Secondary osteoporosis

SUMMARY

Secondary osteoporosis is less common than primary osteoporosis. It may be suspected in patients who present with a fragility fracture despite having no risk factors for osteoporosis. In addition, secondary osteoporosis should be considered if the bone density Z-score is –2.5 or less.

Consider the fracture site and presence of other clinical clues to guide investigations for an underlying cause. The tests to use are those that are indicated for the suspected cause.

Baseline investigations include tests for bone and mineral metabolism (calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone), liver and kidney function, full blood count and thyroid-stimulating hormone. More detailed testing may be required in patients with severe osteoporosis.

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Introduction

Secondary osteoporosis results from specific clinical disorders that are potentially reversible. Up to 30% of postmenopausal women and 50% of men with osteoporosis may have an underlying cause. The underlying pathogenesis of secondary osteoporosis is often multifactorial. Correctly treating the cause may ameliorate fracture risk and avoid unnecessary treatment with antiresorptive drugs.[1,2]

Clinical assessment

Secondary causes of osteoporosis should be considered in patients who suffer a fragility fracture when 'traditional' risk factors are insufficient to explain the injury. People with a bone mineral density Z-score –2.5 or less may also have secondary osteoporosis. (The Z-score is a comparison to age-matched, sex-matched individuals.)

Clues to an underlying secondary cause include an atypical fracture, the severity of osteoporosis and the presence of clinical features found through history and clinical examination (e.g. anaemia, malabsorption, amenorrhoea, constitutional symptoms or specific endocrinopathies) (see Table). A careful drug history may identify possible causes. While corticosteroids are well known to cause osteoporosis and fragility fractures, a number of other drugs also increase fracture risk (see Box). However, not all patients with secondary osteoporosis will present with the classic signs of the underlying condition. They may have subclinical disease at the time of their fracture or when the low bone mineral density is detected, with osteoporosis being the first manifestation of their underlying condition.

Identifying the cause

When a patient has clinical evidence of an underlying cause of osteoporosis, the necessary investigations may be straightforward. In an otherwise healthy patient with no specific clinical signs, a range of investigations may be required to identify a secondary cause of osteoporosis.

The prevalence of undiagnosed secondary causes of osteoporosis is unknown and there are no guidelines regarding appropriate laboratory tests for the otherwise healthy patient. In any patient suspected of having secondary osteoporosis, most experts recommend evaluation of bone and mineral metabolism with blood tests for calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone, liver and kidney function, full blood count and thyroid-stimulating hormone.

In those with severe osteoporosis (multiple fractures or bone mineral density T-score <–3.0) without specific clinical findings, additional tests should be performed. These tests include serum protein electrophoresis, free light chain assay, markers of inflammation, coeliac serology and total IgA, sex steroids (testosterone in men and oestradiol in women) and 24-hour urinary free cortisol.[3-7] A 24-hour urinary calcium collection is indicated if there are abnormalities of serum calcium or parathyroid hormone.

The role of bone turnover markers, such as telopeptides, in the diagnosis of osteoporosis is controversial. Currently, in specialists' clinics, their clinical role is in monitoring treatment efficacy.[8]

Several small cross-sectional studies have evaluated the yield of combined laboratory investigations in identifying an underlying cause of osteoporosis in otherwise asymptomatic patients. In studies of 173[9] and 204[4] postmenopausal women, the three most common findings were hypercalciuria, malabsorption (vitamin D deficiency) and hyperparathyroidism.

Table **Secondary causes of osteoporosis**

Disorder	Most common fracture site	Primary mechanism
Inflammatory conditions		
Rheumatoid arthritis, systemic lupus erythematosus	Hip	High bone turnover due to pro-inflammatory cytokines
Crohn's disease, ulcerative colitis	Vertebrae	High bone turnover due to pro-inflammatory cytokines, malnutrition and malabsorption
Hypogonadism		
Premature menopause (auto-immune, surgical, drugs)	Distal radius (Colles), vertebrae	High bone turnover from low oestrogen or low testosterone
Hypopituitarism (structural or functional)	Distal radius (Colles), vertebrae	High bone turnover from low oestrogen or low testosterone
Endocrinopathies		
Hypercortisolaemia (Cushing's syndrome)	Vertebrae, ribs	Low bone turnover from impaired bone formation and mineralisation
Hyperthyroidism	Hip	High bone turnover from increased bone resorption
Primary hyperparathyroidism	Distal radius, vertebrae	High bone turnover from increased bone resorption
Hyperprolactinaemia	Distal radius, vertebrae	High bone turnover from oestrogen deficiency
Acromegaly	Vertebrae	High bone turnover, increase in bone size and co-existing secondary hypogonadism
Diabetes mellitus	Hip	Low bone turnover from insulinopenia in type 1, mechanism not well understood in type 2
Malabsorption		
Pernicious anaemia	Vertebrae	Low bone turnover from impaired osteoblast recruitment
Coeliac disease	Distal radius, vertebrae	High bone turnover due to malnutrition and malabsorption
Gastrectomy	Vertebrae	High bone turnover due to malnutrition and malabsorption
Haematological conditions		
Multiple myeloma and monoclonal gammopathy of unknown significance	Vertebrae	Uncoupling in bone turnover (high bone resorption and low bone formation) from pro-inflammatory cytokines
Myeloproliferative disorders	Vertebrae	Direct marrow effects on bone
Systemic mastocytosis	Vertebrae	High bone turnover from mast cell mediators
Abnormal bone architecture		
Paget's disease	Long bones	High bone turnover from overactive bone resorption
Osteopetrosis	Hip, long bones	Low bone turnover due to defective bone resorption
Malignancy (primary or secondary)	Affected bones	High bone turnover from paraneoplastic effects
Other conditions		
Chronic liver disease	Vertebrae	Low bone turnover from liver disease and increased bone resorption due to malabsorption, vitamin D deficiency and hypogonadism
Chronic kidney disease	Hip, vertebrae	High bone turnover from osteomalacia, secondary hyperparathyroidism or mixed bone disease, or low bone turnover from adynamic bone disease (from aluminium or iron)
Kidney transplantation	Vertebrae, small bones	High bone turnover and tertiary hyperparathyroidism

In the study of 204 women, hyperparathyroidism was detected in 35%, although less than 10% had primary hyperparathyroidism with hypercalcaemia.[4] A cost–benefit analysis of the investigations was not performed in either of these studies.[4,9] There are no large studies assessing the frequency and cost–benefit of investigations for secondary osteoporosis.

Bone biopsy

In the past, bone histomorphometry was commonly used to assess the severity of osteoporosis before the advent of dual energy X-ray absorptiometry.

Bone biopsies are now rarely performed. In a highly select group of patients, bone biopsy performed and interpreted by an experienced specialist is useful in establishing the underlying aetiology and appropriate therapy of atypical cases if non-invasive methods have been inconclusive. Bone histomorphometry is a specialist tool to diagnose and assess:

- osteomalacia
- renal bone disease
- bone turnover (to differentiate between low- and high-turnover osteoporosis) with potential impact on therapeutic options.

In one specialist centre, 99 transiliac bone biopsies were performed over 14 years on 'atypical' cases of osteoporosis.[10] This represented 0.003% of patients reviewed for bone-related consultations.

Bone marrow and trephine biopsy is only required to exclude an underlying haematological cause for osteoporosis such as plasma cell dyscrasia, lymphoma or mastocyte disorders which will require specific therapies.

Box **Drugs that increase fracture risk**

Corticosteroids (≥5 mg prednisolone daily or equivalent for ≥3 months)
Antiepileptics: carbamazepine, phenytoin, phenobarbitone
Hypoglycaemics: thiazolidinediones, empagliflozin
Selective serotonin reuptake inhibitors
Excess thyroxine
Aromatase inhibitors
Tamoxifen (when used in pre-menopausal women)
Gonadotropin-releasing hormone
Chemotherapy
Immunosuppressants: cyclosporine, tacrolimus, methotrexate
Lithium
Heparin
Proton pump inhibitors
Aluminium-containing antacids
Depot medroxyprogesterone acetate
Antipsychotics

Conclusion

Secondary causes of osteoporosis are less common than primary osteoporosis, but correctly treating an underlying cause may be sufficient to ameliorate the increased fracture risk. Underlying causes should be suspected in patients with very low bone mineral density or in those without 'traditional' risk factors for fractures.

Confirming the diagnosis requires a careful history and physical examination for evidence of known causes and can be confirmed with selected laboratory investigations. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Primary hypoparathyroidism is present in approximately a third of patients with secondary osteoporosis
2. Hyperparathyroidism may be a cause of secondary osteoporosis

Answers on page 107

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