Osteosclerosis

A patient with bone pain and high bone mass

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Increased bone mass is a sporadic finding, especially with routine bone mineral density testing. Causes are predominantly artefactual or systemic, or in rare cases genetic. A patient with unexplained high bone mass is described here, and the possible causes reviewed.

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Case scenario

A 51-year-old perimenopausal woman was referred to an outpatient endocrinology clinic with diffuse bony sclerosis and generalised bone pain. She had a 20-year history of systemic lupus erythematosus, manifesting with Raynaud's phenomenon, skin rash and arthropathy, controlled by regular treatment with azathioprine and hydroxychloroquine and intermittent treatment with prednisone. She had never been treated with bisphosphonates. She had no history of fractures or exposure to fluoride and no family history of bone disorders.

On examination, the patient's body mass index (BMI) was normal. She had oral exostoses and torus mandibularis but no other bone deformities or focal bony tenderness (Figures 1a to c). There were no focal neurological signs or evidence of cranial nerve entrapment. There was no lymphadenopathy or organomegaly.

Key points

- **Osteosclerosis and osteopetrosis are metabolic bone disorders that lead to trabecular and cortical bone thickening, which can be complicated by bone marrow compromise, bony overgrowth and neurological entrapment.**
- **Patients with these disorders may be asymptomatic or may present with generalised bone pain or fractures.**
- **Artefactual causes of high bone mass are common and should be excluded.**
- **Osteosclerosis, which may be focal or diffuse, is often secondary to metabolic, malignant or other processes but can also be due to rare hereditary disorders of osteoblastic bone formation (e.g. mutations in genes such as *SOST* and *LRP5*).**
- **Osteopetrosis is a generalised clinical syndrome due to defective osteoclastic bone resorption, characterised by increased fracture risk, systemic complications and distinctive radiological features.**
- **Unexplained high bone mass is common and is characterised by increased trabecular bone mineral density and cortical bone strength and a generally benign course.**
- **Treatment of osteosclerosis and osteopetrosis should target the underlying cause when possible and associated complications.**

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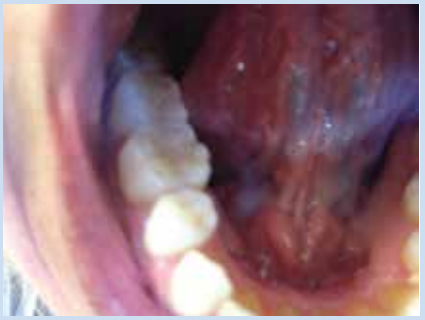


Figures 1a to c. Torus mandibularis (a, left) and oral exostoses (b, centre and c, right) in a woman with bone pain and high bone mass.

Investigations revealed a normal full blood count, normal renal function and normal calcium, phosphate, thyroid stimulating hormone, parathyroid hormone, 25-hydroxyvitamin D and 1,25-dihydroxy-vitamin D levels. Hepatitis C serological testing was negative. Serum protein electrophoresis did not detect a paraprotein. The serum tryptase level was elevated, but 24-hour urinary histamine and methylhistamine levels were within the normal range, and testing for the c-KIT gene mutation (associated with mastocytosis) was negative. Markers of bone formation (bone-specific alkaline phosphatase and procollagen type I propeptide) were high normal or raised, and markers of bone resorption were normal (Table 1).

A skeletal survey revealed generalised osteosclerosis, predominantly in the axial skeleton (Figures 2a to c). Both humeri and femora showed diffuse sclerosis affecting the proximal diaphysis and metaphysis. No signs of osteopetrosis such as fractures, 'rugger jersey spine' (dense sclerotic endplates) or Looser's zones (pseudofractures) were identified. Review of imaging performed 10 years previously showed no significant differences.

CT of the abdomen and pelvis found no pathological lymphadenopathy or organomegaly. MRI of the skull, proximal cervical spine and whole lumbar spine showed prominent low signal in the noncontrast enhanced T1 weighted images, consistent with bony sclerosis. There was no bony expansion or compression of neural foramina.

Bone mineral density (BMD) measured by quantitative CT was elevated at the lumbar spine (511 g/cm^2, corresponding to a Z-score of +14.31) and to a lesser extent at the femoral neck (1.06 g/cm^2, corresponding to a Z-score of +2.75). These findings were confirmed by dual energy x-ray absorptiometry (DXA).

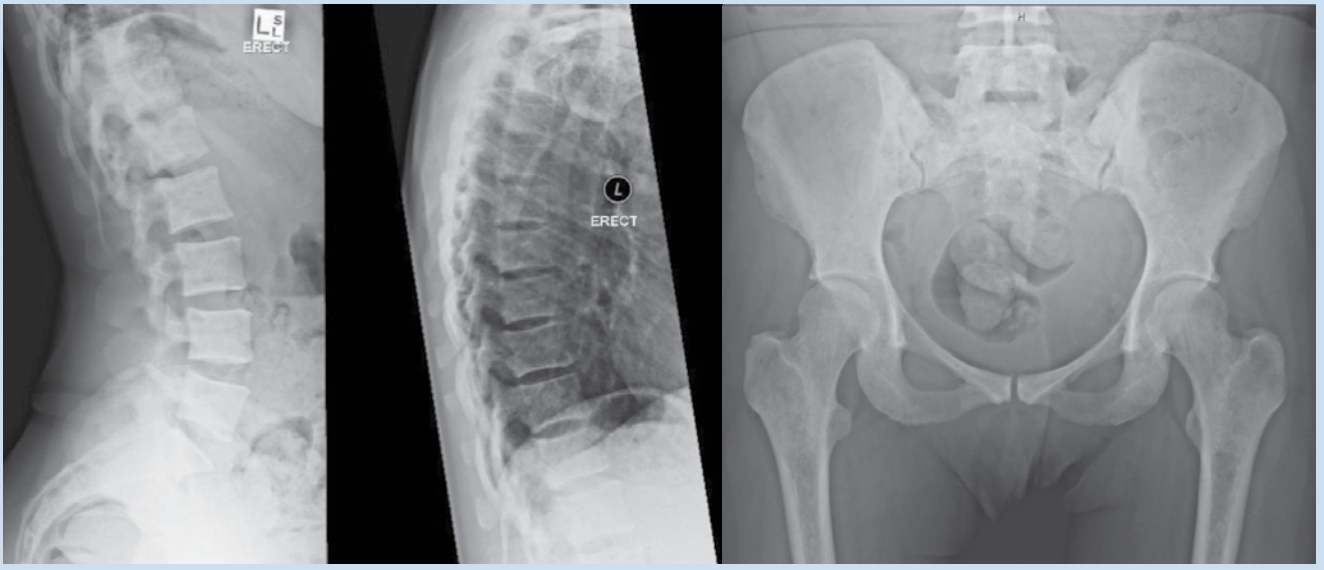
A radionuclide technetium bone scan showed generalised increased uptake in the spine but no focal uptake to suggest malignancy or recent fracture.

The patient underwent bone biopsy of the iliac crest following tetracycline double

Table 1. Investigation results in a woman with bone pain and high bone mass

	Patient result	Reference range
Markers of bone formation*		
Bone-specific alkaline phosphatase (µg/L)	13.2	2.9 to 14.5
Procollagen type I N-terminal propeptide (µg/L)	78	<70
Markers of bone resorption*		
Urine N-telopeptide/creatinine ratio (nmol/mmol)	61	17 to 94
Urine deoxypyridinoline excretion (nmol/mmol)	4.7	3.0 to 7.4
Iliac crest bone histomorphometry†		
Trabecular bone area (%)	78	22 to 28
Relative osteoid area (%)	9.6	1.5 to 3.3
Total osteoid surface (%)	63	8.9 to 14.9
Active resorption surface (%)	6.4	0.8 to 1.9
Total resorption surface (%)	10.6	2.8 to 6.4
Osteoclasts number (cells/cm^2)	4.6	0.5 to 1.5
Double label surface (%)	32.4	5.2 to 11.5
Mineral appositional rate (mm/day)	0.68	0.65 to 0.80
Bone formation rate (mm^3/mm^2/day)	0.22	0.04 to 0.09
Osteoid thickness (µm)	12.8	8.1 to 14.2
Mineralisation lag time (days)	37.6	10.5 to 17.8
Fibrous area (%)	3.6	0

* Reference range is for premenopausal women. † Reference range is for women aged 40 to 60 years.



Figures 2a to c. Radiography showing generalised osteosclerosis in a woman with bone pain. a, b (left and centre). Thoracic and vertebral spine x-rays showing diffuse sclerosis with no fractures. c (right). Pelvic x-ray showing increased density and patchy sclerosis down both femoral shafts, particularly affecting the cortical bone, with evidence of bone remodelling.

Figures 3a to c. Bone biopsy specimens showing severe osteosclerosis in a woman with bone pain. a (left). Reduced Haversian canals, increased cancellous, woven and lamellar bone, and decreased marrow spaces (toluidine blue stain). b (centre). Multiple multinucleated osteoclasts present in the bone marrow (stained red, acid phosphatase stain). No mast cells were detected (toluidine blue stain). c (right). Tetracycline double labelling showing active bone formation, with no smearing to suggest osteomalacia. Tetracycline binds to newly formed bone where it shows as a linear fluorescence. When two doses are given around two weeks apart then the amount of bone formed in the interim can be calculated from the distance between the fluorescent labels and extent of the double-labelled surface.

labelling to assess bone kinetics, which confirmed severe osteosclerosis with increased trabecular bone area, hyperosteoidosis and increased bone turnover (Figures 3a to c). The marrow space was obliterated by woven and trabecular bone, but there was no evidence of primitive or spongiosa bone to suggest osteopetrosis. The rate of bone formation was increased at the basic multicellular unit (Table 1). Increased bone resorption was indicated by the increased active and total resorption surfaces and osteoclast numbers. Mineralisation lag time and fibrous area were not consistent with osteomalacia or fluorosis. Specific staining of the bone biopsy specimen for aluminium and iron was negative.

Genotyping for congenital causes of osteosclerosis was negative for LRP4, LRP5 *and* SOST *gene mutations.*

Discussion

Patients with high bone mass may present with bone pain (as in the patient described above) or a fracture or may be asymptomatic with an incidental finding of a high bone density. Artefactual causes of raised bone density are common and should be excluded (see Box 1).[1]

Osteosclerosis and osteopetrosis

Patients with high bone mass can be classified with osteosclerosis (focal or diffuse) or osteopetrosis. In both conditions, there is increased radiodensity, increased BMD by DXA measurement and trabecular and

1. Artefactual causes of elevations in measured BMD

Vertebral diseases

- Osteoarthritic spondylosis (typically affects lumbar vertebrae and can increase BMD up to 25%)[1]
- Diffuse idiopathic skeletal hyperostosis
- Ankylosing spondylitis
- Vertebral fracture

Extrinsic artefacts

- Overlying abdominal aortic calcification
- Thalassaemia major (soft tissue iron deposition)
- Overlying calculi (e.g. gallstones, renal calculi)
- Secondary calcifications (e.g. abdominal abscess, Gaucher's disease, silicone implants)
- Ingested material (intestinal barium)
- Surgical metalwork (e.g. laminectomy, vertebroplasty, kyphoscolioplasty)

Abbreviation: BMD = bone mineral density.

2. Acquired causes of osteosclerosis

- Renal osteodystrophy
- Fluorosis
- Hepatitis C
- Acromegaly
- Hypothyroidism
- Myelofibrosis
- Systemic mastocytosis
- Oestrogen implants
- Vitamin D insufficiency
- Hypoparathyroidism

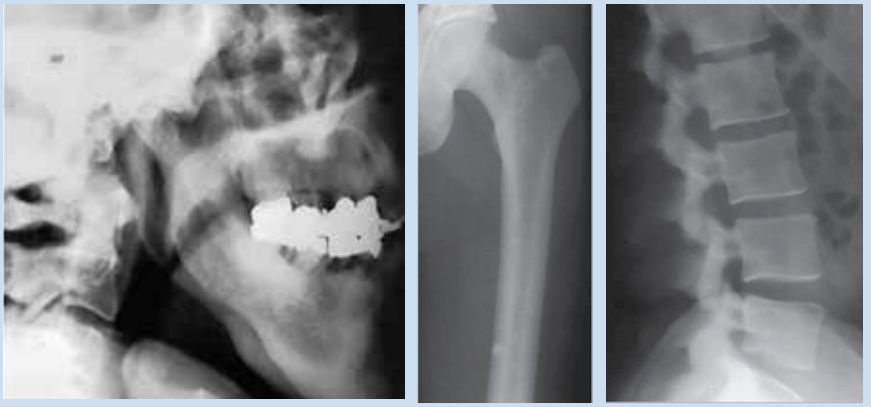
cortical thickening on bone histological examination. However, the underlying mechanisms differ; osteopetrosis involves a defect in osteoclastic resorption of bone, leading to abnormal bone quality, whereas osteosclerosis involves increased osteoblastic bone formation with a relentless increase in bone mass.

The clinical presentation may provide clues to the underlying cause. Osteosclerosis is often secondary to metabolic, malignant, haematological, endocrine or infectious processes (Box 2).[1,2] However, osteopetrosis and some cases of osteosclerosis are due to rare, often hereditary, disorders of bone metabolism (Table 2).[3-13] These have a prevalence

Table 2. Differentiating high bone mass disorders

	Osteosclerosis	Osteopetrosis
Cellular abnormality	Osteoblast[3,4]	Osteoclast[3-5]
Underlying mechanism	**Osteoblast recruitment abnormalities** • Craniometaphyseal dysplasia (*ANKH* gene) • Camurati–Engelmann disease (*TGF-β1* gene) **Osteoblast function abnormalities** • Sclerosteosis and Van Buchem's disease (*SOST* gene)[6] • High bone mass (*LRP5* and *LRP4* genes)[7-12] **Acquired causes (see Box 2)**	**Osteoclast differentiation abnormalities** • Osteoclast deficiency (M-CSF, RANK mutations) **Defects in osteoclast acidification**[5] • Carbonic anhydrase (*CAII* gene) • H^+-ATPase proton pump (*TGIRG1* gene) • Chloride channel (*CLCN7* gene) **Defects in osteoclast proteolysis**[5] • Cathepsin K (*CTSK* gene)
Clinical features	• Usually benign • Fracture resistant • Reduced buoyancy • Calvarial/mandibular thickening and torus mandibularis/palatinus • More severe phenotype in sclerosteosis, Van Buchem's disease, craniometaphyseal dysplasia, Camurati–Engelmann disease	• Clinical severity varies between genotypes • Bone expansion leading to nerve compression (raised intracranial pressure, nerve entrapment, visual impairment, cranial nerve palsies) • Increased fracture risk (due to biomechanically inferior bone) • Short stature, developmental delay • Pancytopenia/hepatosplenomegaly from bone marrow obliteration • Renal tubular acidosis
Bone markers	Increase in bone formation markers: BSAP, P1NP, osteocalcin	Decrease in bone resorption markers: urine NTX, urine DYPD, serum TRACP
X-ray features	Generalised sclerosis affecting predominantly the mandible and axial skeleton, with cortical thickening and bone remodelling without features of osteomalacia or osteopetrosis[7] (Figures 4a to c)	Cortical thickening with medullary encroachment and 'sandwich vertebrae' (dense sclerotic endplates, also known as 'rugger jersey spine')[13] (Figures 5a and b)
Bone biopsy	Increased bone formation (hyperosteoidosis, increased trabecular bone and bone formation rate)	Osteoclast rich or poor, but low resorptive activity (resorption surfaces and increased unresorbed primitive or spongiosa bone)
Treatment	• Target underlying cause • Manage complications of bony overgrowth • Surgical correction, glucocorticoids to reduce bone turnover (severe cases)	• Surgical correction • Bone marrow transplantation (severe cases)

Abbreviations: BSAP = bone-specific alkaline phosphatase; DYPD = deoxypyridinoline excretion; M-CSF = macrophage colony stimulating factor; NTX = N-telopeptide/creatinine ratio; PINP = procollagen type I N-terminal propeptide; RANK = receptor activator of nuclear factor κ B; TRACP = tartrate-resistant acid phosphatase.



Figures 4a to c. Radiographic features of osteosclerosis (increased osteoblast activity). Generalised sclerosis affecting (a, left) the mandible, (b, centre) the femur, with cortical thickening but no medullary encroachment and (c, right) the axial skeleton.

between 0.2 and 5.5 per 100,000 population. Radiographic features of osteosclerosis and osteopetrosis are shown in Figures 4a to c and Figures 5a and b, respectively.

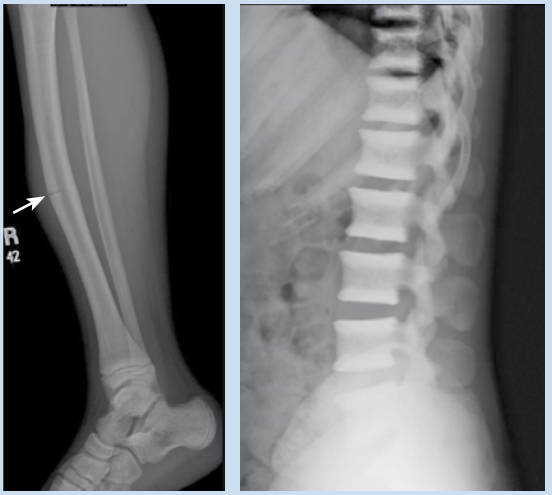
The patient in the case above presented with osteosclerosis on BMD measurement and bone biopsy, with oral exostoses and torus mandibularis but no family history of bone disorders. Secondary causes such as neoplasm or granulomatous or haematological disorders were not evident. Hypothyroidism, renal osteodystrophy, aluminium or vitamin D intoxication and hepatitis C were excluded. Although the serum tryptase level was elevated, suggesting possible mastocytosis, 24-hour urinary histamine and methylhistamine levels were normal and *c-KIT* mutation analysis was negative, making this condition very unlikely.[14]

In the absence of an identifiable secondary cause, a primary genetic bone disorder was considered the most likely cause for this patient's presentation. Bone biopsy confirmed increased bone formation, high-normal osteoclast activity and the absence of osteomalacia. This suggested osteosclerosis and a primary osteoblast-driven disorder rather than osteopetrosis caused by an osteoclast defect. The absence of syndactyly and systemic effects excluded a number of known genetic causes of generalised increased bone mass.

Other causes of increased BMD

Despite the many known causes of increased BMD, a cause cannot be identified in a significant proportion of patients. By definition, if BMD is normally distributed then 0.5% of the population have a BMD corresponding to a T-score of +2.5. Furthermore, pseudoelevations in BMD occur due to artefactual increases in measured calcium content and do not represent true elevations in bone mass.

In up to 35% of patients with an incidental finding of increased BMD on DXA, the cause cannot be identified.[1] Common clinical features in these patients include decreased buoyancy, mandibular enlargement, extra bone at tendon/ligament insertions, broad frame and increased BMI, with no increase in fracture risk, thereby representing a benign condition.[15] Bone geometry shows increased trabecular BMD and alterations in cortical bone density and structure leading to increased cortical strength.[16] BMD does not decline with age, suggesting attenuation of age-related bone loss, contributing to the high bone mass. Family members are also commonly affected, suggesting an underlying genetic disorder that is yet to be identified.



Figures 5a and b. Radiographic features of osteopetrosis (decreased osteoclast activity). a (far left). Tibia and fibula showing cortical thickening with medullary encroachment and a Looser's zone or stress fracture of the anterior aspect of the lower tibial shaft (arrow). b (left). Vertebrae with dense sclerotic endplates, known as 'sandwich vertebrae' or 'rugger jersey spine'.

Conclusion

The patient described here presented with generalised bone pain and torus mandibularis caused by osteosclerosis but had no evidence of bone marrow compromise or neurological sequelae. Secondary causes of osteosclerosis were excluded, suggesting a rare underlying primary sclerosing bone disorder. Normal bone resorption markers with elevated osteoclast numbers excluded an osteoclast defect as the driving cause of the high bone mass, and favoured a mechanism of osteoblast-driven bone formation. The absence of systemic features and the benign, stable clinical course support an undiscovered genetic cause. No association has been identified between the patient's dysregulated bone metabolism and her autoimmune phenotype, but there might be a link. The patient has been treated symptomatically with analgesia. ET

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

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