REVIEW

Approach to the patient with secondary osteoporosis

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Abstract

Secondary osteoporosis is characterized by low bone mass with microarchitectural alterations in bone leading to fragility fractures in the presence of an underlying disease or medication. Scenarios that are highly suspicious for secondary osteoporosis include fragility fractures in younger men or premenopausal women, very low bone mineral density (BMD) values, and fractures despite anti-osteoporotic therapy. An open-minded approach with a detailed history and physical examination combined with first-line laboratory tests are aimed at identifying clinical risk factors for fractures, osteoporosis-inducing drugs, and underlying endocrine, gastrointestinal, hematologic, or rheumatic diseases, which then need to be confirmed by specific and/or more invasive tests. BMD should be assessed with bone densitometry at the hip and spine. Lateral X-rays of the thoracic and lumbar spine should be performed to identify or exclude prevalent vertebral fractures which may be clinically silent. Management of secondary osteoporosis includes treatment of the underlying disease, modification of medications known to affect the skeleton, and specific anti-osteoporotic therapy. Calcium and vitamin D supplementation should be initiated with doses that result in normocalcemia and serum 25-hydroxyvitamin D concentrations of at least 30 ng/ml. Oral and i.v. bisphosphonates are effective and safe drugs for most forms of secondary osteoporosis. Severe osteoporosis may require the use of teriparatide.

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Background

Secondary osteoporosis is defined as bone loss, microarchitecural alterations, and fragility fractures due to an underlying disease or concurrent medication (1). Secondary osteoporosis remains a diagnostic and therapeutic challenge as it frequently affects patient populations, e.g. premenopausal women or younger men who are usually not target populations for routine screening for osteoporosis. In addition, the underlying conditions are diverse and rare, and require specific diagnostic tests (1). Moreover, response to osteoporosis therapy may be limited if the underlying disorder goes unrecognized and if other risk factors are present. For example, alendronate displayed a reduced efficacy in women with postmenopausal osteoporosis and TSH-suppressive L-thyroxine (L-T_4) therapy after treatment for differentiated thyroid cancer (2). As a caveat, the anti-fracture efficacy of many drugs has not been clearly demonstrated, except for glucocorticoid-induced osteoporosis (GIO) and male hypogonadism in secondary osteoporosis, and the use of specific anti-osteoporosis drugs is based on bone mineral density (BMD) as a surrogate.

Apart from the more well-known endocrine disorders, including Cushing's syndrome, hypogonadism, hyperthyroidism, and hyperparathyroidism, the adverse effects of diabetes mellitus have just recently been acknowledged (3). In fact, patients with type 1 diabetes mellitus have a 12-fold higher risk of sustaining osteoporotic fractures, compared with non-diabetic controls (4). In addition, chronic inflammation present in inflammatory bowel disease and rheumatoid arthritis cause osteoporosis, in part because of the pro-inflammatory cytokine milieu and immunosuppressive regimens (5). The emerging use of thiazolidinediones (TZDs) (6), aromatase inhibitors (AIs) (7), androgen-deprivation therapy in men with prostate cancer (8), and the growing field of bariatric surgery (9) have emerged as novel and important etiologies of secondary osteoporosis.

Here, we summarize the current state of knowledge on the mechanisms of secondary osteoporosis, outline a practical diagnostic strategy, and provide management recommendations.

Mechanisms

Endocrine diseases

Glucocorticoid excess Endogenous overexpression or systemic administration of glucocorticoids impairs skeletal health through various cellular effects, of which inhibition of bone formation due to induction of osteoblast and osteocyte apoptosis is the most critical (10). Predominant spinal bone loss and vertebral fractures are characteristic features, as is an increased risk of falls due to muscular atrophy and altered neuromuscular function (11). Even low doses of glucocorticoids (2.5–7.5 mg of prednisolone per day) are associated with a 2.6-fold higher risk of vertebral fractures, whereas doses higher than 7.5 mg of prednisolone per day carry a fivefold higher risk (12). In most patients suffering from rheumatological diseases as listed in Table 1, in particular rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus, rapid bone loss and increased fracture risk are caused by the pro-inflammatory cytokine milieu or the immunosuppressive regimen, which initially includes glucocorticoids, or a balance between both.

Table 1 Common causes for secondary osteoporosis.

Endocrine diseases
  Diabetes mellitus
  GH deficiency (rare)
  Acromegaly (rare)
  Hypercortisolism
  Hyperparathyroidism
  Hyperthyroidism
  Premature menopause
  Male hypogonadism

Gastrointestinal disorders
  Gastrectomy
  Celiac disease
  Inflammatory bowel disease
  Liver cirrhosis
  Chronic biliary tract obstruction
  Chronic therapy with proton pump inhibitors

Hematologic diseases
  Myeloma
  Monoclonal gammopathy of undetermined significance
  Lymphoma/leukemia
  Systemic mastocytosis (rare)
  Disseminated carcinoma
  Chemotherapy

Rheumatological diseases
  Rheumatoid arthritis
  Ankylosing spondylitis
  Systemic lupus erythematosus

Connective tissue diseases
  Osteogenesis imperfecta
  Marfan's syndrome (rare)
  Ehlers–Danlos syndrome (rare)
  Pseudoxanthoma elasticum (rare)

Other
  Anorexia nervosa

Hyperthyroidism A history of overt hyperthyroidism is an established risk factor for osteoporotic fractures (13). A large study of 686 postmenopausal women demonstrated that a serum TSH level <0.1 mU/l was associated with a four- and fivefold risk of hip and vertebral fractures respectively (14). A meta-analysis of 21 studies indicated that thyroid hormone therapy for TSH suppression in differentiated thyroid cancer which results in subclinical hyperthyroidism is associated with osteoporosis in postmenopausal women (15). Based on animal models, thyroid hormone excess (16) as well as suppressed thyrotropin levels (17) has been implicated. Activation of thyroid hormone receptor α on osteoblasts and osteoclasts results in enhanced bone resorption and bone loss (16).

Primary hyperparathyroidism Women are three times more often affected by primary hyperpara-thyroidism than men, and its incidence is as high as 1:500 in elderly women, a high-risk population for osteoporosis (18). Chronic parathyroid hormone (PTH) excess is catabolic to the skeleton, and preferentially affects cortical rather than cancellous bone. Thus, bone loss is most prominent at skeletal sites that consist of cortical bone (middle third of the forearm and femoral neck), while the spine, mainly composed of cancellous bone, is less severely affected (18). Either osteoporotic fractures or a T score of <-2.5 is an indication for parathyroid surgery in otherwise asymptomatic patients (18). A recent observational study over the course of 15 years showed that parathyroidectomy normalized biochemical indices of bone turnover and preserved BMD, whereas cortical bone density decreased in the majority of subjects without surgery during long-term follow-up (19).

Male hypogonadism Androgens are crucial for the accrual of peak bone mass in men and the maintenance of bone strength thereafter (8, 20, 21). The effects of androgens on bone may be mediated by estrogens (22). Hypogonadism is a major risk factor for low BMD and osteoporotic fractures in men, and results in increased bone remodeling with rapid bone loss (21). As androgen-deprivation therapy using GnRH agonists has become a mainstay in the multimodal management of prostate cancer, treatment-related hypogonadism has emerged as an important risk factor for osteoporotic fractures in these men (8, 23).

Pregnancy-associated osteoporosis The mechanisms of this entity are poorly understood. Factors that have been implicated include preexisting vitamin D deficiency, low intake of calcium and protein, low bone mass, increased PTH-related protein, and high bone turnover (24, 25). Multiple pregnancies or prolonged periods of lactation *per se* are not associated with osteoporosis. However, women are at risk of pregnancy-associated

osteoporosis, if they use <u>unfractionated heparins</u> for thromboembolic disorders (26, 27). The skeletal side effects of low-molecular weight heparin are currently unknown (28).

Diabetes mellitus type 1 The risk of osteoporotic fractures is increased by 12-fold in patients with type 1 diabetes (4). <u>Lack of the bone anabolic actions of insulin and other</u> β-cell-derived proteins such as amylin have been postulated to contribute to low BMD and impaired fracture risk (3). In long-standing disease, diabetic complications, such as retinopathy, polyneuropathy, and nephropathy, are the major determinants of low bone mass and increased fracture risk, in part due to the enhanced propensity of falls (3). Data from the Women's Health Initiative Observational Study also indicate a 20% higher risk for fractures after adjustment for frequent falls and increased BMD (4–5% higher at the hip) in women with type 2 diabetes mellitus (29). An important additional risk factor for fractures in postmenopausal women with type 2 diabetes mellitus is the use of a <u>TZD type insulin sen</u>sitizer, associated with fractures of the hip, humerus, and small bones of the hands and feet (30).

GH deficiency Insulin-like growth factor 1 (IGF1) and IGF-binding proteins, which are produced upon stimulation of its hepatic receptor by human GH, represent a potent stimulator of osteoblastic functions and bone formation (31, 32). Patients with untreated adult-onset GH deficiency have a two- to threefold higher risk of osteoporotic fractures (32), and the degree of osteopenia is related to the extent of GH deficiency (33). Accurate measurement of BMD in patients with pediatric-onset GH deficiency is complicated because of short stature and small bone size.

Gastrointestinal diseases

Celiac disease Chronic diarrhea and malabsorption due to villous atrophy are the hallmarks of celiac disease. Intestinal absorption of calcium is impaired, and vitamin D deficiency is common (Table 1), resulting in osteomalacia and secondary hyperparathyroidism (34). Associated autoimmune disorders such as type A gastritis with achlorhydria, Graves' disease with hyperthyroidism, or type 1 diabetes mellitus may further impair skeletal health. A recent study demonstrated a 17-fold higher prevalence of celiac disease among osteoporotic individuals compared with non-osteoporotic individuals, supporting serologic screening of all patients with osteoporosis for celiac disease (35).

Inflammatory bowel disease The pathogenesis of osteoporosis in inflammatory bowel disease is complex, and patients with Crohn's disease are more severely affected compared with those with ulcerative colitis

(36). Chronic inflammation, diarrhea and/or malabsorption, low body mass index (BMI), and intermittent or chronic systemic glucocorticoid therapy for flares are major causes of osteoporosis. In addition, vitamin D deficiency in those with short bowel syndrome or functional loss of terminal ileum integrity, repeated hospitalizations, and prolonged immobility may contribute to low bone mass. Short bowel syndrome is a particular risk factor for bone loss (36).

Gastrectomy and chronic proton pump inhibitor therapy After gastrectomy, osteoporosis develops in up to one-third of patients postoperatively, and may be related to decreased calcium absorption due to the higher gastrointestinal pH value (37). Similarly, a prolonged high-dose use of proton pump inhibitors carries a 3.5-fold increased risk of vertebral fractures in postmenopausal women (38). Loss of gastric acidification may impair the absorption of calcium carbonate compared with calcium gluconate or calcium citrate, which are absorbed in a pH-independent manner, but are used less commonly.

Bariatric surgery Bone loss after bariatric surgery has become a clinical challenge (39). The various procedures, including biliopancreatic diversion with duodenal switch, gastric banding, and Roux-en-Y gastric bypass, the last of which is the preferred method in the US, are associated with variable degrees of reduced fractional calcium absorption and vitamin D malabsorption (9, 39). Bone loss may be moderately severe, and appears to be closely related to the degree of weight loss (9). A preliminary study indicated a doubling of fracture risk after bariatric surgery.

Myeloma bone disease and systemic mastocytosis

Myeloma bone disease and monoclonal gammopathy of undetermined significance Various cellular and humoral communications between myeloma cells and bone cells contribute to osteoporosis, and mainly affect the axial skeleton. Expression of receptor activator of NF-κB ligand (RANKL) and other pro-osteoclastogenic factors by myeloma cells results in enhanced osteoclastogenesis and increased bone resorption (40). In addition, myeloma cells secrete dickkopf-1, a soluble Wnt signaling inhibitor, which markedly suppresses osteoblastic differentiation (41). A population-based retrospective cohort study that followed 165 patients with myeloma for 537 person-years reported that in the year before myeloma was diagnosed, 16 times more fractures were observed than expected, of which two-thirds were pathologic spinal or rib fractures (42). The risk of subsequent osteoporotic fractures was elevated two- to threefold. Up to 1 in 20 patients with newly diagnosed osteoporosis have multiple myeloma or monoclonal gammopathy of undetermined significance

(MGUS) (43). Of note, patients with MGUS, a disease that can progress to multiple myeloma, also carry an increased risk for osteoporotic fractures (44). A retrospective cohort study of 488 patients with MGUS found a 2.7-fold increased risk of axial fractures, but no increase in limb fractures (44).

Systemic mastocytosis Bone loss due to mastocytosis may be rapid and severe, and affects both the long bones and the spine. Osteoporosis results from excessive degranulation of mast cell products, including interleukin (IL)-1, IL-3, IL-6, and histamine, which promote osteoclast differentiation from precursor cells (45). An activating mutation of the tyrosine kinase c-kit (D816V mutation), present in over 90% of adult patients with mastocytosis, contributes to elevated bone resorption.

HIV disease

Women and men with HIV disease are at increased risk of spinal, hip, distal radius, and other fractures due to osteoporosis. In older individuals with HIV disease, fracture risk is increased three- to fourfold compared with non-HIV-infected controls (46). The risk of having osteoporotic bone density is also increased 3.7-fold for HIV-infected individuals compared with controls (47). In addition to anti-retroviral drug use, the increase in osteoporosis risk is related to low BMI, hypogonadism, infection and inflammation, vitamin D deficiency, GH deficiency, smoking, and alcohol abuse. An assessment of bone health and vitamin D status is therefore important in individuals with HIV disease.

Drug-induced osteoporosis

Numerous drugs affect bone metabolism (Table 2) through interaction with the absorption of vitamin D, calcium, and phosphate or vitamin D metabolism and action, direct cellular effects on osteoblasts, osteoclasts, and osteocytes, or interference with either the amount or quality of bone matrix proteins. The adverse skeletal effects of glucocorticoids (11) and calcineurin inhibitor-type immunosuppressants such as cyclosporine A (48) are well established in the management of inflammatory diseases and in transplantation medicine. To minimize skeletal side effects, non-calcineurin inhibitor immunosuppressants and glucocorticoid-sparing regimens are increasingly employed.

The use of the insulin sensitizers TZDs (rosiglitazone and pioglitazone) which act as agonists of the peroxisome proliferator-activated receptor-γ is associated with a three- to five-fold higher risk of fractures of the humerus, femur, and hip in postmenopausal women (49). These alterations may result from shunting pluripotent mesenchymal stem cells toward the adipocyte phenotype at the cost of the osteoblastic lineage, which resembles the bone changes that occur with aging (50). In particular, rosiglitazone decreases bone formation in the face of on-going bone resorption, leading to bone loss (51).

Ablation of androgen or estrogen production or action has become a mainstay in modern therapy of prostate and breast cancer respectively. Androgen-deprivation therapy includes GnRH agonists (goserelin, buserelin, leuprolide, and triptorelin), which cause hypogonadotropic hypogonadism, or anti-androgens (bicalutamide and cyproterone acetate) that block the peripheral action of androgens. Similarly, the use of the AIs anastrozole, letrozole, and exemestane reduces the conversion from adrenal androgens into estrogens. Thus, both strategies are aimed at reducing the amount of bioavailable androgens and estrogens, which act as tumor-promoting hormones; however, they cause severe and rapid high turnover bone loss and fractures (7, 52).

Other drugs known to affect bone metabolism include the injectable contraceptive depot-medroxyprogesterone acetate (53), proton pump inhibitors (54), heparins

Table 2 Drugs known to cause osteoporosis and/or fragility fractures.

Drug class[a]	Examples	Indications
Glucocorticoids[a,b]	Prednisolone	Autoimmune diseases
Calcineurin inhibitors[a,b]	Cyclosporine A	Allogeneic organ transplantation
Chemotherapeutic drugs	Methotrexate, ifosfamide	Miscellaneous
Tyrosine kinase inhibitors	Imatinib	Chronic myelogenous leukemia
Thiazolidinediones[a,b]	Rosiglitazone, pioglitazone	Type 2 diabetes mellitus
GnRH agonists[a,b]	Goserelin, buserelin, flutamide	Prostate cancer, endometriosis
Aromatase inhibitors[a,b]	Anastrozole, letrozole, exemestane	ER-positive breast cancer
Progesterone	Depot-medroxyprogesterone acetate	Contraception
Proton pump inhibitor[a,b]	Omeprazole and pantoprazole	Peptic ulcer and reflux diseases
Unfractionated heparins[a,b]		Thromboembolic diseases
Lipase inhibitors	Orlistat	Morbid obesity
Thyroid hormone[b]	ʟ-thyroxine	Replacement therapy for hypothyroidism, thyroid cancer
Anticonvulsants[a]	Valproic acid	Chronic seizure disorders
Antidepressants[a,b]	Selective serotonin re-uptake inhibitors	Chronic depression
Anti-retroviral drugs	Tenofovir	HIV disease

[a]Strong evidence.
[b]Drug is associated with increased fractures.

(26), antiepileptic drugs that induce hepatic enzymes (phenytoin, phenobarbitone, primidone, and carbamazepine) (55, 56), antidepressants of the selective serotonin re-uptake inhibitor class (57–59), and anti-retroviral drugs used to treat HIV (47).

Diagnosis

The initial evaluation of secondary osteoporosis should include a detailed history of clinical risk factors for fractures and the underlying medical conditions and medications that cause bone loss, a thorough physical examination and laboratory tests (Table 3).

A comprehensive review of all used medications is essential, as is an evaluation of the smoking and alcohol habits, and the hereditary disposition of osteoporosis or fractures. Particular attention should be given to type 1 diabetes mellitus, anorexia nervosa, and prolonged sex hormone deficiency as well as those endocrine disorders that can in principle be cured (Table 1). The risk for falling should be assessed in patients with osteoporotic fractures who reported repeated falls (60). A recommended clinical approach includes evaluation of high-risk medications (sleeping medications, antidepressants, and anticonvulsants), vision, balance and gait, and muscle strength. A reasonable screening test is the 'Timed Up and Go' tests which integrates many of these functions.

Based on these initial findings and the clinical index of suspicion, further laboratory and imaging studies as well as invasive tests are required.

BMD testing using dual-energy X-ray absorptiometry is the method of choice for the diagnosis of secondary osteoporosis and should be conducted at the lumbar spine and hip (61). Aortic calcification and osteophytes, which are particularly common in men, may interfere with spinal BMD measurement, allowing only hip measurement to be used. In the presence of an underlying cause, fracture risk may be increased independently of BMD (57). For example, patients with chronic renal failure may have increased skeletal fragility despite normal BMD values. In addition, there is a higher BMD fracture threshold in patients on systemic glucocorticoids, so that most would support intervention for patients with osteopenia. Spinal X-rays should be performed in those with localized back pain, recent spinal deformities, or a loss of more than 3 cm in height in order to detect prevalent vertebral fractures, osteolytic lesions, or tumors (Table 3). Owing to their low sensitivity, spinal X-rays should not be used to screen for osteoporosis. A recent alternative has been the vertebral fracture assessment tool of the dual-energy X-ray absorptiometry which provides a lateral vertebral morphometry and is associated with less radiation and, when available, is a useful screening test for vertebral fractures. The fracture risk can be easily assessed with the FRAX tool (http://www.shef.ac.uk/FRAX/), a computer-based calculator that,

Table 3 Diagnostic tests in the work-up of secondary osteoporosis.

Diagnostic test	Purpose
History and physical exam	To identify risk factors for fractures, the underlying disease, and potential drugs
Dual-energy X-ray absorptiometry (lumbar spine and hip)	To quantify bone mineral density
Spinal X-rays	To detect prevalent vertebral fractures
	To exclude osteolytic lesions or tumors
Diagnostic test	*To detect or exclude*
Complete blood count	Anemia as in myeloma/celiac disease
	Leukocytosis in leukemia
Renal and liver function test	Renal or liver failure, alcohol abuse
Serum calcium and phosphate levels	Primary hyperparathyroidism, myeloma
Serum C-reactive protein	Chronic infection/inflammation
Serum bone-specific or total AP activity	Paget's disease; osteomalacia
Serum 25-hydroxyvitamin D	Vitamin D deficiency, osteomalacia
Serum levels of basal TSH	Hyperthyroidism
Serum free testosterone levels (in men)	Male hypogonadism
Fasting glucose levels	Diabetes mellitus
Intact parathyroid hormone	Primary hyperparathyroidism
Serum protein electrophoresis, immunofixation	MGUS, myeloma
24-h urinary calcium excretion (with creatinine and sodium control)	Hypercalciuria
Anti-tissue transglutaminase antibodies	Celiac disease
Anti-HIV antibodies	HIV disease, AIDS
Morning fasting serum cortisol after dexamethasone suppression	Cushing's syndrome
Serum tryptase levels, urinary histamine excretion	Systemic mastocytosis
COL1A genetic testing	Osteogenesis imperfecta
Iliac crest bone biopsy	Systemic mastocytosis, MGUS/myeloma, osteomalacia, lymphoma/leukemia

AP, alkaline phosphatase.

in addition to gender, age, BMD, and BMI, also includes risk factors such as smoking, alcohol abuse, glucocorticoid use, and the presence of rheumatoid arthritis and secondary osteoporosis.

We recommend an initial laboratory evaluation with standard renal and liver function tests, a complete blood count, serum calcium and phosphate levels, C-reactive protein, bone-specific (or total) alkaline phosphatase, serum 25-hydroxyvitamin D, serum levels of basal thyrotropin, and serum testosterone levels in men (Table 3). We also recommend free measurements of serum levels of PTH, serum protein electrophoresis, and 24-h urinary calcium excretion. The latter should be performed including measurement of creatinine as internal quality control and sodium excretion to exclude salt restriction with subsequent false-low calcium excretion.

To screen for celiac disease, anti-tissue transglutaminase antibodies should be measured, especially if iron-deficiency anemia and low 25-hydroxyvitamin D levels are present, and if positive, a duodenal biopsy should be performed to confirm the diagnosis. To rule out Cushing's syndrome, we measured morning fasting serum cortisol levels after administration of 1 mg dexamethasone at midnight the previous day. If systemic mastocytosis is suspected, we recommend the measurement of mast cell-derived products, serum tryptase levels, or 24-h urinary excretion of histamine, although these may be normal, in part because histamine is thermolabile. Thus, if available, urinary excretion of N-methylhistamine or 11-β prostaglandin $F_{2\alpha}$ may be more robust and reliable than urinary excretion of histamine. *COL1A* genetic testing is required to confirm the diagnosis of osteogenesis imperfecta. This is most commonly diagnosed based on a positive family history, recurrent fragility fractures, blue sclerae, and hearing loss, and only rarely requires genetic confirmation by *COL1A1* genotyping.

We advocate iliac crest bone biopsy for those individuals where the evaluation described above yields unexplained laboratory findings or remains inconclusive, in young adults with multiple fractures or fractures that occur during antiresorptive treatment. Typical scenarios for a definitive role of bone biopsy are to distinguish osteomalacia from osteoporosis, to establish a diagnosis of systemic mastocytosis, and to assist in diagnosing infiltrating malignant diseases, including multiple myeloma, lymphoma, leukemia, or disseminated carcinoma.

Biochemical markers of bone turnover are of limited use in establishing a secondary cause of osteoporosis; however, they may be used to monitor therapeutic efficacy or the patient's adherence/compliance with treatment.

Treatment

The management of secondary osteoporosis is aimed at i) treating the underlying disease, if known, and ii) treating osteoporosis and preventing further fractures.

A practical approach with patient-centered, individualized therapy is warranted. Because of the various etiologies of secondary osteoporosis and limited randomized placebo-controlled trials in this area, treatment guidelines are largely based on professional opinion rather than the highest level clinical evidence.

Treatment of the underlying disease

Endocrine diseases Complete and sustained therapy of the underlying endocrine disorder can be challenging. Cushing's syndrome and primary hyperparathyroidism should be surgically treated if osteoporosis is present. Endogenous hyperthyroidism should be treated with anti-thyroid drugs, radioiodine therapy, or surgery, while exogenous hyperthyroidism requires adjustment of the L-T_4 dosage with a target serum thyrotropin level within the normal range. If TSH-suppressive therapy for differentiated thyroid carcinoma is required, the lowest L-T_4 dose that suppresses TSH below the limit of detection should be administered.

Sex hormone deficiency in premenopausal women and men with osteoporosis should be replaced, if signs and symptoms of hormone deficiency, such as decreased libido, sarcopenia, and visceral obesity, are present. Fracture risk reduction has not been shown for testosterone replacement therapy, but increases in BMD are seen in hypogonadal men treated with testosterone (8). Specific contraindications, such as breast cancer and thromboembolic diseases in women, and benign prostatic hypertrophy and prostate cancer in men, need to be carefully considered.

While GH replacement therapy in adult GH deficiency increases BMD in men (62, 63), no data on fracture reduction are available, and the cost–effectiveness of this therapy remains unclear. Patients with type 1 diabetes mellitus and low bone mass benefit from intensive insulin therapy (64) and aggressive prevention of diabetic vascular complications, including retinopathy, nephropathy, and polyneuropathy (3). In addition, patients with both type 1 and type 2 diabetes mellitus require assessment of falls risk.

A systematic review on bone health in anorexia nervosa (65) suggests that estrogen replacement therapy resulted in variable increase in BMD, which did not reach that of age-matched controls, whereas bisphosphonates were largely ineffective. As expected, the most consistent finding was that enhanced caloric intake that led to weight gain and ovulations resulted in a substantial gain of BMD.

Gastrointestinal diseases Restoration or maintenance of normal body weight and gastrointestinal absorption are pivotal for patients with osteoporosis due to gastrointestinal diseases (Table 1). Patients with celiac disease require nutritional counseling emphasizing adherence to a gluten-free diet, which may require

close monitoring. Exocrine pancreatic enzymes should be replaced in states of malabsorption due to pancreatic insufficiency. For patients with inflammatory bowel disease, in particular those with Crohn's disease, an attempt should be made to modify the immunosuppressive regimen to control inflammatory activity and to reduce the glucocorticoid dose. The latter strategy should also be applied in other inflammatory disorders complicated by osteoporosis. Two small studies indicate that suppression of the inflammation by tumour necrosis factor-α blockade with infliximab increases BMD in patients with Crohn's disease (66) and rheumatoid arthritis (67). The use of biologicals may also help to reduce the glucocorticoid dose. Small bowel surgery in Crohn's disease should be used sparingly to avoid short bowel syndrome and to thus preserve the terminal ileum. The endocrine and skeletal status of patients who underwent gastrointestinal surgery, particularly those after bariatric surgery, should be monitored for life, as no long-term safety data are available.

Malignant diseases Patients with osteoporosis in the setting of a malignant disease should be referred to a comprehensive cancer center. Patients with breast or prostate cancer and low bone density due to hormone-ablative therapy will be discussed below.

Drug-induced osteoporosis If drugs suspected to promote osteoporosis are being taken (Table 2), their continued use needs to be evaluated and alternatives should be sought. This holds particularly true for alternative routes of administration, especially the use of topical drugs (glucocorticoid aerosol for inflammatory airway disease or enema for inflammatory bowel diseases with rectal involvement). In allogeneic organ transplantation and inflammatory disorders, novel regimens without calcineurin inhibitors and glucocorticoids may be feasible.

For patients with seizure disorders requiring prolonged anticonvulsive therapy, a variety of novel drugs are available that do not interfere with vitamin D and mineral metabolism. In patients with diabetes, TZDs should be discontinued and replaced by other insulin sensitizers, if possible. Patients with heparin-induced osteoporosis who require anticoagulation should be switched to oral vitamin K antagonists. The adverse effects of the injectable contraceptive depot-medroxyprogesterone acetate on BMD need to be balanced against the benefits of preventing unintended pregnancy (53). Particular attention should be paid to anti-hypertensive, sedative, psychotropic, and antidepressant drugs alone or in combination, as they may indirectly cause osteoporotic fractures by enhancing the propensity of falls. We recommend all patients with secondary osteoporosis to limit alcohol consumption to no more than two standard drinks per day and to stop smoking. Patients with hypercalciuria may benefit from a thiazide (12.5–25 mg hydrochlorothiazide per day).

Specific osteoporosis treatment

Vitamin D and calcium An adequate intake of calcium (800–1200 mg/day) via dietary intake or supplements is recommended. Vitamin D supplementation (at least 800 IU/day) is recommended as vitamin D deficiency has a high prevalence and, in addition to various adverse extraskeletal effects, may contribute to low bone mass and increase the propensity to falls (68). In addition, the efficacy of anti-osteoporotic drugs has only been demonstrated in the presence of vitamin D and calcium supplementation. Therapy should be titrated with doses that result in normocalcemia and serum 25-hydroxyvitamin D concentrations of at least 30 ng/ml. In patients with normal renal function, a decrease in serum PTH levels from elevated to normal levels indicates that 25-hydroxyvitamin D deficiency has been corrected. Some anti-epileptic drugs, e.g. phenytoin, phenobarbitone, primidone, and carbamazepine, increase hepatic metabolism of vitamin D, requiring higher vitamin D doses (56).

Intestinal calcium and vitamin D absorption may be severely impaired in widespread Crohn's disease, after gastrectomy or with chronic use of proton pump inhibitors, and after bariatric surgery. In these circumstances, vitamin D should be administered parenterally (100 000–200 000 IU every 3 months) with titration of doses to achieve serum 25-hydroxyvitamin D concentrations of at least 30 ng/ml. An alternative is oral vitamin D preparations administered at 50 000–100 000 IU once or twice a week, or daily, if needed.

A small randomized study comparing alphacalcidol and etidronate in cardiac transplant recipients indicated that alphacalcidol was superior with respect to the preservation of BMD and fracture reduction (69). A larger study that compared alphacalcidol with the more potent aminobisphosphonate alendronate in patients with GIO indicated that alendronate, but not alphacalcidiol, resulted in an increase in BMD and reduced vertebral fractures (70). A meta-analysis suggests that alphacalcidol as well as calcitriol increases BMD and may reduce fractures, in particular in patients not taking systemic glucocorticoids (71). Based on these studies, active vitamin D metabolites may play a role in the management of secondary osteoporosis (other than GIO), if bisphosphonates cannot be used.

Bisphosphonates Both oral and i.v. bisphosphonates have been used in the treatment of secondary osteoporosis. In general, alendronate (70 mg/week) and risedronate (35 mg/week) are reasonable anti-osteoporotic drugs for secondary osteoporosis. However, many patients with osteoporosis secondary to gastrointestinal diseases or concurrent medications not tolerating, or adhering to, oral bisphosphonates and those in whom oral bisphosphonates are contraindicated may benefit from treatment with i.v. ibandronate or zoledronic acid. I.v. bisphosphonates

are also favorable to oral bisphosphonates which are poorly absorbed in malabsorption. Because of its potency and convenient administration, zoledronic acid (4 or 5 mg/year) has recently been evaluated in various forms of secondary osteoporosis. It is important to note that the evidence for an anti-fracture effect of bisphosphonates is limited for most forms of secondary osteoporosis, except for women and men with GIO, men with hypogonadism, and men after cardiac transplantation. In addition, most studies were not powered to assess fracture risk reduction.

The use of bisphosphonates in patients with renal insufficiency has been a concern. However, a *post-hoc* analysis of the fracture intervention trial (FIT) demonstrated that alendronate reduced fractures in postmenopausal women with osteoporosis and impaired renal function (glomerular filtration rate, GFR <45 ml/min) (72). A small study conducted in patients with osteopenia on regular hemodialysis demonstrated an increase in the spinal BMD with ibandronate (2 mg every 4 weeks over 48 weeks) by 5.1%, although no fracture risk reduction was assessed (73).

Glucocorticoid-induced osteoporosis. Oral alendronate (10 mg/day) and risedronate (5 mg/day) increased BMD and reduced vertebral fractures in women and men with GIO (74, 75). In a 12-month study, zoledronic acid was more effective than risedronate in preventing bone loss in men and women with GIO (76). In a randomized head-to-head study, the BMD increase after 12 months was higher in patients with GIO treated with zoledronic acid (5 mg/year) (+4.1%) compared to risedronate (5 mg/day) (2.7%) (76). However, the study had insufficient power to assess differences in fracture reduction.

The use of bisphosphonates in women of childbearing age still represents a therapeutic dilemma, and the decision on its use needs to be made on an individual basis under effective contraception. A systematic review identified 51 cases of bisphosphonate exposure before or during pregnancy, none of which revealed skeletal abnormalities in the offspring (77).

Osteoporosis in men. Studies of treatment in men with osteoporosis have been smaller and fewer in number than those in women. Treatment efficacy in men is mostly based on positive effects on BMD and bone turnover. In hypogonadal and eugonadal men, alendronate (10 mg/day) increased spinal and femoral neck BMD and reduced the incidence of vertebral fractures by 80% over 2 years (78). Risedronate (5 mg/day) increased spinal and femoral neck BMD, and reduced spinal fractures by 60% over 1 year in an uncontrolled study, although it included men with primary and secondary osteoporosis (79). Both studies had insufficient statistical power to measure differences in fracture rates at non-vertebral sites. Zoledronic acid (5 mg annually) given to elderly men (and women) after hip fractures increased femoral neck BMD, reduced risk of all clinical fractures by 35%, and lowered all-cause

mortality by 28% over 3 years (80). This study included patients with primary and secondary osteoporosis, but did not assess those both separately.

Bone loss associated with androgen-deprivation therapy for prostate cancer. Bisphosphonates have been shown to prevent bone loss in men with non-metastatic prostate cancer receiving androgen-deprivation therapy. Oral alendronate (70 mg/week) (81) and i.v. pamidronate (90 mg every 3 months) (82) have prevented bone loss and, in fact, increased BMD at the lumbar spine and the hip, and decreased bone turnover. More recently, i.v. zoledronic acid (5 mg/year) was shown to prevent bone loss associated with androgen-deprivation therapy in men with prostate cancer (83). However, none of these studies were powered to demonstrate anti-fracture efficacy.

Bone loss associated with AI therapy for breast cancer. Two small trials of postmenopausal women with breast cancer taking AI reported that oral risedronate (35 mg/week) (84) and ibandronate (150 mg/month) (85) reduced bone loss. Semi-annual therapy with 4 mg of zoledronic acid for 3 years (Z- and ZO-FAST trials) prevented bone loss in women receiving AI therapy for breast cancer to a greater extent compared with oral bisphosphonates (86, 87). Taken together, both oral and i.v. bisphosphonates reduce bone loss during AI therapy; however, none of the studies had sufficient power to assess anti-fracture efficacy.

Miscellaneous. Oral alendronate (70 mg/week or 10 mg/day) has been shown to increase BMD in patients with primary hyperparathyroidism (88, 89) as well as women with type 2 diabetes mellitus (90) and with pregnancy- and lactation-associated osteoporosis after delivery and lactation (91), although none of these studies were powered to assess fractures. Semi-annual therapy with 4 mg of zoledronic acid prevented bone loss in patients with MGUS (92). Zoledronic acid (4 mg given five times per year) also prevented bone loss after liver transplantation (93) and after allogeneic bone marrow transplantation (94, 95). Similarly, i.v. ibandronate (2 mg given four times per year) prevented bone loss and reduced fractures in men after cardiac transplantation (96). I.v. neridronate increased BMD at the spine and hip and reduced fractures in children with osteogenesis imperfecta (97). Oral alendronate or i.v. pamidronate may work equally well if neridronate is not available (98). A large meta-analysis that included eight studies with 403 participants indicated that oral and i.v. bisphosphonates improved BMD also in adults with OI, although no data were available for fracture reduction (99).

Teriparatide Bone formation is severely impaired in GIO and in many men with osteoporosis, thus providing a rationale to use the bone anabolic teriparatide.

Glucocorticoid-induced osteoporosis. In an 18-month controlled trial that directly compared teriparatide (20 μg/day s.c.) with alendronate (10 mg/day orally) in patients with GIO, teriparatide increased spinal BMD by 7.2% compared with 3.4% in the alendronate group. A superior effect of teriparatide on BMD at the lumbar spine was observed as early as 6 months after the start of the study. While 25–30% of the patients had established vertebral fractures, the incidence of new vertebral fractures was 0.6% in the teriparatide and 6.1% in the alendronate group (100).

Osteoporosis in men. In hypogonadal and eugonadal men with osteoporosis, teriparatide (20 μg/day s.c.) increased spinal and proximal femur BMD (101), and in follow-up studies, it reduced the risk of spinal fractures. The concurrent use of alendronate and teriparatide blunted the bone anabolic effect of teriparatide in men (102). Thus, oral bisphosphonates should be used only after teriparatide has been discontinued. This strategy may preserve the BMD gain. Owing to the high cost and need for daily injection, teriparatide is generally recommended for severe osteoporosis or individuals who do not respond adequately to bisphosphonates.

Denosumab Denosumab is a human MAB directed against RANKL, an essential cytokine for osteoclastogenesis (103). In men receiving androgen-deprivation therapy for prostate cancer, denosumab (60 mg s.c. every 6 months for 2 years) increased spinal BMD by 7% and reduced vertebral fractures by 62% (104). Similarly, in women on AI therapy for breast cancer, denosumab increased BMD at the spine and the femoral neck (105), although this study was not powered to assess fractures. Denosumab has not been approved for primary or secondary osteoporosis, but may expand our armamentarium to treat bone loss conditions.

Conclusion

Fragility fractures in men or premenopausal women, very low values of BMD, and fractures that occur while on anti-osteoporotic therapy should prompt a work-up for secondary osteoporosis. BMD should be assessed with bone densitometry at the hip and spine, and the presence of prevalent vertebral fractures with lateral X-rays of the thoracic and lumbar spine. A detailed history and physical examination combined with first-line laboratory tests may reveal an underlying disease that needs to be confirmed by definitive diagnostic tests. Treatment of the underlying disease is pivotal, if possible, using a regimen that does not harm the skeleton further. All patients with secondary osteoporosis should receive adequate calcium and vitamin D supplementation, ensuring normal calcium and PTH serum levels and 25-hydroxyvitamin D_3 serum concentrations of at least 30 ng/ml. Oral bisphosphonates

(alendronate and risedronate) given once per week are antiresorptive and prevent bone loss. Poor compliance, malabsorption, or impaired gastrointestinal tolerance of oral bisphosphonates may favor the use of parenteral bisphosphonates (ibandronate and zoledronic acid). In this regard, zoledronic acid infused intravenously once or twice per year, depending on the indication for treatment, is potent in preventing bone loss. However, an acute phase reaction is a frequent side effect, particularly after the first infusion. Teriparatide may be used in patients with severe GIO or men with vertebral fractures of very low BMD when anabolic therapy is warranted. New therapies are currently under investigation, including denosumab, a human antibody against RANKL, odanacatib, a specific cathepsin K inhibitor, and third-generation selective estrogen receptor modulators.

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