Osteoporosis Management with Focus on Spine

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Abbreviations

AAOMS	American Association of Oral and Maxillofacial Surgeons
ADT	Androgen deprivation therapy
AIs	Aromatase inhibitors
BMD	Bone mineral density
Dmab	Denosumab
DXA	Dual-energy X-ray absorptiometry
FMP	Final menstrual period
GC	Glucocorticoids
HRT	Hormonal replacement therapy
MOF	Major osteoporotic fractures (the spine, hip, wrist, or humerus)
OFS	Ovarian function suppression
ONJ	Osteonecrosis of the jaw
ROI	Region of interest
SERM	Selective estrogen receptor modulators
TBS	Trabecular bone score
VTE	Venous thromboembolism
ZA	Zoledronic acid

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Osteoporosis is one of the most prevalent bone diseases and is associated with age. Based on the US Census Bureau population estimate, about 115 million people are ≥50 years old among 327 million of the entire population as of July 1, 2018. The number of Americans 65 years and older is projected to increase from 52 million (16%) in 2018 to 95 million (23%) by 2060. Life expectancy was reported as 78.6 years for a total US population in 2017 compared with 69.9 years in 1959 [1].

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [2]. It is a silent disease until fracture/s occur following minimal trauma or, in some cases, with no trauma [3]. Vertebral fractures are the most common manifestation of osteoporosis [4]. The prevalence of radiographic VF increases with age, ranging from 5% to 10% at ages 50–59 years to ≥30% at age 80 years and older in Caucasian women [4, 5]. Vertebral and hip fractures are associated with excess mortality [6]. However, the majority of VF are not diagnosed at the time of occurrence. A previous spine fracture has been reported to increase the risk of next vertebral fracture by fivefold during the following year [7], with almost 20% of women developing a VF within the next 12 months. Patients with no fracture, ≥1 fractures, or ≥2 fractures at baseline developed new vertebral

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fractures in the following 12 months at a rate of 3.6%, 21.9%, and 24.0%, respectively [7].

Screening for Osteoporosis

Recommended Bone Mineral Density (BMD) Testing Based on the Official Positions by ISCD (2019) (https://www.iscd.org/official-positions/2019-iscd-official-positions-adult/)

- Women aged 65 and older and men aged 70 and older.
- Postmenopausal women age <65 and men <70 years if they have a risk factor for low bone mass such as low body weight, prior fracture, high-risk medication use, or disease or condition associated with bone loss.
- Women during the menopausal transition with clinical risk factors for fracture as above.
- Adults with a fragility fracture (any fall from a standing height or less that results in a fracture).
- Adults with a disease or condition associated with low bone mass or bone loss.
- Adults taking medications associated with low bone mass or bone loss.
- Anyone being considered for pharmacologic therapy.
- Anyone being treated, to monitor treatment effect.
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment.
- Women discontinuing estrogen should be considered for bone density testing according to the indications listed above.

Clinical risk factors for fracture that are independent of femoral neck BMD and included in the FRAX® fracture risk calculator are previous fracture, parent with hip fracture, current smoking, long-term glucocorticoid therapy, rheumatoid arthritis, alcohol intake ≥3 units/day, and trabecular bone score.

Other medications associated with low bone mass, bone loss, and/or increased risk of fractures are long-term glucocorticoids (GC, a daily dose ≥5 mg prednisone or equivalent for ≥3 months), calcineurin inhibitors, medications that decrease sex steroids (e.g., androgen deprivation therapy [ADT], aromatase inhibitors [AI], gonadotropin-releasing hormone [GnRH] agonists/antagonists, opioids), antiseizure drugs (e.g., phenytoin, barbiturates), thiazolidinediones, canagliflozin, excessive use of aluminum-containing antacids, H2 receptor blockers, proton pump inhibitors, excessive thyroid hormone, selective serotonin reuptake inhibitors, and heparin [8].

Dual-energy X-ray absorptiometry (DXA) is the gold standard for BMD measurement in clinical practice. Based on the International Society for Clinical Densitometry (ISCD) 2019 Official Position, bone health assessment should be considered in patients before an elective [9] orthopedic or spine surgery. BMD by DXA should include lumbar spine (LS), hip, and in some cases the one-third (33%) radius. Vertebral fracture assessment (VFA) should be considered in patients having spine surgery [10]. Patients with diabetes mellitus, inflammatory arthritis, history of chronic GC use, history of a low-trauma fracture after 50 years of age, chronic kidney disease (CKD) stages 3–5, and limited mobility and smokers who are candidates for an elective orthopedic or spine surgery should have DXA testing. Trabecular bone score (TBS) measurement, when available, should be considered when there is concern about bone quality, such as in patients with diabetes [9, 10]. For patients planning to have a lumbar spinal fusion, preoperative DXA evaluation of both hips and forearm should be considered, since postoperative monitoring of BMD at the LS may not be possible due to the confounding skeletal effects of surgery.

TBS provides assessment of trabecular microarchitecture and is an input for estimating fracture risk with FRAX® (https://www.sheffield.ac.uk/FRAX). Among patients with a median age of 71 years (55.5–85 years), 47% have been demonstrated TBS <1.2, classified as degraded bone microarchitecture; accordingly, it has be suggested that TBS may be useful in assessing skeletal health prior to lumbar spine surgery [11]. Moreover, TBS has been shown to predict spine

fragility fractures in non-osteoporotic patients independently of BMD [12].

Measurement of BMD by DXA before spinal surgery, especially in females older than 50 years, has been proposed [13], with prompt referral to a primary care provider or osteoporosis specialist for workup for secondary causes of low BMD and management of osteoporosis before any planned surgical procedure [14]. Based on the literature, about 74–85% of patients have been shown to be vitamin D deficient before spinal procedures [15, 16]. Vitamin D deficiency can lead to secondary hyperparathyroidism and increase bone resorption. Elevated parathyroid hormone (PTH) was found in 35.4% of patients before spinal surgery [16]. Vitamin D deficiency should be corrected before elective bone surgery.

Since patients who are candidates for an elective spinal procedure typically have extensive imaging of the spine, often including a CT scan, these imaging studies may identify a previously unrecognized vertebral fracture and provide an "opportunistic" measurement of BMD. L1 vertebral body trabecular attenuation by CT was proven to be an alternative and reliable method to determine BMD. L1 trabecular attenuation has been proposed as a method to identify individuals at high risk for fracture [17]. Based on ISCD recommendations, opportunistic CT-based attenuation using Hounsfield Units (HU) can be used to estimate the likelihood of osteoporosis (L1 HU < 100) and normal (L1 HU > 150) and support decisions regarding bone health assessment [10]. Other authors have proposed an L1 HU threshold of 99 and 136 HU for the diagnosis of osteoporosis [18–20].

Algorithm of perioperative assessment and management is described in Fig. 4.2.

Review of Anti-osteoporosis Medication and How to Choose the Appropriate Medication

Mechanism of Action (see Fig. 4.1)

Bisphosphonates (BPs)

Class of medication: antiresorptive, inhibition of bone remodeling

Drug: small molecular drug

Target cells/tissue: osteoclasts/bone tissue

BPs are synthetic, nonhydrolyzable analogues of inorganic pyrophosphate. As pyrophosphate derivatives, BPs have a very high affinity for hydroxyapatite crystals in bone tissue and are

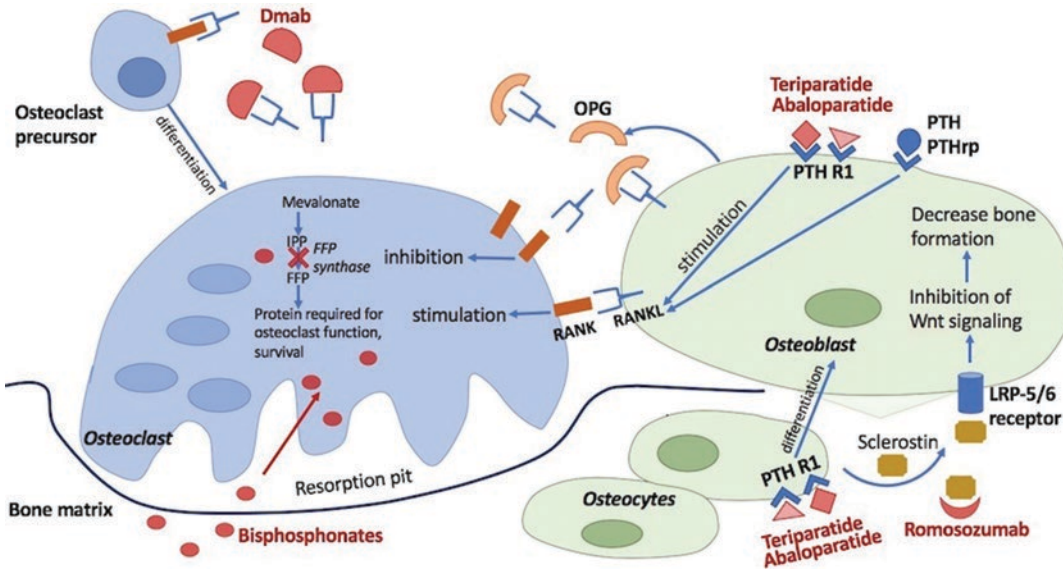

Fig. 4.1 Mechanism of action of the anti-osteoporosis medications. *Dmab* denosumab, *IPP* isopentenyl diphosphate, *FDPS* farnesyl diphosphate, *OPG* osteoprotegerin

preferentially incorporated into sites of active bone remodeling [21].

Oral nitrogen-containing BPs are absorbed throughout the GI tract, but absorption is very low, <1% [21, 22], and only about 50% of BP is retained in the skeleton, with the remainder rapidly eliminated without being metabolized by renal clearance [21]. BPs are probably transferred to bone via entering the bone extracellular space by paracellular transport and bind to free hydroxyapatite that is available on the surface [23]. In vivo BPs bind to bone mineral surfaces at sites of active bone remodeling, particularly areas of resorption [24]. BPs bind to bone mineral and then are released during bone resorption and enter osteoclasts. BPs do not cross cell membranes; however, in the acidic environment that osteoclasts create for the bone matrix resorption, BPs will be accumulated in osteoclasts.

In osteoclasts, BPs disrupt intracellular enzymatic reaction by inhibiting farnesyl diphosphate (FDPS) synthase that leads to inhibition of farnesylated and geranylgeranylated protein synthesis required for osteoclast function and survival [25, 26]. BPs have a highly selective effect on osteoclasts, induce osteoclasts apoptosis, and suppress osteoclast-mediated bone resorption (see Fig. 4.1). Since BPs slow bone remodeling cycle, and in normal bone remodeling, resorption and formation are coupled, formation and resorption are both decreased, although resorption is inhibited more than formation.

The highest skeletal concentration of BP is found in the spine vs. femur shaft [27–29]. Release of BPs from bone matrix depends on bone turnover. BPs also undergo recycling when in bone tissue and can be retained there for many years [30].

There is no improvement in trabecular microarchitecture with BPs. The increase in BMD is due to enhanced secondary mineralization of preformed osteons and closure of the existing skeletal remodeling space [31, 32].

Denosumab (Dmab)

Class of medication: antiresorptive, inhibition of bone remodeling

Drug: human monoclonal antibody

Target cells/tissue: osteoclasts, osteoclast precursors

Dmab is a fully human monoclonal antibody that inhibits receptor activator of NFκB ligand (RANKL). RANKL is expressed by osteoblastic stromal cells and is required for osteoclast precursor differentiation via interaction with RANK which is expressed on many cell types including osteoclast precursors and mature osteoclasts. Preventing binding of RANKL to RANK leads to inhibition of the osteoclast function, decrease in bone resorption, and slow bone resorption.

In contrast to BPs, Dmab does not accumulate in bone tissue but is highly specific to RANKL (see Fig. 4.1). Dmab is cleared by the reticuloendothelial system with half-life of about 26 days [30].

Teriparatide

Class of medications: anabolic

Drug: a recombinant fragment of human PTH (PTH 1–34)

Target cells/tissue: osteoblasts

Intermittent administration of teriparatide upregulates bone remodeling, increases bone formation in excess of bone resorption, and improves bone structure [33]. The bone formed by teriparatide is characterized by increased cancellous bone volume and connectivity, improved trabecular morphology, and a shift toward a more plate-like structure, with increased cortical bone thickness [34]. Teriparatide also activates osteoclasts; however, the anabolic effects dominate [35].

Abaloparatide

Class of medications: anabolic, bone formation via bone modeling mechanism

Drug: a synthetic analogue of PTHrP (1–34)

Target cells/tissue: osteoblasts

Abaloparatide has 41% homology to PTH (1–34) and 76% homology to parathyroid hormone-related protein (PTHrP) (1–34). The effects of abaloparatide on bone metabolism are similar to teriparatide. However, abaloparatide has less pronounced activation effect on osteoclasts vs. teriparatide [36] (see Fig. 4.1).

Romosozumab

Class of medications: anabolic and antiresorptive

Drug: humanized monoclonal antibody

Target cells/tissue: osteocytes, osteoblasts

Romosozumab is a humanized monoclonal antibody against sclerostin. Sclerostin is a glycoprotein produced by osteocytes and an inhibitor of the Wnt pathway, a bone formation regulator. Inhibition of sclerostin leads to increase in osteoblastic differentiation, proliferation, and survival. In the presence of romosozumab, the Wnt signaling pathway is activated, leading to bone formation and bone mineral density gain. Romosozumab also decreases the bone resorption. It binds to the circulating sclerostin [37] (see Fig. 4.1). The metabolism of romosozumab is likely similar to other monoclonal antibodies. Systemic absorption after SC injection is via the lymphatic vessels to the blood compartment. Elimination of monoclonal antibody is expected to be via protein catabolism by degradation into small peptides and amino acids. Partial elimination may occur at the target cells by endocytosis and intracellular degradation that is concentration dependent due to saturation effect [38, 39]. The role of hepatic and renal excretion in elimination is minor [40].

Table 4.1 shows the US Food and Drug Administration (FDA)-approved bone-targeted medications. A suggested approach to decision-making and the precautions regarding anti-osteoporosis medication are described in Figs. 4.2 and 4.3.

Effect of BMD on Spinal Surgery Outcome: Optimization of Spinal BMD Before Spinal Surgery and Postsurgical Management of Osteoporosis

Assessment of bone health before spine surgery is a crucial step for achieving optimal surgical outcomes. Low BMD is a major risk factor for poor screw fixation, screw loosening, and fixation failure, since the ability of screws to resist pullout from bone is directly related to BMD [41, 42]. The vertebral body bone is mostly trabecular bone covered by a thin shell of cortical bone [43]. More metabolically active vertebral trabecular bone is usually more affected by osteoporosis than cortical bone [42].

The prevalence of osteopenia and osteoporosis for patients requiring spine surgery is high and increases with advancing age. Older patients are more prone to VFs and more likely to experience complications from surgery [44]. Osteoporotic bone is less dense and has poor vascularity, discontinuity and thinning of the bony trabeculae, low osteoblast activity, and poor bone marrow quality [42]. In a study of patients having BMD testing with DXA prior to spine surgery, in those age <50 years, 2.3% were classified with osteopenia and 0.3% with osteoporosis [13]. However, for those age >50 years, osteopenia was found in 46.1% of male and 41.4% of female patients, while osteoporosis was diagnosed in 14.5% of male and 51.3% of female patients [13].

Currently, there is no FDA approval for antiresorptive or anabolic medications prior to spine surgery to improve surgical outcomes, although these medications are approved and commonly used to prevent and/or treat osteoporosis. Treatment should be considered in patients prior to spine surgery when the T-score is in the osteoporosis range (≤ -2.5); when fracture probability is high (e.g., T-score between -1.0 and -2.5 and the FRAX® 10-year probability for major osteoporotic fracture is $\geq 20\%$ or $\geq 3\%$ for hip fractures); or when there has been one or more prior adult fractures, especially at the hip or spine within the past year.

The incidence of osteoporosis-related complications, such as revision surgery, compression fracture, proximal junctional kyphosis, pseudarthrosis, or failure of instrumentation following posterior lumbar fusion has been shown to be significantly higher among patients with osteopenia and osteoporosis (33% and 50%, respectively) in comparison to patients with normal BMD (23%) [45]. Nonunion rates are significantly higher for patients with osteoporosis [45].

It is important to note that successful treatment of osteoporosis that increases the T-score to >-2.5 *does not change* the diagnosis of osteo-

Table 4.1 FDA-approved medications for treatment of osteoporosis and in patients with malignancies with and without bone metastases

Drug	FDA-approved indications	Effect on fractures	Effect on BMD	Prevention dose	Treatment dose
Bisphosphonates: antiresorptive effect					
Risedronate Actonel® Atelvia®	*Women and men* *Prevention*: Postmenopausal and glucocorticoid-induced osteoporosis *Treatment*: Postmenopausal, glucocorticoid induced, and in men with osteoporosis Paget disease of bone	Decreased incidence of new and worsening vertebral and non-vertebral fractures	Increased BMD at the spine, hip, and wrist	5 mg/day PO 35 mg/weekly PO 150 mg/mo PO	5 mg/day PO 35 mg/weekly PO 150 mg/mo PO Atelvia® (35 mg/weekly PO) is delayed release form that can be used regardless of food intake, for pts with upper GI problems
Alendronate Fosamax®, Fosamax Plus D® Binosto®	As above	Decreased vertebral, hip, and non-vertebral fractures	Increased BMD at the spine, femoral neck, and trochanter	5 mg/day PO 35 mg/weekly PO	10 mg/day PO 70 mg/weekly PO 70 mg with vitamin D (2800 U or 5600 U) PO Binosto® 70 mg effervescent tablet
Ibandronate Boniva®	*Prevention*: Postmenopausal osteoporosis *Treatment*: Postmenopausal, osteoporosis	Decreased incidence of new and worsening vertebral fractures *No* effect on non-vertebral fractures	Increased BMD at the lumbar spine, total hip, femoral neck, and trochanter	2.5 mg/day PO 150 mg/mo PO	2.5 mg/day PO 150 mg/month PO 3 mgIV q3 mo
Zoledronic acid Reclast®	*Women and men* *Prevention*: Postmenopausal and glucocorticoid-induced osteoporosis *Treatment*: Postmenopausal, glucocorticoid induced, and in men with osteoporosis; Paget disease of bone	Decrease vertebral, hip, and non-vertebral fractures	Increased BMD at the lumbar spine, total hip, femoral neck	5 mg q2 years (q2y is for prevention in women; q1y is for treatment; for Paget disease, often only 1 dose is needed)	5 mg/annually Some providers suggest extending the dosing interval when fracture risk has reached an acceptable level (Bone TeleECHO, Dr. Lewiecki)
Zoledronic acid Zometa®	Hypercalcemia of malignancy (Ca >12 mg/dL) Multiple myeloma for men and women Bone metastases from solid tumors Prostate cancer should have progressed after treatment with at least one hormonal therapy The safety and efficacy have not been established in HPTH or nontumor-related hypercalcemia		Decreased SREs in pts with prostate cancer	Hypercalcemia of malignancy: 4 mg IV over >15 min, retreatment after a minimum of 7 days Multiple myeloma and bone metastasis from solid tumors: 4 mg every 3–4 weeks if CrCl >60 mL/min Reduce the dose for patients with renal impairment	

Table 4.1 (continued)

Drug	FDA-approved indications	Effect on fractures	Effect on BMD	Prevention dose	Treatment dose
Pamidronate Aredia®	Moderate/severe hypercalcemia of malignancy with or without bone metastases Moderate to severe Paget disease of bone Breast cancer osteolytic bone metastases or multiple myeloma osteolytic lesions The safety and efficacy have not been established in HPTH or nontumor-related hypercalcemia		Decrease in SRE, skeletal morbidity rate, time to SRE in pts with breast cancer on chemotherapy Decrease in skeletal morbidity rate when on hormonal therapy Multiple myeloma: Decrease in SRE, pathological fractures, radiation to bone	60–90 mg infused over 2–24 h for moderate hypercalcemia, or 90 mg for severe hypercalcemia; can retreat after a minimum of 7 days Paget disease of bone: 30 mg as a 4-h infusion on 3 consecutive days Breast cancer osteolytic bone metastases: 90 mg IV, 2-h infusion q 3–4 weeks; retreat after renal function recovery Multiple myeloma osteolytic bone lesions: 90 mg as a 4-h infusion q4 weeks; retreat after recovery of renal function	
RANKL inhibitor: antiresorptive effect					
Denosumab (Prolia®)	*Women and men* Postmenopausal osteoporosis at high risk for fracture Increased BMD in men on androgen deprivation therapy for nonmetastatic prostate cancer Increased BMD in women on adjuvant aromatase inhibitor therapy for breast cancer	Decrease of vertebral, hip, and non-vertebral fractures	Increased BMD at the lumbar spine, total hip, femoral neck	No	60 mg SC q6 mo upper arm, upper thigh, or abdomen *Should be administered by a healthcare provider*
Denosumab (Xgeva®)	Prevention of SREs in patients with bone metastases from solid tumors Treatment of giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity Not for the prevention of SREs in patients with multiple myeloma		Prevention/delay of SREs in patients with bone metastases from solid tumors	120 mg Xgeva® SC every 4 weeks *Should be administered by a healthcare provider*	
Sclerostin inhibitor – inhibition of resorption and stimulation bone formation					
Romosozumab (Evenity®)	*Women* Postmenopausal osteoporosis in women at high fracture risk (h/o osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available options)	Decrease of vertebral fractures	Increased BMD at the lumbar spine, total hip, femoral neck	No	2 separate SC injections for total dose of 210 mg q 4 weeks for 12 months in abdomen, thigh, or upper arm *Should be administered by a healthcare provider* No lifetime limit of exposure or contraindication to retreatment

(continued)

Table 4.1 (continued)

Drug	FDA-approved indications	Effect on fractures	Effect on BMD	Prevention dose	Treatment dose
Anabolics: increased bone formation					
Teriparatide Forteo® Bonsity	*Women and men* Glucocorticoid-induced osteoporosis Postmenopausal osteoporosis at high risk for fracture Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture	Decrease in vertebral and non-vertebral fractures	Increased BMD at the lumbar spine, total hip, femoral neck, trochanter	No	20 mcg/daily SC Pre-filled pen for 28 days
Abaloparatide Tymlos®	*Women* Postmenopausal osteoporosis at high risk for fracture	Reduces vertebral and non-vertebral fractures	Increased BMD at the lumbar spine, total hip, femoral neck	No	80 mcg/day SC Pre-filled pen = 3120 mcg for 30 days
Other					
Calcitonin Fortical®, Miacalcin®	*Women* *Injections:* Symptomatic Paget disease of bone when alternative treatments are not suitable Hypercalcemia Postmenopausal osteoporosis when alternative treatments are not suitable *Intranasal spray:* Postmenopausal osteoporosis in women more than 5 years postmenopause when alternative treatments are not suitable	Fracture reduction efficacy has not been demonstrated in osteoporosis Fracture reduction efficacy has not been demonstrated in osteoporosis	No data	No	Paget disease of bone: 100 IU/day Hypercalcemia: 4–8 IU/kg q12 Postmenopausal osteoporosis: 100 IU/day 200 IU/day (one spray) alternating nostrils
Selective estrogen receptor modulators (SERMs): Estrogen-like effect on bones in postmenopausal women only					
Raloxifene Evista®	*Women* Treatment and prevention of postmenopausal osteoporosis Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer	Decreased vertebral fractures	Increased BMD at the spine, total hip, femoral neck, trochanter	60 mg/day PO	60 mg/day PO

BMD bone mineral density, *HPTH* human parathyroid hormone, *SRE* skeletal-related event, *RANKL* receptor activator of NFκB ligand

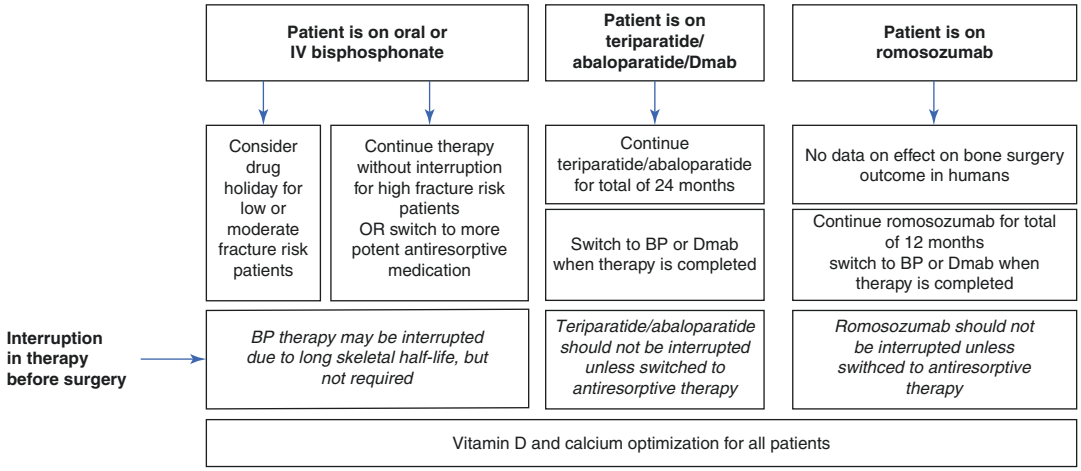

Fig. 4.2 Considerations for patients on osteoporosis treatment before planned surgery. *BP* bisphosphonates, *Dmab* denosumab

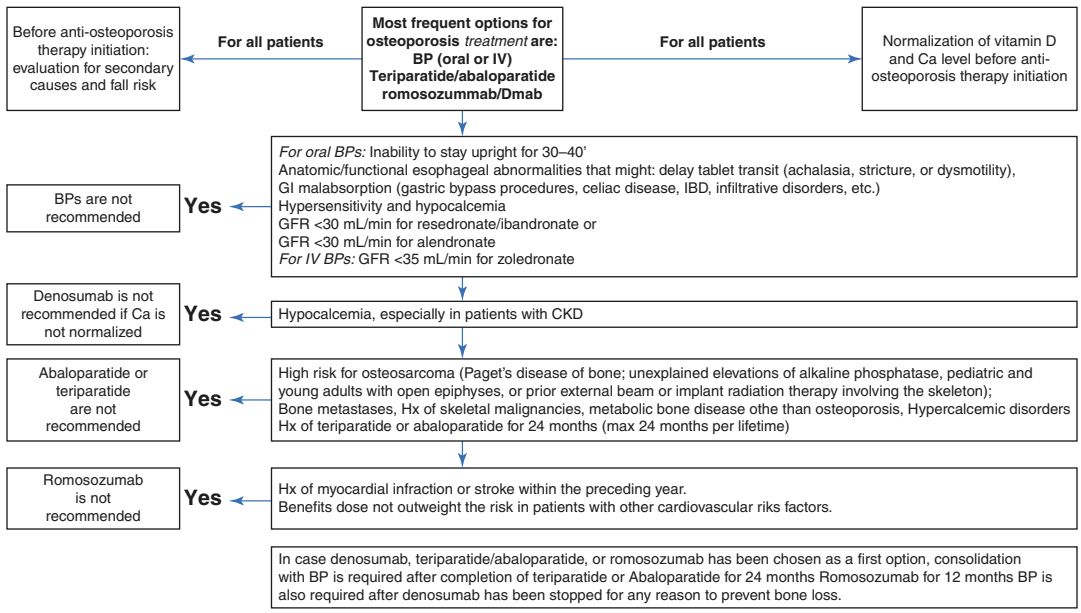

Fig. 4.3 Precautions for the use of osteoporosis medications

porosis, since antiresorptive therapies do not restore degraded bone microarchitecture, which is a key in the osteoporosis definition [46]. Even though anabolic agents may partially improve microarchitecture, the effect will be rapidly lost without consolidation therapy with antiresorptive medication.

Patients who have been treated with zoledronic acid (ZA) within the previous 5 years have been shown to have a prolonged antiresorptive effect and may not need additional anti-osteoporosis treatment. In an open-label extension of a randomized clinical trial, older postmenopausal women with T-score between

−1.0 and −2.0 at either LS or total hip, two doses of 5 mg ZA administered at baseline and 5.5 years later prevented bone loss for almost 11 years [47]. In a post hoc analysis of women in the HORIZON-PFT and HORIZON-RFT trials receiving only one of multiple planned annual doses of ZA, fracture risk was significantly reduced over 3 years compared with placebo and similar to the fracture risk reduction observed in those who received annual infusions [48]. Moreover, a single dose of ZA in late postmenopausal women with T-score between −1.0 and −2.5 at either LS or total hip showed that lumbar spine BMD increased by 5.7% at 2 years and 5.1% at 5 years, consistent with persistence of antiresorptive effect for at least 5 years after a 5-mg dose of ZA [49].

Multiple studies have shown a beneficial effect of the anabolic agent teriparatide in patients requiring spinal surgery. In general, teriparatide has been shown to increase LS BMD by 9% with 12 months of treatment and 14% with 24 months of treatment [50]. The efficacy of teriparatide treatment to reduce pedicle screw loosening after instrumented lumbar fusion in postmenopausal women with osteoporosis has been reported [51, 52]. The risk of screw loosening has been shown to be 10% for the teriparatide group in comparison with the control group (27.3%) [51]. Postoperative teriparatide injections significantly decreased pedicle screw loosening during 6–12 months after spinal surgery in comparison with oral risedronate (2.3% vs. 9.2%, respectively) [52]. Teriparatide has also been shown to significantly improve the rate of bone union (82%) vs. therapy with risedronate (68%) 12 months after spinal surgery; facet fusion was in 79% of patients in the teriparatide group and 65% in the bisphosphonate group [53].

A recent report of a post hoc analysis of a randomized controlled clinical trial suggests that abaloparatide (80 mcg/day subcutaneously) is superior to alendronate (70 mg/week, oral) in reducing the risk of VFs in postmenopausal women with osteoporosis, with a further decrease in fracture risk after transitioning from abaloparatide to alendronate [54]. In another study evaluating a different transition, from Dmab to alendronate, it was found that BMD was maintained or increased for the following year; only 16% of patients lost LS BMD with this approach [55], which likely might be also considered in the presurgical period. These studies and others illustrate differences in the efficacy of medications in the treatment high-risk patients and the importance of the sequence of therapy [56].

In a retrospective study of 45 postmenopausal women with osteoporosis having lumbar posterolateral fusion, the effects of 3 medication regimens on fusion across the transverse processes and bone union of facet joints by CT were compared [57]. The long-duration teriparatide group received a dose of 20 mcg daily for 3 months pre-op and an average total of 13.0 months; the short-duration group received a dose of 20 mcg daily for 3 months pre-op and an average total of 5.5 months; and the risedronate group received 2.5 mg daily for 3 months pre-op and an average total of 13.0 months. Fusion at 12 months was 86% for long duration teriparatide, 78% for short-duration teriparatide, and 70% for risedronate. Bone union at 12 months was 81% for long-duration teriparatide, 61% for short-duration teriparatide, and 50% for risedronate. These findings suggest that teriparatide is superior to risedronate and that long-duration teriparatide is superior to short-duration for bone healing after lumbar fusion.

Recently, an open-label randomized controlled trial compared the BMD response with teriparatide given as high dose (40 mcg/day) or standard dose (20 mcg/day) for 9 months overlapping with Dmab 60 mg administered at the 3- and 9-month time points [58]. Almost all patients achieved a BMD increase at the lumbar spine >3% from baseline, regardless of the teriparatide dose [58]. It was found that the high-dose teriparatide regimen resulted in larger and more rapid BMD gains than the standard dose, suggesting clinical applications in high-risk patients and perhaps for those having spine surgery as well.

The sequence of medications is important (see Fig. 4.2). In postmenopausal women switching from Dmab to teriparatide, transient bone loss at

the spine, hip, and the radius has been reported, in contrast to BMD increases observed after transitioning from teriparatide to Dmab (DATA Switch Study) [59]. In an observational study of long-term BP users, switching to Dmab or teriparatide was shown to increase spine BMD, with a more significant increase in the teriparatide group [60]. However, there is a transient loss of hip BMD 1 year after switching to teriparatide, with no overall increase over 2 years, compared with an increase of hip BMD switching to Dmab. These findings suggest that switching from BP to teriparatide should be done with caution especially for patients at high risk of hip fracture [60].

A recent systematic review and meta-analysis compared the efficacy of BPs and teriparatide on radiographic and functional outcomes after thoracolumbar spinal fusion [61]. Teriparatide was associated with higher fusion rates than BPs and similar risk of screw loosening. Compared with controls, the risk of cage subsidence and vertebral fracture was reduced with BPs, with no difference in fusion rates or screw loosening. Another systematic review and meta-analysis found no difference in screw loosening between BP and controls in patients who underwent lumbar fusion [62]. Moreover, BP use was associated with decreased odds of cage subsidence and VF.

Infusion of ZA administered 3 days and 1 year after the lumbar interbody fusion surgery was associated with a rate of solid fusion of 75% compared with 56% in the control group and lower incidence of subsequent compression fractures (19% vs. 51%, respectively), pedicle screw loosening (18% vs. 45%, respectively), and cage subsidence >2 mm (28% vs. 54%, respectively) after 2 years of follow-up [63].

Currently, there is no information on the effect of romosozumab on postsurgical outcomes in patients undergoing spinal surgery. Based on the animal studies, anti-sclerostin antibodies have been shown to enhance the bone formation, fracture healing, and ultimate load and induce an increase in neovascularization around the fracture site [64, 65]. Sclerostin, which is a negative regulator of bone formation, was found to be elevated at 48 weeks after fracture with physiological healing and in patients with the immobilization-induced bone loss [66, 67]. Thus, romosozumab injections for 12 months might be an effective therapy in the peri- and postoperative period. However, dedicated clinical trials are needed.

Evaluation Before Antiresorptive Therapy Initiation

Dental Clearance The vast majority of osteonecrosis of the jaw (ONJ) cases, about 95% in many studies, is in cancer patients who are receiving a much higher dose of antiresorptive medication than osteoporosis patients and often have many comorbidities. The annual dose of BPs is about 10 times and Dmab dose is 12 times higher in cancer patients compared with the doses that are used for osteoporosis treatment [68]. Moreover, in cancer patients, the risk of ONJ is as high as 1–2% even without bone-targeted therapy [69]. In contrast, ONJ is a very rare complication of antiresorptive therapy with oral or IV bisphosphonate therapy for osteoporosis. Thus, for cancer patients, a comprehensive dental examination and appropriate preventive dentistry is recommended before starting bone-modifying therapy [70]. Osteoporosis patients, in contrast, do not necessarily require as much attention to oral health before starting treatment, but good oral hygiene is advised, and any planned invasive oral surgery should probably be completed and healed before starting a potent antiresorptive agent [68].

Risk factors for ONJ are not well defined due to the rarity of the condition, but include age older than 65 years, glucocorticoid use, periodontitis, and prolonged use of BP [71–73]. Tooth extraction is the most common immediate cause of ONJ (48%), followed by marginal and apical periodontitis (24%) and nonconformity of a denture (8%). Spontaneous onset was described in 13.6% of ONJ cases [74, 75]. In a case series from Scotland, the incidence of ONJ with alendronate was <0.004% per drug patient-years for

men and women with age-related or hormone-related osteoporosis, but much higher (>0.1%) for those treated for GC-induced osteoporosis [76]. The duration of BP treatment is correlated with the risk of ONJ. In a survey of patients in a large healthcare delivery system, the prevalence of ONJ was greater with ≥4 years of exposure compared with those with <4 years of exposure (0.21% vs. 0.04%, respectively, $P = 0.03$) [73]. The risk of ONJ has been shown to be 0.017% after IV BP use for 3 years with no increase after 6 years (1 case among 616 participants) [77]. In contrast, estimates for the development of ONJ after tooth extraction in cancer patients on IV BPs are about 1.6–14.8% [78, 79]. Dmab is also associated with ONJ, especially with doses higher than for osteoporosis treatment. An analysis of 8963 patients revealed ONJ in 1.7%, a rate higher than in BP and control groups [74].

In the FRAME trial, postmenopausal women with osteoporosis were treated with romosozumab or placebo for 12 months followed by Dmab administration for the next 12 months [80]. There was only one case of ONJ in the intervention arm (0.03%, 1/3581 patients) and two cases after Dmab use (0.06%). All cases were related to dental issues such as ill-fitting dentures, tooth extraction, and subsequent osteomyelitis of the jaw.

Teriparatide and abaloparatide have not been shown be associated with ONJ. In general, any pending dental or oral health problems should be completed before starting treatment, if possible. Patients should be aware of possible, even rare complications of bone-targeted therapy, and they should inform their dental providers of planned therapy [81, 82].

While receiving therapy, patients should maintain good oral hygiene and avoid invasive dental procedures, if possible [70]. If invasive dental treatment is needed and the patient has received a low cumulative dose of BP (<2 years) or Dmab, the anti-osteoporosis therapy can be continued [83]. For patients with extended history of BP use (>4 years) for osteoporosis, a 2-month drug holiday before the procedure has been suggested by the *American Association of Oral and Maxillofacial Surgeons* (AAOMS); however, there are limited supporting data [69].

All planned invasive dental procedures should be done before starting BP or Dmab therapy, and if ONJ develops, discontinuation of antiresorptive therapy may be considered until soft tissue closure occurs [69].

Kidney Function Check BP product labels recommend against their use for the treatment of osteoporosis when creatinine clearance is <30 (ibandronate, risedronate) or <35 mL/min (alendronate, ZA). Serum creatinine should be monitored before each ZA dose [70]. The renal safety profile is excellent when used as recommended, with no evidence of long-term decline in renal function [82]. When ZA is used for the treatment of cancer-related conditions in patients with impaired renal function, the dosage can be reduced and/or the infusion time lengthened.

Dmab does not require monitoring of renal function and dose modification [70]. Anabolic agents such as teriparatide and abaloparatide have not been shown to affect kidney function. Administration of teriparatide to patients with severe renal impairment (Cr/Cl <30 mL/min) did not increase maximum serum concentration of teriparatide.

Level of Vitamin D and Calcium Serum calcium and 25-hydroxyvitamin D levels should be evaluated regularly. Patients should be calcium and vitamin D repleted before initiation of therapy since hypocalcemia is one of the complications of antiresorptive therapy. Dmab can cause symptomatic hypocalcemia in some patients, especially those with pre-dose calcium or vitamin D deficiency or severe CKD [84]. The Institute of Medicine reports vitamin D 4000 IU/day as upper limit intake [85]. However, in a Calgary study, a comparison of vitamin D doses of 400, 4000, and 10,000 IU/day for 3 years showed a similar safety profile across the range of doses assessed [86].

Suggested perioperative approach for evaluation and management of osteoporosis is described in Fig. 4.4.

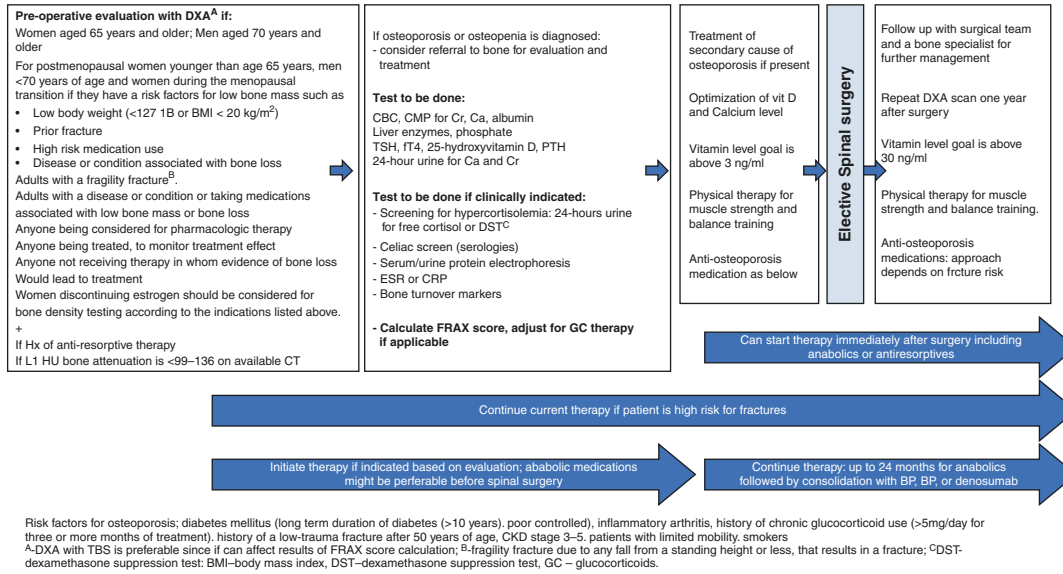

Fig. 4.4 Suggested perioperative approach for evaluation and management of osteoporosis

Osteoporosis Management

Postmenopausal Osteoporosis Management

Estrogen plays an important role in bone growth, bone maturation, and bone turnover, and estrogen deficiency leads to accelerated bone loss. 50-year-old white women have about 15–20% lifetime risk of hip fracture and 50% risk of any osteoporotic fracture [8]. During menopause the mean annual decrease in BMD is about 1.9 ± 0.7% measured by DXA [87]. The annual rate of postmenopausal bone loss has been shown to be 1.3–1.5% at the LS and 1.4% at the femoral neck [88, 89]. The SWAN study demonstrated the greatest cumulative bone loss between a year before the final menstrual period (FMP) and 2 years after the FMP (transmenopause) [90].

Descriptions of anti-osteoporosis medications, dosing, indications, and effect on BMD are listed in Table 4.1.

In postmenopausal women, treatment is indicated in patients with high or very high risk for fractures and can be considered for moderate fracture risk patients (Table 4.2) [91, 92]. Initially, BP therapy with alendronate, risedronate, ZA, or Dmab is recommended to reduce the hip, non-vertebral, and spine fracture risk [68]. Ibandronate has not been shown to reduce non-vertebral or hip fractures [93].

For very high fracture risk patients, abaloparatide, teriparatide, Dmab, romosozumab, or ZA is recommended. *Very-high-risk patients* are defined as patients with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, history of multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term GC therapy), very low T-score (e.g., less than −3.0), high risk for falls or history of injurious falls, and a very high fracture probability by the fracture risk assessment tool, FRAX® (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) [68].

Fracture reassessment is recommended every 1–2 years until findings are stable [68]. If there is a BMD loss or failure to respond as expected, evaluation and consideration of a change in treatment may be needed. Monitoring is also done to reassess fracture risk and assess whether the patient is on track to achieving an acceptable level of risk.

A new alternative approach of treat-to-target has been recently proposed [94]. The concept is to identify a treatment target that represents an acceptable fracture risk and choose a medication that is likely to reach the target. BMD expressed as T-score is the leading candidate for a treatment target since there is a robust relationship between T-score and fracture risk. For each SD decrease of BMD (1.0 T-score unit), there is an approximate of doubling of risk for fracture [95]. Osteoporosis can be diagnosed according to T-score, and patients are often selected for treatment because of T-score. Greater increases of BMD with treatment are associated with greater reductions of fracture risk [96]. For example, to achieve the T-score target of >−2.0 when the baseline T-score is −2.5, this might be achievable with an oral BP. However, if pre-treatment T-score is −3.0 or lower, anabolic therapy followed by an antiresorptive agent may be needed to reach the target. Therapy should be reconsidered when the target is not reached or the patient is not on a path to reach the target with initial therapy [94].

BPs have a long skeletal-half life that is associated with persistence of antiresorptive effects for a period of time after long-term therapy. For this reason, the concept of a BP "holiday" has emerged. Temporary discontinuation of BP therapy may be considered after 5 years of oral or 3 years of IV BP therapy if the patient is at low or moderate risk of fracture (see Table 4.2) [68, 91]. In contrast, administration of Dmab cannot be delayed for more than 7 months after the last

Table 4.2 Risk stratification for bone loss. (**a**) Postmenopausal osteoporosis (data from Eastell et al. [91]). (**b**) Glucocorticoid-induced osteoporosis (from Buckley et al. [92], with permission John Wiley & Sons)

A. Fracture risk category, postmenopausal osteoporosis	**History of fractures**	**DXA assessment, T-score**	**10-year risk of hip fracture (%)**	**10-year risk of major osteoporotic fractures (%)**
Low risk	*No* prior hip or spine fractures	Hip and spine both are above −1.0	<3	<20
Moderate risk	*No* prior hip or spine fractures	Hip and spine both are above −2.5	<3	<20
High risk	Yes – prior hip or spine fractures *Or*	Hip or spine are −2.5 or below *or*	≥3 *or*	≥20
Very high risk	Yes – multiple spine fractures *And*	Hip or spine are −2.5 or below		
B. Fracture risk category, GC-induced osteoporosis	**Adults >40 years old** **FRAX® score is GC-adjusted**		**Adults <40 years old** **FRAX® score is GC-adjusted**	
Low risk	FRAX 10-year risk of MOF <10% FRAX 10-year risk of hip fracture <1%		None of above risk factors other than GC treatment	
Moderate risk	FRAX 10-year risk of MOF 10–19% FRAX 10-year risk of hip fracture >1% and <3%		Hip or spine BMD Z-score <−3.0 Rapid bone loss (≥10% at the hip or spine over 1 year) Continuing GC treatment at ≥7.5 mg/day for ≥6 months	
High risk	Prior osteoporotic fracture(s) Hip or spine BMD T score <−2.5 in men age >50 years and postmenopausal women FRAX 10-year risk of MOF ≥20% FRAX 10-year risk of hip fracture ≥3%		Prior osteoporotic fracture(s)	

Glucocorticoid therapy-related FRAX® adjustment: recommended to increase the FRAX® risk by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is >7.5 mg/day. The example: if hip fracture risk is 2.0%, the adjusted risk is 2.4%

MOF major osteoporosis fractures (fractures of the spine [clinical], hip, wrist, or humerus)

injection due to rapid BMD loss and increased risk of fracture. Delay in Dmab administration leads to an increase of bone turnover markers (BTMs) and a decrease in BMD to baseline in about a year [97]. Return of VF risk to baseline has been described within 7–20 months after the last Dmab injection, with some patients having multiple VFs, especially those with one or more prevalent VFs. For patients who remain in high or very high fracture risk categories despite therapy, continuation of current therapy or switching to another medication is appropriate.

Anabolic therapy such as teriparatide (anabolic effect), abaloparatide (anabolic effect), or romosozumab (dual antiresorptive and anabolic effect) is recommended for a very-high-risk patient (as described above) [68, 93]. Teriparatide and abaloparatide are approved for a total of 24 months of treatment during the lifetime. Romosozumab can be given for 12 months with no restrictions on repeat treatment.

If BPs, Dmab, anabolics, or romosozumab cannot be given due to contraindications or intolerance, hormonal replacement therapy (HRT), selective estrogen receptor modulators (SERM), HRT/tibolone, or calcitonin can be recommended to eligible patients. Based on the International Menopause Society (2016) and North American Menopause Society (2017) recommendations, in women <60 years old or within 10 years of menopause onset, HRT benefits overweigh the risks and can be considered as first-line therapy for prevention of bone loss and fractures [98, 99]. Asymptomatic menopausal patients can be treated with a SERM, such as raloxifene or bazedoxifene. For patients who are older than 60 years, the therapy options are SERM, HRT/tibolone, calcitonin, and vitamin D with calcium supplementation (in order) (see Table 4.2).

Osteoporosis Management in Patients with Chronic Kidney Disease (CKD)

Based on Kidney Disease Improving Global Outcomes (KDIGO) guidelines, CKD is classified according to GFR as follows: GFR ≥90 mL/min (G1, normal and high); 60–89 mL/min (G2, mild reduction); 45–59 mL/min (G3a, mild-moderate reduction); 30–44 mL/min (G3b, moderate-severe reduction); 15–29 mL/min (G4, severe reduction); and <15 mL/min (G5, kidney failure).

In general, in patients with CKD G1–G2 (GFR ≥60) with osteoporosis and/or high risk of fracture and G3a–G3b (GFR 30–59) with normal PTH level and osteoporosis and/or high risk of fracture, treatment approach as for general population is recommended [84]. BPs are excreted by kidneys, and their use in patients with GFR <30–35 mL/min is usually avoided since there are no large-scale data on BP use in this category of patients. Alendronate is not recommended if GFR <35 mL/min. Risedronate and ibandronate are not recommended in patients with GFR <30 mL/min. ZA is not recommended in patients with creatinine clearance <35 mL/min. Dmab and romosozumab are not affected by kidney function. Administration of teriparatide to patients with severe CKD (Cr/Cl <30 mL/min) has not been shown to increase the medication serum concentration. In patients with osteoporosis and stage 4 or 5 CKD, teriparatide administration for 24 months has been reported to increase BMD and bone formation marker (P1NP) with no new safety concerns [100]. Analysis of 1882 patients, including patients with CKD stage 4 and 5 (33 patients), showed a significant increase in LS and hip BMD after 24 months of teriparatide administration. The greatest increase from the baseline was documented in LS being 12% in 24 months of therapy [101].

During the first 12 months after kidney transplant in patients with an estimated GFR >30 mL/min/1.73 m^2 and low BMD, treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents can be considered [84]. Treatment choice should be determined based on the presence of CKD-mineral and bone disorder (MBD), as indicated by abnormal biochemical workup (calcium, phosphate, PTH, ALP, and 25(OH)D levels). Bone biopsy to guide treatment might also be considered when the results are likely to affect management approach [84]. Measurement of BTM is generally not helpful in differentiating

among bone disorders such as PTH-mediated high-turnover bone disease, adynamic bone disease (if PTH <100 pg/mL), suspected osteomalacia, unexplained bone pain or fragility fractures, or progressive loss of BMD when on antiresorptive therapy.

Osteoporosis in Patients on Chronic Glucocorticoid (GC) Therapy

Chronic preoperative GC therapy is an independent risk factor for multiple perioperative complications, including superficial and deep surgical site infection, wound dehiscence, urinary tract infection, pulmonary embolism, non-home discharge, and readmission [102]. Patients on chronic GC therapy had longer hospital stays, higher reoperation rates, and infectious complications such as urinary tract infection (UTI), sepsis, and postoperative pneumonia [103]. Inhibition of endochondral ossification and delay in bone healing are associated with chronic GC therapy [104].

Since GC therapy affects trabecular more than cortical bone, patients taking supraphysiological GC doses are at particularly high risk for VFs, since the spine has a high component of trabecular bone. The highest bone loss is observed during the first 3–6 months of GC use. The American College of Rheumatology suggested checking initial BMD within 6 months of GC therapy initiation for patients who are 40 years of age or older [92]. In younger patients, BMD should be measured if a history of osteoporotic fracture or other significant factors for osteoporosis is present. Calculated with the FRAX® tool, the risk of major osteoporotic fracture (MOF) is estimated to increase by 1.15, and the risk of hip fracture to increase by 1.2, if the prednisone dose is >7.5 mg/day (equivalent to 30 mg of hydrocortisone = 1.1 mg of dexamethasone or betamethasone = 6 mg of methylprednisolone or triamcinolone) [92]. For example, if hip fracture risk is 2.0%, the adjusted risk is 2.4%. For patients on high-dose GCs (prednisone >7.5 mg/day or equivalent), the FRAX® risk of major osteoporotic fracture (MOF) also can be adjusted upward by 15%, so that a risk of 20% would be adjusted to 23% [105]. Treatment with oral BP is recommended for moderate-high-risk patients (see Table 4.1) regardless of age. If oral BPs are not appropriate, IV BP, teriparatide, or Dmab can be used (in order of preference) [92].

A recent network meta-analysis (4328 patients) demonstrated that teriparatide and Dmab are more efficacious than BPs in preventing GC-induced VF, with safety and tolerability that is similar to oral BPs which are currently recommended as first-line therapy [106]. IV ibandronate was shown to be effective for the primary prevention of CG-induced osteoporosis. Oral risedronate was also effective in fracture risk reduction among patients on CG therapy. Oral alendronate, but not oral ibandronate, reduced this risk of fractures in patients receiving GCs with at least 7.5 mg/day [106].

While there is a theoretical risk of adverse immune effects with Dmab, it has never been clearly demonstrated in humans. Based on clinical phase 3 pivotal fracture trial that represented >10,000 patients-years of Dmab exposure, there was no difference between control and Dmab groups in the overall incidence of infections [107]. There was no clear pattern suggesting a relationship to time or duration of Dmab exposure and no indication of any effect on defense mechanisms against infection [107].

Monitoring the Effect of Anti-osteoporosis Therapy

BMD monitoring by DXA of the LS and hip to assess the response to treatment and risk fracture stratification is recommended. Based on the American Association for Clinical Endocrinology osteoporosis guidelines (2020), repeat DXA is recommended every 1–2 years until findings are stable. However, intervals can be less frequent interval, depending on clinical circumstances [68]. Endocrine Society Guidelines (2020) suggest reassessment of fracture risk in postmenopausal women with a low BMD and at high or very high risk of fractures on anti-osteoporosis therapy every 1–3 years [93]. Patients with low

BMD and low to moderate fracture risk can be reassessed every 2–4 years [93].

BMD is the best tool to measure a clinical response to therapy since a greater increase in BMD is associated with greater fracture risk reduction [108, 109]. Ideally, repeat DXA evaluation should be done with the same DXA unit, with measurements of the same regions of interest (ROI), and by the same technologist if possible [68].

Measurement of BTMs is also useful for therapy monitoring [68]. There are two classes of BTMs that are available for use in clinical practice, representing bone resorption and bone formation that occurs with skeletal remodeling. Widely used bone resorption markers are type 1 collagen amino- or carboxyl-terminal peptides (NTX, CTX). Bone formation markers include type 1 procollagen amino- or carboxyl-terminal peptides (P1CP, P1NP), osteocalcin (OC), and alkaline phosphatase (ALP). The International Osteoporosis Foundation and the International Federation of Clinical Chemistry (IFCC) Bone Marker Standards Working Group have recommended serum PINP and CTX as bone turnover reference markers for the fracture risk prediction and monitoring of osteoporosis treatment [110].

Serum CTX for antiresorptive therapy or P1NP for bone anabolic therapy is suggested as an alternative way of identifying poor response or compliance with therapy [93].

Of note, some bone formation (osteocalcin) and resorption markers (pyridinoline [PYD], deoxypyridinoline [DPD], CTX, NTX) are affected by renal function. But bone alkaline phosphatase (BAP), P1NP, and tartaric acid-resistant acid phosphatase (TRACP-5b) are not influenced by the renal function and can be used in patients with CKD [111].

A recent fracture and bone surgery can significantly affect BTM levels. BTMs have been shown to be on a pre-fracture level in the first few hours after fracture and then steeply increase during the first weeks and may remain elevated for more than 1 year post-fracture [112, 113]. Elevation of BTMs after a vertebral fracture has been shown on day 3 after the fracture [113]. Higher levels of BTMs can be seen with large fracture surface [113]. The extent of the peak varied depending on BTM type. Peak for osteocalcin and CTX has been documented between 12 and 24 weeks, P1NP between 4 and 24 weeks, and ALP between 2 and 4 weeks [113]. Of note, lower serum P1NP has been proposed as a novel marker predicting nonunion after spinal surgery [114].

Compliance with antiresorptive therapy is critical in BMD changes and fracture prevention. Discontinuation or noncompliance with some medications such as teriparatide/abaloparatide or Dmab will lead to a rapid reversal of gained therapeutic bone effect. Compliance with Dmab has been shown to decline beyond 24 months to be in proportions as low as 28% at 36 months, 13% at 48 months, and 8% at 60 months [115]. Patients with poor (an interval of ≥10 months between two doses), moderate (7–10 months between two doses), and good compliance (≤7 months between two doses) showed annualized percentage in BMD of 1.4%, 3%, and 3.9% for the spine and 0.6%, 1.3%, and 2.1% for the hip, respectively [115]. If compliance is an issue with medications that require frequent administration such as oral BP, switching to injectable forms might be beneficial. If the patient is on an anabolic agent or Dmab, noncompliance can lead to rapid bone loss, and switching to BP might be warranted.

Management of Bone Health in Malignancy (Multiple Myeloma and Solid Cancers) with and without Bone Involvement

Multiple myeloma and breast, prostate, thyroid, kidney, and lung cancers are common malignancies that spread to the bone, with the spine being one of the most common bone locations. BPs (ZA, pamidronate) and Dmab have been shown to effectively reduce the skeletal-related morbidity from metastatic cancer [116]. BPs have been shown to have an anticancer effect by inhibiting growth, migration, invasion, and induction apoptosis of cancer cells [117].

Teriparatide, abaloparatide, and romosozumab are not approved for use in cancer patients at this time. However, the use of sclerostin inhibitor setrusumab in bone metastases-bearing mice has been shown to alleviate bone tumor growth and bone destruction and to protect from cancer-induced muscle fiber atrophy and loss of muscle function and has increased the animal life span, thus proving potentially helpful to breast cancer patients [118]. Further investigations are needed to prove the clinical utility of sclerostin inhibition in cancer patients.

Bone-modifying medications and some published regiments in cancer patients are described in Table 4.3 [70, 81, 119–131].

Multiple Myeloma

Multiple myeloma (MM) is a plasma cell disorder with clonal plasma cell bone marrow infiltration, production of paraprotein, presence of lytic lesions in the bones (myeloma bone disease, MBD), renal impairment, hypercalcemia, and anemia [132]. In MM, about 80–90% of patients will have osteolytic lesions affecting the axial and appendicular skeleton [133]. The bone involvement can be presented by lytic lesion/s (radiolucent, plasmacytoma), widespread osteopenia, or multiple lytic lesions most commonly affecting the spine, skull, and long bones [134]. In contrast to other cancers such as prostate and breast, where both the osteoclastic and osteoblastic activity are increased, in MM the coupling mechanism is lost with an increase in osteoclastogenesis and suppressed osteoblastic activity [135, 136].

Due to bone involvement, many patients (70–80%) will have bone pain, fractures (50–60%), and hypercalcemia (15%) [137]. BP therapy is one of the main standard therapies for MM bone symptoms with a preference for IV forms over oral therapy [138]. Infusion of ZA every 12 weeks vs. 4 weeks in patients with cancer, including MM, has not resulted in SRE increase over 2 years of follow-up [128]. Dmab (Xgeva®) was recently approved by the FDA (2018) for adjuvant therapy of MM (see Table 4.3).

Breast Cancer

Based on the current recommendations on early breast cancer management, prophylactic use of BPs in women undergoing ovarian function suppression (OFS) or in postmenopausal state is recommended since it leads to prolongation of disease-free survival (DFS) and breast cancer-specific survival. BP therapy is also recommended for treatment-related bone loss and fractures [81, 139, 140]. However, no beneficial outcome has been demonstrated for premenopausal women [140].

The Japanese Society for Bone and Mineral Research recommends starting therapy with ZA or Dmab for patients on AI therapy who have been diagnosed with osteoporosis, in patients with T-score <−2.0, and in patients with T-score between −2.0 and −1.5 and family history of hip fracture or 15% or more risk of major osteoporotic fracture [126].

AIs can also cause about two times an increase in fracture risk compared to tamoxifen treatment [126]. Estrogen deprivation in women with breast cancer will accelerate bone turnover leading to a decrease in BMD and a 40–50% increase in fracture incidence [141, 142].

AIs lead to an increase in bone loss and incidence of fractures in both pre- and postmenopausal women. AIs have been reported to cause approximately two times increase in fracture risk compared to tamoxifen treatment.

Premenopausal Women Based on the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial, in premenopausal women receiving adjuvant therapy for hormone-responsive breast cancer, ZA had been shown to prevent cancer treatment-induced bone loss and was given 4 mg every 6 months for 3 years. Overall bone

Table 4.3 Bone-targeted therapy in patients with selected malignancies

Disease	Indications for bone-targeted therapy	Dose, intervals, duration	Comments
Multiple myeloma	Lytic disease on imaging studies Osteopenia in the absence of lytic disease Adjunct to pain control for osteolytic disease and those receiving other interventions for fractures or impending fractures Osteopenia (osteoporosis) but no radiographic evidence of lytic bone disease Prevention of SRE in patients with multiple myeloma and in patients with bone metastases from solid tumors Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy	Intravenous pamidronate 90 mg delivered over at least 2 h or zoledronic acid 4 mg delivered over at least 15 min every 3–4 weeks is recommended. Alternative treatment includes the use of denosumab [70] Therapy can be stopped in a year in case of remission and no active bone disease and in 2 years in case of less than good partial response and can be used longer in case of ongoing bone disease [119] Denosumab: 120 mg every 4 weeks	For severe renal impairment (serum creatinine level >3.0 mg/dL or CrCl <30 mL/min): Pamidronate 90 mg over 4–6 h; consider reducing the initial pamidronate dose Avoid infusion <2 h with pamidronate or <15 min with zoledronic acid CrCL <30 mL/min or patients on dialysis are at risk for hypocalcemia
Breast cancer	Non-metastatic early-stage breast cancer [81] *For:* Postmenopausal patients Premenopausal patients before treatment who have menopause induced by ovarian suppression who are deemed candidates for adjuvant systemic therapy	*Adjuvant bone-remodeling therapy:* ZA 4 mg every 6 months IV for 3–5 years [81] Clodronate 1600 mg/day PO for 2–3 years [81] Ibandronate 50 mg p.o. daily [120] Clodronate 1600 mg/day [120] Ibandronate 6 mg IV monthly [121] Denosumab 60 mg SC every 6 months [122]	If low risk for cancer recurrence, the use of bisphosphonates may not result in clinically meaningful effect Optimal duration is not defined
Prostate cancer	Non-metastatic bone disease on ADT [123] Metastatic castrate-resistant prostate cancer to bone Not approved for patients with bone metastases from castrate-sensitive prostate cancer	*Prevention of treatment-induced bone loss:* Denosumab 60 mg SC 6 months [124, 125] Oral bisphosphonates *or* IV ZA 5 mg annually *or* Denosumab 60 mg SC q6mo *SRE prevention:* IV ZA based on GFR every 3–4 weeks: >60 mL/min – 4 mg 50–60 mL/min – 3.5 mg 40–49 mL/min – 3.3 mg 30–39 mL/min – 3 mg	Serum Cr should be measured before each ZA dose, and treatment should be withheld for renal deterioration: Normal baseline Cr –> ⇑ of 0.5 mg/dL Abnormal baseline Cr –> ⇑ 1.0 mg/dL ZA treatment to be resumed only when Cr returned to within 10% of the baseline value Re-initiation: Same dose as that prior to treatment interruption (FDA package insert)

(continued)

Table 4.3 (continued)

Disease	Indications for bone-targeted therapy	Dose, intervals, duration	Comments
Breast and prostate cancer [126]	ADT or AI therapy: Diagnosed osteoporosis *or* T-score <−2.0 *or* T-score between −2.0 and −1.5 + FH of hip fracture OR 15% or more 10-year probability of major osteoporotic fractures by FRAX®	ZA or denosumab	All other patients should have BMD checked every 1–2 years More frequent measurements are recommended for patients who are at risk of rapid progression of CTIBL due to powerful ADT such as apalutamide and abiraterone with prednisolone
MM, breast and prostate cancer [127]	Bone metastases	ZA every 12 weeks [128] vs. every 4 weeks infusions	No difference in SRE, pain scores, performance status scores, incidence of JON, kidney dysfunction, skeletal morbidity rates C-terminal telopeptide levels were higher in patients on ZA every 12 weeks
Differentiated thyroid cancer Anaplastic thyroid cancer Medullary thyroid cancer	Consider for high-risk patients such as peri- or postmenopausal on LT4 suppressive therapy (no known bone metastases) Multiple progressing and/or symptomatic DTC bone metastases Known osseous metastases Painful osseous metastases	No recommendations on dose and frequency were provided by ATA guidelines; IV ZA 5 mg annually *or* Denosumab 60 mg SC q6mo most likely should be used [129] IV ZA q3mo [129] BP or RANKL inhibitor (denosumab); no recommendations available on frequency [130] BP or RANKL inhibitor (denosumab); no recommendations available on frequency [127]	Expert consensus: Bone-directed therapy should be used in the setting of diffuse bone metastases even if TKI therapy is intended or ongoing
Lung cancer	Bone metastatic disease	Denosumab 60 mg SC monthly *or* ZA 4 mg IV monthly	Denosumab improves overall survival [131]

AI aromatase inhibitors, *ADT* androgen deprivation therapy, *CTIBL* cancer treatment-induced bone loss, *TKI* tyrosine kinase inhibitor, *ZA* zoledronic acid

loss after 3 years of treatment was shown to be more severe in anastrozole/goserelin group (BMD, 17.3%; mean T-score reduction, 2.6) vs. tamoxifen/goserelin group (BMD, 11.6%; mean T-score reduction, 1.1). Thirty-six months of tamoxifen treatment showed 46% of patients with osteopenia in the LS in contrast to only 16% of patients having osteopenia at baseline. However, a combination of ZA with tamoxifen resulted in only 23% of patients with osteopenia and 4% with osteoporosis vs. 23% of patients with osteopenia and 1% of patients with osteoporosis of the LS at baseline. Thirty-six months of anastrozole therapy led to 54% of patients with osteopenia and 25% with osteoporosis in the LS, compared to only 24% having osteopenia and 1% having osteoporosis at baseline. However, BMD remained stable in patients additionally receiving ZA [143]. A combination of anastrozole with ZA showed 44% of osteopenia with an absolute increase of 15% from baseline with no patients who developed osteoporosis of the LS [143].

Postmenopausal Women ZA administered immediately with the aromatase inhibitor letrozole increased BMD in LS and total hip in dose 4 mg every 6 months for 5 years in contrast to a decreased BMD if ZA was initiated during the follow-up for BMD worsening or nontraumatic fracture [144]. Subgroup analysis in the AZURE

trial demonstrated a significant difference in the rates of invasive disease-free survival and 5-year overall survival (OS) rate among postmenopausal women (defined as >5 years since menopause), however, with no difference in distant skeletal recurrence [145].

The ZO-FAST trial showed increased BMD with immediate vs. delayed initiation of ZA with a difference in BMD being 9.29% at 3 years. The immediate-ZA group had a significant 41% relative risk reduction for DFS events [146].

The use of ZA with adjuvant therapy was shown to reduce the rate of fractures [145]. No effect on DFS and OS was demonstrated in women with early breast cancer in the AZURE trial [145].

Oral clodronate in dose 1600 mg/day for 2 years significantly reduced the risk of bone metastases by 31% over the 5-year period with an improvement of OS, especially in stage II/III patients [147].

An increase in LS BMD was also demonstrated for risedronate and ibandronate in contrast to placebo in patients receiving adjuvant endocrine therapy for early-stage breast cancer.

Based on the SWOG S0307 trial, a comparison of IV ZA, oral clodronate, and oral ibandronate has not shown a difference in DFS or OS in the early stage of breast cancer [120]. However, fracture rates (mostly in the LS) were significantly higher for clodronate (9.3%) vs. ibandronate (7.4%) and ZA (7.1%) [120].

Dmab injections every 6 months has been shown to significantly improve DFS with no toxicity difference in postmenopausal women with early breast cancer and on AI therapy based on ABCSG-18 clinical trial [122]. However, the D-CARE trial did not show improvement in bone metastases-free survival and DFS in early breast cancer after Dmab 120 mg every 3–4 weeks with 5-year follow-up [148].

Prostate Cancer

Testosterone promotes the growth and proliferation of androgen-sensitive tumor cells in prostate cancer, and testosterone-deprived prostate cells undergo apoptosis [149]. Medical castration with ADT is defined as testosterone level <50 ng/dL [150]. ADT reduces serum testosterone levels to less than 5% of the normal range and serum estradiol to less than 20% of the normal level with estrogen deficiency being the primary mediator of bone loss [123].

Androgen deprivation therapy has been shown to increase the risk of fractures by three times (10.8% vs. 3.2%), with the highest risk in patients who received combined androgen blockade and bilateral orchiectomy with pharmacologic ADT [151]. ADT induces high bone turnover with annual bone loss of about 4–4.6%, significantly higher than aging bone loss [123].

Based on the position statement by the International Osteoporosis Foundation, preventive measures in prostate non-metastatic bone cancer should not differ from those used for primary prevention of idiopathic osteoporosis [123]. The antiresorptive regimen includes oral BP (weekly alendronate, or risedronate) or IV ZA (5 mg once a year) or SC Dmab (60 mg every 6 months) with injectable forms to be preferable.

PSA ≥8 μg/l and a PSA doubling time ≤10 months (or both) have been indicated as risk factors for the development of bone metastases in castrate-resistant prostate cancer (CRPC) [152]. Dmab has been shown to significantly increase bone metastases-free survival in high-risk patients with 33% of risk reduction for the development of symptomatic metastases. Metastatic prostate cancer to the bone can lead to skeletal-related events (SREs) in 42% of patients within 2 years after diagnosis [153] that can be decreased by 36% using ZA [154]. ZA treatment of CRPC with bone metastases has been shown to decrease in SREs, to prolong time to the first SRE, and to better control metastases-related pain [154]. In castrate-sensitive prostate cancer, ZA was not proved to delay SRE or improve OS [155–157].

The optimal regimen for ZA in patients on ADT has yet to be established. There was no significant difference in the BMD gain between groups receiving ZA 4 mg every month, every 2 months, every 3 months, or every 6 months [158]. No difference in SRE over 2 years has been shown in patients receiving ZA every 4 weeks vs. every 12 weeks [128].

Other Solid Tumors (Other than Breast and Prostate Cancers)

Lung Cancer Squamous cell carcinoma and adenocarcinoma metastasize to vertebrae, and multiple spine levels are often involved with a mean survival of 7 months after the diagnosis of vertebral metastasis [159]. ZA was shown to significantly delay development of SRE (39% vs. 46% in control) and time to first SRE (236 vs. 155 days) and to reduce annual incidence of SREs (1.74 per year vs. 2.71 per year) [160]. Comparison of Dmab and ZA in patients with bone metastases of solid tumors (predominantly non-small cell lung cancer, NSCLC) or myeloma showed non-inferiority of Dmab to ZA and delaying the first SRE in favor of Dmab [161]. Dmab 120 mg SC monthly compared with ZA 4 mg per month has been shown to improve survival in NSCLC (9.5 vs. 8 months) and squamous cell lung cancer (8.6 vs. 6.4 months) among patients with NSCLC with bone involvement [131].

Thyroid Cancer Analysis of 30,063 patients with all types of thyroid cancer revealed 3.9% of patients have bone metastases and 5.5% developed SRE [162]. In general, bone metastases are more common in follicular thyroid cancer (7–28%) and medullary thyroid cancer (16–19%) in comparison to papillary thyroid cancer (1.4–7%) [163]. The 5- and 10-year OS from initial bone metastases in patients with differentiated thyroid cancer were described as 61% and 27% and only 15% in poorly differentiated thyroid cancer [164, 165].

Differentiated Thyroid Cancer (DTC) Adjunctive therapy with calcium, vitamin D, and bone-enhancing agents such as a BP or Dmab should be considered in pre- and postmenopausal women with DTC who are on suppressive thyroid hormone therapy [129]. In patients with multiple progressing and/or symptomatic DTC bone metastases, the bone-directed therapy should be strongly considered, and ZA therapy is suggested every 3 months. The bone-directed therapy is recommended even if kinase inhibitor therapy is intended or ongoing [129]. 4 mg ZA every month has been shown to diminish new SRE in patients with DTC [166]. Significantly lower SRE (14% vs. 50%) and delayed onset of the first SRE were shown with monthly ZA but with 9.1% (2 cases) of ONJ despite regular dental follow-up [167]. Another approach that was described is to give 4 mg of ZA every 3 months for the first year and every 6 months thereafter [168]. In patients with bone metastases and no pathological fractures, 4 mg of ZA every 6 months might be sufficient [168].

Medullary Thyroid Cancer (MTC) Bone metastases in MTC, described in 19% of patients [169], are usually multifocal, primarily involving the spine (86–92%) and pelvis (60–69%) with SRE in 47–48% of patients [169, 170]. SRE was seen more frequently in osteolytic (42%) vs. osteoblastic bone metastases [170]. SREs have been shown to be less frequent in patients on monthly antiresorptive treatment [170].

The American Thyroid Association (ATA) guidelines on MTC management recommend treatment with Dmab or BP for patients with painful osseous metastases, and recommendations are based on expert opinion [127].

Anaplastic Thyroid Cancer (ATC) Based on ATA recommendations on ATC management, patients with known osseous metastases should be considered for periodic IV BP infusions or Dmab injections. However, no definitive recommendations regarding frequency and duration have been provided [130].

Kidney Cancer As many as 50% of patients with renal carcinoma develop bone metastases with 15% involving the spine [171]. Thirty percent of patients will have a pathological fracture as primary presentation and an average life expectancy of 1–2 years in the presence of metastases [171, 172]. The addition of ZA to everolimus in patients with RCC showed a significant delay in the development of first SRE in comparison with everolimus alone (9.6 months vs. 5.2 months) [173]. However, no improvement in

DFS or OS was shown with bisphosphonate use [174]. The addition of bone-targeting therapy (Dmab 120 mg or ZA 4 mg every 4 weeks) to tyrosine kinase inhibitors resulted in a trend favoring OS with the use of Dmab or ZA, but no difference in time to SRE was found. However, the group of patients who received antiresorptive therapy was small (nine patients) [175].

Neuroendocrine Tumors (NETs) In general, BPs are not commonly used for NET with bone metastases, possibly due to a lack of survival benefit [176]. Bone metastases are reported in 7–18% of patients with neuroendocrine tumors [177]. Analysis of 74 patients with NET of the pancreas (30%), small and large bowel (35%), lung (15%), thymus (3%), breast (1%), and unknown origin (16%) showed the spine to be the most common site of the bone metastases (85%) with prevalent involvement of the dorsal (60%), LS (58%), and sacrum (38%) [177]. The monthly administration of BP did not show a benefit over less intense schemes in overal outcome. However, monthly therapy was given in cases of more advanced bone involvement [177], which could have affected the results. The BP or Dmab treatment has been recommended for NET metastatic bone disease to improve survival independently from their dosing, at least for BP administration.

Medullary Thyroid Cancer (MTC) MTC is a neuroendocrine thyroid tumor that is described in the thyroid cancer section.

Pheochromocytoma/Paraganglioma (Pheo/PGL) Overall, 71% of patients with metastatic Pheo/PGL have bone involvement and about 72% will have at least one SRE. The spine is the most common location (81%) of bone metastases in patients with pheo/PGL [178]. The median OS was reported 12 years for patients with only bone metastases and 5 years if bone metastases and non-osseous metastases [178]. Pathological fracture has been described as one of the most common SREs (27%). Thus, close follow-up and antiresorptive therapy in patients with bone metastases and systemic therapy in any patient with the progressive bone disease despite the lack of symptoms have been recommended [178].

In general, as for other NETs, bisphosphonate or Dmab is recommended in the case of bone metastases [179].

Non-pharmacological Treatment of Low BMD

An ounce of prevention is worth a pound of cure.
—Benjamin Franklin

Physical Activity and Fall Prevention Exercises can prevent or reverse almost 1% of bone loss in LS and femoral neck per year in pre- and postmenopausal women [180]. Based on a systematic review, exercise interventions have led to a decrease in the incidence of falls ranging from 22% to 58% and mean improvement in gait ranging from 4% to 50% and in balance from 5% to 80% [181]. Weight-bearing exercise, especially resistance training, showed greater gains in strength. This type can also improve a neuromuscular activity and functional capacity, such as gait velocities and stair climbing abilities [181]. The American Geriatrics Society and British Geriatrics Society (2011) recommended the inclusion of strength, balance, gait, and coordination training as part of an intervention for fall prevention in older persons [182].

If a patient is at high risk for falls, daily balance exercises can be introduced. As an example, the patient can be encouraged to stand with feet together and to shift forward and backward to limits of stability, to dance, or to perform walking lunges or Tai Chi [183].

Cognitive and balance exercises can be improved by introducing patients to the Clock Yourself app (http://www.clock yourself.com.au). Fall prevention is a critical part of osteoporosis management; a fall can impact independence and lead to disability, social isolation, and increased mortality. There are known risk factors for falls in older people – *modifiable* and *non-modifiable*.

Potentially *modifiable* risk factors include sensory deficits (vision, auditory); musculoskeletal causes (balance and gait impairment, foot problems, muscle weakness in low extremities, musculoskeletal pain); cardiac abnormalities (arrhythmias, CHF, HTN); diabetes mellitus; low BMI; and vitamin D deficiency. Neurological causes of falls include dizziness, vertigo, movement disorders, and neuropathies [184]. Depression is an important fall risk factor. Fear of falling has been shown to develop in 32% of elderly patients who experienced a fall [185]. Fallers with fear of falling experience a greater increase in balance and cognitive disorders and decrease in mobility [185]. Systemic diseases such as cancer, obstructive sleep apnea, nocturia, postural hypotension, and urinary incontinence can also increase the risk of falls [184]. A review of the medication list of the patient is important to identify the medications that can increase the risk of falls. Based on the 2015 American Geriatrics Society Beers Criteria for non-anti-infective medications, older adults should consider decreasing their dose of, or entirely avoiding, anticholinergics, antipsychotics, benzodiazepines, non-benzodiazepines hypnotics, and opioid receptor agonist analgesics [186].

Non-modifiable factors include age, especially >80 years old, female gender, white race, cognitive impairment, dementia, recent hospital discharge, history of stroke or transient ischemic attack, history of previous falls and fractures, and presence of arthritis [184].

Detailed recommendations on steps to prevent falls can be found on the International Osteoporosis Foundation website.

Suggested patient-related measures include:

- Regular vision check, eyeglass cleaning, careful stair use if wearing bi-focal glasses, sunglasses use to reduce glare during sunny days
- Comfortable shoes with a broad heel and non-slip soles
- Medication reconciliation during doctor visits
- A healthy diet, smoking cessation, and decrease in alcohol intake
- Regular weight-bearing and muscle-strengthening exercises
- Consideration of using hip protectors

Environment-related measures:

- Regular home check for removal of objects patient could trip over (clutter, throw rugs, electrical cords)
- Wiping all floor spills immediately
- Extra light in hallways, stairways, outside walkways
- Handrails in bathrooms/restrooms, stairs
- Use of nonskid floor wax
- Keeping frequently used items at an easy-to-reach level

Smoking and Alcohol Use Smoking is included as a risk factor in the FRAX® score calculator. Nicotine has direct and indirect effects on bone mass. One of the indirect effects is low body mass that causes a decrease in mechanical loading, low-fat tissue component, and decreased estrogen fat production by decreased conversion of androgen to estrogen [187]. Furthermore, estrogen metabolism can be enhanced by tobacco smoking, and smokers have been shown to have 0.8–1.7 years earlier onset of menopause in comparison with non-smokers [188].

Also, smoking is associated with high levels of free radicals that may contribute to bone resorption and lower bone mass [189]. Alcohol intake ≥30 g/day (one glass of wine (4 oz or 120 mL = 10 g of alcohol), one glass of beer (4 oz or 120 mL = 4 g of alcohol), or one shot of liquor (10 g of alcohol)) has been shown to significantly decrease total body BMD in elderly women [190].

Post-Fracture Care It is critical to follow patients who have been diagnosed with osteoporosis or already developed a fragility fracture. Fracture liaison Service (FLS) is a program that might be effective in inpatient and outpatient settings to identify, evaluate, treat, and follow patients after a fracture (https://www.capturethefracture.org/about) [191]. FLS is multispecialty team including FLS coordinator, surgeons, primary care

providers, bone specialists, physical therapist, and dietician who participate in the patient's care, providing osteoporosis education, evaluation, and further management. Implementation of FSL has been shown to improve the rate of BMD testing, to increase treatment initiation, and to reduce risk of re-fracture and mortality [192].

Summary

Fractures due to osteoporosis can lead to social isolation, decreased quality of life, and increased morbidity and mortality. Evaluation of BMD and risk for fractures is critical for the planning and outcome of spinal interventions. A multidisciplinary approach is important for early diagnosis, identification of the modifiable factors that are known to have negative effect of BMD, and timely treatment initiation.

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