

Pathophysiology, diagnosis and management of secondary osteoporosis

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Abstract

Age-related decline in sex hormones is the most frequent cause of primary osteoporosis; however, secondary causes contribute to osteoporosis in a substantial proportion of cases. These causes are diverse and often overlooked, ranging from endocrine diseases to chronic inflammatory conditions and medication use. The identification and exclusion of secondary causes of osteoporosis is crucial, because treatment typically begins by addressing the underlying condition. Investigation to exclude common secondary causes is recommended for everyone presenting with fractures indicative of osteoporosis. Advanced investigations are reserved for premenopausal individuals and those aged <50 years, and for older people in whom common risk factors, comorbidities or drugs predisposing to osteoporosis are absent. The risk of fracture can be underestimated by bone mineral density in some chronic diseases and overestimated in others. Specific adjustments can be made to the criteria in the online fracture risk FRAX calculator to provide a more accurate estimation of fracture risk in people with some forms of secondary osteoporosis. The response to conventional anti-osteoporosis treatments can be suboptimal if the underlying condition remains unrecognized and untreated. In most conditions, the evidence for antiresorptive or anabolic therapy is based on changes in bone mineral density rather than fracture. This Review covers the aetiology, pathogenesis, diagnosis and management of secondary osteoporosis, together with key areas for future research.

Sections

Introduction

Prevalence of secondary osteoporosis

Pathogenesis of secondary osteoporosis

Management of secondary osteoporosis

Conclusions

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Key points

- Secondary osteoporosis is common, often overlooked and should be systematically investigated in people with unexplained low bone mineral density, fragility fractures or both.
- A wide range of diseases and medications can impair bone strength through effects on bone mass, turnover, mineralization and microarchitecture.
- Endocrine conditions (such as diabetes mellitus), inflammatory conditions (such as rheumatoid arthritis), haematological conditions (such as multiple myeloma), anorexia nervosa and various medications, including glucocorticoids and aromatase inhibitors, are among the most frequent contributors to secondary osteoporosis.
- Accurate diagnosis relies on a structured evaluation including medical history, clinical examination, imaging (dual-energy X-ray absorptiometry and preferably vertebral fracture assessment), laboratory tests and targeted investigations when indicated.
- Multimorbidity increasingly contributes to bone fragility in older adults, complicating diagnosis and treatment decisions.
- Management of secondary osteoporosis requires treatment of the underlying cause, optimization of lifestyle and nutritional factors and selective use of anti-osteoporosis therapies.

Introduction

Osteoporosis is a highly prevalent skeletal disorder, characterized by low bone mass and impaired bone microarchitecture, leading to an increased risk of fragility fractures. Globally, osteoporosis affects an estimated 200 million individuals, particularly postmenopausal and older people, and is associated with substantial morbidity, mortality and healthcare costs¹. Fragility fractures, especially of the hip and vertebrae, are linked to chronic pain, reduced mobility, loss of independence and increased risk of death, with mortality one year after hip fracture reaching 20–30% in older adults¹. According to the World Health Organization, osteoporosis in postmenopausal individuals and those aged ≥ 50 years is defined as a *T*-score ≤ -2.5 for bone mineral density (BMD) at the lumbar spine, total hip or femoral neck measured by dual-energy X-ray absorptiometry (DXA)². In addition to BMD, many guidelines include a history of specific fractures or a high risk of fracture, as estimated by tools such as the FRAX calculator³, as criteria for initiating anti-osteoporosis treatment⁴. In premenopausal individuals and those aged < 50 years the use of *Z*-scores is preferable, and osteoporosis is usually defined as low BMD (*Z*-score ≤ -2.0) accompanied by low-energy fractures².

Primary osteoporosis, associated with age-related sex hormone decline, is the most common form of the disease. However, other factors including chronic medical conditions, medication use and endocrine disorders can contribute to skeletal fragility, collectively termed secondary osteoporosis, which is common, but under-recognized⁵. The classification of osteoporosis into primary and secondary forms is somewhat arbitrary, and these conditions can coexist. Secondary osteoporosis describes the finding of low BMD, fragility fracture or both in a person who has one or more secondary causes of bone impairment.

Importantly, secondary osteoporosis can affect people without traditional risk factors for primary osteoporosis. Secondary osteoporosis should be systematically ruled out before a diagnosis of primary osteoporosis is made, particularly in premenopausal individuals and men^{5,6}. Early identification of secondary osteoporosis also enables targeted management to reduce the individual and societal burden of this condition. Comprehensive evaluation, including detailed personal and family history, physical examination and laboratory testing, is essential to identify clinical risk factors for fractures, medication use that might affect bone health and underlying conditions^{6,7}.

In this Review, we describe the spectrum of diseases and drugs associated with secondary osteoporosis, provide guidance on appropriate diagnostic approaches and summarize current recommendations for management. We also discuss the effect of multimorbidity on the prevalence of secondary osteoporosis in older adults and highlight areas requiring further research to improve patient outcomes. This Review is timely because growing multimorbidity in older adults and the widespread use of bone-affecting medications are increasing the clinical burden and diagnostic complexity of secondary osteoporosis.

Prevalence of secondary osteoporosis

Although primary osteoporosis is the most prevalent form of the disease, in 2006 a comprehensive literature review revealed that secondary causes are present in nearly two-thirds of men, more than half of premenopausal and perimenopausal women and about one-fifth of postmenopausal women with osteoporosis⁸. These secondary causes were diverse and included Cushing's syndrome, gastrointestinal diseases, haematological diseases, hyperthyroidism, hypogonadism, idiopathic hypercalcaemia, medication use, primary hyperparathyroidism, rheumatic diseases and solid organ transplantation⁸ (Box 1).

The most common form of secondary osteoporosis is induced by the use of oral glucocorticoids⁹, which are widely used worldwide. In population-based studies, the annual percentage of corticosteroid use varies between countries, ranging from 2% to 17% (6.8% in the USA, 17.5% in Taiwan and 2.2% in Denmark)¹⁰ (see the section 'Medication use'). Individuals receiving long-term oral glucocorticoid therapy have an estimated prevalence of osteoporosis, fractures or both as high as 30–50%^{11,12}. A retrospective cohort study using data from the UK General Practice Research Database on 244,235 users of oral glucocorticoids and 244,235 control individuals (mean age 57 years; 58.6% women) showed a dose-dependent increase in fracture risk with glucocorticoid use¹³. With a standardized daily dose of ≤ 2.5 mg prednisolone, the risk of hip fracture was 0.99 (95% confidence interval (CI) 0.82–1.20) relative to control, rising to 1.77 (95% CI 1.55–2.02) at daily doses of 2.5–7.5 mg and 2.27 (95% CI 1.94–2.66) at doses of ≥ 7.5 mg. For vertebral fracture, the relative risks were 1.55 (95% CI 1.20–2.01), 2.59 (95% CI 2.16–3.10) and 5.18 (95% CI 4.25–6.31), respectively¹³. Importantly, an increased risk of vertebral fractures was demonstrated even with low daily doses of glucocorticoids (≤ 2.5 mg prednisolone)¹³, underscoring the need for early fracture risk assessment and prevention strategies in people taking these drugs.

Diabetes mellitus, a growing global health concern, is another common condition associated with increased risk of fracture. According to the International Diabetes Federation, the global prevalence of diabetes mellitus (combined type 1 (T1DM) and type 2 (T2DM)) was estimated at 9.3% in 2019, and is expected to increase to 10.9% by 2045¹⁴. Numerous population-based studies have demonstrated an increased risk of fracture among individuals with diabetes mellitus^{15,16}, and a 2023 meta-analysis of observational studies showed that the prevalence of osteoporosis (defined as a BMD *T*-score ≤ -2.5 in the

Box 1 | Conditions associated with secondary osteoporosis^a

Endocrine diseases

Cushing syndrome (adipose tissue deposition in the face and upper back, easy bruising and thin skin, facial plethora, muscle wasting and purple striae)
Hyperparathyroidism
Hyperthyroidism (enlarged thyroid and rapid pulse)
Sex hormone deficiency (atrophic testes in male hypogonadism)

Gastrointestinal diseases and interventions

Bariatric surgery (surgical scars)
Coeliac disease
Inflammatory bowel disease
Small bowel resection (surgical scars)

Genetic disorders^b

Hypophosphatasia (bone pain or tenderness, chronic musculoskeletal pain, fractures (especially recurrent, atypical or poorly healing, including stress fractures, particularly metatarsal) and poor dentition)
Osteogenesis imperfecta (blue sclerae, hearing loss and poor dentition)
X-linked hypophosphataemia (diffuse pain, poor dentition and proximal muscle weakness)

Haematological diseases

Monoclonal gammopathy of unknown significance (MGUS)
Multiple myeloma
Systemic mastocytosis (skin rash and urticaria)
Thalassaemia

Hepatic disease

Chronic liver disease (hepatomegaly)

Metabolic diseases

Hypophosphataemic osteomalacia (musculoskeletal pain and poor proximal muscle strength)
Obesity-related bone fragility

Musculoskeletal diseases

Inflammatory arthritis
Ehlers–Danlos syndrome (arachnodactyly, hyperlaxity, joint hypermobility and long limbs)

Neurological and mental health disorders

Anorexia nervosa
Dementia
Parkinson disease
Stroke

Pulmonary diseases

Chronic obstructive pulmonary disease
Cystic fibrosis

Renal diseases

Chronic kidney disease
Idiopathic hypercalcaemia
Tubular disorders

Other causes

HIV infection
Immobilization
Iron overload
Organ transplantation
Pregnancy- and lactation-associated osteoporosis

Draws on ref. 8. ^aClinical findings have been included in parentheses, where relevant. ^bConditions linked to bone fragility that are not direct causes of secondary osteoporosis, included here to aid differential diagnosis.

lumbar spine, femoral neck or total hip, or a *T*-score ≤ -2.5 plus a history of fracture) was 27.7% among 11,603 people with T2DM¹⁷. A systematic review and meta-analysis of observational studies in people with diabetes mellitus showed an increase in the risk of hip fracture (T1DM: risk ratio (RR) 4.93, 95% CI 3.06–7.95; T2DM: RR 1.33, 95% CI 1.19–1.49) and all non-vertebral fractures (T1DM: RR 1.92, 95% CI 0.92–3.99; T2DM: RR 1.19, 95% CI 1.11–1.28)¹⁸. In addition, a meta-analysis of eight cohort studies demonstrated that, in a sample of 738,018 individuals, those with T2DM were at increased risk of incident vertebral fractures (odds ratio (OR) 1.35, 95% CI 1.27–1.44)¹⁹.

Pathogenesis of secondary osteoporosis

Secondary osteoporosis can be caused by a variety of underlying diseases (Box 1) and the use of several medications (Table 1), most of which share common mechanisms affecting bone remodelling and strength. The presence of these mechanisms in conditions that underly secondary osteoporosis provides a practical framework to understand patterns of bone loss and fracture risk in clinical practice. In many cases of secondary osteoporosis, pathogenesis

is multifactorial. Drugs used to treat the underlying condition, particularly glucocorticoids, are often contributing factors, and the presence of comorbidities, poor nutrition, low body mass index (BMI), reduced physical mobility, sarcopenia and an increased risk of falls also have an important role in disease progression. The diseases listed in Box 1 are characterized by a reduction in BMD with accompanying disruption of bone microarchitecture and increased bone fragility. In diabetes mellitus, abnormalities of bone matrix and minerals that contribute independently to reduced bone strength have also been demonstrated²⁰. The underlying conditions selected for detailed discussion were chosen from the wider list in Box 1 on the basis of their prevalence.

Underlying conditions

Anorexia nervosa. Anorexia nervosa is an eating disorder that affects about 1.0% of women and 0.3% of men, and is characterized by extreme food restriction, very low body weight, an intense fear of gaining weight and a distorted body image²¹. This condition is more common in adolescents and young adults, with peak onset between the ages of

Table 1 | Medications associated with secondary osteoporosis

Medication	Bone formation	Bone resorption	BMD	Fractures	Notes
Androgen receptor inhibitors	↓	↑	↓	↑	↓ Androgen binding to androgen receptors can induce compensative ↑ androgen production or AR gene expression; accelerated and persistent bone loss (3–5% annually); ↓ muscle mass; ↑ risk of falls
Antidepressants (TCAs and SSRIs)	↓	↑	↓ (to a greater extent in total hip than lumbar spine)	↑ (mostly non-vertebral fracture and hip fracture)	No difference between TCAs and SSRIs in risk of fracture; ↑ risk of falls
Antiepileptics	↑	↑	↓	↑	↑ P450 activity; vitamin D metabolism
Antiretroviral therapy	↓	↑	↓	↑	Effects most prominent with tenofovir disoproxil fumarate
Aromatase inhibitors	↑	↑	↓	↑	↓ Endogenous oestrogens
Cyclosporin	↑	↑	↓	?	None
Deferoxamine	↓	↑	↓	↓	Hypercalciuria; several confounding factors for bone loss in people with β-thalassaemia
Glucocorticoids	↓	↑	↓ (to a greater extent in lumbar spine than total hip)	↑ (vertebral fracture to a greater extent than non-vertebral fracture)	Highest BMD loss and risk of fracture in the first year
Gonadotropin-release hormone analogues	↑	↑	↓	↑	↓ Endogenous sex hormones
Histamine-2 blockers	?	?	Neutral (or ↓)	↑ or neutral	↓ Ca, Mg and vitamin absorption
Heparin	↓	↑	↓ (total hip and forearm)	↑ or neutral	Therapy is usually of short duration; no data for BMD of the lumbar spine; effects reduced with low-molecular-weight heparin
Levothyroxine	↑	↑	↓	↑	Only in supranormal doses
Loop diuretics	↑	↑	↓	↑ (hip) or neutral	↑ Renal Ca excretion
Medroxyprogesterone acetate	Neutral	↑	↓	↑ or neutral	Indirect effects through oestrogen deficiency; highest BMD loss in first 1–2 years
Methotrexate	↓	↑	↓	↑	↑ Risk of fracture with high doses used in oncology, but rarely with low doses used in rheumatology
Opioids	↓	?	↓	↑	Can induce hypogonadism; ↑ risk of falls
PPIs	Neutral (or ↑)	Neutral (or ↑)	Neutral (or ↓)	↑	↓ Ca, Mg and vitamin absorption
Tacrolimus	Neutral	↑	↓	?	None
Thiazolidinediones	↓	↑	↓	↑	Especially in postmenopausal people
Vitamin A (retinoids)	↓	↑	?	↑ (hip)	U-shaped effect (low and high levels ↑ risk of hip fracture)
Warfarin	↓	↑	↓ or neutral	↑ or neutral	↓ Vitamin K pathway and γ-carboxylation of osteocalcin

Draws on ref. 60. BMD, bone mineral density; Ca, calcium; Mg, magnesium; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants. ↓ indicates a decrease, ↑ indicates an increase.

15 and 19 years. Anorexia nervosa has been associated with an increased long-term risk of fracture, with a 40-year cohort study showing a 46% increase in fracture rate compared with the general population²². Impaired bone metabolism is caused not only by malnutrition, but is also mediated by functional hypogonadotropic hypogonadism and suppression of insulin-like growth factor 1 (IGF1), distinguishing it from bone changes due to constitutional leanness²³.

Chronic inflammation. Many of the underlying causes of secondary osteoporosis are characterized by chronic inflammation, often with intermittent episodes of acute inflammation. The prevalence of fractures is 6–35% in adults with chronic liver disease²⁴, ~10% in adults aged >40 years with chronic obstructive pulmonary disease²⁵,

0.5–1.0% in adults with rheumatoid arthritis²⁶ and ~0.3% in adults with inflammatory bowel disease²⁷. These, and other chronic inflammatory conditions, are associated with increased production of pro-inflammatory, pro-resorptive cytokines, such as tumour necrosis factor (TNF), IL-1, IL-6 and IL-17 (ref. 28). Together with dysregulation of signalling between TNF ligand superfamily member 11 (also known as receptor activator of nuclear factor β ligand, RANKL) and TNF receptor superfamily member 11B (also known as osteoprotegerin, OPG), these processes stimulate osteoclastogenesis and increase osteoclast activity and lifespan²⁹. In addition, chronic inflammation can impair bone formation through downregulation of Wingless and Int-1 (Wnt) signalling³⁰, and contributes indirectly to bone loss via weight loss, reduced mobility and sarcopenia.

Endocrine conditions. Endocrine abnormalities have direct adverse effects on bone. Parathyroid and thyroid disorders³¹, sex hormone deficiency owing to hypogonadism or menopause^{32,33} and excess levels of endogenous glucocorticoids (such as cortisol) accelerate bone resorption and reduce formation, leading to rapid skeletal fragility. Primary hyperparathyroidism can also lead to hypercalcaemia-related bone loss (0.1–0.4% of adults)³⁴, although this condition can also occur in the context of malignancy, haematologic diseases or ectopic calcitriol production (as in sarcoidosis)³⁵. Secondary hyperparathyroidism is common in chronic kidney disease and can also occur as a result of vitamin D insufficiency or deficiency, the prevalence of which increases in many conditions associated with secondary osteoporosis^{36,37}.

In diabetes mellitus, low bone turnover and the accumulation of advanced glycation end products impair bone quality and strength. In addition, disruption of the bone microvasculature, together with an increased risk of falls related to hypoglycaemia, peripheral neuropathy, sarcopenia and visual impairment, contributes to fracture risk^{20,38,39}. A large-scale study of data from the UK Biobank indicates that fracture risk is increased in both types of diabetes mellitus, but is greatest in T1DM⁴⁰. In T2DM, disease duration is associated with a time-dependent increase in fracture risk, and the presence of microvascular complications further amplifies this risk⁴⁰. Moreover, fracture risk can be increased despite normal or even increased BMD^{18,19}. However, in people with T2DM, fracture risk can be underestimated by standard FRAX calculations because this condition is not included in the model³. Specific approaches for correction have, therefore, been proposed by the Bone and Diabetes Working Group of the International Osteoporosis Foundation to improve risk assessment⁴¹, such as substituting rheumatoid arthritis with T2DM in FRAX.

Haematological conditions. In multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS), tumour plasma-cell-induced stimulation of bone resorption and inhibition of bone formation leads to local lesions and generalized bone loss⁴². DXA-based studies show that osteoporosis is present in approximately 30% of people with newly diagnosed multiple myeloma, and in 25–40% of people with MGUS, compared with 15–20% of age-matched control individuals⁴³. In systemic mastocytosis, activated mast cells release factors that increase bone resorption and inhibit bone formation, resulting in osteolytic lesions and generalized osteoporosis although, paradoxically, osteosclerotic lesions can also occur⁴⁴. In a cohort of 157 patients (65 men; 92 women, mean age 54 ± 12 years) with indolent systemic mastocytosis, osteoporotic fractures (62% vertebral) were common, affecting 37% of patients, whereas osteoporosis (low BMD) was present in 28% of patients⁴⁵.

Hypophosphataemic osteomalacia. A rare metabolic disease that results from impaired bone mineralization secondary to chronic phosphate wasting. Aetiologies can be classified as fibroblast growth factor 23 (FGF23)-mediated (for example, X-linked hypophosphataemia and tumour-induced osteomalacia) or FGF23-independent (for example, Fanconi syndrome either inherited or acquired, such as by tenofovir disoproxil fumarate use for the treatment of HIV or hepatitis B infection)⁴⁶. Clinically, patients present with bone pain, muscle weakness, fatigue and stress or insufficiency fractures. Typical laboratory findings (low serum level of phosphate with an elevated level of alkaline phosphatase) at initial assessment serve as key diagnostic clues and can avoid unnecessary bone biopsies and inappropriate treatment with antiresorptive drugs, which offer no benefit in these people⁴⁷.

Obesity-related bone fragility. In people living with obesity, despite normal or increased BMD, bone quality and strength can be adversely affected by increased amounts of adipose tissue and by failure of the skeleton to adapt to the increased mechanical loading⁴⁸. The risk of falling is also increased in people living with obesity, with various biomechanical characteristics of falls increasing the risk of fractures at certain sites. Bariatric surgery for obesity, especially malabsorptive procedures, is associated with high-turnover bone loss, alterations in bone microarchitecture and an increased risk of fractures^{48,49}. In 2016, Rousseau et al. introduced the concept of fracture site patterns, describing a shift from an ‘obesity-related’ fracture pattern observed prior to bariatric surgery to a more classical ‘osteoporotic’ pattern during surgical follow-up⁵⁰. In this retrospective study, individuals with obesity had a higher risk of distal lower limb fractures than control individuals without obesity. In the group of people with obesity who underwent bariatric surgery, a higher rate of fractures occurred at typical osteoporotic sites, including the femur, hip, pelvis and upper limb, than in individuals with obesity who did not undergo surgery or in control individuals without obesity⁵⁰.

Pregnancy- and lactation-associated osteoporosis. Bone fragility and fracture occurring during pregnancy or the lactation period is termed pregnancy- and lactation-associated osteoporosis (PLO)⁵¹. At the population level, PLO has been estimated to occur in approximately 4–8 cases per million individuals, highlighting its rarity⁵². Although multiple vertebral fractures are common, fractures of the hip, pelvis, sacrum or other sites can also occur. In a retrospective cohort study of individuals with PLO, 78.9% of fractures were vertebral, 17.5% were pelvic and 3.5% affected the proximal femura⁵³. Transiliac bone biopsy with histomorphometry and micro-computed tomography demonstrates that people often have substantial deficits in bone structure and a low bone-formation rate⁵⁴. Most such patients have no other identifiable secondary cause of osteoporosis, although a history of childhood fractures, a family history of osteoporosis or both is frequently reported⁵². The pathogenesis of PLO is not fully understood, but is likely to be multifactorial. The combination of disease onset at a young age, severity (multiple vertebral fractures), family history and pattern of fractures has led to the hypothesis that genetic factors might be involved⁵⁵. Other proposed mechanisms include hormonal changes, alterations in calcium and vitamin D metabolism and disrupted bone remodelling. PLO resolves once the pregnancy and lactation period is over.

Multimorbidity and osteoporosis

Multimorbidity, typically defined as the presence of two or more chronic conditions in the same person, has emerged as a major public health concern worldwide. Multimorbidity is particularly common among older adults and, with increasing life expectancy across many countries, its prevalence is expected to rise⁵⁶. The coexistence of multiple conditions is linked to early death, declines in physical function and quality of life and increased use of healthcare services. The pathways leading to multimorbidity are complex and interconnected, involving biological ageing, physiological processes and wider social determinants of health, such as socioeconomic disadvantage⁵⁷.

A study conducted in Germany involving 10,660 adults aged ≥50 years (53.5% women) found that two-thirds of those with osteoporosis (8.7% of participants) also had more than two additional conditions⁵⁸. Moreover, multimorbidity at the time of fracture was substantially associated with a lower likelihood of being investigated and treated for osteoporosis. Chronic kidney disease, dementia and

T2DM have been associated with low rates of referral for DXA and treatment for osteoporosis among individuals at high risk of fracture⁵⁹. In older people (aged ≥ 70 years) with multimorbidity and an already high risk of fracture, an extensive biological work-up to identify secondary causes of osteoporosis is often unnecessary, as the results would not substantially alter management. However, such an evaluation should be conducted in younger individuals when no apparent cause of osteoporosis is identified.

Medication use

Medications that adversely affect the skeleton and can lead to secondary osteoporosis are shown in ref. 60 and Table 1. The five drug types selected for discussion – glucocorticoids, aromatase inhibitors, levothyroxine, proton-pump inhibitors and antiretroviral therapy – were chosen from the wider list in Table 1 on the basis of their well-documented skeletal effects and clinical relevance in populations at risk of osteoporosis.

Glucocorticoids. Glucocorticoid therapy is the most common cause of medication-induced osteoporosis⁹. By inhibiting osteoblast proliferation, inducing osteocyte apoptosis and disrupting calcium and vitamin D metabolism, glucocorticoids lead to an increase in the risk of fractures even at low doses¹³. Adverse outcomes result both from direct effects on bone cells and the indirect effects of decreased sex hormone and IGF1 secretion, decreased intestinal calcium absorption and increased renal calcium excretion, which can be accompanied by secondary hyperparathyroidism⁹. Increased osteoclastogenesis and osteoclast activity results in an early and transient increase in bone resorption, accompanied by inhibition of osteoblast proliferation, differentiation and survival, resulting in reduced bone formation, which persists for the duration of glucocorticoid therapy⁶¹. Increased apoptosis of osteocytes has also been observed⁶¹. Glucocorticoid administration for at least 3 months is associated with a significant elevation in fracture risk⁶². Trabecular bone is affected to a greater extent than cortical bone, and vertebral fractures are the most common fracture type associated with glucocorticoid therapy⁶¹. A meta-analysis showed that bone loss is rapid during the first 3–6 months of treatment, with a high risk of vertebral fractures that diminishes with the continuation of therapy beyond 6 months⁶³. By contrast, the rate of non-vertebral fractures increases with chronic glucocorticoid therapy⁶³. In addition to duration of use, the dose of glucocorticoid is also important. Although a prednisone dose of 7.5 mg daily is often considered to be the threshold for harmful skeletal effects, fractures have been described with daily doses as low as 2.5 mg (ref. 64). Limited evidence suggests that administration of glucocorticoids through alternative routes, for example, inhaled, epidural or topical, might also adversely affect the skeleton, although to a lesser extent⁶⁵.

Aromatase inhibitors. These drugs are administered to approximately 70% of people with hormone-receptor-positive breast cancer⁶⁶. Aromatase inhibitors induce oestrogen deficiency, which increases bone turnover and bone resorption, resulting in bone loss and an increased risk of fractures⁶⁷. The rate of bone loss is greater than that observed during natural menopause, and is positively associated with the speed and magnitude of oestrogen reduction⁶⁸. Fracture risk should be evaluated in everyone initiating aromatase inhibitor therapy. In premenopausal individuals receiving a combination of gonadotropin-releasing hormone analogues and aromatase inhibitors

for hormone-receptor-positive breast cancer, the decline in oestrogen is particularly abrupt. The rate of bone loss is markedly accelerated compared with natural menopause or aromatase inhibitors alone, thus necessitating early assessment and proactive management of fracture risk⁶⁹.

Levothyroxine. Thyroid hormones stimulate osteoclast activity. Therefore, the high doses of levothyroxine used for thyroid-stimulating hormone (TSH) suppression therapy in people with thyroid cancer can induce subclinical hyperthyroidism, resulting in increased bone turnover and bone loss, especially in postmenopausal people⁷⁰. Fracture risk seems to be related to the degree of TSH suppression⁷¹. The priority is to address the underlying condition, but bone resorption inhibitors can also be used to treat people with substantial or continuous bone loss, especially in those with thyroid cancer who are receiving long-term levothyroxine therapy⁷².

Proton-pump inhibitors. Proton-pump inhibitors (PPIs) are widely prescribed for the management of acid-related gastrointestinal disorders. However, concerns have emerged regarding their long-term, and sometimes inappropriate, use (prolonged use without an ongoing indication)⁷³. Observational studies have demonstrated an increased risk of fractures, particularly vertebral, with PPI use⁷³. In a 2020 meta-analysis, a dose-dependent association between PPI use and the risk of fractures was reported⁷⁴, and this dose-dependent risk is supported by data from prospective cohort studies^{75,76}. In a 2019 meta-analysis, the PPI dose significantly altered the risk of hip fracture (RR 1.17 for low-dose therapy; RR 1.30 for high-dose therapy)⁷⁷. However, the effect of treatment duration on fracture risk remains uncertain, given that available studies have produced inconsistent findings^{76,77}.

Antiretroviral therapy. Bone loss in people living with HIV results from both the infection itself and antiretroviral therapy⁷⁸. HIV-mediated mechanisms include chronic immune activation, elevated pro-resorptive cytokines and impaired osteoblast function, whereas antiretroviral therapy (particularly tenofovir disoproxil fumarate) leads to bone loss through renal phosphate wasting, secondary hyperparathyroidism and direct effects on bone cells⁷⁸. Together, these overlapping mechanisms lead to decreased BMD and an increased risk of fractures, with antiretroviral therapy amplifying the bone loss already caused by HIV infection⁷⁹. DXA studies have shown that osteoporosis and osteopaenia are present in 4–15% and 30–40% of people with HIV, respectively⁷⁸. The prevalence of fractures is around 6–7%, with an incidence approximately 1.5–2.0 times higher than in the general population⁸⁰.

Management of secondary osteoporosis Guidelines

Many clinical guidelines suggest that extensive work-up for secondary causes of osteoporosis should be performed in people who meet certain criteria, including men, premenopausal individuals and those without classical risk factors, comorbidities or medication use associated with osteoporosis (Box 2). Several societies and organizations have provided recommendations for testing people with osteoporosis for underlying, secondary aetiologies^{4,81}. Although most current clinical practice guidelines for osteoporosis primarily address primary, postmenopausal osteoporosis, increasingly recommendations are being included for various causes of secondary osteoporosis, such as diabetes mellitus⁴¹, glucocorticoid use^{82,83}, organ transplantation⁸⁴ and bariatric

surgery⁸⁵. Specific guidelines for osteoporosis secondary to the use of aromatase inhibitors for breast cancer⁸⁶ and androgen deprivation therapy for prostate cancer⁸⁷ have also been published. In addition, guidelines pertaining to osteoporosis in men incorporate a section addressing the secondary causes⁸⁸.

Diagnosis of secondary osteoporosis

Clinical suspicion. The need for vigilance and a high clinical suspicion for secondary osteoporosis stems from its frequent occurrence, particularly in cases of unexplained low BMD or fractures in people who are not typically considered at risk for osteoporosis (Box 3), as well as in those without comorbidities or medication use associated with the condition. Notably, secondary osteoporosis is associated with younger age, unexpectedly low BMD and multiple vertebral or non-vertebral fractures (Box 2). Secondary osteoporosis should also be considered when people have a suboptimal response to bone-acting therapies, such as persistently elevated carboxy-terminal collagen crosslinks despite treatment with bisphosphonates or denosumab, inadequate BMD gains or recurrent fractures despite anti-osteoporosis treatment.

Although there is no clear distinction in *T*-scores between primary and secondary osteoporosis, a 65-year-old woman with a *T*-score of -3.0 who is a heavy smoker, has a low body mass index (BMI) and a family history of osteoporosis is likely to have primary osteoporosis. By contrast, a 55-year-old woman with the same *T*-score, a normal BMI and no classical clinical risk factors for fracture, presenting with fatigue and an elevated level of C-reactive protein probably has secondary osteoporosis. Importantly, in young adults, a low BMD (*Z*-score ≤ -2.0) alone does not always indicate osteoporosis, but a low BMD combined with vertebral or non-vertebral fractures provides substantial evidence of osteoporosis in these individuals³². For people with low BMD, fractures or both, particularly men and younger individuals, the following clinical approach can help to exclude a diagnosis of primary osteoporosis and identify underlying secondary causes for targeted management (Fig. 1).

Medical history. A full medical history should be obtained, including previous and existing medical conditions (Box 1) and the long-term use of medications (Table 1) known to affect bone metabolism or accelerate bone loss. Clinical risk factors for both primary and secondary osteoporosis include age, menopausal status, low BMI ($<19 \text{ kg m}^{-2}$), eating disorders, tobacco smoking, excessive alcohol consumption (≥ 2 units per day) and lack of physical exercise or immobilization. The person's history of fractures, and the family history of osteoporosis, should also be recorded.

Physical examination. The person's height and weight should be measured, and BMI calculated. Weight loss, both intentional and unintentional, is associated with a decrease in BMD and an increase in fracture risk⁴⁸. Current height should be compared with the person's historical maximum height to determine height loss. Although frequently overlooked, a thorough physical examination is crucial to exclude other conditions, such as osteomalacia or inherited skeletal disorders (Box 1), and inform the investigation of secondary causes of osteoporosis.

Imaging. Measurement of BMD by DXA is central to the diagnosis of secondary osteoporosis and determination of fracture risk. The DXA criteria for diagnosing secondary osteoporosis are the same as for primary osteoporosis: *T*-score ≤ -2.5 at the lumbar spine, femoral neck or total hip. Assessment of vertebral fractures by DXA or conventional

Box 2 | Secondary osteoporosis in clinical practice: a hypothetical case study

A 65-year-old man with a 15-year history of chronic obstructive pulmonary disease presents for routine follow-up. He reports mild back pain, but no previous major fractures. His treatment includes long-term inhaled glucocorticoids and several short courses of oral glucocorticoids (<3 months each) to treat symptom exacerbations. Physical examination reveals mild kyphosis and decreased spinal mobility. A 6 cm loss in height is noted compared with previous records. Dual-energy X-ray absorptiometry shows a *T*-score of -2.6 at the lumbar spine and -2.1 at the femoral neck. Thoracic spine radiography reveals multiple dorsal vertebral fractures. Laboratory tests do not indicate other secondary causes. The man is diagnosed with secondary osteoporosis due to chronic obstructive pulmonary disease, with both inhaled and intermittent oral glucocorticoid use contributing to bone fragility⁶⁵. Although the short, oral courses of glucocorticoids alone are insufficient to meet the criteria for glucocorticoid-induced osteoporosis, they represent an additional risk factor in this context. Treatment of osteoporosis with teriparatide and pain management with simple analgesics led to a favourable clinical outcome, with no new vertebral fractures occurring during follow-up.

radiography should be considered when height loss is ≥ 4 cm. Other imaging modalities, such as computed tomography and MRI, can be used when conventional radiography is inconclusive for diagnosing vertebral fractures, although these modalities do not provide useful information for evaluating secondary osteoporosis.

Biochemical assessment. Before initiating treatment, basic laboratory tests should be conducted for everyone with osteoporosis, and further assessment might be required for some individuals based on their clinical circumstances and the initial laboratory results. These tests can identify conditions contributing to skeletal fragility that require additional intervention. Certain findings can also be pertinent when selecting the initial treatment for osteoporosis. Routine tests include serum levels of 25-hydroxyvitamin D, albumin, alkaline phosphatase, calcium, creatinine, C-reactive protein, liver enzymes, parathyroid hormone, phosphorus and TSH, as well as estimated glomerular filtration rate (eGFR), a complete blood cell count and protein electrophoresis. Further tests, where indicated, include 24-hour urinary excretion of calcium, cortisol, creatinine and phosphate, as well as serum levels of 1,25-dihydroxyvitamin D, antibodies for coeliac disease, bone alkaline phosphatase, iron, related peptide, testosterone and tryptase⁸⁹.

Bone marrow biopsy. In some people, bone marrow aspiration and biopsy might be warranted to confirm or exclude the presence of clonal mast cell diseases, such as systemic mastocytosis⁴⁴. Current clinical practice guidelines recommend that most people with MGUS should undergo bone marrow biopsy for multiple myeloma^{89,90}, which is characterized by $\geq 10\%$ monoclonal plasma cells in the bone marrow as well as other criteria.

Genetic testing. Genetic testing can help to diagnose inherited, monogenic skeletal disorders, such as osteogenesis imperfecta, hypophosphatasia, X-linked osteoporosis and X-linked hypophosphataemia⁹¹.

These are not secondary causes of osteoporosis, but rather skeletal disorders associated with increased bone fragility. Genetic testing is indicated in premenopausal individuals and those aged <50 years, in whom secondary causes of osteoporosis have been excluded, who present with low BMD and fractures and a family history of fractures⁹¹. Owing to the rarity of these conditions, such patients should be referred to a specialist centre with the relevant expertise for further assessment and appropriate treatment.

Defects in genes involved in type I collagen biosynthesis, as well as in *LRPS*, *PLS3*, *SGMS2* and *WNT1* are among the most common known contributors to osteoporosis in young adults, many of whom were previously classified as having idiopathic osteoporosis⁹¹. However, despite these discoveries, the majority of cases of osteoporosis in young adults still lack a defined genetic cause, and the underlying mechanisms remain largely unknown. Notably, a *RUNX1* gene variant was identified in 2023 in a 40-year-old man with osteoporosis, highlighting the expanding spectrum of monogenic contributors⁹².

Treatment of secondary osteoporosis

The first step in treating secondary osteoporosis is to identify and treat the underlying disease or alter the medication causing bone loss. Extrapolating from evidence in people with primary, postmenopausal osteoporosis, lifestyle modifications are recommended in the management of secondary osteoporosis. Adequate calcium and vitamin D intake should be ensured through diet or supplements, and weight-bearing exercise, smoking cessation and avoidance of excess alcohol intake are advised, together with the implementation of fall-prevention strategies to reduce fracture risk.

Anti-osteoporosis treatments can be beneficial in people with secondary osteoporosis. However, many clinical trials of these therapies have excluded individuals with comorbidities and so the evidence on which to base therapeutic decisions (such as type of drug, dose and treatment duration) for these individuals is limited. Additionally, some secondary causes of osteoporosis have drug contraindications (for example, bisphosphonates in people with severe chronic kidney disease; $\text{eGFR} < 30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$), and medication compliance can be an issue in people with multimorbidity. Treatment should be individualized based on the underlying cause, fracture risk, comorbidities and contraindications.

When low BMD is suspected to overlap with osteomalacia or other mineralization defects, careful evaluation is warranted before initiating

antiresorptive therapies, such as bisphosphonates or denosumab, as these agents can further impair mineralization. However, zoledronic acid or denosumab are the preferred therapies when malabsorption has been identified (for example, following gastric bypass)^{93,94}. In people with severe chronic kidney disease ($\text{eGFR} < 30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$), management of secondary osteoporosis is complicated by the need to distinguish true osteoporosis from chronic kidney disease mineral and bone disorders (CKD-MBD), such as adynamic bone disease, which affects the safety and efficacy of antiresorptive therapies⁹⁵. Bone biopsy is the gold standard for diagnosis of CKD-MBD, although low levels of parathyroid hormone and bone-specific alkaline phosphatase are often diagnostic in clinical practice. There are specific guidelines for the management of common causes of secondary osteoporosis, such as diabetes mellitus⁴¹, glucocorticoid therapy^{82,83}, organ transplantation⁸⁴ and bariatric surgery⁸⁵, and for osteoporosis related to the use of aromatase inhibitors⁸⁶ and androgen deprivation therapy⁸⁷.

In 2024, the European Calcified Tissue Society recommended that oral bisphosphonates should be the first-line treatment in people with glucocorticoid-induced osteoporosis at medium risk of fractures, denosumab or zoledronate in those at high risk and romosozumab or teriparatide in those at very high risk⁸². Both the American College of Rheumatology and National Osteoporosis Guideline Group guidelines include abaloparatide and romosozumab as treatment options for very-high-risk individuals receiving glucocorticoid therapy^{83,89}. By contrast, the European Calcified Tissue Society does not currently recommend abaloparatide for glucocorticoid-induced osteoporosis because of the limited clinical evidence available in this population⁸².

Several guidelines on the treatment of osteoporosis in people receiving aromatase inhibitors for breast cancer have been published. The criteria for intervention vary, but all agree that treatment should be started at a lower threshold than in postmenopausal osteoporosis (BMD *T*-score < -2.0 , or < -1.0 with additional risk factors)^{86,95}. Bisphosphonates and denosumab both increase BMD and are valid treatment options for these people⁹⁵, but only denosumab has been shown to reduce fracture risk⁹⁶. Data from clinical trials suggest that bisphosphonates and denosumab might also improve disease-free survival^{97,98}. If denosumab is the chosen therapy, an 'exit' strategy should be planned to reduce the risk of multiple vertebral fractures upon its discontinuation⁹⁹. People who discontinue denosumab should receive follow-up antiresorptive therapy (such as zoledronic acid)

Box 3 | Clinical suspicion for secondary osteoporosis

Secondary osteoporosis^{5–7,32} should be considered in the following situations:

- (1) Premenopausal individuals and those aged <50 years with:
 - Multiple vertebral fractures or low-trauma peripheral fractures without identifiable clinical risk factorsand/or
 - Low BMD ($Z\text{-score} \leq -2.0$) not explained^a by lifestyle, nutrition or family history
- (2) Postmenopausal individuals and those aged ≥ 50 years with:
 - Unexpectedly low BMD ($T\text{-score} \leq -2.5$) despite the absence of classical risk factors or comorbidities

and/or

- Multiple vertebral or non-vertebral fractures in the absence of underlying conditions or medication use known to be associated with secondary osteoporosis
- (3) Other clinical indicators (all ages/sexes):
 - Suboptimal response to anti-osteoporosis therapy (for example, recurrent fractures or persistently elevated levels of bone turnover markers)
 - Rapid decline in BMD despite anti-osteoporosis therapy
 - Underlying conditions or medication use known to affect bone metabolism are absent, but fractures or low BMD are present

^aFindings not associated with clinical risk factors, comorbidities or medications known to contribute to primary osteoporosis.

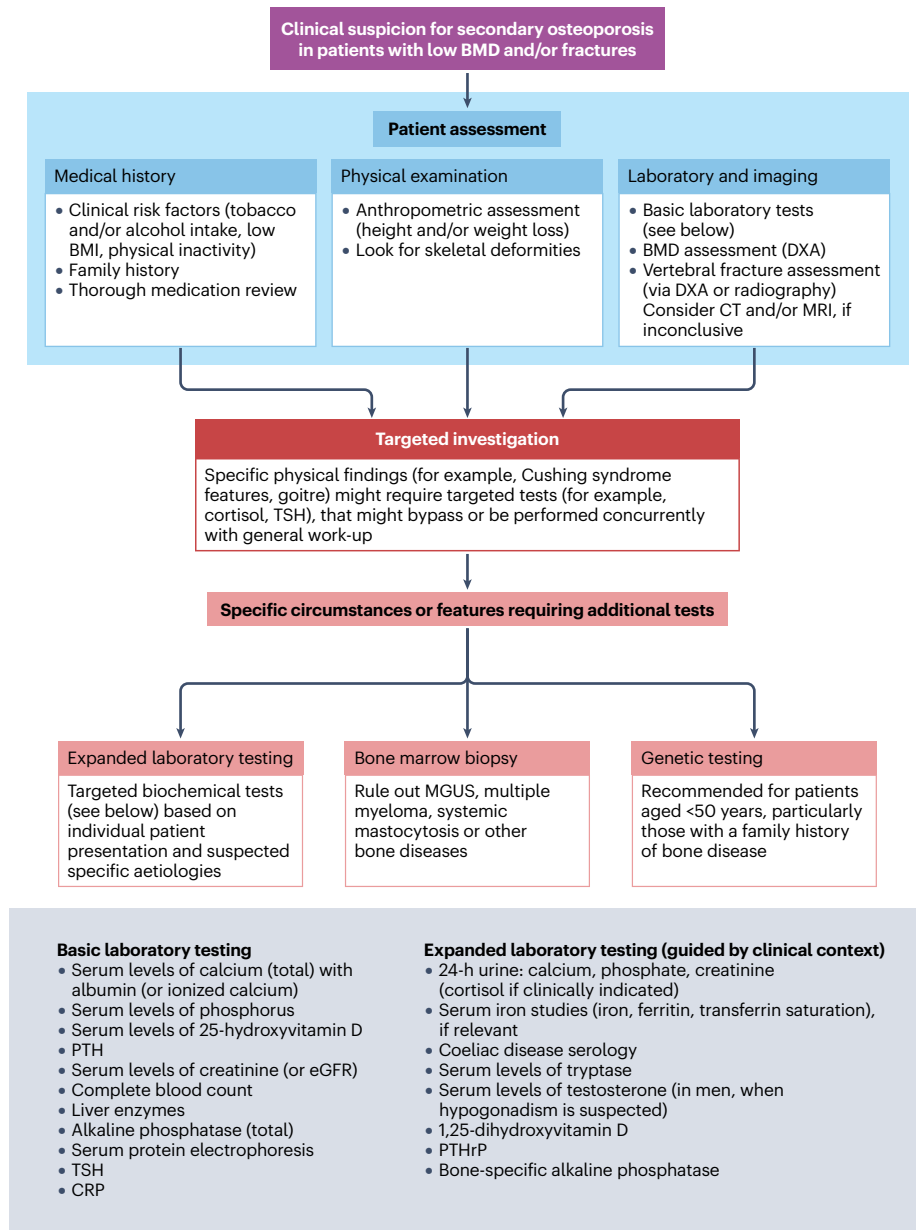


Fig. 1 | Diagnostic flow chart for secondary osteoporosis. For people in whom secondary osteoporosis is suspected (Box 3), diagnostic steps include taking a full medical history including assessment of clinical risk factors and a medication review, anthropometric assessment and physical examination, imaging studies and biochemical analyses (basic and expanded, where indicated). In some cases, bone marrow biopsy and genetic testing can be indicated to identify the underlying or associated condition. BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; PTH, parathyroid hormone; PTHrP, PTH-related protein; TSH, thyroid-stimulating hormone.

accompanied by close monitoring during the first year, because the majority of bone loss typically occurs within the first 12 months after denosumab cessation⁹⁹. Unlike for primary, postmenopausal osteoporosis, drug holidays are generally not recommended in secondary osteoporosis when the underlying cause persists (for example, those on ongoing glucocorticoid therapy), because continued antiresorptive treatment is typically required to maintain bone protection¹⁰⁰.

Conclusions

This Review underscores the growing recognition of secondary osteoporosis as a substantial contributor to bone fragility, highlighting both well-established and emerging causes, along with their underlying mechanisms. The advances discussed herein have deepened our understanding of how multimorbidity, medications and hormonal or

metabolic disturbances influence bone metabolism, bone density and fracture risk, emphasizing the importance of a comprehensive and individualized diagnostic approach. Clinically, these insights reinforce the need for heightened clinical awareness in people presenting with bone fragility, so that underlying conditions are identified early and managed appropriately, thereby improving patient outcomes.

Despite these advances, several important knowledge gaps remain, representing key opportunities for future research. These include defining the optimal use of anabolic therapies in premenopausal individuals with secondary osteoporosis³², investigating the effects of gender-affirming hormone therapies on skeletal development and peak bone mass in young transgender populations¹⁰¹, and assessing the effect of emerging therapies (such as GLP1 receptor agonists in people with obesity) on bone turnover, BMD and fracture risk¹⁰². Addressing

these questions will be critical to refine treatment strategies, guide clinical decision-making, and ultimately reduce fracture risk in individuals with secondary osteoporosis.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The authors declare no competing interests.

Additional information

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Review criteria For this narrative Review, we conducted a literature search using the MEDLINE database (https://www.nlm.nih.gov/medline/medline_home.html) up to March 2025. Relevant studies were selected using a combination of keywords for secondary osteoporosis and bone health outcomes (bone, bone turnover or remodelling, BMD, osteoporosis, bone microarchitecture and fractures). Additional studies were identified through an extensive manual search of the bibliographic references in the original papers and reviews initially selected. We reviewed observational and interventional studies, focusing on randomized controlled trials. Particular attention was paid to identifying the available meta-analyses on the subject. The relevance of the studies was assessed using a hierarchical approach based on the title, abstract and full manuscript.

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