, some herbs have been designated to treat OP and prevent bones from fractures [203]. Herbal treatment is helpful and slow; many patients are satisfied using them. They offer prevention and maintenance rather than over-active treatment [204].

Some useful herbs are studied here.

7.3.1 *Cimicifuga racemosa*

Cimicifuga racemosa is a perennial dicot of the Buttercup family native to the USA and the eastern half of Canada. It is also known as baneberry, black cohosh, black snakeroot, bugbane, and bug root. Data from the clinical trials proposed the beneficial effects of the herb on bone mineral density and metabolism [205]. Additionally, the investigators hint at the conceivable reduction of the cumulative dose of HRT for the prophylaxis of the disease in patients taking the herb [206].

It contains phytoestrogens that would help to stop OP. Phytoestrogens are polyphenolic compounds formed naturally in beans, cereals, flax seeds, hops, legumes, nuts, sesame seeds, and soybeans that might exert estrogenic activities. The two main composites are flavonoids and non-flavonoids. Isoflavones, coumestans, and prenylflavonoids belong to flavonoids, and lignans belong to non-flavonoids. A study showed that the herb was talented in promoting bone formation in mice.

7.3.2 *Drynaria fortunei*

The dried rhizome of Drynaria fortunei (Kunze) J. Sm., or Rhizoma Drynariae, is stated to prevent age-associated bone loss. It contains mostly flavonoids, glycosides, triterpenoids, and phenolic acids [142]. In animals whose ovaries were surgically excised, extract of this herb prevented estrogen deficiency-induced weight gain without an unfavorable effect on the uterus [143]. Moreover, it exerted a protective effect on bone, increasing trabecular number and bone fraction and decreasing trabecular separation in calcaneus bone. In vitro studies show that its extract inhibits RANK activity [143]. It has been stated that polysaccharides extracted from the herb showed an anti-osteoporotic effect in ovariectomized rats. It maintained trabecular microarchitecture and bone biomechanical properties and enhanced femoral and tibial bone mineral density [144].

7.3.3 *Elaeagnus angustifolia*

Elaeagnus angustifolia is a species of Elaeagnus native to Afghanistan, West and Central Asia, from southern Russia and Kazakhstan to Iran and Turkey. It is now extensively established in North America as a well-known species rich in folic acid and vitamin C. In addition, the fruit contains plant compounds that activate hormone receptors, thus preventing the loss of calcium during menopause in women. Consumption of elecampane powder with milk, which is rich in calcium, is very helpful in preventing the occurrence or progression of this disease and osteoarthritis. In addition, people should seek medical help if needed under the supervision of a specialist. Consumption of elecampane powder with milk, which is rich in calcium, is very helpful in preventing the development or progression of osteoporosis and osteoarthritis. Some clinical investigations on the analgesic and inflammatory effects of its fruit extract in osteoarthritis have shown a comparable effect of this extract with acetaminophen or ibuprofen [207]. It is also helpful for strengthening bones and can be mixed with milk or coconut milk.

7.3.4 *Glycine max L*

Glycine max L. is an annual plant from the Fabaceae family. It is a rich source of genistein, daidzein, biochanin A, and glycitein. Its other name is soybean. It also has proteins and grows mainly in Southwest Asia [202]. The aglycones and conjugate forms of genistein account for 60% of isoflavones and daidzein for up to 30% [208] in this herb. These estrogen-like compounds help the

bones from bone diseases and prevent bone loss. It is generally recommended that OP patients should consult with their physicians before using soy, especially if they have a high risk of estrogen-dependent breast cancer for some reason.

Soy foods have been part of old-style Asian cuisine for several years. Soy products have recently become public worldwide. Soy foodstuffs are also used as a healthy analog for meat and as a common food choice for vegetarians due to their high protein content. Varied types of soy foods include unfermented soy foods, for example, soy milk, tofu, whole soybeans, adamant, and fermented soy foodstuffs such as fermented bean paste, miso, natto, soy sauce, and tempeh.

7.3.5 *Sesamum indicum*

Sesame seeds (*Sesamum indicum* L.) contain calcium, magnesium, copper, zinc, manganese, phosphorus, and vitamins K and D [209].

7.3.6 *Trifolium pretense*

The red clover (*Trifolium pretense*) contains phytoestrogens. Since natural estrogen can help protect bones, this plant may help treat OP [210]. However, there is little scientific evidence that it is effective in slowing down bone loss. The compounds in it might upsurge the risk of bleeding during and after surgery. Therefore, it should be stopped no less than two weeks before a scheduled surgery. In hormone-sensitive conditions such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids, it might act like estrogen. Any condition that might be made worse by estrogen should not use red clover. Also, patients with protein S deficiency have a high risk of forming blood clots. There is some concern that the herb might increase the risk of clot formation in these patients because it seems that it has some estrogen-like effects. It may also slow the natural blood clotting process.

Phytoestrogens may interact with other medications and should not be appropriate for some persons. Birth control pills interact with it. It may have some of the same effects as estrogen. However, it is not as strong as the estrogen in birth control pills. Some birth control pills include ethinyl estradiol and levonorgestrel, ethinyl estradiol, and norethindrone. Taking it along with estrogen pills might decrease the effects of estrogen pills, such as conjugated equine estrogens, ethinyl estradiol, and estradiol.

Medications changed by the cytochrome P450 1A2 substrates such as amitriptyline, haloperidol, ondansetron, propranolol, theophylline, and verapamil interact with red clover. Other medications changed by the cytochrome P450 2C19 substrates interact with red clover, such as omeprazole, lansoprazole, pantoprazole, diazepam, carisoprodol, and nelfinavir. Medications changed by the Cytochrome P450 2C9 substrates interact with it, such as diclofenac, ibuprofen, meloxicam, and piroxicam; celecoxib; amitriptyline; warfarin; glipizide; and losartan. Also, medications changed by the Cytochrome P450 3A4 substrates interact with red clover, such as lovastatin, ketoconazole, itraconazole, fexofenadine, and triazolam.

Anticoagulant/antiplatelet medications interact with red clover. Taking considerable amounts of this herb might slow blood clotting. Taking it along with medications that also slow clotting, including NSAIDs such as aspirin, diclofenac, ibuprofen, naproxen, and other slow clotting medicines such as clopidogrel, dalteparin, enoxaparin, heparin, and warfarin might increase the risks of bleeding and bruising.

Some types of tumors are affected by estrogen levels in the body, such as estrogen-sensitive tumors. Tamoxifen is used as a medicine to help treat and prevent estrogen-sensitive tumors. Tamoxifen and red clover interact with each other. It seems the herb also affects estrogen levels in the human body. By affecting estrogen in the body, it may decrease the efficacy of tamoxifen.

In pregnant and breast-feeding women, taking this herb is likely safe when taken orally in amounts commonly found in food. However, it is likely unsafe when used in pharmacological doses. It acts like estrogen and may disturb hormone balances during pregnancy or breast-feeding.

7.3.7 *Labisia pumila*

Labisia pumila is native to Malaysia and belongs to the family Myrsinaceae. The water extract has shown bioactive chemicals, for example, anthocyanin, ascorbic acid, flavonoids, β-carotene, and phenolic acid, which have extensive antioxidant, anti-inflammatory, antimicrobial, and antifungal properties. The superior antioxidant activity in the herb is related to its high phenolic and flavonoid compounds. The herb is used for the treatment of painful menstruation and disorders of sexual life in females due to its oestrogenic properties in Malaysia. As a phytoestrogen-containing herb, it is also a treatment approach in patients with OP.

7.3.8 *Eurycoma longifolia*

Eurycoma longifolia Jack, or tongkat ali, is a flowering plant of the family Simaroubaceae. The herb is native to Indonesia, Malaysia, Vietnam, Cambodia, Myanmar, Laos and Thailand. In these countries, the herb is one of the well-known folk medicines for aphrodisiac effects in addition to intermittent fever and malaria. Decoctions of its leaves are used for washing itches, while its fruits are used in curing dysentery. Its bark is used as a vermifuge, while the taproots are used to control hypertension, and the root barks are used to treat diarrhea and fever. Mostly, the root extract is used as a folk medicine for sexual dysfunction, aging, aches, constipation, exercise recovery, malaria, cancer, DM, anxiety, fever, increased energy and strength, leukemia, OP, stress, syphilis, and glandular swelling. The herb's roots are also used as an aphrodisiac, antibiotic, appetite stimulant, and health supplement. The herb has various classes of bioactive chemicals like quassinoids, canthin-6-one alkaloids, β-carboline alkaloids, triterpene tirucallane type, squalene derivatives, and biphenyl neolignan, eurycolactone, laurycolactone, and eurycomalactone, and bioactive steroids. Among these phytoconstituents, quassinoids account for most herb-root phytochemicals [211].

For other valuable herbs, see Table 5.

Table 5 Summary of anti-osteoporotic and important properties of herbs.

Scientific name	Plant parts	Relevant ethnomedical uses	Ref.
Achyranthes bidentata Blume	Root	Bone related diseases	[212, 213]
Berberis aristata DC	Stem bark	Menopausal disorders, OP	[214]
Butea monosperma (L.) Kuntze	Stem bark	Bone fracture	[215]
Cissus quadrangularis L.	Aerial parts, root	Hemorrhoids, menstrual disorders, scurvy, flatulence, bone fractures & diseases	[216-218]

Cuscuta chinensis Lam.	Seed	Sexual dysfunction, OP, senescence	[219, 220]
Davallia formosana Hayata	Rhizome	Bone diseases, OP	[221]
Dipsacus asperoides C. Y. Cheng et T. M. Ai	Root	Bone fractures, traumatic ecchymoma, injury of muscles	[222, 223]
Drynaria fortunei (Kunze) J. Sm.	Rhizome	Joint diseases, bone fractures	[224-228]
Epimedium brevicornu Maxim *Epimedium koreanum* Nakai *Epimedium pubescens* Maxim *Epimedium sagittatum* (Sieb. et Zucc.)	Leaf Leaf Leaf Leaf	Hypertension, impotence, prospermia, hyperdiuresis, OP, menopause syndrome, RA, and chronic tracheitis	[229-239]
Glycine max (Linn.) Merr.	Seed	Cardiovascular diseases, cancer, OP, renal dysfunction	[240-246]
Heimia myrtifolia Cham.	Leaf	OP	[247]
Lepidium meyenii Walp.	Root	Hot flushes, tender breast, vaginal dryness, OP	[248, 249]
Linum usitatissimum L.	Seed	Postmenopausal osteoporosis	[250-253]
Psoralea corylifolia L.	Fruit	Bone fracture, OP & osteomalacia	[254-257]
Panax notoginseng (Burk.) F. H. Chen	Root	Trauma, injury of muscles, bone fracture	[258, 259]
Salvia miltiorrhiza Bunge (also known as ‘dan shen’ or ‘red sage root’)	Root	Cardio-cerebral diseases, prevents the decrease in trabecular bone mass and bone mineral density	[260]
Sambucus williamsii Hance	Stem	Bone fractures, joint diseases, inflammation,	[261]
Ulmus wallichiana Planch.	Bark	Bone fractures	[262-265]

7.4 Natural Remedies

The goal of using natural remedies is to control and treat OP without the use of medications. However, these should be done under specialist and trained supervision. Osteoporosis is currently treated with various natural remedies [162]. Other remedies include coriander tea, almond milk, nettle tea, turmeric, nettle, fennel, and eggshell concoction. Pour a tablespoon of turmeric, 2 tablespoons of each nettle and fennel plant, and a tablespoon of eggshell jam into three cups of boiling water and infuse for 10 minutes. A tablespoon of honey would be added when consuming it. The amount of this potion is three times a day. This combination should be used for a week. To prepare a sesame concoction, add a teaspoon of roasted seeds to a cup of warm milk and drink this mixture twice a day. Another remedy is powdered elm with skin, flesh, and core (complete elm powder). Another remedy is one to two glasses of celery juice. Luteolin is a flavonoid. It originates in celery, green pepper, parsley, perilla leaf and seeds, and chamomile. The active compound has anti-inflammatory effects, inhibits osteoclast differentiation, and protects against OVX-induced bone loss [266].

Honey has promising helpful effects in stopping OP due to its high concentration of antioxidant and anti-inflammatory compounds. Several types of honey have been given away to prevent bone

loss in various animal models [267]. Cow's milk with honey is a useful remedy. Consuming 7 almond nuts in the evening [268], consuming 21 raisins daily in the morning fasting, and beets with leaves in soup or stew are also useful. Calf thigh bone and mutton are healing diets after bone fracture. Momenia, or Momijo medicine, which traditional Iranian physicians have considered, is a blackish-brown substance spontaneously found in cracks and fractures adjacent to underground oil reserves in the highlands.

Chamomile tea promotes bone repair and growth [269]. This result may be predominantly effective for females who are prone to the disease after menopause, estrogen depletion, and bone loss. The results of an investigation showed that the body identifies chamomile as being almost like estrogen and that chamomile may have the ability to stimulate bone-forming cells. However, more research needs to be done [269].

Consuming Ardeh or Tahini (100% crushed sesame seeds), 3 tablespoons in combination with grape juice at breakfast is also recommended [270, 271]. Ardeh is also named fermented sesame. To make sesame seeds, sesame seeds are first soaked after collection so that the thin black or brown skin can be easily removed. The white, peeled sesame seeds are then crushed in a mill to form relatively loose dough called Ardeh. Raw or toasted sesame seeds are easy to sprinkle onto dishes, or people can use sesame seed oil or tahini in various recipes. People with a sesame allergy background must avoid any foodstuffs containing sesame in any form, including sesame seeds, sesame oil, and tahini. A tablespoon of raw sesame jam with dinner, curd with mint, walnut, and dates, a traditional Iranian food, is also useful. Curd is made by concentrating or drying the buttermilk after buttering or from nonfat yogurt. Eating foods rich in calcium and phosphorus, such as curd and dates, is the best food to protect bones.

Walnuts have nutritional properties and are a valuable source of protein, healthy fats, fiber, plant sterols, and many vitamins and minerals. Just 30 grams of walnut provide 100% of your daily omega-3 needs. The vitamins in walnuts include vitamin C, thiamine, riboflavin, niacin, pantothenic acid, vitamin B_6, folic acid, and vitamins B_{12}, E, K, and A. Walnuts also include beta-carotene, lutein and xanthine. Walnuts are also rich in calcium, copper, iron, magnesium, manganese, phosphorus, potassium, selenium, and zinc source. Walnuts, like other nuts, are high in fiber and protein. After all, walnut tastes good. It can be eaten as a healthy snack or with breakfast cereals, oats, smoothies, or salads. Walnut cakes and biscuits are popular.

Barberry root decoction daily in a glass is also useful [272].

7.5 Physiotherapy

Physiotherapy intervention for patients with OP or reduced bone density should include the following. Weight training, exercise flexibility, endurance exercise, situational practice, and balance practice. Considerable attention and care must be taken before manual procedures such as manipulations or joint assessments that may increase fracture risk in patients, especially in the spine.

Treadmill exercises are not recommended for people with severe OP or fractures of the lower limbs, pelvis, or ribs.

7.6 Exercise

Regular exercise, apart from its many benefits for other parts of the body, especially the bone, will make it stronger and stronger. Like calcium and vitamin D, adequate consumption, and other principles of proper nutrition, standing exercise can significantly increase bone density. Standing exercises can strain the body's weight, the bones of the spine, the pelvis, and the lower limbs. Stress on the bone is one of the most important factors in strengthening it. The bone becomes stronger where more force and tension are applied, and if no force or tension is applied to it, it gradually loses density. This is why people who rest in bed for a long time due to chronic illness or those who are in a state of weightlessness in space for a long time suffer from this disease. The important fact is that sports in which little weight is applied to the bones (such as swimming) will not significantly increase their density. Walking and running, tennis, basketball, mountaineering, and weightlifting are sports that increase bone density. Standing exercises strengthen bones; at least half an hour of exercise daily is essential. This period should be longer in adolescents and children. Lack of physical activity during childhood and adolescence causes the bones not to be strong enough, and these not-so-strong bones will certainly develop earlier in old age. Standing exercises are important in old age, and without them, OP progresses rapidly.

7.7 Magnetic Therapy

Supportive therapy to maintain bone tissue quality and reduce pain in patients with OP includes low-frequency pulse bio-magnetic therapy, which aids metabolic processes in the bones and leads to better cooperation of bone-building agents and a significant reduction in pain. In patients with OP, magnetic therapy speeds up the healing process, as it stimulates the formation of new bone (accelerates bone formation and calcification) and increases sensitivity to PTH. The analgesic frequencies of 4 to 6 Hz are applied first, and when the pain subsides, therapeutic frequencies in the 36 to 44 Hz range can be performed.

8. Conclusion

Osteoporosis is a skeletal disease that occurs mainly in geriatrics. Its characteristic feature is a reduction in bone mass and strength with aging, putting men and women at risk of bone fractures. It appears less often in men than in women because they have stronger and larger bones, their bone loss initiates later and develops more slowly, and they have no period of rapid hormonal change and bone loss. Women above 65 should be asked for a bone density scan. In addition to producing fractures, this disease leads to severe mental disorders, disabilities, and financial consequences. The disease has many risk factors. Referral of patients to experienced physicians is a beneficial recommendation. Educating patients is crucial because many are unaware of the severe consequences of the disease. Early prevention can help reduce the high complications. Patients are asked to balance their lifestyle, take prescribed medications, quit smoking, and abstain from alcohol. The nutritionist must suggest to the patient a diet rich in calcium and the need to take vitamin D supplements and other necessary nourishments and vitamins. Herbs and natural remedies should be taken under specialist supervision. Attending a physiotherapy schedule is recommended for exercising and participating in a supervised activities program.

Author Contributions

The author did all the research work of this study.

Competing Interests

The author has declared that no competing interests exist.

References

1. Sheng B, Li X, Nussler AK, Zhu S. The relationship between healthy lifestyles and bone health: A narrative review. Medicine. 2021; 100: e24684.
2. Porter JL, Varacallo M. Osteoporosis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
3. Johnell O, Kanis J. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006; 17: 1726-1733.
4. Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA. Race and sex differences in mortality following fracture of the hip. Am J Public Health. 1992; 82: 1147-1150.
5. Boskey AL, Coleman R. Aging and bone. J Dent Res. 2010; 89: 1333-1348.
6. Boskey AL, Imbert L. Bone quality changes associated with aging and disease: A review. Ann N Y Acad Sci. 2017; 1410: 93-106.
7. Berger C, Goltzman D, Langsetmo L, Joseph L, Jackson S, Kreiger N, et al. Peak bone mass from longitudinal data: Implications for the prevalence, pathophysiology, and diagnosis of osteoporosis. J Bone Miner Res. 2010; 25: 1948-1957.
8. Baxter-Jones AD, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: An estimation of peak bone mass. J Bone Miner Res. 2011; 26: 1729-1739.
9. Zhu X, Zheng H. Factors influencing peak bone mass gain. Front Med. 2021; 15: 53-69.
10. Openstax. 6.6 Exercise, nutrition, hormones, and bone tissue [Internet]. Houston, TX: Openstax; 2017. Available from: https://openstax.org/books/anatomy-and-physiology/pages/6-6-exercise-nutrition-hormones-and-bone-tissue.
11. Cao S, Wang Z, Li C, Wang Q. The effect of whole-body vibration exercise on postmenopausal women with osteoporosis: A protocol for systematic review and meta-analysis. Medicine. 2021; 100: e25606.
12. ElDeeb AM, Abdel-Aziem AA. Effect of whole-body vibration exercise on power profile and bone mineral density in postmenopausal women with osteoporosis: A randomized controlled trial. J Manipulative Physiol Ther. 2020; 43: 384-393.
13. Weber-Rajek M, Mieszkowski J, Niespodziński B, Ciechanowska K. Whole-body vibration exercise in postmenopausal osteoporosis. Prz Menopauzalny. 2015; 14: 41-47.
14. Sandhu SK, Hampson G. The pathogenesis, diagnosis, investigation and management of osteoporosis. J Clin Pathol. 2011; 64: 1042-1050.
15. Greendale GA, Sowers M, Han W, Huang MH, Finkelstein JS, Crandall CJ, et al. Bone mineral density loss in relation to the final menstrual period in a multiethnic cohort: Results from the Study of Women's Health Across the Nation (SWAN). J Bone Miner Res. 2012; 27: 111-118.

16. Barnsley J, Buckland G, Chan PE, Ong A, Ramos AS, Baxter M, et al. Pathophysiology and treatment of osteoporosis: Challenges for clinical practice in older people. Aging Clin Exp Res. 2021; 33: 759-773.
17. Colangelo L, Biamonte F, Pepe J, Cipriani C, Minisola S. Understanding and managing secondary osteoporosis. Expert Rev Endocrinol Metab. 2019; 14: 111-122.
18. Lee RH, Lyles KW, Colón-Emeric C. A review of the effect of anticonvulsant medications on bone mineral density and fracture risk. Am Geriatr Pharmacother. 2010; 8: 34-46.
19. Chawla A, Wang C, Patton C, Murray M, Punekar Y, de Ruiter A, et al. A review of long-term toxicity of antiretroviral treatment regimens and implications for an aging population. Infect Dis Ther. 2018; 7: 183-195.
20. Waqas K, Ferreira JL, Tsourdi E, Body JJ, Hadji P, Zillikens MC. Updated guidance on the management of cancer treatment-induced bone loss (CTIBL) in pre-and postmenopausal women with early-stage breast cancer. J Bone Oncol. 2021; 28: 100355.
21. Kulak CA, Borba VZ, Kulak Júnior J, Custódio MR. Bone disease after transplantation: Osteoporosis and fractures risk. Arq Bras Endocrinol Metabol. 2014; 58: 484-492.
22. Wang W, Gao Y, Liu H, Feng W, Li X, Guo J, et al. Eldecalcitol, an active vitamin D analog, effectively prevents cyclophosphamide-induced osteoporosis in rats. Exp Ther Med. 2019; 18: 1571-1580.
23. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: Pathogenesis and management. J Clin Oncol. 2000; 18: 1570-1593.
24. Panday K, Gona A, Humphrey MB. Medication-induced osteoporosis: Screening and treatment strategies. Ther Adv Musculoskelet Dis. 2014; 6: 185-202.
25. di Munno O, Mazzantini M, Sinigaglia L, Bianchi G, Minisola G, Muratore M, et al. Effect of low dose methotrexate on bone density in women with rheumatoid arthritis: Results from a multicenter cross-sectional study. J Rheumatol. 2004; 31: 1305-1309.
26. Uehara RI, Suzuki YA, Ichikawa YO. Methotrexate (MTX) inhibits osteoblastic differentiation in vitro: Possible mechanism of MTX osteopathy. J Rheumatol. 2001; 28: 251-256.
27. Torstensson M, Leth-Møller K, Andersson C, Torp-Pedersen C, Gislason GH, Holm EA. Danish register-based study on the association between specific antipsychotic drugs and fractures in elderly individuals. Age Ageing. 2017; 46: 258-264.
28. Xiao F, Qu X, Zhai Z, Jiang C, Li H, Liu X, et al. Association between loop diuretic use and fracture risk. Osteoporos Int. 2015; 26: 775-784.
29. Paik JM, Rosen HN, Gordon CM, Curhan GC. Diuretic use and risk of vertebral fracture in women. Am J Med. 2016; 129: 1299-1306.
30. Lee TH, Song YJ, Kim H, Sung YK, Cho SK. Intervention thresholds for treatment in patients with glucocorticoid-induced osteoporosis: Systematic review of guidelines. J Bone Metab. 2020; 27: 247-259.
31. Dore RK. Long-term safety, efficacy, and patient acceptability of teriparatide in the management of glucocorticoid-induced osteoporosis. Patient Preference Adherence. 2013; 7: 435-446.
32. Chotiyarnwong P, McCloskey EV. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. Nat Rev Endocrinol. 2020; 16: 437-447.
33. Dennison E, Cooper C. Epidemiology of glucocorticoid-induced osteoporosis. Front Horm Res. 2002; 30: 121-126.

34. Signorelli SS, Scuto S, Marino E, Giusti M, Xourafa A, Gaudio A. Anticoagulants and osteoporosis. Int J Mol Sci. 2019; 20: 5275.
35. Mohamad NV, Ima-Nirwana S, Chin KY. The skeletal effects of gonadotropin-releasing hormone antagonists: A concise review. Endocr Metab Immune Disord Drug Targets. 2021; 21: 1713-1720.
36. Sharafeldeen M, Elsaqa M, Sameh W, Elabbady A. Effect on bone mineral density in surgical versus medical castration for metastatic prostate cancer. Turk J Urol. 2021; 47: 120-124.
37. Sathe A, Gerriets V. Medroxyprogesterone. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
38. Delitala AP, Scuteri A, Doria C. Thyroid hormone diseases and osteoporosis. J Clin Med. 2020; 9: 1034.
39. de Vries F, Bruin M, Lobatto DJ, Dekkers OM, Schoones JW, van Furth WR, et al. Opioids and their endocrine effects: A systematic review and meta-analysis. J Clin Endocrinol Metab. 2020; 105: 1020-1029.
40. Briganti SI, Naciu AM, Tabacco G, Cesareo R, Napoli N, Trimboli P, et al. Proton pump inhibitors and fractures in adults: A critical appraisal and review of the literature. Int J Endocrinol. 2021; 2021: 8902367.
41. Gorgas MQ, Torres F, Vives R, Lopez-Rico I, Capella D, Pontes C. Effects of selective serotonin reuptake inhibitors and other antidepressant drugs on the risk of hip fracture: A case–control study in an elderly Mediterranean population. Eur J Hosp Pharm. 2021; 28: 28-32.
42. Blau JE, Taylor SI. Adverse effects of SGLT2 inhibitors on bone health. Nat Rev Nephrol. 2018; 14: 473-474.
43. Kumari C, Yagoub G, Ashfaque M, Jawed S, Hamid P. Consequences of diabetes mellitus in bone health: Traditional review. Cureus. 2021; 13: e13820.
44. Khanra D, Mukherjee A, Deshpande S, Khan H, Kathuria S, Kella D, et al. A network meta-analysis comparing osteoporotic fracture among different direct oral anticoagulants and vitamin K antagonists in patients with atrial fibrillation. J Bone Metab. 2021; 28: 139-150.
45. Yokoyama S, Wakamoto S, Tanaka Y, Nakagawa C, Hosomi K, Takada M. Association between antipsychotics and osteoporosis based on real-world data. Ann Pharmacother. 2020; 54: 988-995.
46. Jacquot J, Delion M, Gangloff S, Braux J, Velard F. Bone disease in cystic fibrosis: New pathogenic insights opening novel therapies. Osteoporos Int. 2016; 27: 1401-1412.
47. Dolan AL, Arden NK, Grahame R, Spector TD. Assessment of bone in Ehlers Danlos syndrome by ultrasound and densitometry. Ann Rheum Dis. 1998; 57: 630-633.
48. Hughes D, Mikosch P, Belmatoug N, Carubbi F, Cox T, Goker-Alpan O, et al. Gaucher disease in bone: From pathophysiology to practice. J Bone Miner Res. 2019; 34: 996-1013.
49. Jacoby JT, Bento dos Santos B, Nalin T, Colonetti K, Farret Refosco L, FM de Souza C, et al. Bone mineral density in patients with hepatic glycogen storage diseases. Nutrients. 2021; 13: 2987.
50. Minarich LA, Kirpich A, Fiske LM, Weinstein DA. Bone mineral density in glycogen storage disease type Ia and Ib. Genet Med. 2012; 14: 737-741.
51. Powell LW, Seckington RC, Deugnier Y. Haemochromatosis. Lancet. 2016; 388: 706-716.
52. Weber DR, Coughlin C, Brodsky JL, Lindstrom K, Ficicioglu C, Kaplan P, et al. Low bone mineral density is a common finding in patients with homocystinuria. Mol Genet Metab. 2016; 117: 351-354.

53. Villa-Suárez JM, García-Fontana C, Andújar-Vera F, González-Salvatierra S, de Haro-Muñoz T, Contreras-Bolívar V, et al. Hypophosphatasia: A unique disorder of bone mineralization. Int J Mol Sci. 2021; 22: 4303.
54. Salik I, Rawla P. Marfan Syndrome. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
55. Ramani PK, Parayil Sankaran B. Menkes kinky hair disease. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
56. El-Gazzar A, Högler W. Mechanisms of bone fragility: From osteogenesis imperfecta to secondary osteoporosis. Int J Mol Sci. 2021; 22: 625.
57. Lo SS. Prevalence of osteoporosis in elderly women in Hong Kong. Osteoporos Sarcopenia. 2021; 7: 92-97.
58. Neeleman RA, Wensink D, Wagenmakers MA, Mijnhout GS, Friesema EC, Langendonk JG. Diagnostic and therapeutic strategies for porphyrias. Neth J Med. 2020; 78: 149-160.
59. Bertelloni S, Baroncelli GI, Federico G, Cappa M, Lala R, Saggese G. Altered bone mineral density in patients with complete androgen insensitivity syndrome. Horm Res Paediatr. 1998; 50: 309-314.
60. Brotman AW, Stern TA. Osteoporosis and pathologic fracture in anorexia nervosa. Am J Psychiatry. 1985; 142: 495-496.
61. Gibson JH, Mitchell A, Reeve J, Harries MG. Treatment of reduced bone mineral density in athletic amenorrhea: A pilot study. Osteoporos Int. 1999; 10: 284-289.
62. Andereggen L, Frey J, Andres RH, Luedi MM, Widmer HR, Beck J, et al. Persistent bone impairment despite long-term control of hyperprolactinemia and hypogonadism in men and women with prolactinomas. Sci Rep. 2021; 11: 5122.
63. Mazziotti G, Frara S, Giustina A. Pituitary diseases and bone. Endocr Rev. 2018; 39: 440-488.
64. Okeke TC, Anyaehie UB, Ezenyeaku CC. Premature menopause. Ann Med Health Sci Res. 2013; 3: 90-95.
65. Thomas-Teinturier C, El Fayech C, Oberlin O, Pacquement H, Haddy N, Labbé M, et al. Age at menopause and its influencing factors in a cohort of survivors of childhood cancer: Earlier but rarely premature. Hum Reprod. 2013; 28: 488-495.
66. Augoulea A, Zachou G, Lambrinoudaki I. Turner syndrome and osteoporosis. Maturitas. 2019; 130: 41-49.
67. Nour MA, Perry RJ. Current concepts surrounding bone health and osteoporosis in Turner syndrome. Expert Rev Endocrinol Metab. 2014; 9: 515-524.
68. Landin-Wilhelmsen K, Bryman I, Windh M, Wilhelmsen L. Osteoporosis and fractures in Turner syndrome-importance of growth promoting and oestrogen therapy. Clin Endocrinol. 1999; 51: 497-502.
69. Rubin K. Turner syndrome and osteoporosis: Mechanisms and prognosis. Pediatrics. 1998; 102: 481-485.
70. Hiéronimus S, Lussiez V, Le Duff F, Ferrari P, Bständig B, Fénichel P. Klinefelter's syndrome and bone mineral density: Is osteoporosis a constant feature? Ann Endocrinol. 2011; 72: 14-18.
71. Ferlin A, Schipilliti M, Di Mambro A, Vinanzi C, Foresta C. Osteoporosis in Klinefelter's syndrome. Mol Hum Reprod. 2010; 16: 402-410.
72. Horowitz M, Wishart JM, O'Loughlin PD, Morris HA, Needt AG, Nordin BE. Osteoporosis and Klinefelter's syndrome. Clin Endocrinol. 1992; 36: 113-118.

73. Zhao LJ, Jiang H, Papasian CJ, Maulik D, Drees B, Hamilton J, et al. Correlation of obesity and osteoporosis: Effect of fat mass on the determination of osteoporosis. J Bone Miner Res. 2008; 23: 17-29.
74. Stachowska B, Halupczok-Żyła J, Bolanowski M. Decreased trabecular bone score in patients with active endogenous Cushing's syndrome. Front Endocrinol. 2021; 11: 593173.
75. Wongdee K, Charoenphandhu N. Osteoporosis in diabetes mellitus: Possible cellular and molecular mechanisms. World J Diabetes. 2011; 2: 41-48.
76. Utiger RD. When tiny glands cause big problems. Kidney stones or osteoporosis may signal hyperparathyroidism, a disease that disrupts the distribution of calcium in the body. Health News. 2003; 9: 5.
77. Reddy PA, Harinarayan CV, Sachan A, Suresh V, Rajagopal G. Bone disease in thyrotoxicosis. Indian J Med Res. 2012; 135: 277-286.
78. Wartofsky L. Bone disease in thyrotoxicosis. Hosp Pract. 1994; 29: 69-80.
79. Duerksen DR, Lix LM, Johansson H, McCloskey EV, Harvey NC, Kanis JA, et al. Fracture risk assessment in celiac disease: A registry-based cohort study. Osteoporos Int. 2021; 32: 93-99.
80. Heikkilä K, Pearce J, Mäki M, Kaukinen K. Celiac disease and bone fractures: A systematic review and meta-analysis. J Clin Endocrinol Metab. 2015; 100: 25-34.
81. Elaine WY, Kim SC, Sturgeon DJ, Lindeman KG, Weissman JS. Fracture risk after Roux-en-Y gastric bypass vs adjustable gastric banding among medicare beneficiaries. JAMA Surg. 2019; 154: 746-753.
82. Yu EW, Lee MP, Landon JE, Lindeman KG, Kim SC. Fracture risk after bariatric surgery: Roux-en-Y gastric bypass versus adjustable gastric banding. J Bone Miner Res. 2017; 32: 1229-1236.
83. Seo HS, Na Y, Jung J. Analysis of the occurrence of diseases following gastrectomy for early gastric cancer: A nationwide claims study. J Gastric Cancer. 2021; 21: 279-297.
84. Osataphan S, Patti ME. Trim the gut, lose the weight—and the bone. J Clin Investig. 2019; 129: 2184-2186.
85. Bravenboer N, Oostlander AE, Van Bodegraven AA. Bone loss in patients with inflammatory bowel disease: Cause, detection and treatment. Curr Opin Gastroenterol. 2021; 37: 128-134.
86. Sipponen P, Härkönen M. Hypochlorhydric stomach: A risk condition for calcium malabsorption and osteoporosis? Scand J Gastroenterol. 2010; 45: 133-138.
87. Chaudhary A, Domínguez-Muñoz JE, Layer P, Lerch MM. Pancreatic exocrine insufficiency as a complication of gastrointestinal surgery and the impact of pancreatic enzyme replacement therapy. Dig Dis. 2020; 38: 53-68.
88. Glass LM, Su GL. Metabolic bone disease in primary biliary cirrhosis. Gastroenterol Clin North Am. 2016; 45: 333-343.
89. Wang H, Bai X. Mechanisms of bone remodeling disorder in hemophilia. Semin Thromb Hemost. 2021; 47: 43-52.
90. Rajakumar SA, Danska JS. Bad to the bone: B cell acute lymphoblastic leukemia cells mediate bone destruction. Mol Cell Oncol. 2021; 8: 1835423.
91. Bryant ML, Worthington MA, Parsons K. Treatment of osteoporosis/osteopenia in pediatric leukemia and lymphoma. Ann Pharmacother. 2009; 43: 714-720.
92. Cabanillas ME, Lu H, Fang S, Du XL. Elderly patients with non-Hodgkin lymphoma who receive chemotherapy are at higher risk for osteoporosis and fractures. Leuk Lymphoma. 2007; 48: 1514-1521.

93. Chauhan S, Varma S, Tahlan A, Sachdev A, Singh KK, Jaiparkash MP, et al. Osteoporosis-An unusual presentation of T-cell lymphoma. Am J Hematol. 2007; 82: 85-86.
94. Kaseb H, Annamaraju P, Babiker HM. Monoclonal gammopathy of undetermined significance. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
95. Pop V, Parvu A, Craciun A, Farcas AD, Tomoaia G, Bojan A. Modern markers for evaluating bone disease in multiple myeloma. Exp Ther Med. 2021; 22: 1329.
96. Al Farii H, Zhou S, Albers A. Management of osteomyelitis in sickle cell disease. J Am Acad Orthop Surg Glob Res Rev. 2020; 4: e20.00002-10.
97. Pardanani A. Systemic mastocytosis in adults: 2021 Update on diagnosis, risk stratification and management. Am J Hematol. 2021; 96: 508-525.
98. Wong P, Fuller PJ, Gillespie MT, Milat F. Bone disease in thalassemia: A molecular and clinical overview. Endocr Rev. 2016; 37: 320-346.
99. Hinze AM, Louie GH. Osteoporosis management in ankylosing spondylitis. Curr Treat Options Rheumatol. 2016; 2: 271-282.
100. Abdulkhaliq A, Cheikh M, Almuntashri F, Alzahrani H, Nadwi H, Kadi E, et al. A comparison of demographics, disease activity, disability, and treatment among rheumatoid arthritis patients with and without osteoporosis. Open Access Rheumatol. 2021; 13: 275-283.
101. Li L, Xie H, Lu N, Esdaile JM, Aviña-Zubieta JA. Impact of systemic lupus erythematosus on the risk of newly diagnosed hip fracture: A general population-based study. Arthritis Care Res. 2021; 73: 259-265.
102. Pack AM, Morrell MJ. Adverse effects of antiepileptic drugs on bone structure: Epidemiology, mechanisms and therapeutic implications. CNS Drugs. 2001; 15: 633-642.
103. Fitzpatrick LA. Pathophysiology of bone loss in patients receiving anticonvulsant therapy. Epilepsy Behav. 2004; 5: 3-15.
104. Dobson R, Ramagopalan S, Giovannoni G. Bone health and multiple sclerosis. Mult Scler J. 2012; 18: 1522-1528.
105. Iolascon G, Paoletta M, Moretti A. Neuromuscular diseases and bone. Front Endocrinol. 2019; 10: 794.
106. Figueroa CA, Rosen CJ. Parkinson's disease and osteoporosis: Basic and clinical implications. Expert Rev Endocrinol Metab. 2020; 15: 185-193.
107. Thakkar P, Prakash NB, Tharion G, Shetty S, Paul TV, Bondu J, et al. Evaluating bone loss with bone turnover markers following acute spinal cord injury. Asian Spine J. 2020; 14: 97-105.
108. Voor MJ, Brown EH, Xu Q, Waddell SW, Burden Jr RL, Burke DA, et al. Bone loss following spinal cord injury in a rat model. J Neurotrauma. 2012; 29: 1676-1682.
109. Carda S, Cisari C, Invernizzi M, Bevilacqua M. Osteoporosis after stroke: A review of the causes and potential treatments. Cerebrovasc Dis. 2009; 28: 191-200.
110. Emerson B, Haden M. A public health based vision for the management and regulation of opioids. Int J Drug Policy. 2021; 91: 103201.
111. Panayiotopoulos A, Bhat N, Bhangoo A. Bone and vitamin D metabolism in HIV. Rev Endocr Metab Disord. 2013; 14: 119-125.
112. Ofotokun I, Weitzmann MN. HIV and bone metabolism. Discov Med. 2011; 11: 385-393.
113. Miller PD. Unrecognized and unappreciated secondary causes of osteoporosis. Endocrinol Metab Clin North Am. 2012; 41: 613-628.

114. Zhang L, Sun Y. Muscle-bone crosstalk in chronic obstructive pulmonary disease. Front Endocrinol. 2021; 12: 724911.
115. Xing W, Lv X, Gao W, Wang J, Yang Z, Wang S, et al. Bone mineral density in patients with chronic heart failure: A meta-analysis. Clin Interv Aging. 2018; 13: 343-353.
116. Xie L, Hu X, Li W, Ouyang Z. A retrospective study of end-stage kidney disease patients on maintenance hemodialysis with renal osteodystrophy-associated fragility fractures. BMC Nephrol. 2021; 22: 23.
117. Leslie SW, Sajjad H. Hypercalciuria. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
118. Dayer R, Haumont T, Belaieff W, Lascombes P. Idiopathic scoliosis: Etiological concepts and hypotheses. J Child Orthop. 2013; 7: 11-16.
119. Kovvuru K, Kanduri SR, Vaitla P, Marathi R, Gosi S, Anton DF, et al. Risk factors and management of osteoporosis post-transplant. Medicina. 2020; 56: 302.
120. Park SB, Kim J, Jeong JH, Lee JK, Chin DK, Chung CK, et al. Prevalence and incidence of osteoporosis and osteoporotic vertebral fracture in Korea: Nationwide epidemiological study focusing on differences in socioeconomic status. Spine. 2016; 41: 328-336.
121. Rizzato G. Clinical impact of bone and calcium metabolism changes in sarcoidosis. Thorax. 1998; 53: 425-429.
122. Papageorgiou M, Kerschan-Schindl K, Sathyapalan T, Pietschmann P. Is weight loss harmful for skeletal health in obese older adults? Gerontology. 2020; 66: 2-14.
123. Xu Y, Ye J, Zhou D, Su L. Research progress on applications of calcium derived from marine organisms. Sci Rep. 2020; 10: 18425.
124. Coxam V. Current data with inulin-type fructans and calcium, targeting bone health in adults. J Nutr. 2007; 137: 2527S-2533S.
125. He B, Lyu Q, Yin L, Zhang M, Quan Z, Ou Y. Depression and osteoporosis: A Mendelian randomization study. Calcif Tissue Int. 2021; 109: 675-684.
126. Wu Q, Liu J, Gallegos-Orozco JF, Hentz JG. Depression, fracture risk, and bone loss: A meta-analysis of cohort studies. Osteoporos Int. 2010; 21: 1627-1635.
127. Reginster JY, Rabenda V. Patient preference in the management of postmenopausal osteoporosis with bisphosphonates. Clin Interv Aging. 2006; 1: 415-423.
128. Svedbom A, Hernlund E, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: A compendium of country-specific reports. Arch Osteoporos. 2013; 8: 137.
129. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: Medical management, epidemiology and economic burden: A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013; 8: 136.
130. Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Miner Res. 2014; 29: 2520-2526.
131. Looker AC, Fan B, Shepherd JA. FRAX-based estimates of 10-year probability of hip and major osteoporotic fracture among adults aged 40 and over: United States, 2013 and 2014. HHS, CDC, NCHS; 2017; 103.

132. Bartl R, Bartl C. The Osteoporosis manual: Prevention, diagnosis and management. Cham, Switzerland: Springer International Publishing; 2019.
133. Shetty S, John B, Mohan S, Paul TV. Vertebral fracture assessment by dual-energy X-ray absorptiometry along with bone mineral density in the evaluation of postmenopausal osteoporosis. Arch Osteoporos. 2020; 15: 25.
134. Wade SW, Strader C, Fitzpatrick LA, Anthony MS, O'Malley CD. Estimating prevalence of osteoporosis: Examples from industrialized countries. Arch Osteoporos. 2014; 9: 182.
135. Kimlin MG. Geographic location and vitamin D synthesis. Mol Aspects Med. 2008; 29: 453-461.
136. Kimlin MG, Olds WJ, Moore MR. Location and vitamin D synthesis: Is the hypothesis validated by geophysical data? J Photochem Photobiol B Biol. 2007; 86: 234-239.
137. Maggi S, Noale M, Giannini S, Adami S, Defeo D, Isaia G, et al. Quantitative heel ultrasound in a population-based study in Italy and its relationship with fracture history: The ESOPO study. Osteoporos Int. 2006; 17: 237-244.
138. Prince RL, Lewis JR, Lim WH, Wong G, Wilson KE, Khoo BC, et al. Adding lateral spine imaging for vertebral fractures to densitometric screening: Improving ascertainment of patients at high risk of incident osteoporotic fractures. J Bone Miner Res. 2019; 34: 282-289.
139. Omrani GR, Masoompour SM, Hamidi A, Mardanifard HA, Taghavi SM, Talezadeh P, et al. Bone mineral density in the normal Iranian population: A comparison with American reference data. Arch Osteoporos. 2006; 1: 29-35.
140. Wu XP, Liao EY, Luo XH, Dai RC, Zhang H, Peng J. Age-related variation in quantitative ultrasound at the tibia and prevalence of osteoporosis in native Chinese women. Br J Radiol. 2003; 76: 605-610.
141. Xia WB, He SL, Xu L, Liu AM, Jiang Y, Li M, et al. Rapidly increasing rates of hip fracture in Beijing, China. J Bone Miner Res. 2012; 27: 125-129.
142. Iki M. Epidemiology of osteoporosis in Japan. Clin Calcium. 2012; 22: 797-803.
143. Cheung CL, Ang SB, Chadha M, Chow ES, Chung YS, Hew FL, et al. An updated hip fracture projection in Asia: The Asian Federation of Osteoporosis Societies study. Osteoporos Sarcopenia. 2018; 4: 16-21.
144. Mithal A, Bansal B, Kyer CS, Ebeling P. The Asia-pacific regional audit-epidemiology, costs, and burden of osteoporosis in India 2013: A report of international osteoporosis foundation. Indian J Endocrinol Metab. 2014; 18: 449-454.
145. Delmas PD, van de Langerijt L, Watts NB, Eastell R, Genant H, Grauer A, et al. Underdiagnosis of vertebral fractures is a worldwide problem: The IMPACT study. J Bone Miner Res. 2005; 20: 557-563.
146. Griffith JF. Identifying osteoporotic vertebral fracture. Quant Imaging Med Surg. 2015; 5: 592-602.
147. Gourlay ML, Overman RA, Ensrud KE. Bone density screening and re-screening in postmenopausal women and older men. Curr Osteoporos Rep. 2015; 13: 390-398.
148. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. Eur J Rheumatol. 2017; 4: 46-56.
149. Oberkircher L, Ruchholtz S, Rommens PM, Hofmann A, Bücking B, Krüger A. Osteoporotic pelvic fractures. Deutsch Ärztebl Int. 2018; 115: 70-80.
150. Soles GL, Ferguson TA. Fragility fractures of the pelvis. Curr Rev Musculoskelet Med. 2012; 5: 222-228.

151. Wong CC, McGirt MJ. Vertebral compression fractures: A review of current management and multimodal therapy. J Multidiscip Healthc. 2013; 6: 205-214.
152. WHO Study Group on Assessment of Fracture Risk, its application to Screening for Postmenopausal Osteoporosis. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Report of a WHO study group. Geneva: World Health Organization; 1994; 843.
153. Chakhtoura M, Dagher H, Sharara S, Ajjour S, Chamoun N, Cauley J, et al. Systematic review of major osteoporotic fracture to hip fracture incidence rate ratios worldwide: Implications for Fracture Risk Assessment Tool (FRAX)-derived estimates. J Bone Miner Res. 2020; 36: 1942-1956.
154. Morse LR, Biering-Soerensen F, Carbone LD, Cervinka T, Cirnigliaro CM, Johnston TE, et al. Bone mineral density testing in spinal cord injury: 2019 ISCD official position. J Clin Densitom. 2019; 22: 554-566.
155. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality—A review of recent evidence. Autoimmun Rev. 2013; 12: 976-989.
156. Weycker D, Li X, Barron R, Bornheimer R, Chandler D. Hospitalizations for osteoporosis-related fractures: Economic costs and clinical outcomes. Bone Rep. 2016; 5: 186-191.
157. Mangano KM, Sahni S, Kerstetter JE. Dietary protein is beneficial to bone health under conditions of adequate calcium intake: An update on clinical research. Curr Opin Clin Nutr Metab Care. 2014; 17: 69-74.
158. Plantz MA, Bittar K. Dietary calcium. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2021.
159. Reid IR, Bolland MJ, Grey A. Does calcium supplementation increase cardiovascular risk? Clin Endocrinol. 2010; 73: 689-695.
160. Behar JO. Effect of calcium on magnesium absorption. Am J Physiol. 1975; 229: 1590-1595.
161. Cook JD, Dassenko SA, Whittaker P. Calcium supplementation: Effect on iron absorption. Am J Clin Nutr. 1991; 53: 106-111.
162. Yasmeen A, Arshad MS, Ahmad RS, Saeed F, Imran A, Anjum FM, et al. Formulation and biochemical evaluation of designer diet enriched with botanicals for bone health. Food Sci Nutr. 2020; 8: 2984-2992.
163. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357: 266-281.
164. US Department of Health and Human Services. Bone health and osteoporosis: A report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, Office of the Surgeon General; 2004; 87.
165. Rizzoli R, Stevenson JC, Bauer JM, van Loon LJ, Walrand S, Kanis JA, et al. The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: A consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Maturitas. 2014; 79: 122-132.
166. Groenendijk I, den Boeft L, van Loon LJ, de Groot LC. High versus low dietary protein intake and bone health in older adults: A systematic review and meta-analysis. Comput Struct Biotechnol J. 2019; 17: 1101-1112.

167. Dai Z, Butler LM, van Dam RM, Ang LW, Yuan JM, Koh WP. Adherence to a vegetable-fruit-soy dietary pattern or the Alternative Healthy Eating Index is associated with lower hip fracture risk among Singapore Chinese. J Nutr. 2014; 144: 511-518.
168. Shin S, Joung H. A dairy and fruit dietary pattern is associated with a reduced likelihood of osteoporosis in Korean postmenopausal women. Br J Nutr. 2013; 110: 1926-1933.
169. Benetou V, Orfanos P, Pettersson-Kymmer U, Bergström U, Svensson O, Johansson I, et al. Mediterranean diet and incidence of hip fractures in a European cohort. Osteoporos Int. 2013; 24: 1587-1598.
170. Benetou V, Orfanos P, Feskanich D, Michaëlsson K, Pettersson-Kymmer U, Byberg L, et al. Mediterranean diet and hip fracture incidence among older adults: The CHANCES project. Osteoporos Int. 2018; 29: 1591-1599.
171. Malmir H, Saneei P, Larijani B, Esmaillzadeh A. Adherence to Mediterranean diet in relation to bone mineral density and risk of fracture: A systematic review and meta-analysis of observational studies. Eur J Nutr. 2018; 57: 2147-2160.
172. Ho-Pham LT, Nguyen ND, Nguyen TV. Effect of vegetarian diets on bone mineral density: A Bayesian meta-analysis. Am J Clin Nutr. 2009; 90: 943-950.
173. Appleby P, Roddam A, Allen N, Key T. Comparative fracture risk in vegetarians and nonvegetarians in EPIC-Oxford. Eur J Clin Nutr. 2007; 61: 1400-1406.
174. Fairweather-Tait SJ, Skinner J, Guile GR, Cassidy A, Spector TD, MacGregor AJ. Diet and bone mineral density study in postmenopausal women from the TwinsUK registry shows a negative association with a traditional English dietary pattern and a positive association with wine. Am J Clinl Nutr. 2011; 94: 1371-1375.
175. Sahni S, Mangano KM, McLean RR, Hannan MT, Kiel DP. Dietary approaches for bone health: Lessons from the Framingham Osteoporosis Study. Curr Osteoporos Rep. 2015; 13: 245-255.
176. Finck H, Hart AR, Jennings A, Welch AA. Is there a role for vitamin C in preventing osteoporosis and fractures? A review of the potential underlying mechanisms and current epidemiological evidence. Nutr Res Rev. 2014; 27: 268-283.
177. Malmir H, Shab-Bidar S, Djafarian K. Vitamin C intake in relation to bone mineral density and risk of hip fracture and osteoporosis: A systematic review and meta-analysis of observational studies. Br J Nutr. 2018; 119: 847-858.
178. Sun Y, Liu C, Bo Y, You J, Zhu Y, Duan D, et al. Dietary vitamin C intake and the risk of hip fracture: A dose-response meta-analysis. Osteoporos Int. 2018; 29: 79-87.
179. Griel AE, Kris-Etherton PM, Hilpert KF, Zhao G, West SG, Corwin RL. An increase in dietary n-3 fatty acids decreases a marker of bone resorption in humans. Nutr J. 2007; 6: 2.
180. Sun D, Krishnan A, Zaman K, Lawrence R, Bhattacharya A, Fernandes G. Dietary n-3 fatty acids decrease osteoclastogenesis and loss of bone mass in ovariectomized mice. J Bone Miner Res. 2003; 18: 1206-1216.
181. Mangano KM, Sahni S, Kerstetter JE, Kenny AM, Hannan MT. Polyunsaturated fatty acids and their relation with bone and muscle health in adults. Curr Osteoporos Rep. 2013; 11: 203-212.
182. Shen D, Zhang X, Li Z, Bai H, Chen L. Effects of omega-3 fatty acids on bone turnover markers in postmenopausal women: Systematic review and meta-analysis. Climacteric. 2017; 20: 522-527.
183. Fonolla-Joya J, Reyes-García R, García-Martín A, López-Huertas E, Muñoz-Torres M. Daily intake of milk enriched with n-3 fatty acids, oleic acid, and calcium improves metabolic and bone biomarkers in postmenopausal women. J Am Coll Nutr. 2016; 35: 529-536.

184. Lavado-García J, Roncero-Martin R, Moran JM, Pedrera-Canal M, Aliaga I, Leal-Hernandez O, et al. Long-chain omega-3 polyunsaturated fatty acid dietary intake is positively associated with bone mineral density in normal and osteopenic Spanish women. PloS One. 2018; 13: e0190539.
185. Sadeghi O, Djafarian K, Ghorabi S, Khodadost M, Nasiri M, Shab-Bidar S. Dietary intake of fish, n-3 polyunsaturated fatty acids and risk of hip fracture: A systematic review and meta-analysis on observational studies. Crit Rev Food Sci Nutr. 2019; 59: 1320-1333.
186. Fratoni V, Brandi ML. B vitamins, homocysteine and bone health. Nutrients. 2015; 7: 2176-2192.
187. Van Wijngaarden JP, Doets EL, Szczecińska A, Souverein OW, Duffy ME, Dullemeijer C, et al. Vitamin B_{12}, folate, homocysteine, and bone health in adults and elderly people: A systematic review with meta-analyses. J Nutr Metab. 2013; 2013: 486186.
188. Nielsen FH, Lukaski HC, Johnson LK, Roughead ZF. Reported zinc, but not copper, intakes influence whole-body bone density, mineral content and T score responses to zinc and copper supplementation in healthy postmenopausal women. Br J Nutr. 2011; 106: 1872-1879.
189. Arjmandi BH, Khalil DA, Lucas EA, Georgis A, Stoecker BJ, Hardin C, et al. Dried plums improve indices of bone formation in postmenopausal women. J Womens Health Gend Based Med. 2002; 11: 61-68.
190. Hooshmand S, Chai SC, Saadat RL, Payton ME, Brummel-Smith K, Arjmandi BH. Comparative effects of dried plum and dried apple on bone in postmenopausal women. Br J Nutr. 2011; 106: 923-930.
191. Simonavice E, Liu PY, Ilich JZ, Kim JS, Arjmandi B, Panton LB. The effects of a 6-month resistance training and dried plum consumption intervention on strength, body composition, blood markers of bone turnover, and inflammation in breast cancer survivors. Appl Physiol Nutr Metab. 2014; 39: 730-739.
192. Hooshmand S, Kern M, Metti D, Shamloufard P, Chai SC, Johnson SA, et al. The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: A randomized, controlled trial. Osteoporos Int. 2016; 27: 2271-2279.
193. Arjmandi B, George K, Ormsbee L, Akhavan N, Munoz J, Foley E, et al. The short-term effects of prunes in preventing inflammation and improving indices of bone health in osteopenic men. Curr Dev Nutr. 2020; 4: nzaa040_005.
194. Horikawa A, Miyakoshi N, Hongo M, Kasukawa Y, Shimada Y, Kodama H, et al. The effects of trends in osteoporosis treatment on the incidence of fractures. J Osteoporos. 2021; 2021: 5517247.
195. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, et al. Osteoporosis in men: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012; 97: 1802-1822.
196. O'Connor MB, Bond U, Yousif T. Osteoporosis management following teriparatide therapy for vertebral fractures: Are patients on correct maintenance therapy? Ir Med J. 2018; 111: 724.
197. Sikon A, Batur P. Profile of teriparatide in the management of postmenopausal osteoporosis. Int J Womens Health. 2010; 2: 37-44.
198. Migliaccio S, Brama M, Malavolta N. Management of glucocorticoids-induced osteoporosis: Role of teriparatide. Ther Clin Risk Manag. 2009; 5: 305-310.
199. Bodenner D, Redman C, Riggs A. Teriparatide in the management of osteoporosis. Clin Interv Aging. 2007; 2: 499-507.
200. Marx D, Yazdi AR, Papini M, Towler M. A review of the latest insights into the mechanism of action of strontium in bone. Bone Rep. 2020; 12: 100273.

201. Yang S, Nguyen ND, Eisman JA, Nguyen TV. Association between beta-blockers and fracture risk: A Bayesian meta-analysis. Bone. 2012; 51: 969-974.
202. Jolly JJ, Chin KY, Alias E, Chua KH, Soelaiman IN. Protective effects of selected botanical agents on bone. Int J Environ Res Public Health. 2018; 15: 963.
203. Chen J, Lin Z. The efficacy and safety of Chinese herbal medicine Xianling Gubao capsule combined with alendronate in the treatment of primary osteoporosis: A systematic review and meta-analysis of 20 randomized controlled trials. Front Pharmacol. 2021; 12: 695832.
204. Leung PC, Siu WS. Herbal treatment for osteoporosis: A current review. J Tradit Complement Med. 2013; 3: 82-87.
205. Fait T. Menopause hormone therapy: Latest developments and clinical practice. Drugs Context. 2019; 8: 212551.
206. Henneicke-von Zepelin HH. 60 years of Cimicifuga racemosa medicinal products: Clinical research milestones, current study findings and current development. Wien Med Wochenschr. 2017; 167: 147-159.
207. Panahi Y, Alishiri GH, Bayat N, Hosseini SM, Sahebkar A. Efficacy of Elaeagnus Angustifolia extract in the treatment of knee osteoarthritis: A randomized controlled trial. EXCLI J. 2016; 15: 203-210.
208. Collison MW. Determination of total soy isoflavones in dietary supplements, supplement ingredients, and soy foods by high-performance liquid chromatography with ultraviolet detection: Collaborative study. J AOAC Int. 2008; 91: 489-500.
209. Andargie M, Vinas M, Rathgeb A, Möller E, Karlovsky P. Lignans of sesame (*Sesamum indicum* L.): A comprehensive review. Molecules. 2021; 26: 883.
210. Clifton-Bligh PB, Baber RJ, Fulcher GR, Nery ML, Moreton T. The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism. Menopause. 2001; 8: 259-265.
211. Rehman SU, Choe K, Yoo HH. Review on a traditional herbal medicine, Eurycoma longifolia Jack (Tongkat Ali): Its traditional uses, chemistry, evidence-based pharmacology and toxicology. Molecules. 2016; 21: 331.
212. He CC, Hui RR, Tezuka Y, Kadota S, Li JX. Osteoprotective effect of extract from Achyranthes bidentata in ovariectomized rats. J Ethnopharmacol. 2010; 127: 229-234.
213. Zhang R, Hu SJ, Li C, Zhang F, Gan HQ, Mei QB. Achyranthes bidentata root extract prevent OVX-induced osteoporosis in rats. J Ethnopharmacol. 2012; 139: 12-18.
214. Yogesh HS, Chandrashekhar VM, Katti HR, Ganapaty S, Raghavendra HL, Gowda GK, et al. Anti-osteoporotic activity of aqueous-methanol extract of Berberis aristata in ovariectomized rats. J Ethnopharmacol. 2011; 134: 334-338.
215. Pandey R, Gautam AK, Bhargavan B, Trivedi R, Swarnkar G, Nagar GK, et al. Total extract and standardized fraction from the stem bark of Butea monosperma have osteoprotective action: Evidence for the nonestrogenic osteogenic effect of the standardized fraction. Menopause. 2010; 17: 602-610.
216. Shirwaikar A, Khan S, Malini S. Antiosteoporotic effect of ethanol extract of Cissus quadrangularis Linn. on ovariectomized rat. J Ethnopharmacol. 2003; 89: 245-250.
217. Muthusami S, Senthilkumar K, Vignesh C, Ilangovan R, Stanley J, Selvamurugan N, et al. Effects of *Cissus quadrangularis* on the proliferation, differentiation and matrix mineralization of human osteoblast like SaOS-2 cells. J Cell Biochem. 2011; 112: 1035-1045.

218. Muthusami S, Ramachandran I, Krishnamoorthy S, Govindan R, Narasimhan S. Cissus quadrangularis augments IGF system components in human osteoblast like SaOS-2 cells. Growth Horm IGF Res. 2011; 21: 343-348.
219. Yang L, Chen Q, Wang F, Zhang G. Antiosteoporotic compounds from seeds of Cuscuta chinensis. J Ethnopharmacol. 2011; 135: 553-560.
220. Yang HM, Shin HK, Kang YH, Kim JK. *Cuscuta chinensis* extract promotes osteoblast differentiation and mineralization in human osteoblast-like MG-63 cells. J Med Food. 2009; 12: 85-92.
221. Ko YJ, Wu JB, Ho HY, Lin WC. Antiosteoporotic activity of Davallia formosana. J Ethnopharmacol. 2012; 139: 558-565.
222. Niu Y, Li Y, Huang H, Kong X, Zhang R, Liu L, et al. Asperosaponin VI, a saponin component from *Dipsacus asper* wall, induces osteoblast differentiation through bone morphogenetic protein-2/p38 and extracellular signal-regulated kinase 1/2 pathway. Phytother Res. 2011; 25: 1700-1706.
223. Liu ZG, Zhang R, Li C, Ma X, Liu L, Wang JP, et al. The osteoprotective effect of Radix Dipsaci extract in ovariectomized rats. J Ethnopharmacol. 2009; 123: 74-81.
224. Jeong JC, Lee JW, Yoon CH, Kim HM, Kim CH. Drynariae Rhizoma promotes osteoblast differentiation and mineralization in MC3T3-E1 cells through regulation of bone morphogenetic protein-2, alkaline phosphatase, type I collagen and collagenase-1. Toxicol Vitro. 2004; 18: 829-834.
225. Wang XL, Wang NL, Zhang Y, Gao H, Pang WY, Wong MS, et al. Effects of eleven flavonoids from the osteoprotective fraction of Drynaria fortunei (K UNZE) J. S M. on osteoblastic proliferation using an osteoblast-like cell line. Chem Pharm Bull. 2008; 56: 46-51.
226. Wang X, Zhen L, Zhang G, Wong MS, Qin L, Yao X. Osteogenic effects of flavonoid aglycones from an osteoprotective fraction of Drynaria fortunei—An in vitro efficacy study. Phytomedicine. 2011; 18: 868-872.
227. Chang EJ, Lee WJ, Cho SH, Choi SW. Proliferative effects of flavan-3-ols and propelargonidins from rhizomes of *Drynaria fortunei* on MCF-7 and osteoblastic cells. Arch Pharm Res. 2003; 26: 620-630.
228. Guo D, Wang J, Wang X, Luo H, Zhang H, Cao D, et al. Double directional adjusting estrogenic effect of naringin from Rhizoma drynariae (Gusuibu). J Ethnopharmacol. 2011; 138: 451-457.
229. Zhang G, Qin L, Hung WY, Shi YY, Leung PC, Yeung HY, et al. Flavonoids derived from herbal Epimedium Brevicornum Maxim prevent OVX-induced osteoporosis in rats independent of its enhancement in intestinal calcium absorption. Bone. 2006; 38: 818-825.
230. Zhang DW, Cheng Y, Wang NL, Zhang JC, Yang MS, Yao XS. Effects of total flavonoids and flavonol glycosides from Epimedium koreanum Nakai on the proliferation and differentiation of primary osteoblasts. Phytomedicine. 2008; 15: 55-61.
231. Qian G, Zhang X, Lu L, Wu X, Li S, Meng J. Regulation of Cbfa1 expression by total flavonoids of Herba epimedii. Endocr J. 2006; 53: 87-94.
232. Songlin P, Ge Z, Yixin H, Xinluan W, Pingchung L, Kwoksui L, et al. Epimedium-derived flavonoids promote osteoblastogenesis and suppress adipogenesis in bone marrow stromal cells while exerting an anabolic effect on osteoporotic bone. Bone. 2009; 45: 534-544.

233. Zhang JF, Li G, Chan CY, Meng CL, Lin MC, Chen YC, et al. Flavonoids of Herba Epimedii regulate osteogenesis of human mesenchymal stem cells through BMP and Wnt/β-catenin signaling pathway. Mol Cell Endocrinol. 2010; 314: 70-74.
234. Nian H, Ma MH, Nian SS, Xu LL. Antiosteoporotic activity of icariin in ovariectomized rats. Phytomedicine. 2009; 16: 320-326.
235. Hsieh TP, Sheu SY, Sun JS, Chen MH. Icariin inhibits osteoclast differentiation and bone resorption by suppression of MAPKs/NF-κB regulated HIF-1α and PGE2 synthesis. Phytomedicine. 2011; 18: 176-185.
236. Mok SK, Chen WF, Lai WP, Leung PC, Wang XL, Yao XS, et al. Icariin protects against bone loss induced by oestrogen deficiency and activates oestrogen receptor-dependent osteoblastic functions in UMR 106 cells. Br J Pharmacol. 2010; 159: 939-949.
237. Hsieh TP, Sheu SY, Sun JS, Chen MH, Liu MH. Icariin isolated from Epimedium pubescens regulates osteoblasts anabolism through BMP-2, SMAD4, and Cbfa1 expression. Phytomedicine. 2010; 17: 414-423.
238. Choi HJ, Eun JS, Park YR, Kim DK, Li R, Moon WS, et al. Ikarisoside A inhibits inducible nitric oxide synthase in lipopolysaccharide-stimulated RAW 264.7 cells via p38 kinase and nuclear factor-κB signaling pathways. Eur J Pharmacol. 2008; 601: 171-178.
239. Choi HJ, Park YR, Nepal M, Choi BY, Cho NP, Choi SH, et al. Inhibition of osteoclastogenic differentiation by Ikarisoside A in RAW 264.7 cells via JNK and NF-κB signaling pathways. Eur J Pharmacol. 2010; 636: 28-35.
240. Potter SM, Baum JA, Teng H, Stillman RJ, Shay NF, Erdman Jr JW. Soy protein and isoflavones: Their effects on blood lipids and bone density in postmenopausal women. American J Clini Nutr. 1998; 68: 1375S-1379S.
241. Taku K, Melby MK, Nishi N, Omori T, Kurzer MS. Soy isoflavones for osteoporosis: An evidence-based approach. Maturitas. 2011; 70: 333-338.
242. Bitto A, Polito F, Burnett B, Levy R, Di Stefano V, Armbruster MA, et al. Protective effect of genistein aglycone on the development of osteonecrosis of the femoral head and secondary osteoporosis induced by methylprednisolone in rats. J Endocrinol. 2009; 201: 321-328.
243. Bitto A, Burnett BP, Polito F, Levy RM, Marini H, Stefano VD, et al. Genistein aglycone reverses glucocorticoid-induced osteoporosis and increases bone breaking strength in rats: A comparative study with alendronate. Br J Pharmacol. 2009; 156: 1287-1295.
244. Atteritano M, Mazzaferro S, Frisina A, Cannata ML, Bitto A, D'Anna R, et al. Genistein effects on quantitative ultrasound parameters and bone mineral density in osteopenic postmenopausal women. Osteoporos Int. 2009; 20: 1947-1954.
245. Filipović B, Šošić-Jurjević B, Ajdžanović V, Brkić D, Manojlović-Stojanoski M, Milošević V, et al. Daidzein administration positively affects thyroid C cells and bone structure in orchidectomized middle-aged rats. Osteoporos Int. 2010; 21: 1609-1616.
246. Komrakova M, Sehmisch S, Tezval M, Schmelz U, Frauendorf H, Grueger T, et al. Impact of 4-methylbenzylidene camphor, daidzein, and estrogen on intact and osteotomized bone in osteopenic rats. J Endocrinol. 2011; 211: 157-168.
247. Ayoub N, Singab AN, El-Naggar M, Lindequist U. Investigation of phenolic leaf extract of Heimia myrtifolia (Lythraceae): Pharmacological properties (stimulation of mineralization of SaOS-2 osteosarcoma cells) and identification of polyphenols. Drug Discov Ther. 2010; 4: 341-348.

248. Zhang Y, Yu L, Ao M, Jin W. Effect of ethanol extract of *Lepidium meyenii* Walp. on osteoporosis in ovariectomized rat. J Ethnopharmacol. 2006; 105: 274-279.
249. Gonzales GF. Ethnobiology and ethnopharmacology of *Lepidium meyenii* (Maca), a plant from the Peruvian highlands. Evid Based Complementary Altern Med. 2012; 2012: 193496.
250. Sacco SM, Jiang JM, Reza-López S, Ma DW, Thompson LU, Ward WE. Flaxseed combined with low-dose estrogen therapy preserves bone tissue in ovariectomized rats. Menopause. 2009; 16: 545-554.
251. Boulbaroud S, Mesfioui A, Arfaoui A, Ouichou A, El-Hessni A. Preventive effects of flaxseed and sesame oil on bone loss in ovariectomized rats. Pak J Biol Sci. 2008; 11: 1696-1701.
252. Kettler DB. Can manipulation of the ratios of essential fatty acids slow the rapid rate of postmenopausal bone loss? Altern Med Rev. 2001; 6: 61-77.
253. Arjmandi BH. The role of phytoestrogens in the prevention and treatment of osteoporosis in ovarian hormone deficiency. J Am Coll Nutr. 2001; 20: 398S-402S; discussion 417S-420S.
254. Wang D, Li F, Jiang Z. Osteoblastic proliferation stimulating activity of Psoralea corylifolia extracts and two of its flavonoids. Planta Med. 2001; 67: 748-749.
255. Xin D, Wang H, Yang J, Su YF, Fan GW, Wang YF, et al. Phytoestrogens from Psoralea corylifolia reveal estrogen receptor-subtype selectivity. Phytomedicine. 2010; 17: 126-131.
256. Park CK, Lee Y, Chang EJ, Lee MH, Yoon JH, Ryu JH, et al. Bavachalcone inhibits osteoclast differentiation through suppression of NFATc1 induction by RANKL. Biochem Pharmacol. 2008; 75: 2175-2182.
257. Tang DZ, Yang F, Yang Z, Huang J, Shi Q, Chen D, et al. Psoralen stimulates osteoblast differentiation through activation of BMP signaling. Biochem Biophys Res Commun. 2011; 405: 256-261.
258. Shen Y, Li YQ, Li SP, Ma L, Ding LJ, Ji H. Alleviation of ovariectomy-induced osteoporosis in rats by Panax notoginseng saponins. J Nat Med. 2010; 64: 336-345.
259. Li XD, Wang JS, Chang B, Chen B, Guo C, Hou GQ, et al. Panax notoginseng saponins promotes proliferation and osteogenic differentiation of rat bone marrow stromal cells. J Ethnopharmacol. 2011; 134: 268-274.
260. Lee SY, Choi DY, Woo ER. Inhibition of osteoclast differentiation by tanshinones from the root of *Salvia miltiorrhiza* bunge. Arch Pharm Res. 2005; 28: 909-913.
261. Zhang Y, Li Q, Wan HY, Xiao HH, Lai WP, Yao XS, et al. Study of the mechanisms by which *Sambucus williamsii* HANCE extract exert protective effects against ovariectomy-induced osteoporosis in vivo. Osteoporos Int. 2011; 22: 703-709.
262. Siddiqui JA, Sharan K, Swarnkar G, Rawat P, Kumar M, Manickavasagam L, et al. Quercetin-6-C-β-D-glucopyranoside isolated from Ulmus wallichiana planchon is more potent than quercetin in inhibiting osteoclastogenesis and mitigating ovariectomy-induced bone loss in rats. Menopause. 2011; 18: 198-207.
263. Sharan K, Swarnkar G, Siddiqui JA, Kumar A, Rawat P, Kumar M, et al. A novel flavonoid, 6-C-β-d-glucopyranosyl-(2S,3S)-(+)-3',4',5,7-tetrahydroxyflavanone, isolated from Ulmus wallichiana Planchon mitigates ovariectomy-induced osteoporosis in rats. Menopause. 2010; 17: 577-586.
264. Swarnkar G, Sharan K, Siddiqui JA, Chakravarti B, Rawat P, Kumar M, et al. A novel flavonoid isolated from the steam-bark of Ulmus Wallichiana Planchon stimulates osteoblast function and inhibits osteoclast and adipocyte differentiation. Eur J Pharmacol. 2011; 658: 65-73.

265. Sharan K, Siddiqui JA, Swarnkar G, Tyagi AM, Kumar A, Rawat P, et al. Extract and fraction from Ulmus wallichiana Planchon promote peak bone achievement and have a nonestrogenic osteoprotective effect. Menopause. 2010; 17: 393-402.
266. Kim TH, Jung JW, Ha BG, Hong JM, Park EK, Kim HJ, et al. The effects of luteolin on osteoclast differentiation, function in vitro and ovariectomy-induced bone loss. J Nutr Biochem. 2011; 22: 8-15.
267. Kamaruzzaman MA, Chin KY, Mohd Ramli ES. A review of potential beneficial effects of honey on bone health. Evid Based Complementary Altern Med. 2019; 2019: 8543618.
268. O'Keefe JH, Bergman N, Carrera-Bastos P, Fontes-Villalba M, DiNicolantonio JJ, Cordain L. Nutritional strategies for skeletal and cardiovascular health: Hard bones, soft arteries, rather than vice versa. Open Heart. 2016; 3: e000325.
269. Kassi E, Papoutsi Z, Fokialakis N, Messari I, Mitakou S, Moutsatsou P. Greek plant extracts exhibit selective estrogen receptor modulator (SERM)-like properties. J Agric Food Chem. 2004; 52: 6956-6961.
270. Sochett E. Healthy bones–Activity and nutrition. Paediatr Child Health. 2002; 7: 315-317.
271. Hohman EE, Weaver CM. A grape-enriched diet increases bone calcium retention and cortical bone properties in ovariectomized rats. J Nutr. 2015; 145: 253-259.
272. Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI. Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. Front Pharmacol. 2018; 9: 557.