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A review of osteoporosis management in younger premenopausal women

Amber N McLendon*[1] & C Brock Woodis[2]

The purpose of this review is to describe the available evidence for osteoporosis treatments in young and premenopausal women. A review of articles evaluating the treatment or prevention of osteoporosis in young (age less than 50 years) or premenopausal women was conducted. Several trials evaluating the treatment of anorexia nervosa and use of hormone therapy in those women, the use of bisphosphonates in women undergoing chemotherapy for breast cancer and the use of bisphosphonates, teriparatide and vitamin D in women with glucocorticoid-induced osteoporosis are described. Limited data were found to support the treatment of osteoporosis in women with idiopathic osteoporosis or cystic fibrosis, or after kidney transplant. The evidence for treatment of osteoporosis in premenopausal women is not nearly as robust as that for postmenopausal osteoporosis. Although fracture risk in the premenopausal population is low, women with secondary osteoporosis may benefit from treatment with various agents, depending upon the condition.

Osteoporosis in younger women results from either a low peak bone mass, increased bone loss prior to menopause or both [1]. Peak bone mass is reached by 30 years of age with 90% of the development completed by 18 years of age [2]. For most women, bone mass remains stable until menopause, when the loss of estrogen in conjunction with aging is associated with a decline in bone mineral density (BMD). Family history, gender and race are responsible for the majority of peak bone mass; however, diet and exercise behaviors are responsible for up to 25%. Peak bone mass variations are genetic in 60–70% of cases [3]. Osteoporosis is a disease of the bone, with effects including decreased BMD and increased risk of fractures, especially at the spine, hip and wrist [4]. The loss of bone results from an imbalance in bone formation by osteoblasts and bone resorption by osteoclasts. Most treatments for osteoporosis aim to adjust this imbalance [5]. In the case of premenopausal osteoporosis, secondary causes are responsible for at least half of cases [1]. Secondary causes are listed in Table 1 [1]. In the Michigan Bone Health Study, over 600 premenopausal women followed for 6 years showed varied changes in lumbar spine (LS) BMD but a 1.6% decrease in femoral neck (FN) BMD starting in a woman's mid 20s [6]. Risk factors for low BMD in premenopausal women include low body weight, amenorrhea, lack of physical activity, smoking, low dietary calcium or vitamin D, personal or family history of fracture, pregnancy and Caucasian or Asian race [3]. Minimal bone loss is noted during pregnancy and breastfeeding; however, this loss is usually corrected shortly after pregnancy and breastfeeding are complete [7].

Healthy premenopausal women experience a 0.25–1% loss in BMD annually after reaching peak bone mass (commonly at the FN); however, no link has been established between this gradual loss in BMD and fracture risk in healthy women. Low Z-scores (2.5 standard deviations below other young females) are seen in 0.5% of premenopausal women [3]. In Spanish women 20–44 years of age, 0.34% will have osteoporosis at the LS and 0.17% will have osteoporosis at the FN based on BMD alone [1]. Overall, 50–90% of premenopausal women have a secondary cause for osteoporosis (e.g., eating disorders or glucocorticoid use, among others), with the remaining women diagnosed with idiopathic osteoporosis [8]. Fracture risk in premenopausal women with osteoporosis remains low due to the small baseline fracture risk in younger women. The incidence of fractures in females under the age of 35 years is more difficult to detect due to the low incidence of three fractures per 100,000 patient-years but is noted to increase to 21 per 100,000 patient-years in women aged 35–44 years [1]. Premenopausal fractures are associated with a 1.5- to 3-fold increase in the risk of postmenopausal fractures [3]. Fracture risk is doubled or tripled once a loss of 10% in BMD has occurred; however, treatments resulting in a 5% increase in BMD may decrease fracture risk [9].

Premenopausal women referred to a bone disease referral program at a tertiary medical center were evaluated for secondary versus idiopathic osteoporosis [10]. A retrospective review of all

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Keywords

• bisphosphonates • bone loss • female • hormone therapy • osteoporosis • premenopausal • teriparatide • treatment • vitamin D • young

Table 1. Secondary causes of osteoporosis in young women.

Causes	Examples
Medications	Glucocorticoids, anticonvulsants, aromatase inhibitors, heparin, alcohol, LHRH agonists, medroxyprogesterone acetate, high-dose levothyroxine, cytotoxic chemotherapy
Endocrine diseases	Hypogonadism, hyperthyroidism, Cushing's disease, growth hormone deficiency, hypopituitarism, hyperparathyroidism, Type 1 diabetes
Malnutrition or malabsorption	Anorexia nervosa, inflammatory intestinal disease, celiac disease, intestinal resection
Inflammatory disease	Rheumatoid arthritis, systemic lupus erythematous
Transplant patients	Solid organ and bone marrow transplants
Other causes	Liver disease, osteogenesis imperfecta, HIV infection, hemochromatosis, idiopathic osteoporosis, pregnancy, systemic mastocytosis, chronic kidney disease, malignancies, hyperprolactinemia, multiple myeloma, depression

LHRH: Luteinizing hormone-releasing hormone.
Data taken from [1,3].

premenopausal women referred for fracture or low bone mass over 1 year (n = 61) was conducted, and 39% were found to have idiopathic osteoporosis, while 49% of the 29 women with a history of low-trauma fracture had idiopathic osteoporosis. This is consistent with other measures in premenopausal women. Low-trauma fracture was defined as that occurring due to a fall from standing height or less, with the exception of digit or skull fracture. Over half of the women (57%) reported a family history of osteoporosis. Secondary osteoporosis was due to amenorrhea in 34%, anorexia nervosa (AN) in 16%, glucocorticoid use in 13% and celiac disease in 10%. Premenopausal women with secondary osteoporosis had lower BMD at the spine (Z-score: -2.39 vs -1.58; p = 0.001) and hip than those with idiopathic osteoporosis, indicating a greater need for treatment in those women with secondary causes. Of the women referred due to a fracture, 28% did not have a low BMD. Bisphosphonates were used by 47% of women with low BMD but no history of fracture and by 50% of women with idiopathic osteoporosis, which may indicate overuse of osteoporosis treatments in this population. Therefore, a need to clarify the role of osteoporosis treatments in younger, premenopausal women is needed.

The purpose of this review is to describe the available evidence for osteoporosis treatments in young and premenopausal women (Table 2).

Diagnosis

The International Society for Clinical Densitometry has developed standards for measuring BMD in premenopausal women [11]. They advocate the use of Z-scores rather than T-scores (used in postmenopausal women to describe standard deviations from a young, normal female BMD), with Z-scores of less than -2.0 at the LS or femur to determine BMD "below the expected range for age." The Z-score combined with risk factors including a history of fragility fracture is then used to make a diagnosis of osteoporosis in this younger cohort. In addition to BMD, a full medical history, family history, menstrual history, diet and exercise, lifestyle, medication history and laboratory workup should be performed to determine the underlying cause [1,3].

The US Preventive Services Task Force does not recommend BMD screening in healthy premenopausal women with no risk factors for osteoporosis [3]. Women with AN or with amenorrhea over 6 months to a year are recommended to obtain BMD screening, although the results should be interpreted carefully, as many of these young women have yet to reach peak bone mass [9].

Osteoporosis prevention in young women

The National Osteoporosis Foundation recommends that women aged 18–50 years should consume 1000 mg of calcium and 600 IU of vitamin D daily [2]. Regular weight-bearing exercise is also associated with increased BMD. Other recommended lifestyle factors are to avoid smoking and alcohol, and limit caffeine consumption.

A 2013 systematic review of calcium intake and its effects on bone health concluded that data supporting the benefits in premenopausal women were limited, although positive effects on BMD were found in children and postmenopausal women [12]. In comparison, calcium, vitamin D and increased physical activity demonstrated a positive effect in 16 premenopausal women (average age 36 years) with idiopathic osteoporosis [13]. All secondary causes of osteoporosis were excluded. The study design was observational and followed women over an average of 3 years. The subjects were instructed to take calcium 500–1000 mg/day based on dietary calcium intake, take vitamin D 400–800 IU/day, increase physical activity and avoid smoking. The exact formulation and amount of calcium, vitamin D and type and amount of exercise for each subject was not reported. Half of the

Table 2. Evidence for treatment of osteoporosis in young, premenopausal women.

Study type (length)	Population	Intervention	Results	Ref.
Diet & exercise				
Observational (3 years)	16 premenopausal women with idiopathic osteoporosis (LS Z-score: -2.04; FN Z-score: -1.47)	Ca: 500–1000 mg (dose based on dietary intake) VitD: 400–800 IU Increase physical activity and avoid smoking	↑ LS BMD 1.9% (p = 0.021) ↑ FN BMD 5.6% (p = 0.04) No fractures	[13]
Case–control (2 years)	71 premenopausal women with RA 29 controls (age: 38 years)	Sedentary Moderate exercise	Osteopenia HR: 0.53 (95% CI : 0.37–0.76) No fractures	[18]
Anorexia nervosa				
Observational	75 women with AN (age: 24 years; LS T-score: -1.8; hip T-score: -1.4)	Oral contraceptive (n = 30) Control (n = 45)	No difference between groups Controls that resumed menses: ↑ LS BMD 3.1% (p = 0.02) Controls that increased in weight: ↑ hip BMD 0.6% (p = 0.05)	[26]
Observational cohort (1 year)	38 women with AN and amenorrhea for 1 year (age: 17 years; LS T-score: -2.1)	Ethinyl estradiol 50 µg/norgestrel 0.5 mg	LS T-score: -1.8 (NSS)	[27]
Longitudinal cohort (2 years)	45 women with AN and T-score <-2.5 (age: 25 years; AN for average 8 years; amenorrhea: 7 years; LS Z-score: -2.3; FN Z-score: -3.4; hip Z-score: -3.4 Ca/VitD only in those with deficiencies)	17-β estradiol 0.5 mg days 1–21/dydrogesterone 10 mg days 11–21 (n = 12) Control (n = 33)	No difference between groups Subjects that resumed menses: ↑ LS BMD 4% (p = 0.008); ↑ hip BMD 3% (p = 0.05); ↑ FN BMD 3% (p = 0.04) Subjects that increased in weight: ↑ LS BMD (p = 0.04); ↑ hip BMD (p = 0.04); ↑ LS BMD (p = 0.04); ↑ hip BMD (p = 0.04)	[25]
Observational (1 year)	50 women with AN (age: 16 years; amenorrhea: 16 months; LS Z-score: -1.58; FN T-score: -1.58; VitD: 400 IU; Ca: 1200–1500 mg)	Oral contraceptive/standard treatment with AN 30 months (n = 22) Standard treatment with AN 16 months (n = 28)	No difference between groups	[28]
RCT (18 months)	48 women with AN and amenorrhea (age: 24 years)	Estrogen/progesterone (n = 22) Placebo (n = 26)	No difference between groups Subjects that resume menses: ↑ BMD 19.3%	[29]
RCT (13 months)	112 women with AN (age: 15 years; LS Z-score: -0.8; VitD: 400 IU; Ca: 500 mg)	Ethinyl estradiol/norgestimate (n = 53) Placebo (n = 59)	6 months: LS BMD: 2.4 vs 1% (p = 0.013) 13 months: LS BMD: 3.1 vs 2.4% (NSS)	[30]
Breast cancer				
Open label (12 months)	112 premenopausal women undergoing chemotherapy for breast cancer (n = 112; age: >40 years)	ZA 4 mg iv. every 6 months Observational group	LS BMD: ↓1.1 vs 7.5% (p < 0.001); FN BMD: ↑1.1 vs ↓3.4% (p < 0.001)	[35]

AN: Anorexia nervosa; b.i.d.: Twice daily; BMD: Bone mineral density; Ca: Calcium; CF: Cystic fibrosis; FN: Femoral neck; GIO: Glucocorticoid-induced osteoporosis; HR: Hazard ratio; im.: Intramuscular; IU: International units; iv.: Intravenous; LS: Lumbar spine; MPA: Medroxyprogesterone acetate; NSS: Not statistically significant; p.o.: Orally; QOD: Every other day; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; sc.: Subcutaneously; VitD: Vitamin D; ZA: Zoledronic acid.

Table 2. Evidence for treatment of osteoporosis in young, premenopausal women (cont.).

Study type (length)	Population	Intervention	Results	Ref.
Breast cancer (cont.)				
Open label, Phase III (3 years; and 2-year follow-up)	401 premenopausal women with hormone-responsive breast cancer undergoing treatment	ZA 4 mg iv. every 6 months Observational group	LS BMD no change vs ↓14.4% ($p < 0.001$); LS T-score no change vs ↓1.4 2-year follow-up: LS BMD ↑4% in treatment ($p = 0.02$); LS BMD ↓6.6% in observational group ($p < 0.01$); fractures zero vs two (NSS)	[36,37]
RCT (1 year; and 1-year follow-up)	103 premenopausal women with newly diagnosed breast cancer undergoing chemotherapy (age: 42 years; VitD: 400–800 IU; Ca: 1000 mg)	ZA 4 mg iv. every 3 months (n = 50) Placebo (n = 53)	LS BMD: ↓0.6 vs 4.39% ($p < 0.05$) FN BMD: ↑0.4 vs ↓1.5% ($p < 0.05$) Hip BMD: ↑2.8 vs ↓0.12% ($p < 0.05$) 1-year follow-up: LS BMD stable vs ↓ ($p < 0.01$); hip BM stable vs ↓ ($p < 0.01$)	[32,38]
RCT, Phase III (1 year)	216 premenopausal women with breast cancer preparing for chemotherapy (age: 43 years; VitD: 400 IU; Ca: 600 mg)	Risedronate 35 mg weekly (n = 108) Placebo (n = 108)	LS BMD: ↓4.3 vs 5.4% (NSS)	[39]
RCT (2 years)	53 women with breast cancer and ovarian failure	Risedronate 30 mg daily for 2 weeks every 12 weeks (n = 27) Placebo (n = 26)	LS BMD 2.5% between groups ($p = 0.041$); FN BMD 2.6% between groups ($p = 0.029$)	[42]
Glucocorticoid-induced osteoporosis				
RCT (1 year)	231 subjects with GIO or at risk for GIO on ≥7.5-mg prednisone (age: <35 years [n = 86]; 35–50 years [n = 231]; premenopausal: n = 195; VitD: 400–1200 IU; Ca: 1000 mg)	ZA 5 mg iv. for one dose Risedronate 5 mg p.o. daily	Total hip BMD: ZA > risedronate ($p = 0.025$) Vertebral fractures: five vs three (NSS) LS (age: 35–50 years) BMD: ZA > risedronate ($p = 0.0041$) Premenopausal women with GIO: ↑ LS BMD 3.1% ZA; ↑ LS BMD: 1.7% risedronate (NSS); Total hip BMD ZA > risedronate ($p = 0.025$) Premenopausal women at risk for GIO: ↑ LS BMD 1.8% ZA; ↑ LS BMD 0.7% risedronate (NSS); total hip BMD ZA > risedronate ($p = 0.049$)	[47]
RCT (18 months)	201 subjects with GIO taking prednisone ≥7.5 mg daily	Alendronate 10 mg daily (n = 99; n = 7 premenopausal women) Alphacalcidol 1 µg daily (n = 101; n = 10 premenopausal women)	LS BMD ↑2.1 vs ↓1.9%; difference 4% (95% CI: 2.4–5.5%); hip BMD ↑1.4 vs ↓2%; difference 3.4% (95% CI: 1.3–5.5); vertebral fractures: three vs 13; HR: 0.4 (95% CI: 0.1–1.4); nonvertebral fractures two vs three; HR: 0.7 (95% CI: 0.1–4)	[47,49]

AN: Anorexia nervosa; b.i.d.: Twice daily; BMD: Bone mineral density; Ca: Calcium; CF: Cystic fibrosis; FN: Femoral neck; GIO: Glucocorticoid-induced osteoporosis; HR: Hazard ratio; im.: Intramuscular; IU: International units; iv.: Intravenous; LS: Lumbar spine; MPA: Medroxyprogesterone acetate; NSS: Not statistically significant; p.o.: Orally; QOD: Every other day; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; sc.: Subcutaneously; VitD: Vitamin D; ZA: Zoledronic acid.

Table 2. Evidence for treatment of osteoporosis in young, premenopausal women (cont.).

Study type (length)	Population	Intervention	Results	Ref.
Glucocorticoid-induced osteoporosis (cont.)				
RCT (18-month interim with subset population; 36 months total for full study population)	428 subjects with GIO taking prednisone ≥5 mg daily and LS/hip (subset of 67 premenopausal women; T-score: ≤-2 or ≤-1 with fracture VitD: 800 IU; Ca: 1000 mg)	Teriparatide 20 µg sc. daily (n = 37; age 40 years; LS T-score -2.4; hip T-score -1.7; average prednisone dose 8 mg for 1.8 years; history of fracture 33%) Alendronate 10 mg daily (n = 30; age 36 years; LS T-score -2.6; hip T-score -1.8; average prednisone dose 10 mg for 0.9 years; history of fracture 28%)	↑ LS BMD 7 vs 0.7% ($p < 0.001$); ↑ hip BMD 4 vs 1% ($p < 0.01$); vertebral fractures zero for both; nonvertebral fractures two vs zero ($p = 0.32$) Full study population at 36 months: ↑ LS BMD 11 vs 5.3% ($p < 0.001$); ↑ hip BMD: 5.2% vs 2.7% ($p < 0.001$); ↑ FN BMD: 6.3 vs 3.4% ($p < 0.001$); vertebral fractures: 1.7 vs 7.7% ($p = 0.007$)	[50,51]
RCT (24 months)	20 premenopausal women with systemic lupus erythematous and osteopenia taking prednisone ≥10 mg (age: 37 years; amenorrhea: 2 years; Ca: 1000 mg)	Conjugated estrogens 0.625 mg days 1–21/MPA 10 mg days 11–21 Calcitriol 0.5 µg daily	LS BMD ↑2% ($p < 0.05$ from baseline) vs ↓1.74% ($p < 0.05$ from baseline; $p < 0.03$); no fractures	[52]
Cystic fibrosis				
RCT (12 months)	48 subjects with CF and LS/FN T-score ≤-1 (age: 27.5 years; LS T-score: -1.785; LS Z-score: -1.695; VitD: 800 IU; Ca: 1000 mg)	Alendronate 10 mg daily (n = 24; n = 9 females) Placebo (n = 24; n = 14 females)	LS BMD: ↑4.9 vs ↓1.8% ($p < 0.001$); hip BMD: ↑2.8 vs ↓0.7% ($p = 0.003$); no fractures	[54]
RCT (12 months)	56 subjects with CF and T-score <-1 (subset of 22 women; age: 29 years; LS T-score: -1.6; VitD: 800 IU; Ca: 500 mg plus 500 mg diet)	Alendronate 70 mg weekly (n = 10) Placebo (n = 10)	LS BMD: ↑ 5.2 vs ↓0.08% ($p < 0.001$); hip BMD: ↑2.1 vs ↓1.3% ($p < 0.001$); fractures NSS	[53]
Kidney transplant				
RCT (6 months; and 3 year follow-up)	20 subjects with kidney transplant (age: 49–55 years)	ZA 4 mg iv. 2 weeks and 3 months after transplant (n = 10; n = 4 women) Placebo (n = 10; n = 4 women)	LS Z-score: ↑0.23 vs ↓0.27 (significant but no p-value given); FN Z-score: ↑0.02 vs ↓0.57 (significant but no p-value given) 6 months to 3 years: Z-score ZA: -1.6 to -1.2 ($p = 0.044$); Z-score placebo: -1.3 to -0.2 ($p = 0.021$); vertebral fractures: two in each group	[55,56]
RCT (12 months)	80 subjects with kidney transplant (n = 13 premenopausal women; age: 43 years; Ca: 1000 mg)	Ibandronate iv. 1 mg before transplant and 2 mg 3 months after transplant Placebo	↓ LS BMD: 0.9 vs 6.5% ($p < 0.001$); FN BMD: ↑0.5% vs ↓7.7% ($p < 0.0001$)	[57]

AN: Anorexia nervosa; b.i.d.: Twice daily; BMD: Bone mineral density; Ca: Calcium; CF: Cystic fibrosis; FN: Femoral neck; GIO: Glucocorticoid-induced osteoporosis; HR: Hazard ratio; im.: Intramuscular; IU: International units; iv.: Intravenous; LS: Lumbar spine; MPA: Medroxyprogesterone acetate; NSS: Not statistically significant; p.o.: Orally; QOD: Every other day; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; sc.: Subcutaneously; VitD: Vitamin D; ZA: Zoledronic acid.

Table 2. Evidence for treatment of osteoporosis in young, premenopausal women (cont.).

Study type (length)	Population	Intervention	Results	Ref.
Other				
RCT (12 months)	61 female athletes with menstrual irregularities (age: 21–45 years)	Cyclic MPA 10 mg daily for 10 days with Ca 1000 mg Cyclic MPA 10 mg daily for 10 days Calcium 1000 mg daily Double placebo	LS BMD: ↑1.7% MPA plus Ca ($p = 0.004$ compared with baseline); LS BMD: ↑1.7% in MPA group; ($p = 0.004$ compared with baseline); LS BMD no change in Ca group	[58]
Observational	60 subjects with β-thalassemia major and hypogonadism (n = 30 women; age: 19 years)	17-β estradiol 50 µg daily for 21 days with MPA 10 mg for 11 days each cycle (n = 10) Untreated (n = 10) Control (n = 10)	LS BMD ↓ more in β-thalassemia groups than controls ($p < 0.001$); LS BMD ↑ more in treated than untreated group ($p < 0.001$); FN BMD ↓ more in untreated than treated group ($p < 0.001$); FN BMD ↓ more in untreated vs control group ($p < 0.001$)	[59]
RCT (12 months)	60 women with stem cell transplant and ovarian failure (age: 26 years; LS T-score: -1.4; FN T-score: -1.5)	Calcium 1000 mg/vitamin D 800 IU daily (n = 15) Estradiol 2 mg/dihydroprogesterone 10 mg for 4 days plus Ca/VitD (n = 15) Risedronate 35 mg weekly plus Ca/VitD (n = 15) ZA 4 mg iv. monthly for 3 months plus Ca/VitD (n = 15)	LS BMD: ↓ 4.3% in Ca/VitD ($p < 0.05$ from baseline); FN BMD: ↓ 4.2% in Ca/VitD ($p < 0.05$ from baseline); LS BMD stable in hormone group; FN BMD stable in hormone group; LS BMD: ↑5.8% in risedronate ($p < 0.05$ from baseline); FN BMD: ↑1.2% in risedronate (NSS from baseline); LS BMD: ↑ 8.6% in ZA ($p < 0.01$ from baseline); FN BMD: ↑ 5.4% in ZA ($p < 0.05$ from baseline) Bisphosphonates vs hormone and Ca/VitD group at LS: ($p < 0.05$); ZA vs risedronate at FN ($p < 0.001$)	[60]
RCT (6 months)	40 women with endometriosis treated with gonadotropin-releasing hormone agonists (age: 30 years; Ca: 1200 mg)	Parathyroid hormone 40 µg sc. daily (n = 20) Placebo (n = 20)	LS BMD: ↑3.4 ($p = 0.01$ from baseline) vs ↓2.8% ($p = 0.01$ from baseline; $p < 0.001$ between groups) FN BMD NSS	[61]
RCT (12 months)	32 subjects with Crohn's disease and hip T-score <-1 (VitD: 400 IU; Ca: 1000 mg)	Alendronate 10 mg daily (n = 17) Placebo (n = 15)	LS BMD: ↑4.6 vs ↓0.9% ($p < 0.01$)	[62]
RCT (6 months)	28 premenopausal women with oophorectomy (Ca: 500 mg b.i.d.)	Salmon calcitonin 100 units im. QOD Placebo	BMD stable in calcitonin group but ↓ in placebo group	[63]

AN: Anorexia nervosa; b.i.d.: Twice daily; BMD: Bone mineral density; Ca: Calcium; CF: Cystic fibrosis; FN: Femoral neck; GIO: Glucocorticoid-induced osteoporosis; HR: Hazard ratio; im.: Intramuscular; IU: International units; iv.: Intravenous; LS: Lumbar spine; MPA: Medroxyprogesterone acetate; NSS: Not statistically significant; p.o.: Orally; QOD: Every other day; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; sc.: Subcutaneously; VitD: Vitamin D; ZA: Zoledronic acid.

women had a family history of osteoporosis and 25% had experienced a fragility fracture. Nearly 40% of the subjects had low calcium intake (less than 500 mg/day) at baseline and five patients smoked. Z-scores at baseline were -2.04 at the LS and -1.47 at the FN, meeting the definition for low bone mass. Over half of the women increased their calcium intake through diet rather than supplementation. All subjects reported an increase in physical activity. A significant 1.9% increase was seen in LS BMD after 2 years ($p = 0.021$) and a 5.6% increase was seen at the FN after 3 years ($p = 0.04$). The significant increase at the FN is sufficient to reduce fracture risk. No fractures were found during the study period. This is the only study evaluating the impact of treatment in idiopathic osteoporosis and demonstrates that lifestyle changes can have a significant impact on bone health.

A meta-analysis of resistance exercise on BMD in premenopausal women did not find a statistically significant difference in LS or FN BMD [14]. Walking, jumping and resistance exercises have demonstrated a 1.2–2.6% increase in FN BMD per year ($p < 0.05$), while resistance training and weight lifting demonstrated a 0.02% increase in spinal BMD ($p < 0.05$) in healthy premenopausal women [15–17]. In a cohort study of premenopausal women with rheumatoid arthritis in Brazil (n = 71; average age: 38 years) with 29 healthy controls, women who were sedentary were found to have a higher risk of osteopenia (no hazard ratio reported; $p = 0.044$), while women with moderate levels of activity had a relative risk of 0.53 (95% CI: 0.37–0.76) [18]. No fractures were reported during the 2-year course of the study. Women with rheumatoid arthritis may limit exercise due to pain and deformities associated with the disease process. Overall, these results support the idea that an increase in exercise as tolerated can have a positive impact on BMD in premenopausal women.

Treatment

The American Association of Clinical Endocrinologists recommends the bisphosphonates alendronate, risedronate and zoledronic acid, and denosumab as first-line treatments for postmenopausal osteoporosis [19]. Ibandronate is recommended as a second-line agent, raloxifene second or third line, and calcitonin as a last-line therapy. Teriparatide is recommended for women who have failed bisphosphonates or have very high fracture risk. Oral bisphosphonates are associated with gastrointestinal (GI) adverse effects, such as heartburn, indigestion and esophageal irritation. Intravenous (iv.) bisphosphonates are associated with flu-like symptoms (fever and muscle aches), especially with the first infusion in nearly one-third of women. Osteonecrosis of the jaw (ONJ) is associated with bisphosphonate use, but is generally seen more often with iv. bisphosphonates at higher doses than those used for osteoporosis. Nausea and orthostatic hypotension have been experienced with those women using teriparatide. Calcitonin injections may be accompanied by nausea, local reactions, sweating and flushing.

Consideration of the risks of osteoporosis treatment in premenopausal women must also include risks for those women who are pregnant or breastfeeding. Concerns for placental transfer of bisphosphonates have resulted from rat studies of fetal skeletal development and hypocalcemia. Most case reports in humans have found no congenital abnormalities; however, bisphosphonates carry a US FDA category C pregnancy risk, and use of bisphosphonates without contraception is not recommended in younger females [20]. Case reports of two women with osteogenesis imperfecta treated with bisphosphonates report hypocalcemia in one newborn and club feet in the other infant [10]. Concern also exists due to the long duration of bisphosphonate incorporation in the bone [3]. One case series consisting of four infants born to three mothers (one with osteogenesis imperfecta and two with polyostotic fibrous dysplasia) who received iv. pamidronate prior to conception did not find any adverse maternal or fetal effects [21]. The FDA pregnancy risk for teriparatide is category C and iv. zoledronic acid is category D [3]. Selective estrogen receptor modulators (SERMs) should not be used in premenopausal women due to increased bone loss [8]. Although use of oral contraceptives have demonstrated mixed results in BMD of premenopausal women, the American College of Rheumatology no longer recommends estrogen as a treatment of osteoporosis in pre- or postmenopausal women [22,23]. It is important to note potential limitations when evaluating choice of drug therapy based on the FDA pregnancy risk categories. The successive categories can be misleading and it may appear that there is increasing risk of severity of malformation between categories. Furthermore, there is no distinction between source of data (i.e., animal versus human) within each category. The FDA pregnancy category classification scheme also does not address that the lack of treatment of certain comorbid conditions (e.g., diabetes mellitus, pregnancy-induced hypertension and asthma) may outweigh the risk of drug exposure to the fetus [24].

Anorexia nervosa

In women with AN, 20–50% develop osteoporosis and 44% experience a fracture [9,25]. The development of amenorrhea with AN leads to a decrease in estrogen and bone loss within 12 months. Restoring body weight is the primary treatment for osteoporosis associated with AN, while recommending exercise may prove harmful in those who have used exercise to purge. Most studies of osteoporosis in AN have focused on the replacement of estrogen as a treatment strategy. Bisphosphonate treatment in women with a history of purging may be limited due to the potential for esophageal ulcer development.

In an observational study of 75 women with AN, the average age of included subjects was 24 years with a spine T-score of -1.8 and a hip T-score of -1.4 [26]. Calcium and vitamin D intake were not analyzed. Women were followed from 6 months to 5 years. In the 45 women who did not take oral contraceptives, resuming a menstrual cycle was associated with an increase in spine BMD of 3.1% ($p = 0.02$), while an increase in weight (to greater than 85% of expected weight and/or a 10% increase) was associated with an increase in hip BMD of 0.6% ($p = 0.05$). The use of oral contraceptives was not associated with a significant change in BMD at either site, whether or not weight was gained or menses resumed. The authors summarized that weight restoration is more associated with an increase in hip BMD, while the return of menses is more associated with spinal BMD improvement.

Adolescents with AN were followed for 1 year after administration of hormone therapy to determine the medication's effect on BMD (n = 38) [27]. Baseline BMD was measured for each woman after 1 year of amenorrhea and they were treated with ethinyl estradiol 50 µg/norgestrel 0.5 mg daily. After 1 year, 22 women were available for analysis. The mean age at baseline was 17 years and the LS BMD T-score was -2.1. Calcium and vitamin D intake was not discussed. After 1 year, the LS T-score in treated women was -1.8; however, this was not significantly different from baseline.

In a longitudinal study of 45 women with AN, women with a T-score less than -2.5 were treated with 17-β estradiol 0.5 mg percutaneously for days 1–21 of each cycle and dydrogesterone 10 mg on days 11–21 for 2 years (n = 12) [25]. The mean age of women was 25 years, and those with osteoporosis had AN for 8 years, amenorrhea for 7 years and Z-scores at LS of -2.3, FN -3.4 and total hip -3.4. Calcium and vitamin D were only given to those with noted deficiencies. No significant changes in BMD were found at any site in either the treatment or control group, and there were no differences between the groups. Although hormone therapy did not result in a change in BMD, weight increase at 1 year did result in a significant increase in LS and total hip BMD ($p = 0.04$ for both), as well as a return of the menstrual cycle at the spine, total hip and FN (4%, $p = 0.008$; 3%, $p = 0.05$; and 3%, $p = 0.04$, respectively). This study further demonstrates the benefit of weight gain and return of menses in women with AN. Hormone therapy did not demonstrate a benefit, even in those women with very low BMD.

An observational study of 50 women with AN (average age: 16 years) demonstrated no benefit of hormone therapy for increasing BMD [28]. Women with anorexia were given the option, along with their treatment team and family, of standard treatment for AN (n = 28) or standard treatment plus an oral contraceptive to prevent bone loss (n = 22). Standard treatment involved medical, nutritional and psychiatric approaches. Five different oral contraceptives were used in the women. All women received a multivitamin with 400 IU of vitamin D daily and calcium 1200–1500 mg daily was given to those women without adequate dietary calcium intake. At baseline, women had experienced amenorrhea for an average of 16 months and had a LS Z-score of -1.58 and a FN T-score of -1.58 (Z-score not reported). A significant difference between the groups at baseline was a longer duration of AN in the oral contraceptive group (15.7 vs 29.8 months; $p = 0.02$). After 1 year, women in both groups gained 3–4 kg on average. However, no significant change in BMD at either the LS or FN was observed. The authors note that use of oral contraceptives in the absence of clear benefit for BMD may mask the natural return of menses that is often used to mark progress in treating AN.

Another study evaluating the effect of estrogen/progesterone on BMD in young women with AN randomized 48 women with amenorrhea to active drug (n = 22) or placebo (n = 26) for 18 months. The mean age of the subjects was 24 years. After 18 months, no difference was found between the BMD of either group [29]. Those who resumed menses had a 19.3% increase in BMD. They also noted that women with a lower weight at baseline had less recovery in their bone mass. This study further supports the role of weight gain and menses recovery over hormone therapy in women with AN.

A randomized, double-blind, placebo-controlled study of a triphasic oral contraceptive in females with AN demonstrated a significant change in LS BMD at 6 months; however, by the conclusion of the study at 13 months, the difference was no longer significant [30]. Young women were randomized to norgestimate/ethinyl estradiol (n = 53) or placebo (n = 59). The average age of subjects included was 15 years and they took a multivitamin with 500-mg calcium and 400-IU vitamin D. The baseline LS Z-score was -0.8. After six cycles, the change in BMD at the LS was 2.4% in the treatment group and 1% in the placebo group (p = 0.013). After 13 cycles, LS BMD was increased by 3.1% in the treatment group and 2.4% in the placebo group (p = 0.268). There were no significant differences in hip BMD at any time point. For those in the treatment group, adverse events were reported as follows: dysmenorrhea: 16.4%, abdominal pain: 11.5%, flu-like symptoms: 11.5% and sinusitis: 11.5%. Although this trial was shorter than the others described, it demonstrates a possible early benefit for hormone therapy on BMD but no long-term benefit. With the development of adverse events in several women, the risks of hormone therapy in these women likely outweigh any potential benefit.

Overall, the evidence does not suggest a benefit for estrogen or progesterone therapy in young women with AN. Calcium and vitamin D consumption was not analyzed in the majority of the trials; however, incorporating lifestyle changes into the treatment of AN may prove beneficial. Other osteoporosis treatments have not been evaluated in this population. The strongest evidence for improvement of BMD in women with AN is for weight gain and return of the menstrual cycle.

Breast cancer

Breast cancer treatment with gonadotropin-releasing hormone analogs, tamoxifen and aromatase inhibitors are associated with bone loss [31]. Use of these medications results in a hypogonadal state in women and contributes to accelerated bone loss of up to 13% within the first year of treatment, which is often more severe than age-related bone loss. Studies have estimated the bone loss to be 3–8% in the LS and 2–4% in the total hip [32]. Although tamoxifen is associated with increases in BMD for postmenopausal women, it is associated with a decrease in LS and hip BMD in premenopausal women due to its antagonistic effects at the bone in the presence of premenopausal estrogen. Bisphosphonates have been evaluated in this population for the prevention of bone loss associated with breast cancer treatments. Increased concerns exist for the development of ONJ in cancer patients receiving bisphosphonates beyond that of women with osteoporosis. A systematic review reported 6–10% of cancer patients receiving bisphosphonates may develop ONJ over 2–3 years [33]. The Belgian Bone Club recommends that breast cancer patients treated with aromatase inhibitors be treated with zoledronic acid 4 mg every 6 months [31]. Raloxifene is not recommended in women with a history of breast cancer who have been treated with tamoxifen due to cross-resistance [34]. Estrogens and teriparatide are also not recommended by the ASCO due to their potential to increase cancer or metastases.

An open-label trial evaluating the effect of zoledronic acid 4 mg iv. every 6 months in premenopausal women over age 40 (mean age: 44–45 years) who were undergoing chemotherapy for breast cancer (n = 112) was conducted to evaluate the effect on BMD [35]. All women took calcium 500 mg and vitamin D 1000 IU daily. At baseline, the LS BMD was 1.09 g/cm^2 and FN BMD was 0.88 g/cm^2. After 12 months, LS BMD decreased 1.1% in the zoledronic acid group (n = 56) and by 7.5% in the observation group (n = 56; p < 0.001 between groups), and FN BMD increased by by 1.1% in the zoledronic acid group and decreased by 3.4% in the observation group (p < 0.001 between groups). The only adverse events reported were chills, arthralgia and myalgia in the zoledronic acid group at the time of infusion. Although not a randomized controlled trial (RCT), these results suggest a benefit for zoledronic acid in preserving LS BMD and improving FN BMD in women with breast cancer.

An additional, open-label, Phase III trial evaluated the impact of zoledronic acid on bone loss in premenopausal women (average age: 44–46 years) receiving treatment for hormone-responsive breast cancer [36]. The Austrian Breast and Colorectal Cancer Study Group Trial 12 examined the use of goserelin in combination with aromatase inhibitors. Goserelin is associated with a 5% BMD loss in premenopausal women and aromatase inhibitors are also associated with bone loss of 4–5% over 2 years. The BMD substudy was performed to evaluate the effects of combination treatment on bone health and the impact of prevention on expected bone loss. Premenopausal women (n = 401) were randomized to goserelin plus tamoxifen or goserelin

plus anastrazole for 3 years. Each group was then further randomized to those who would receive zoledronic acid 4 mg iv. every 6 months (n = 204) or not (n = 197). Calcium and vitamin D were not discussed by the authors. At baseline, the LS BMD was 1.0 g/cm^2 and the hip BMD was 0.7 g/cm^2. Women who did not receive zoledronic acid experienced significant bone loss in the LS over 3 years (-14.4%; $p < 0.001$), with a T-score drop of -1.4; however, those who received zoledronic acid did not demonstrate a significant change in LS BMD over 3 years. Infusion reactions were the most commonly reported adverse effect of zoledronic acid therapy and most often occurred during the first infusion. Bone pain was reported in 36%, arthralgia in 28% and fever in 11% of women who received zoledronic acid ($p = 0.0003$, $p = 0.12$ and $p < 0.001$, respectively compared with placebo). There were no reports of ONJ or fractures for any women in the trial. A follow-up was conducted 2 years after the completion of the study (5 years from baseline), and women who did not receive zoledronic acid had continued declines in BMD, with a total of 6.6% loss at the LS ($p < 0.01$ from baseline) [37]. Those in the zoledronic acid group saw a 4% increase in LS BMD ($p = 0.02$) at the 60-month mark. Two fractures were reported by women in the placebo group, with none in the zoledronic acid group; however, this was not statistically significant ($p = 0.242$). In women at risk for osteoporosis while being treated for breast cancer, the use of zoledronic acid for bone protection was supported by evidence of stable BMD over 5 years compared with a sharp decline in the placebo group.

Zoledronic acid was also evaluated for prophylaxis of bone loss in women receiving chemotherapy for breast cancer [32]. The iv. route is preferred to minimize the GI adverse effects of oral bisphosphonates in women receiving chemotherapy. Premenopausal women with new diagnoses of breast cancer were randomized to zoledronic acid 4 mg iv. every 3 months (n = 50) or placebo (n = 53) for 1 year while receiving chemotherapy. The average age of participants was 42 and all were given calcium 1000 mg daily and vitamin D 400–800 IU daily. At baseline, LS Z-scores were 0.2, FN Z-scores were 0.15 and hip Z-scores were 0.17–0.25. After 12 months, women in the placebo group experienced a 4.39% decrease in LS BMD compared with 0.6% in the zoledronic acid group ($p < 0.05$). Similar results were seen for the FN (1.5% loss in the placebo group compared with a gain of 0.4% in the zoledronic acid group; $p < 0.05$) and total hip (2.8 gain vs -0.12% loss, respectively; $p < 0.05$). There were no reports of renal failure or ONJ with bisphosphonate therapy; however, 47% complained of eye discomfort, which was significantly different from placebo ($p < 0.01$). A follow-up study of the women 12 months with no intervention after the original study demonstrated significant continued bone loss in the following year at the LS and total hip for women who received placebo ($p < 0.001$ for both) but remained stable for those who had received zoledronic acid [38]. This study further describes the benefit of zoledronic acid for osteoporosis prevention in women undergoing chemotherapy for breast cancer. Adverse events experienced by women in this population are similar to those experienced by postmenopausal women.

Risedronate was evaluated for the prevention of bone loss in premenopausal women with breast cancer in a placebo-controlled, double-blind, randomized, Phase II trial of 216 women (mean age: 43 years) [39]. All patients received calcium 600 mg and vitamin D 400 IU daily. Premenopausal women preparing to undergo chemotherapy for breast cancer were randomized to risedronate 35 mg weekly (n = 108) or placebo (n = 108) for 1 year. LS BMD at baseline was 1.2 g/cm^2. At 1 year, the change in BMD at the LS was -4.3% for risedronate and -5.4% for placebo; however, the difference was not statistically significant. Adverse events were similar in both groups. This differs from studies in postmenopausal women where risedronate demonstrated an increase in BMD in women with breast cancer undergoing chemotherapy [40,41]. Another trial evaluating risedronate in 53 women with breast cancer and ovarian failure randomized women to risedronate 30 mg daily for 2 weeks every 12 weeks for 2 years (n = 27) or placebo (n = 26) [42]. After 2 years, the BMD decreased in the placebo group but increased in the risedronate group for a difference of 2.5% at the LS ($p = 0.041$) and 2.6% at the FN ($p = 0.029$). Although these studies have mixed results, overall, the data for the benefit of risedronate are not as convincing as those for zoledronic acid.

The overall data for breast cancer support the role of bisphosphonates (particularly iv. bisphosphonate zoledronic acid) for the prevention of osteoporosis associated with breast cancer treatment in premenopausal women. The safety profile in these women appears to be comparable with that for postmenopausal women, despite increased administration (every 6 months vs every year).

Glucocorticoid-induced osteoporosis

In the setting of glucocorticoid use, BMD is noted to decrease precipitously after 3 months of treatment up to 6 months with a slower, continued decline thereafter [23]. Glucocorticoids contribute to osteoporosis by inhibiting osteoblast activity and decreasing calcium absorption in the GI tract. The 2010 American College of Rheumatology guidelines report an increased risk of fracture in patients who currently receive or in the past have received 2.5–7.5 mg daily of prednisone or its equivalent. Fractures are noted to develop in patients taking glucocorticoids regardless of BMD and may occur in premenopausal women at higher BMDs than those seen in postmenopausal women. Recommendations are rated as follows: Level A (multiple RCTs or meta-analysis); Level B (single RCT or nonrandomized study); and Level C (expert consensus or case series). The authors recommend that premenopausal women on glucocorticoid treatment with history of a prevalent fragility fracture should be treated for osteoporosis, with the exception of those of child-bearing potential on therapy for less than 3 months. They also recommend that women with no child-bearing potential taking prednisone ≥5 mg or its equivalent daily for 1–3 months should take alendronate or risedronate (Level A and studied for 3–4 years); however those taking ≥7.5 mg or its equivalent should receive zoledronic acid (Level B, studied for 3 years) [43–45]. Those receiving glucocorticoid treatment for greater than 3 months may take alendronate or risedronate (Level A), zoledronic acid or teriparatide (Level B) [23]. Women with child-bearing potential taking prednisone ≥7.5 mg or its equivalent daily for more than 3 months should take alendronate (Level A), risedronate or teriparatide (Level C). These therapies were selected for their shorter half-lives. No recommendations are made for those taking less than 7.5 mg of prednisone or its equivalent for greater than 3 months. All women, regardless of dose or duration of glucocorticoid therapy, should take calcium 1200–1500 mg/day and vitamin D to achieve normal 25-hydroxyvitamin D levels, or 800–1000 IU daily. Glucocorticoid use may require the need for higher vitamin D doses in order to maintain normal levels. The authors noted a lack of data in premenopausal women that limited the strength and number of recommendations. Alendronate and risedronate have data demonstrating both improvement in BMD and a decrease in vertebral fracture risk in patients with glucocorticoid-induced osteoporosis (GIO). The American College of Rheumatology (ACR) also recommends using the lowest dose of glucocorticoid for the shortest duration possible in order to minimize osteoporosis risk.

Following the revision of the ACR guidelines in 2010, a Joint Guideline Working Group was established by the International Osteoporosis Foundation (IOF) and the European Calcified Tissue Society (ECTS) to update GIO recommendations for Europe. The Joint IOF–ECTS Working Group provided a framework for the use of oral glucocorticoid therapy at any dose for a period of 3 months or longer in male and female patients aged 18 years and older [46]. Similar to the ACR guidelines, the Joint IOF–ECTS Working Group position statement discussed epidemiology and pathophysiology of GIO as well as the Fracture Risk Assessment Tool (FRAX®, WHO, Sheffield, UK [101]). The Working Group recommended alendronate, etidronate, risedronate, zoledronic acid and teriparatide as first-line therapies for GIO in the majority of patients. Even though recommendations from the ACR were discussed in this position statement by the IOF and the ECTS, the document explicitly stated that local factors specific to each country should be taken into account when considering intervention.

As the evidence for each of the agents is well established and supported by the guidelines, trials that compare the various treatments are reviewed below.

Infused versus oral bisphosphonates were compared among different age groups and menopausal state in a *post hoc* analysis of a trial comparing zoledronic acid and risedronate [47]. The authors felt that adherence would be greater with an iv. infusion than with an oral medication and thus the chance of fractures may be reduced [48]. Subjects ranging in age from 18 to 85 years with or at risk for GIO (taking prednisone 7.5 mg or equivalent daily) were randomized to zoledronic acid 5 mg iv. once or risedronate 5 mg by mouth daily for 1 year. Pregnant women or those not using contraception were excluded. All subjects also received calcium 1000 mg and vitamin D 400–1200 IU daily. At baseline, 86 women aged less than 35 years and 231 women aged 35–50 years were included. For menopausal state, 195 premenopausal women were included. Baseline LS T-score was -1.3 to -1.4 in the treatment group and -0.9 in the at-risk group. BMD was assessed at baseline and at 12 months, and was found to be increased at the LS in women aged 35–50 years, with GIO more for zoledronic acid than risedronate ($p = 0.0041$). No significant difference was found in LS BMD

in women less than 35 years of age. The authors report that this may be due to the low sample size of women in this age range (n = 86 out of 833 total). In the subgroup of premenopausal women with GIO, zoledronic acid increased LS BMD by 3.1% compared with 1.7% by risedronate, and in premenopausal women at risk for GIO, zoledronic acid increased LS BMD by 1.8% compared with 0.7% by risedronate; however, these findings did not reach statistical significance. Total hip BMD increased significantly more in the zoledronic acid group compared with risedronate, both in women with GIO and those at risk for GIO (1.34%; p = 0.025 and 1.45%; p = 0.049, respectively). Differences between the groups appeared at 6 months. The sponsor of the study and manufacturer of zoledronic acid was involved in all aspects of the design, data collection and reporting of results. In all HORIZON (Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly) participants, five vertebral fractures developed in the zoledronic acid group and three in the risedronate group; however, the difference was not significant. No cases of ONJ were reported during the study. Adverse events were more common in the zoledronic acid group than the risedronate group overall in both the treatment and prevention groups (p = 0.0159 and 0.0272, respectively). The significant zoledronic acid adverse reactions included pyrexia 12–15%, myalgia 6–11%, vomiting 2–6%, influenza-like illness 6–7%, musculoskeletal chest pain 1–3%, sciatica 2–3% and chills 2–4%. Overall, participants preferred the iv. route for both convenience (81%) and satisfaction (78%). Based on the results of this large, well-designed trial, zoledronic acid was superior to risedronate at the hip and well tolerated in younger women with GIO.

Alendronate was compared with activated vitamin D in 201 patients with GIO over 18 months in a randomized, double-blind, double-dummy study [49]. Participants were included if they planned to start or had started prednisone 7.5 mg or its equivalent daily within the previous 12 weeks and anticipated to stay on therapy for at least 6 months due to a rheumatic condition. Subjects were randomized to alendronate 10 mg daily (n = 99) and alfacalcidol 1 µg daily (n = 101), including seven and ten premenopausal women, respectively. The average age of those in the study was 61 years with prednisone doses of 22–23 mg/day. All subjects took calcium 1000 mg and vitamin D 400 IU daily. At baseline, FN T-scores demonstrated low bone mass (-1.2 to -1.4). After 18 months, LS BMD increased by 2.1% in the alendronate group and declined by 1.9% in the alfacalcidol group, with an absolute difference of 4% (95% CI: 2.4–5.5), while hip BMD increased by 1.4% in the alendronate group and declined by 2.0% in the alfacalcidol group, for an absolute difference of 3.4% (95% CI: 1.3–5.5). Over the course of the study, three vertebral fractures developed in the alendronate group compared with 13 in the alfacalcidol group (hazard ratio: 0.4; 95% CI: 0.1–1.4). Other fractures occurred in two alendronate subjects and three alfacalcidol subjects (hazard ratio: 0.7; 95% CI: 0.1–4). Adverse events were similar in both groups, including GI complaints and hypocalcemia. This study definitively proves the superiority of GIO treatment with bisphosphonates over that of activated vitamin D. Notably, this study demonstrated a reduction in fractures with bisphosphonate treatment.

The effects of teriparatide and alendronate on LS BMD were compared in a subset of 67 premenopausal women (age: ≥21 years) with GIO from a total of 428 [50]. Men and postmenopausal women were also evaluated over 18 months. Subjects were included if they had taken ≥5-mg prednisone for ≥3 months and had a LS or hip BMD T-score ≤-2.0 or ≤-1.0 with one fragility fracture. Subjects were randomized to teriparatide 20 µg subcutaneously daily (n = 37) or alendronate 10 mg by mouth daily (n = 30). Calcium 1000 mg daily and vitamin D 800 IU daily were also given over the course of the study. The average age of women in the alendronate group was 36 and 40 years in the teriparatide group, LS T-scores of -2.6 and -2.4, total hip T-scores of -1.8 and -1.7, and a history of daily prednisone use 10 and 8 mg for 0.9 and 1.8 years, with 28 and 33% having a history of fracture, respectively. Indications for glucocorticoid use included joint, autoimmune, respiratory and bowel diseases. Five women in the teriparatide group and nine women in the alendronate group discontinued from the study (p = 0.06); most discontinued due to adverse events or subjects' decision to withdraw. Premenopausal women treated with teriparatide demonstrated a 7% increase in LS BMD compared with 0.7% in the alendronate group (p < 0.001) at 18 months. A 4% increase in hip BMD in the teriparatide group versus 1% in the alendronate group (p < 0.01) was also noted. The differences were significant at 6 months and maintained during the duration of the study. In the subjects treated with alendronate, LS BMD did not significantly differ from baseline at any time point in the study. No new vertebral fractures were detected in any premenopausal women

during the study period. Two nonvertebral fractures occurred in the teriparatide group and none in the alendronate group; however, the difference was not significant ($p = 0.32$). Adverse effects, including influenza (10%), back pain (17%), dyspnea (10%) and rash (10%), were reported in the alendronate group, and nausea (14%), influenza (11%), headache (11%), depression (8%), vomiting (14%), dyspepsia (8%), cough (8%) and myalgia (8%) were reported in the teriparatide group. The authors speculated that teriparatide demonstrated a greater impact on BMD in premenopausal women due to the mechanism of action directly altering the effects of glucocorticoids on bone, whereas alendronate does not mechanistically correct the effects of glucocorticoids in the presence of estrogen in premenopausal women [5]. A final report was issued after 36 months of treatment [51]. Although not broken down by menopausal state, teriparatide continued to significantly improve BMD at the LS (11 vs 5.3%; $p < 0.001$), total hip (5.2 vs 2.7%; $p < 0.001$) and FN (6.3 vs 3.4%; $p < 0.001$) compared with alendronate. A significant difference in vertebral fractures was also noted after 36 months, with 1.7% of participants in the teriparatide group experiencing a fracture and 7.7% of participants in the alendronate group experiencing a vertebral fracture ($p = 0.007$). Nonvertebral fractures were not significantly different. Adverse effects were significantly greater for teriparatide in the following categories: nausea 17 versus 8% for alendronate ($p = 0.007$), dyspnea 7 versus 3% ($p = 0.028$), insomnia 6 versus 1% ($p = 0.017$), viral infection 2 versus 0% ($p = 0.023$) and hypercalcemia 21 versus 7% ($p < 0.001$). Alendronate was significantly greater for weight loss 4 versus 0% ($p = 0.002$). Although bisphosphonates are commonly recommended for treatment of GIO, teriparatide has demonstrated superiority at the hip and spine, with a possible reduction in fractures compared with alendronate.

Hormone therapy was compared with calcitriol in 20 premenopausal women treated for systemic lupus erythematous with chronic steroids [52]. Women in the trial had received more than 10 mg of prednisone daily and were randomized to conjugated estrogen 0.625 mg daily days 1–21 of menstrual cycle and medroxyprogesterone acetate (MPA) 10 mg daily days 11–21, or calcitriol 0.5 µg daily. The average age of women at baseline was 37 years, they had experienced amenorrhea for 2 years, had osteopenia (LS BMD: 0.9 g/cm^2 and hip BMD: 0.7 g/cm^2) and all participants took calcium 1000 mg daily. After 24 months, LS BMD decreased significantly by 1.74% ($p < 0.05$) in the calcitriol group but increased by 2% in the hormone therapy group ($p < 0.05$). The difference between groups at the LS was significant ($p < 0.03$). No fractures were reported over the course of the study. In women with lupus, hormone therapy was superior to calcitriol for treatment of GIO.

Overall, FDA-approved treatments for osteoporosis are superior to vitamin D alone. Teriparatide and zoledronic acid have demonstrated superiority to oral bisphosphonates in women with GIO. Therapy should be based on ACR recommendations, patient history and prescriber preference.

Cystic fibrosis

With the increase in life expectancy for cystic fibrosis (CF) patients comes an increase in the development of CF-related bone disease [53]. Although the precise mechanism of bone loss in CF patients is unknown, several factors probably contribute, including lower peak bone mass due to poor nutrition and physical activity, delayed puberty and hypogonadism, use of glucocorticoids, and inflammatory cytokines. Due to the increase in osteoporosis in this population, studies have been conducted to evaluate appropriate treatments in these younger patients.

A randomized, double-blind, placebo-controlled trial of alendronate 10 mg daily was carried out in CF patients with a T-score of less than or equal to -1 at the spine or FN for 12 months [54]. Forty-eight patients were included and equally divided between the two groups. The alendronate group contained nine females and the placebo group contained 14. The average age of the participants was 27.5 years, the average LS T-score at baseline was -1.785 and the Z-score was -1.695. All subjects received 800 IU of vitamin D and 1000-mg calcium daily. The alendronate group demonstrated a significant increase in BMD at the hip (4.9 vs -1.8%; $p < 0.001$) and spine (2.8 vs -0.7%; $p = 0.003$) compared with placebo. The authors noted a greater BMD response at the spine in male subjects than female subjects. No new vertebral fractures occurred during the study period. While placebo subjects with baseline osteopenia continued to experience bone loss after 1 year, subjects taking alendronate experienced a significant increase. This demonstrates the efficacy of oral bisphosphonates in the CF population; however, as adverse events were not discussed, safety in this younger population still needs to be evaluated.

Alendronate 70 mg weekly was evaluated in 56 patients, including 22 women with CF and

a BMD T-score less than -1 in a randomized, double-blind, placebo-controlled 12-month trial [53]. All women also took vitamin D 800 IU daily and calcium 500 mg from supplementation and 500 mg from the diet daily. The average age of the participants was 29 years and the average T-score at baseline in the LS was -1.6. After 12 months, LS BMD increased by 5.2% in the alendronate group (n = 10) and decreased by 0.08% in the placebo group (n = 12), $p < 0.001$. Hip BMD increased by 2.1% in the alendronate group and decreased by 1.3% in the placebo group, $p < 0.001$. There was no significant difference in the development of new vertebral fractures over the course of the study. Adverse events were similar in both groups. This study further demonstrates the role of alendronate in improving BMD in patients with CF and demonstrates no additional safety risks in this population.

Although data are limited to small studies with one active ingredient, the future looks promising for the use of oral bisphosphonates in patients with CF and demonstrated bone loss. Additional research is needed to evaluate the long-term risks in this population.

Kidney transplantation

Fracture risk for kidney transplant patients is as high as 10% within the first 2 years, probably due to the high doses of corticosteroids used to prevent rejection. Post-transplant osteodystrophy is also due to the comorbity of diabetes in many transplant patients, along with high doses of loop diuretics. Zoledronic acid was evaluated in 20 patients for prevention of bone loss following kidney transplantation in a randomized, double-blind, placebo-controlled trial [55]. All patients received methylprednisolone as part of their antirejection regimen, with a cumulative dose of 3 g over the course of the study. They also received calcium citrate 1000 mg daily and daily injections of 0.25–0.5 µg of activated vitamin D. Participants were randomized to either zoledronic acid 4 mg iv. at 2 weeks and again at 3 months after transplant (n = 10) or placebo (n = 10). The average age of participants was 49–55 years and four out of the ten in each group were women. LS Z-scores were -0.5 to -1 and FN Z-scores were -0.8 to -1.1 at baseline. At 6 months, the LS Z-score decreased by 0.27, while the zoledronic acid group increased by 0.23. The authors report that this was a significant difference from baseline in each group; however, p-values were not listed. At the FN, the Z-score decreased by 0.57 in the placebo group (listed as significant) and remained stable (a 0.02 increase) in the zoledronic acid group. A follow-up study 3 years after transplant was performed and the Z-score in the placebo group increased from -1.3 at 6 months to -0.2 at 3 years ($p = 0.021$) and from -1.6 to -1.2 in the zoledronic acid group ($p = 0.044$) [56]. Overall, the effect of zoledronic acid was temporary as all groups experienced improvement in BMD after 3 years. Two vertebral fractures occurred in each group over 3 years. These results suggest that osteoporosis prevention may not be required in kidney transplant patients due to limited long-term benefit on BMD or fractures.

iv. ibandronate was evaluated in 80 patients (average age: 43 years) after kidney transplant, a population which included 13 premenopausal women [57]. Dietary counseling to encourage 1000 mg of daily calcium consumption was provided and supplementation of 500 mg was supplied for those with dairy intolerance. The treatment group received ibandronate 1 mg iv. before transplant (lower dose adjusted for renal function) and 2 mg iv. every 3 months after transplant for a total of four infusions over 12 months (n = 36 with six premenopausal women), while other subjects were randomized to placebo (n = 36 with seven premenopausal women). All patients received cyclosporine, prednisone (average: 12–13 mg/day) and mycophenolate mofetil to prevent rejection. At baseline, LS T-score was -0.7 and FN T-score was -0.7. BMD decreased in both groups at the LS after transplant; however, a significantly greater percentage of bone loss was noted in the control group (-0.9% ibandronate vs -6.5% control; $p < 0.0001$). Different responses at the FN were also noted (+0.5 ibandronate vs -7.7% control at the FN; $p < 0.0001$). Benefits of ibandronate were noted by the authors to occur at all sites in the subgroup of premenopausal women. Adverse effects of ibandronate included bone pain and flatulence. This study demonstrated a benefit for frequent dosing of an iv. bisphosphonate, although the long-term benefits have not been elucidated.

In the setting of kidney transplant, data are limited to support the use of any osteoporosis treatment, including iv. bisphosphonates.

Other

In athletes with resulting menstrual cycle irregularities, cyclic MPA 10 mg daily for 10 days per month was evaluated with and without calcium 1000 mg/day supplementation in a 12-month, randomized, double-blind, placebo-controlled trial. Women aged 21–45 years (n = 61) were randomized to four groups (n = 16 in both MPA groups, n = 15 in active calcium group and n = 14

in placebo group). LS BMD was increased by 1.7% ($p = 0.004$) in both MPA groups, while the calcium alone group experienced no change in BMD [58]. Calcium supplementation may be sufficient to minimize bone loss in female athletes with menstrual irregularities; however, additional evidence is needed to determine the role of hormone therapy in this population.

Hormone therapy for treatment of hypogonadism associated with β-thalassemia major was evaluated in an observational study of 60 patients, including 30 women [59]. The average age of the women was 19 years. Women were divided into three groups: those receiving hormone therapy with 17-β estradiol 50 µg daily for 21 days each month and MPA 10 mg for 11 days each cycle ($n = 10$), those untreated ($n = 10$) and a control group of women without β-thalassemia ($n = 10$). Women with β-thalassemia had decreased spine BMD compared with controls ($p < 0.001$), while estradiol/medroxyprogesterone-treated women had increased BMD at the LS compared with untreated women with β-thalassemia ($p < 0.001$). At the FN, the untreated women had significantly lower BMD than both the control group ($p < 0.001$) and the estradiol/medroxyprogesterone-treated group ($p < 0.001$). The authors concluded that osteoporosis is found at the LS and FN in untreated women with thalassemia, while osteoporosis is only present in the LS for women treated with estradiol/medroxyprogesterone. The application of these results is limited at this time due to the limited population studied.

Various osteoporosis treatments were compared in women with ovarian failure after a stem cell transplant [60]. Bone loss after stem cell transplant is often associated with ovarian failure. The authors report that standard treatment after stem cell transplant is for women to receive calcium/vitamin D and hormone replacement. Those who go on to develop osteoporosis are then treated with bisphosphonates. Four groups of 15 women were randomized to calcium 1000 mg/vitamin D 800 IU once daily alone, estradiol 2 mg daily with dihydroprogesterone 10 mg for 14 days per month with calcium/vitamin D, risedronate 35 mg weekly with calcium/vitamin D or zoledronic acid 4 mg iv. monthly for 3 months with calcium/vitamin D for 12 months. The average age of women in the trial was 26 years and baseline LS BMD was -1.4, while FN BMD was -1.5. The calcium/vitamin D group experienced a significant decrease in BMD from baseline at the spine (-4.3%; $p < 0.05$) and FN (-4.2%; $p < 0.05$), while the hormone therapy group remained stable at all sites. The risedronate group demonstrated a significant increase in BMD at the LS (5.8%; $p < 0.05$) and the zoledronic acid group demonstrated a significant increase at the LS (8.6%; $p < 0.01$) and FN (5.4%; $p < 0.05$). Both bisphosphonates were significantly different from the calcium/vitamin D and hormone treatment groups at both sites ($p < 0.05$), while the zoledronic acid group experienced a significantly greater increase in BMD at the FN than the risedronate group (5.4 vs 1.2%; $p < 0.0001$). Vertebral fractures were found in five women at baseline and three additional vertebral fractures occurred during the 12 months. The study was not powered to detect a difference in fractures. Adverse effects occurred in six out of 15 women in the hormone treatment group (headache and breast tenderness), three out of 15 women in the risedronate group (gastric pain) and flu-like symptoms in 12 out of 15 women in the zoledronic acid group. Overall, nonhormonal osteoporosis treatment proved superior to placebo or hormone replacement in women with ovarian failure after stem cell transplant. Either oral or iv. bisphosphonates may prove beneficial in this population, although further studies on fracture reduction should be carried out to determine overall benefit.

Women with endometriosis who were treated with gonadotropin-releasing hormone agonists were randomized to treatment with parathyroid hormone 40 µg subcutaneously daily ($n = 20$) or placebo ($n = 20$), and followed for 6 months [61]. Subjects (average age: 30 years) remained on nafarelin 200 µg intranasally twice daily throughout the study and were encouraged to maintain daily consumption of calcium at 1200 mg through diet or supplements. LS BMD was 0.8 g/cm^2 and FN BMD was 0.9 g/cm^2 at baseline. At the LS, BMD decreased by 2.8% from baseline ($p < 0.001$) in the placebo group, while BMD in the treated group increased by 3.4% ($p = 0.01$). The difference between the two groups reached significance ($p < 0.001$). No differences were noted between the groups at the FN. Adverse effects in the parathyroid hormone group were reported as follows: emotional instability 40%, nausea 35%, arthralgia 30%, weight gain 15% and hair loss 10%. Due to the limited evidence in this population and comparison with placebo rather than other active treatments, no recommendations can be made at this time. Multiple adverse events were associated with parathyroid hormone, which may also limit its use in this population.

Alendronate was evaluated in patients with Crohn's disease and low BMD (T-score less than -1 in either the hip or spine) in a randomized, double-blind, placebo-controlled trial of 32 patients over 12 months [62]. Subjects were randomized to alendronate 10 mg daily (n = 17) or placebo (n = 15), with vitamin D 400 IU daily and calcium if dietary intake was below 1000 mg daily. LS BMD increased by 4.6% in the alendronate group and decreased by 0.9% in the placebo group ($p < 0.01$). BMD was noted to increase in premenopausal, as well as postmenopausal women. In women with low T-scores and Crohn's disease, this study supports the use of alendronate to improve BMD. Additional studies are needed to ascertain the benefits for fracture prevention.

Calcitonin was evaluated in 28 premenopausal women with recent oophorectomy to prevent bone loss [63]. Women were randomized to 100 IU of salmon calcitonin or placebo intramuscular every other day starting 7 days after oophorectomy for 6 months, then all women were given active calcitonin for an additional 6 months. Additionally, the participants received calcium 500 mg twice daily. While the placebo-treated patients experienced a significant decrease in BMD after 12 months, the calcitonin-treated group did not see a decline. Due to the small and limited studies, calcitonin cannot be recommended for prevention of bone loss in premenopausal women with oophorectomy.

Conclusion

Osteoporosis diagnosis and management is clearly defined for postmenopausal women, where the risks for fractures and benefits of treatment have been well studied. Osteoporosis discovery and treatment in younger, premenopausal women is less well defined due to the minimal risk of fractures and lack of large RCTs. Premenopausal osteoporosis is often a result of an underlying condition or medication, and management is

Executive summary

Background

- Healthy premenopausal women experience a 0.25–1% loss in bone mineral density (BMD) annually after reaching peak bone mass, and osteoporosis may be seen in 0.5% of premenopausal women.
- Many cases are due to secondary causes; however, the remaining cases are idiopathic in nature.

Diagnosis

- The International Society for Clinical Densitometry advocates the use of Z-scores rather than T-scores to determine BMD "below the expected range for age."
- The Z-score combined with risk factors, including a history of fragility fracture, is then used to make a diagnosis of osteoporosis in younger women.

Osteoporosis prevention in young women

- The National Osteoporosis Foundation recommends that women aged 18–50 years should consume 1000 mg of calcium and 600 IU of vitamin D daily.
- This, along with regular weight-bearing exercise, avoiding smoking and alcohol, and limiting caffeine consumption, are important lifestyle factors to prevent or minimize osteoporosis in young women.

Anorexia nervosa

- Hormone therapy does not demonstrate benefit in young women with anorexia nervosa.
- The strongest evidence for improvement of BMD is for weight gain and return of the menstrual cycle.

Breast cancer

- The overall data for bone loss associated with breast cancer and chemotherapy support the role of bisphosphonates (particularly the intravenous bisphosphonate zoledronic acid).
- The safety profile is similar to that for postmenopausal women, although risks in pregnancy and breastfeeding have not been established.

Glucocorticoid-induced osteoporosis

- In younger women with glucocorticoid-induced osteoporosis, recommendations from the American College of Rheumatology and the International Osteoporosis Foundation/European Calcified Tissue Society are available.

Cystic fibrosis

- Alendronate has demonstrated benefit in young women with cystic fibrosis and demonstrated bone loss.
- Additional research is needed to evaluate the long-term risks in this population.
- Data are limited to support the use of any osteoporosis treatment in other conditions not listed above.
- The evidence for treatment of osteoporosis in premenopausal women is not nearly as robust as that for postmenopausal osteoporosis. Data are limited to recommend osteoporosis treatment outside the setting of a previous fracture or an underlying secondary cause.

dependent on the underlying cause. Although fracture risk in the premenopausal population is low, women with secondary osteoporosis may benefit from treatment. For young women with AN, treatment of the underlying disease is associated with increases in BMD, while hormone therapy does not demonstrate a benefit. In the setting of women undergoing chemotherapy for breast cancer, zoledronic acid has shown promise for improving BMD and may also prevent fractures. GIO may be treated with either the bisphosphonates or teriparatide, since safety and efficacy of these agents are well established in this population. Evidence is also supportive for alendronate in women with CF-associated bone loss. In other conditions, the data are limited to recommend osteoporosis treatment in premenopausal women.

Future perspective

The American College of Rheumatology has called for additional studies of the fracture risk and risks of long-term osteoporosis treatment in premenopausal women receiving glucocorticoids. Ongoing studies will provide additional information on long-term risks of fetal exposure to osteoporosis treatments [23]. Denosumab, one of the newer osteoporosis treatments, is currently being investigated in young women with breast cancer [102]. Overall, studies for indications beyond those discussed here may elucidate further roles for treatment in younger women, particularly in the settings of premature menopause and CF. With increased attention to the issue, additional understanding of the fracture risk in this population will also allow for improved treatment decisions, as the FRAX fracture risk assessment tool has done for postmenopausal women.

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