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Treatment of osteoporosis: current state of the art

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Summary Osteoporosis can be treated with medications and lifestyle changes, including avoiding a sedentary lifestyle, alcohol, and smoking. We will identify medications that protect against hip fractures in addition to vertebral fractures, and explore new evidence of adverse effects and risks. Bisphosphonates are used as first-line treatment. We will discuss the latest osteoporosis medications, drug interactions, potential bone protective effects of other drug classes, and the evidence of exercise and kyphoplasty.

Keywords Osteoporosis treatment · Osteoporosis medications · Adverse effects · Contraindications · Interactions

Behandlung der Osteoporose: State of the Art

Zusammenfassung Osteoporose kann medikamentös und durch Lebensstilveränderungen, wie Einschränkung von Bewegungsarmut, Rauchen und Alkohol-Gebrauch, beeinflusst werden. Wir unterscheiden Medikamente, die nur Vertebralfrakturen oder Vertebral und Hüftfrakturen verhindern. Anhand von aktueller Literatur werden die Risiken und Nebenwirkungen beschrieben. Bei der Auswahl stehen Bisphosphonate an erster Stelle. Besprochen werden auch Medikamentenreaktionen, möglicher Osteoporoseschutz anderer Medikamentenklassen, Fitness und Kyphoplastie.

Schlüsselwörter Osteoporose Behandlung · Osteoporose Medikamente · Nebenwirkungen · Gegenindikationen · Wechselwirkungen

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Importance

A 50-year-old Caucasian woman has a 40 % risk of an osteoporotic fracture during her lifetime, yet available treatment options are suboptimal [1]. Particularly concerning is that only 7–38 % of women with an established fracture receive treatment with an approved osteoporosis prevention medication [2–9]. Minority women are even less likely to be treated for established osteoporosis [9]. An article based on dual-energy X-ray absorptiometry (DXA) conducted in the Women's Health Initiative (WHI) found that of those diagnosed with osteoporosis, only 72.6 % discussed the results with a healthcare provider and 56 % initiated drug treatment [10]. Although medication compliance drops to about half after 1 year [11], treatment is effective in preventing osteoporotic fractures. This article will discuss the latest evidence on pharmacologic and nonpharmacologic treatment options.

Medications

Medications for the treatment of osteoporosis can be divided into anabolic and antiresorptive categories. Bisphosphonates, estrogen, selective estrogen receptor modulators, and denosumab, a monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), are antiresorptive, which slow bone remodeling so that bone formation exceeds resorption. Recombinant parathyroid hormone (PTH) is an anabolic agent which increases osteoblast activity building bone. Strontium ranelate has a dual mechanism (Table 1).

Table 1 Medical options for treatment of osteoporosis

Class	Drug/dosage/route	Contraindications	Adverse effects
Bisphosphonates	Alendronate[a] 70 mg PO weekly Risendronate 35 mg PO weekly or 150 mg PO monthly Ibandronate 150 mg PO monthly, 3 mg IV q 3 months Zoledronic acid[a] 5 mg IV yearly	Hypocalcemia Abnormalities of the esophagus Inability to be upright for 30 min Increase risk of aspiration Renal clearance <30 ml/min	Dyspepsia 1–4 % Hypocalcemia 18 % Hypophosphatemia 10 % Atypical femoral fractures <0.1 % Osteonecrosis of the jaw <0.1 %
Selective estrogen reuptake modulators (SERMs)	Raloxifene 60 mg PO daily Bazedoxifene 22.6 mg PO daily Lasofoxifene 0.5 mg PO daily	Venous thromboembolic disorder Pregnancy Breast-feeding	Peripheral edema 3–14 % Hot flashes 8–29 % Arthralgia 11–16 % Cramps 6–12 % Flu syndrome 14–15 % Infection 11 %
Recombinant human parathyroid hormone (PTH) analog	Teriparatide 20 mcg SQ daily	Bone metastases History of skeletal malignancies Hypercalcemia Paget's disease of bone Young patients with open epiphyses External beam or implant radiation involving the skeleton	Arthralgia 10 % Nausea 9–14 % Hypercalcemia 6–11 % Increase serum uric acid Dizziness 8 %
Receptor activator of nuclear factor kappa-B ligand (RANKL)	Denosumab[a] 60 mg SQ every 6 months	Pregnancy Hypocalcemia	Arthralgia/pain 7–14 % Hypercholesterolemia 7 % Dermatitis/rash 3–11 % Atypical femoral fractures
Strontium[b]	Strontium ranelate 2 g PO daily	Renal clearance <30 ml/min Risk of heart problems History of thromboembolism Immobilization Patients with phenylketonuria (contains phenylalanine) Blood pressure >160/90 mmHg	Myocardial infarction Venous thromboembolism
Calcium	Calcium carbonate[a] PO 500–600 mg, two to three times daily	Hypercalcemia	Constipation
Vitamin D	Cholecalciferol[a] or Ergocalciferol[a] 400–4000 IU PO daily Alfacalcidol 0.25–1 mcg daily	Hypercalcemia Hypervitaminosis D	Hypervitaminosis D
Estrogen[b]	Conjugated estrogens 0.3–1.25 mg PO daily Estradiol 0.5–2.0 mg PO daily, 0.025–0.1 mg patch once or twice a week Estradiol acetate 0.05–0.1 mg intravaginal ring Ethinyl estradiol 0.02–0.05 mg PO daily	Thromboembolic disorders (DVT, PE, MI, CVA) Breast cancer Estrogen-dependent tumor Hepatic dysfunction or disease Antithrombin deficiency Undiagnosed abnormal vaginal bleeding Migraine with aura Endometrial hyperplasia Pregnancy	Abdominal pain (15–17 %) Back pain (13–14 %) Vaginal hemorrhage (2–14 %) Breast cancer Thromboembolic event Stroke

PO oral, *IV* intravenous, *SQ* subcutaneous, *DVT* deep venous thrombosis, *PE* pulmonary embolism, *MI* myocardial infarction, *CVA* cerebrovascular
[a]Protective of hip fractures
[b]The benefit in osteoporosis does not justify the risks in most patients

Bisphosphonates

Bisphosphonates are structurally very similar to pyrophosphate and are incorporated into bone. They bind tightly to bone and prevent cytokine release that activates osteoclasts and osteoblast apoptosis [12–14].

Bisphosphonates are first-line treatment of osteoporosis as this class of drugs has the best evidence for fracture reduction [15]. Alendronate, risedronate, and zoledronic acid have supporting evidence for vertebral and nonvertebral fracture reduction, whereas ibandronate prevents vertebral but not nonvertebral fractures [16–19].

Oral bisphosphonates should be taken on an empty stomach with only water to facilitate their absorption. Gastrointestinal side effects include esophageal and gastric erosions which can be reduced by large amounts >240 ml of water and staying upright for 30 min after taking the pills [20]. A delayed release formulation of risedronate can be taken after breakfast and has been shown to be as effective as immediate release risedronate [21].

Rarer adverse effects includes atypical femoral fractures (3.2–50 cases per 100,000 person years); these fractures also occur in denosumab users [22]. Another concern is osteonecrosis of the jaw with an incidence

of 1 in 100,000 patient years, most common (94%) in cancer patients [23]. Considering the high risk of osteoporotic fractures, the treatment benefit likely outweighs the risks. The question of whether bisphosphonates suppress bone turn over sufficiently to impair fracture healing was answered by a prospective study of 90 hip fracture patients. Healing (in weeks) was no different in the groups receiving risedronate 1 week (10.7 weeks), 1 month (12.9), or 3 months (12.3) after surgery [24].

A longer duration of treatment seems to increase the risk of complications [25]. Yet bisphosphonates stays in bone for a very long time, prompting the question how long after stopping benefits remain. This was answered by the FLEX trial where 1099 patients age 55–81, who had been on alendronate for 5 years, were randomized to continue on alendronate or placebo [26]. The alendronate group had fewer clinical vertebral fractures, but no difference in fractures was found on X-ray measurement.

Menopause and estrogen

After menopause, bone resorption is uncoupled from bone formation, causing a net loss of bone. Bone resorption is accelerated while bone formation continues at the pre-menopausal rate. Trabecular bone is affected more than cortical bone. In the perimenopausal years, women lose about 5% of bone mineral density (BMD) in the femoral neck and 10% in the spine [27]. In the WHI, women who took standard dose estrogen plus progestin therapy had 46 fewer total fractures and 6 fewer hip fractures per 10,000 patient years than placebo [28]. Women who took standard dose estrogen only therapy had 56 fewer total fractures and 7 fewer hip fractures per 10,000 patient years [28]. Owing to its potential for harm (increased risk of breast cancer, thromboembolic disease, and stroke), estrogen is no longer indicated for treatment or prevention of postmenopausal osteoporosis.

Selective estrogen reuptake modulators

Selective estrogen reuptake modulators (SERMs) are compounds that lack the steroid structure of estrogen, but bind to estrogen receptors throughout the body with varying agonist and antagonist effects. Raloxifene is Food and Drug Administration (FDA) approved for prevention and treatment of osteoporosis in the USA. Although tamoxifen was the first SERM developed, its agonist activity on the endometrium which may lead to endometrial hyperplasia and cancer limits its usefulness in osteoporosis prevention. Two other SERMs, bazedoxifene and lasofoxifene, are available in Europe; the latter has possible safety concerns [29].

Raloxifene in doses of 60 mg or the pooled higher doses of 120 or 150 mg daily reduced the risk of vertebral fractures by 40% (relative risk (RR): 0.6, 95% confidence interval (CI): 0.49–0.74) and 49% (RR: 0.51, 95% CI: 0.41–0.64) [30]. Raloxifene also significantly reduced the incidence of estrogen receptor-positive breast cancers. A reduced incidence of nonvertebral fractures has been documented with lasofoxifene [31] but not for other SERMs.

Alendronate was shown in one study to have significantly greater increases in hip BMD than raloxifene (2.3 vs 0.8%, $p<0.001$) [32]. In another randomized trial of 619 postmenopausal women comparing raloxifene 60 or 150 mg daily with conjugated equine estrogen 0.625 mg a daily or placebo, all treatment groups improved BMD compared with placebo. The differences in the estrogen group were greater than in either of the raloxifene groups, but again no fracture data are reported [33].

Calcitonin

Calcitonin is an endogenous peptide that binds to osteoclasts and impedes bone resorption. Calcitonin is present in many different species, but salmon calcitonin is used therapeutically in humans because it binds strongly to human calcitonin receptors. Calcitonin is available in the USA to be used via intranasal, subcutaneous, and intramuscular routes. Intranasal calcitonin has the fewest side effects and is used most of the time. Calcitonin is approved for treatment of osteoporosis in women who are at least 5 years beyond menopause. Its antiresorptive effects are less potent than other medications, which is why it is used as a second-line treatment [34]. The PROOF study showed vertebral fracture risk reduction of 23% (CI: 0.47–0.97) number needed to treat (NNT) 11 over 3 years but no significant effect on the hip [35]. It is very effective for treating bone pain after an osteoporotic vertebral compression fracture which is its main use in the USA, but may take up to 2 weeks to reduce pain [36, 37]. In March of 2014, a warning of increased risk of malignancy was added based on a meta-analysis of 21 studies with 10,883 patients. The overall incidence of malignancies reported in these 21 trials were higher among calcitonin-salmon-treated patients (254/6151 or 4.1%) compared with placebo-treated patients (137/4732 or 2.9%). Although a definitive causal relationship between the calcitonin-salmon use and malignancies cannot be established from this meta-analysis, the benefits for the individual patient should be carefully evaluated against all possible risks [38]. In 2012, the European Medicines Agency had concluded that calcitonin should no longer be used in the treatment of osteoporosis [39].

Recombinant human parathyroid hormone analog

PTH regulates calcium and phosphate in the kidneys as well as bone metabolism and facilitates calcium resorption from bone. However, PTH given intermittently stimulates osteoblasts, the bone building cells, whereas continuous administration stimulates osteoclasts [40]. Teriparatide is recombinant human PTH analog (1–34). Teriparatide increases trabecular and cortical bone turn-

over by increasing osteoblast activity over osteoclast activity. Teriparatide is indicated by the FDA for treatment of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis in both men and women, and bone loss in men with primary or hypogonadal osteoporosis at high risk for fracture. Avoid using PTH in patients with bone metastases, history of skeletal malignancies, or hypercalcemic disorders.

Teriparatide shows benefit over placebo in reduction of fracture and increase in BMD at all sites. A meta-analysis of three studies of postmenopausal women showed a decrease in vertebral fractures from 14.68 to 4.46 % and reduction in nonvertebral fractures from 8.87 to 5.43 % [41]. In the largest study of postmenopausal women, the NNT was 26 for preventing fractures over 18 months [42]. Patients taking calcium supplementation of greater than 1500 mg/day had the greatest benefit [41]. After completion of teriparatide treatment patients who then took a bisphosphonate had continued improvement in BMD and the risk of vertebral fractures was sustained for 1 year [43–45].

Teriparatide has been studied in combination with antiresorptive agents. Concomitant administration with alendronate decreases the efficacy of teriparatide at improving BMD, so combination therapy is not recommended [46]. Patients with prior exposure to a bisphosphonate show an increase in BMD on teriparatide but less than in patients who had never taken a bisphosphonate [47]. There is a greater increase in BMD with hormone replacement therapy (HRT) combined with teriparatide compared with HRT alone in four trials [41]. Combination with denosumab showed increased benefit [48].

Patients inject 20 mcg subcutaneously once a day in the thigh or abdominal wall using a prefilled pen containing 28 doses. An alternative dose of 56.5 mcg weekly showed a decrease in vertebral fractures in Japanese patients [49]. Patients were advised to lie down with the first dose in case transient hypotension occurs within the first 4 h (5 %). No dosage adjustments are recommended in renal impairment, but use in severe renal impairment is contraindicated in the Canadian labeling. Limit use to 2 years per lifetime as bone mass does not continue to increase with use after 2 years.

Adverse effects were minimal with 16 % of patients having a serious adverse effect in the teriparatide group compared with 19 % taking placebo. Adverse effects with a greater than 10 % incidence include arthralgia, pain, and nausea. Teriparatide may increase serum calcium, urinary calcium, and serum uric acid (3 vs 1 %). Use caution in patients on digoxin as hypercalcemia may predispose to digoxin toxicity. Osteosarcoma has occurred in rats. To decrease the risk, avoid teriparatide in patients with Paget's disease of bone, young patients with open epiphyses, and patients with prior external beam or implant radiation involving the skeleton.

Antibody against receptor activator of nuclear factor kappa-B ligand

Denosumab is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL. It binds to RANKL, a transmembrane on osteoclasts, decreasing bone resorption and reducing bone turnover. Bone mass as well as strength in cortical, subcortical, and trabecular bone increase [50].

Denosumab is FDA approved for treatment of osteoporosis in postmenopausal women and men, including those on androgen-deprivation therapy for prostate cancer and aromatase inhibitor therapy for breast cancer. In postmenopausal women, the FREEDOM trial showed a NNT of 62 for 3 years to prevent a clinical vertebral fracture and a NNT of 230 for hip fracture [51]. On follow-up for 6 years, patients continued to see suppression in bone turnover, increase in BMD, and decrease in fractures [52]. In the DECIDE trial, denosumab 60 mg every 6 months showed a statistically significant increase in BMD compared with alendronate 70 mg/week (3.5 vs 2.6 %, respectively) [53]. A 2-year crossover study showed greater adherence with a 6-month injection compared with a weekly tablet 87.3 vs. 76.6 % ($p=0.014$) [54]. Patients treated with denosumab and teriparatide together had a greater increase in BMD at all three sites than either drug alone [48].

Denosumab is administered by a healthcare professional every 6 months as a 60 mg subcutaneous injection in the upper arm, upper thigh, or abdomen. It can be given at the same dose in severe renal impairment and dialysis patients, but should be avoided in pregnancy (category x). Patients taking denosumab should take calcium and vitamin D daily. Hypocalcemia needs to be corrected prior to therapy and monitored closely especially in patients with a creatinine clearance < 30 ml/min as these patients have a greater risk of hypocalcemia. Osteonecrosis of the jaw (2 % at 3 years) and atypical femoral fractures have been reported [22, 55–57]. The only significant adverse effects were eczema (RR: 1.91, 95 % CI: 1.43–2.55, $p<0.001$) and infections (RR: 1.26, 95 % CI: 1.01–1.58, $p=0.041$) [58].

Strontium ranelate

Strontium in vitro enhances the replication of pre-osteoblast cells and decreases osteoclast differentiation [59, 60]. This leads to significant changes in microarchitecture with higher cortical thickness (+18 %, $p=0.008$) and trabecular number (+14 %, $p=0.05$) as shown on bone biopsy [61]. In the Treatment of Peripheral Osteoporosis (TROPOS) Study, of the 5091 patients, 2479 in the strontium group showed a 24 % relative risk (RR) reduction of vertebral fractures compared with placebo over 5 years [62]. Hip fracture reduction reached statistical significance only in a high risk subgroup of 1128 patients, with a mean age of 79.2, +4.4 years, mean lumbar spine T-score −4.2, and mean femoral neck T score −3.6 (incidence 7.2

vs 10.2 %) [63]. In January of 2014, the Pharmacovigilance Risk Assessment Committee recommended against the use of strontium due to heart problems including heart attacks [64]. The European Medicines Agency has concluded to further restrict the use of strontium to patients who cannot be treated with other medicines approved for osteoporosis. In addition, these patients should continue to be evaluated regularly by their doctor and treatment should be stopped if patients develop heart or circulatory problems, such as uncontrolled high blood pressure or angina. As recommended in a previous review, patients who have a history of certain heart or circulatory problems, such as stroke and heart attack, must not use the medicine [65].

Calcium

Calcium is deposited in bone and is necessary for bone strength. Calcium has been shown to reduce fractures at a rate of 10–24 % [66–69]. There is also consistent epidemiological evidence that low vitamin D levels and low calcium intake are associated with increased rates of osteoporosis and fractures. Some studies have shown no effect on fracture reduction in intention to treat analysis thought to be due to low compliance (54–59 %) [70–72]. In the subgroups with >80 % compliance fracture protection was statistically improved.

The United States Preventive Services Task Force cites insufficient evidence (I recommendation) for supplementation of either calcium or vitamin D in postmenopausal women [73]. The Cochrane database recommends calcium and vitamin D supplementation for older adults and patients on corticosteroids [74, 75]. The Institute of Medicine (IOM) in 2010 released recommendations for 1000 mg elemental calcium in adults aged 50 years and younger, 1200 mg in those older than 50 years, and 1300 mg in teenagers, pregnant, and lactating women [74–76]. Upper limits of intake are 2000 mg daily for >50-year olds and 2500–3000 for younger adults [76]. Owing to decreasing absorption of doses over 500 mg, calcium should be taken in divided doses [77]. Reducing sodium in the diet to <2 g daily improves calcium retention [78]. While calcium citrate was touted to be better absorbed in low acid stomach environments, absorption is similar to calcium carbonate as long as formulations are taken with food [79].

Calcium has been implicated in increased risk of myocardial infarction but no difference was identified in stroke or overall death [80]. None of the studies, however, was designed to assess cardiovascular risk and only 4 of the 15 studies included information on important comorbidities. A systematic review completed in the same year found no difference in cardiovascular risk, [81] nor did a meta-analysis of 65,364 women taking calcium supplements with or without vitamin D [82]. In a randomized controlled trial (RCT) designed to look for cardiovascular disease in 1460 women with an average age of 75 years, no difference was found in death, hospitalization, ischemic heart disease, arrhythmia, heart failure, cerebrovascular disease, or peripheral artery disease over 9.5 years of follow-up [83].

Vitamin D

Vitamin D is both a hormone and a vitamin. Although we make vitamin D in our skin through use of ultraviolet (UV) rays from the sun, its production is highly variable and for most of the population insufficient. Environmental factors affecting cutaneous vitamin D production in response to sun exposure include: time of day, season, latitude, altitude, UV index, which is dependent on clouds, pollution, and humidity. Patient factors affecting skin production include skin tone, from the darkest to the lightest skin tone there is a six-fold difference in vitamin D production [84], and age, with a 70-year-old patient making 75 % less vitamin D than a 20-year-old patient [85]. A certain amount of sun exposure can therefore not be recommended to supply sufficient vitamin D. Sunscreen blocks UV rays, thereby making the skin unable to produce vitamin D. Dietary intake is mostly insufficient, especially in older adults [86], leading to deficiency rates as high as 92.8 % in nursing home patients [87].

There is controversy over whether vitamin D prevents fractures. A recent meta-analysis found that supplemental vitamin D did not affect BMD or fracture rates, possibly because of insufficient power or inappropriate doses, or because the intervention was not targeted to deficient populations [88]. A 26 % hip and 23 % vertebral fracture reduction was found with 700–800 IU cholecalciferol daily (CI: 0.61–0.88 and 0.68–0.87) but no reduction in the group taking 400 IU [89]. A health economic evaluation of treating the UK population aged 65 and over with 800 IU of vitamin D daily showed a hip fracture reduction from 65,400 to 45,700, saving almost 1700 associated deaths, while saving the UK taxpayer £22 million per year [90].

Although vitamin D is stored in the adipose tissue, blood levels drop below baseline in 2 weeks after a 50,000 IU dose of vitamin D2 and remain above baseline after 30 days of a dose of vitamin D3 [91]. Infrequent high dosing showed increased fractures and falls in a study of elderly given 500,000 IU of vitamin D3 once a year [92]. The IOM recommends 600 IU daily for 70-year olds and 800 IU for >70-year olds with 4000 IU upper level intake for adults [76]. The National Osteoporosis Foundation of the USA and the American Geriatrics Society recommend 1000 IU daily [93, 94]. Replacement of vitamin D deficiency is usually done with weekly 50,000 IU for 3 months, but a small study of 163 women over age 57 showed that 800 IU daily increased serum levels to 50 mmol/l in 97.5 % [95].

Other medications

Vitamin B-12 stimulates osteoblast proliferation, and B-12 deficient patients have a higher rate of osteoporosis (odds ratio (OR): 6.9; 95 % CI: 1.2–39.4) [96]. Patients with pernicious anemia are at increased risk of fractures and 1500 mcg vitamin B-12 and 5 mg folate daily reduced hip fractures in patients over age 65 years with a NNT of 14 (95 % CI: 9–28) [97].

Statins inhibit osteoclast activation and increase osteoblast formation. A meta-analysis of 21 mostly observational studies showed modest increase in BMD, especially in the hip, and greater effect from lipophilic statins such as lovastatin and simvastatin [98]. A case-control study of 6110 patients age 65 years and older showed a 71 % reduction in hip fracture risk (adjusted OR: 0.29; 95 % CI: 0.10–0.81) [99].

Beta-blockers are thought to increase bone formation and impair osteoclastic bone resorption by inactivating the sympathetic nervous system. An Australian case-control study showed higher BMD and lower fracture rates (OR: 0.68; 95 % CI: 0.49–0.96) [100]. A very large (n>150,000) British case-control study showed a reduced OR for fracture of 0.77 (95 % CI: 0.72–0.83); for current use of beta-blockers and OR: 0.80 (95 % CI: 0.74–0.86); for current use of thiazides only OR: 0.80 (95 % CI: 0.74–0.86); and for combined current use of beta-blockers and thiazides OR: 0.71 (95 % CI: 0.64–0.79) compared with patients who did not use either beta-blockers or thiazide diuretics [101].

The other medications in this section are not approved for the treatment of osteoporosis, and the results are mostly based on observational data. RCTs are needed that may provide a starting point for the development of future osteoporosis treatments.

Risk factors

The management of osteoporosis does not only include medication treatment but also includes management of risk factors contributing to bone density loss. Both smoking and chronic heavy alcohol intake have been consistently associated with increases in osteoporotic fracture in both men and women. Smokers have decreased peripheral estrogen levels and elevated levels of cortisol, both of which decrease BMD. In addition, nicotine may have direct negative effects on osteoblasts in a dose-dependent relationship [102]. People who smoke have lower BMD and increased fracture rates [103]. Clinicians should encourage smoking cessation, cutting down on smoking, and avoidance of second hand smoke to decrease the risk of osteoporotic fractures. Quitting tobacco use decrease the excess risk of hip fracture after 10 years (RR 0.7; 95 % CI: 0.5–0.9) [104].

Heavy alcohol use can cause nutritional deficiencies and increased fall risk. In women, the level above which alcohol confers an increased risk is 7 units a week. In men, it is about 14 units a week [105].

Patients with inflammatory diseases and celiac disease are at increased risk of osteoporosis [106]. Patients with celiac disease have disordered bone metabolism due to malabsorption and chronic inflammation. Osteoporosis can even be an atypical presentation of celiac disease in adults [106].

Additionally, many medications contribute to osteoporosis. Corticosteroids decrease calcium absorption from the gut, increase calcium excretion in the kidney and interfere with replication, maturation of osteoblasts, and cause their apoptosis [107]. Most bone density is lost within the first 4 months, making early treatment essential if steroids are continued [108]. Selective serotonin reuptake inhibitors block serotonin transporters in bone and increase hip bone loss [109]. Proton pump inhibitors decrease calcium absorption due to low gastric acidity and inhibit osteoclast proton pumps that affect bone remodeling [110]. Carbamazepine induces the CYP 450 system and increases metabolism of vitamin D [111].

Epidemiologic studies have found associations between amount of caffeine intake and fracture risk [112]. Caffeine can contribute to osteoporosis by affecting bone marrow-derived mesenchymal stem cells, the precursor of osteoblasts [113], and vitamin D receptor protein expression and vitamin D-mediated actions in human osteoblast cells [114]. It also increases urinary calcium excretion for 1–3 h but has only a modest effect on bone if calcium intake is >800 mg daily [115].

Obese patients have 50 % lower serum levels of vitamin D, probably due to sequestration in the adipose tissue [116]. Bariatric surgery adds a component of malabsorption, so that 40–68 % of these patients are vitamin D deficient [117, 118]. Guidelines recommend screening for vitamin deficiency every 6 months for 2 years then annually and supplementation of calcium and vitamin D [118].

Exercise

Physical Activity has been shown to increase BMD in RCTs [119]. Strength training with non-weight bearing exercise, such as swimming [120], does not seem to have an effect on BMD, [121] and walking by itself does not improve BMD [122]. For fracture prevention, pull on the muscle seems to be the determining factor in building bone. In a 10-year follow-up, study of 2 years of back exercises showed an incidence of vertebral compression fracture of 1.6 % in the exercise group and 4.3 % (p=0.0290) in the control group [123]. A Cochrane review of 47 RCT showed no evidence that exercise prevents fractures (OR: 0.61; 95 % CI: 0.23–1.64) [124].

Fall prevention

Women with osteoporosis who fall are at increased risk of hip fracture. Research has focused on exercise to improve stability and core strength. Multicomponent

group and home exercise programs decrease the rate of falls in community dwelling elderly [125]. This exercise program includes balance training, strength, and gait training. Other interventions that decrease the risk of falling include home safety assessments, reduction in psychotropic medications, and pacemakers in people with bradycardia [125]. In addition, treatment of foot ailments and improvement in footwear as well as limiting the number of medications that an elderly person takes can also impact risk of falls [126].

Hip protectors

Hip protectors, or physical cushions worn over the hips, in an early study showed benefit when worn [127] but a subsequent intention to treat analysis showed no benefit [128]. A trial where nursing home patients wore hip protectors on one hip but not on the other side, even with 80 % adherence, showed no statistically significant difference [129]. A Cochrane Review found a small benefit in institutionalized patients, but no benefit in community dwelling patients and a small increase in pelvic fractures [130].

Kyphoplasty

Kyphoplasty in contrast to vertebroplasty uses a balloon to inflate the collapsed vertebra before injecting cement to stabilize the fracture [131]. It improves pain, function, and restores some of the vertebral body height [131]. Recent RCTs showed no benefit of vertebroplasty on pain reduction or vertebral fracture incidence [132, 133]. In a study of 63 patients with average age 75.3 years undergoing kyphoplasty, intraoperative, and postoperative complications occurred in 26.9 %, including bone cement complications in nine cases (14.3 %) [134].

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Conflict of interest
The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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