Bone Diseases

Osteoporosis
&
Osteomalacia

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راجعت سيدة عمرها 60 سنة بكسر كوليس (رض بسيط)، ما هي النقاط الأساسية في استجوابها؟

- .....
- القصة الطمثية
- العادات: تدخين، وكحول
- التغذية والفعالية الفيزيائية
- القصة الدوائية
- القصة العائلية

اتصل صديقك الذي يعاني من نوبة ربوية شديدة وقد وصف له الطبيب العلاج بالكورتيزون. ماذا تقول له

- إياك إياك
- ممكن لكن لا تتناوله بجرعة عالية
- ممكن لكن لفترة لا تتجاوز الأسبوع لأنه يخلخل العظام
- .....

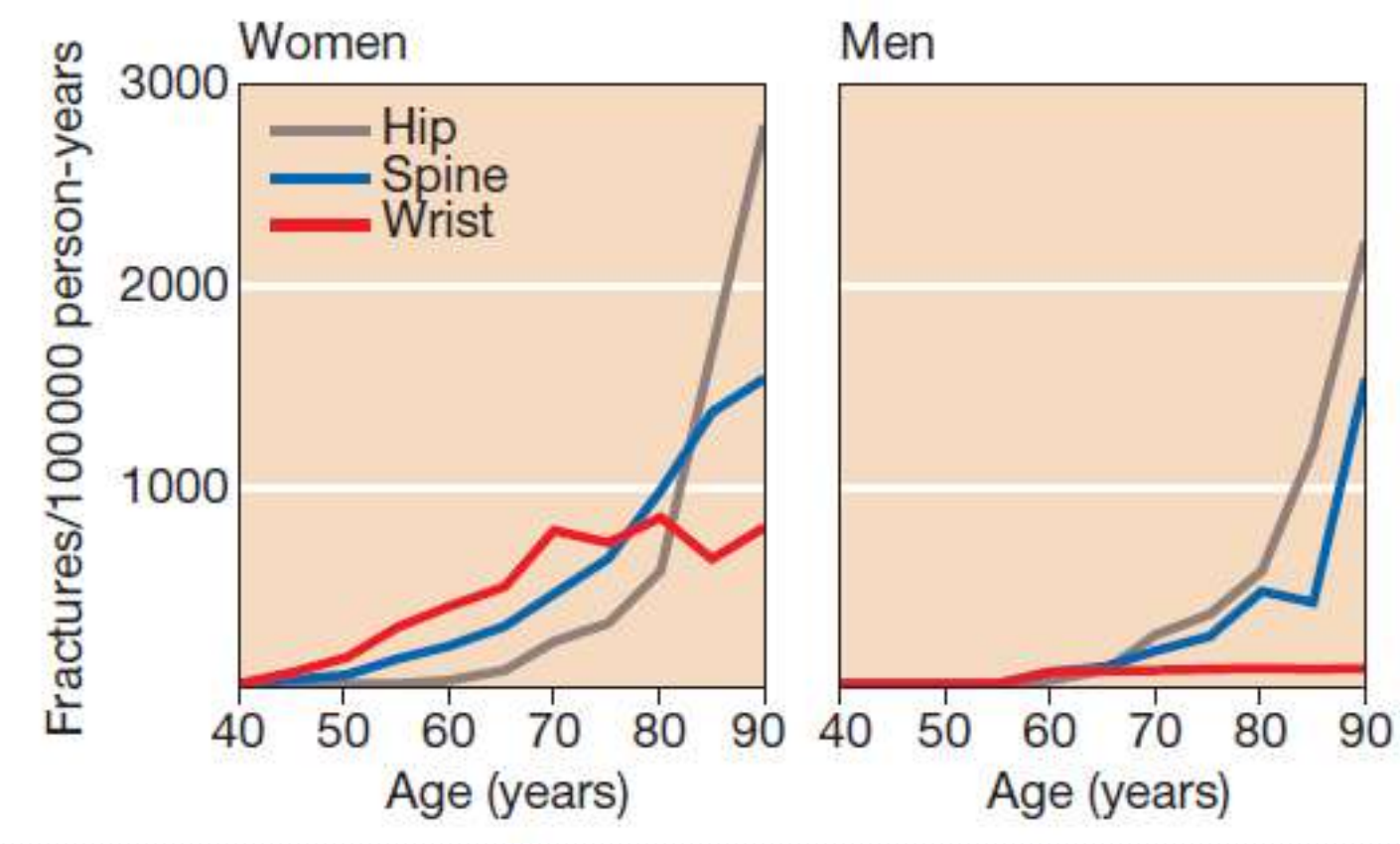
Corticosteroid induced osteoporosis

- Dose and duration
- No ‘safe’ dose of corticosteroid,
- Risk increases: prednisolone exceeds 7.5 mg daily for more than 3 months.

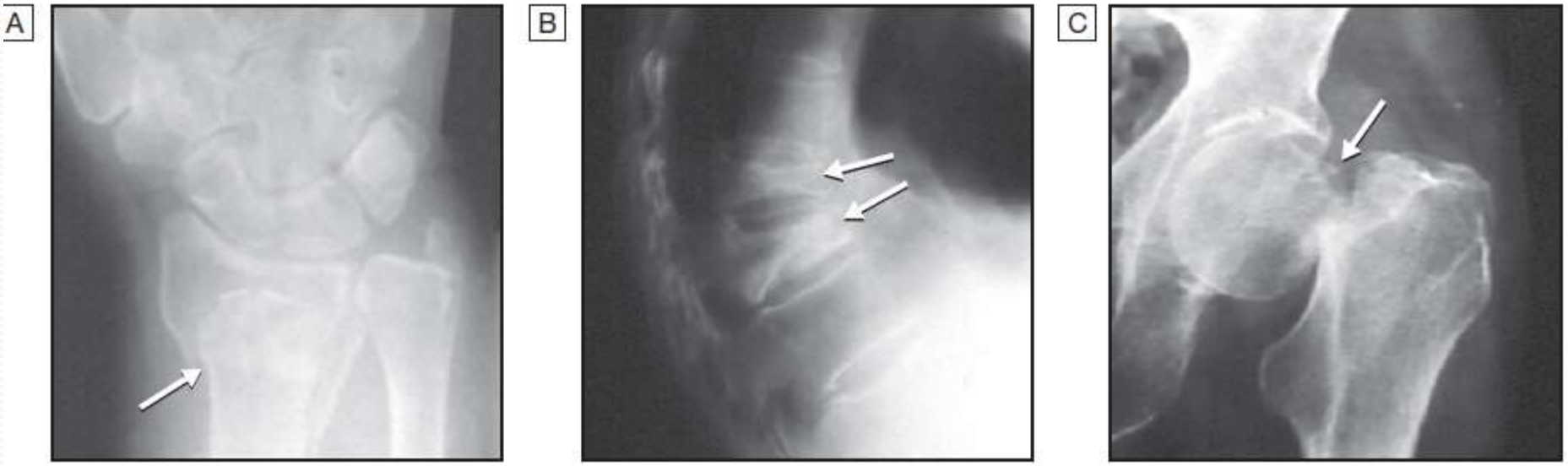
Corticosteroids

- **Reduced bone formation**:
  - direct inhibitory effect on osteoblast function
  - induced osteoblast and osteocyte apoptosis.
- **Inhibit intestinal calcium absorption**
- **Cause a renal leak of calcium**
  - reduce serum calcium
  - secondary hyperparathyroidism
- **Hypogonadism** (high-dose steroids).

Relationship between age and incidence of osteoporotic fractures

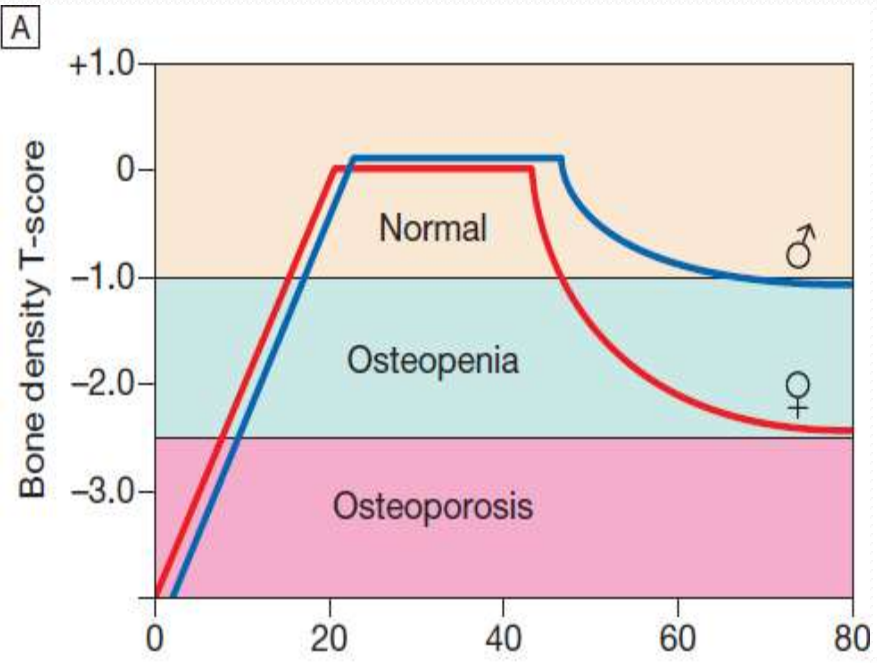


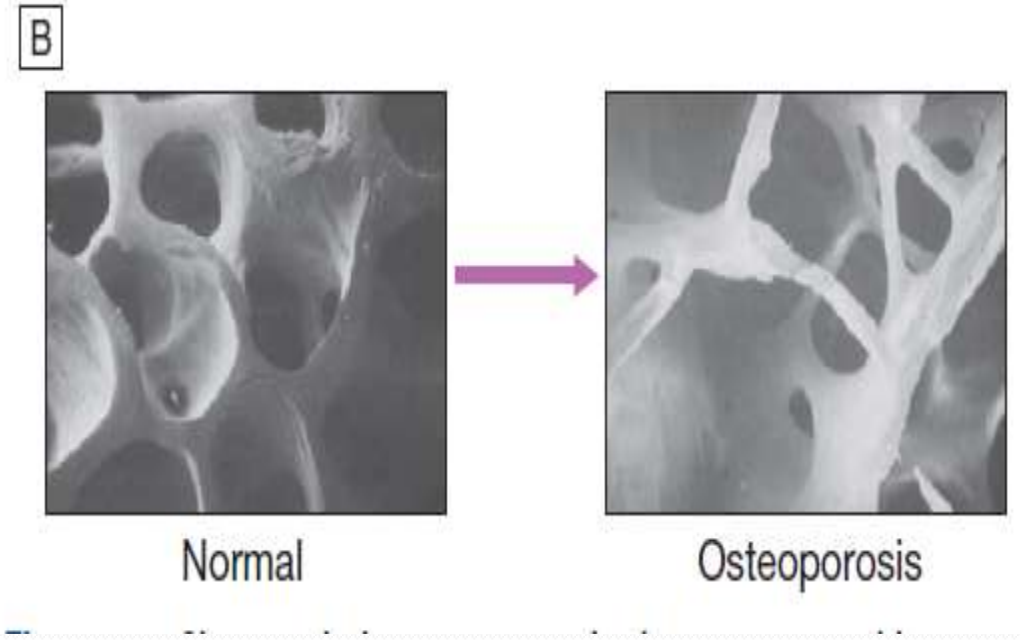
Osteoporosis



1 Osteoporotic fractures: X-rays. A Wrist (Colles fracture). B Spine. C Hip.

Changes in bone mass microstructure with age





A Changes in bone mass with age in men (blue line) and women (red line). **B** Scanning electron micrographs of normal bone (left) and osteoporotic bone (right).

Secondary causes of osteoporosis and osteoporotic fractures

Endocrine disease

- Hypogonadism
- Hyperthyroidism
- Hyperparathyroidism
- Cushing's syndrome

Inflammatory disease

- Inflammatory bowel disease
- Ankylosing spondylitis
- RA

Drugs

- Corticosteroids
- Gonadotrophin-releasing hormone (GnRH) agonists
- Aromatase inhibitors
- Thyroxine over-replacement
- Thiazolidinediones
- Sedatives
- Anticonvulsants
- Alcohol intake > 3 U/day
- Heparin

Gastrointestinal disease

- Malabsorption
- Chronic liver disease

Lung disease

- Chronic obstructive pulmonary disease
- Cystic fibrosis

Miscellaneous

- Myeloma
- Homocystinuria
- Anorexia nervosa*
- Highly trained athletes*
- HIV infection
- Gaucher's disease
- Systemic mastocytosis
- Immobilisation
- Body mass index < 18
- Heavy smokers
- Autoantibodies to osteoprotegerin (OPG)

*Hypogonadism also plays a role in osteoporosis associated with these conditions.

12 Get up and go test

To assess gait and balance, ask the patient to stand up from a sitting position, walk 10 m, turn and go back to the chair. A normal performance takes less than 12 seconds.

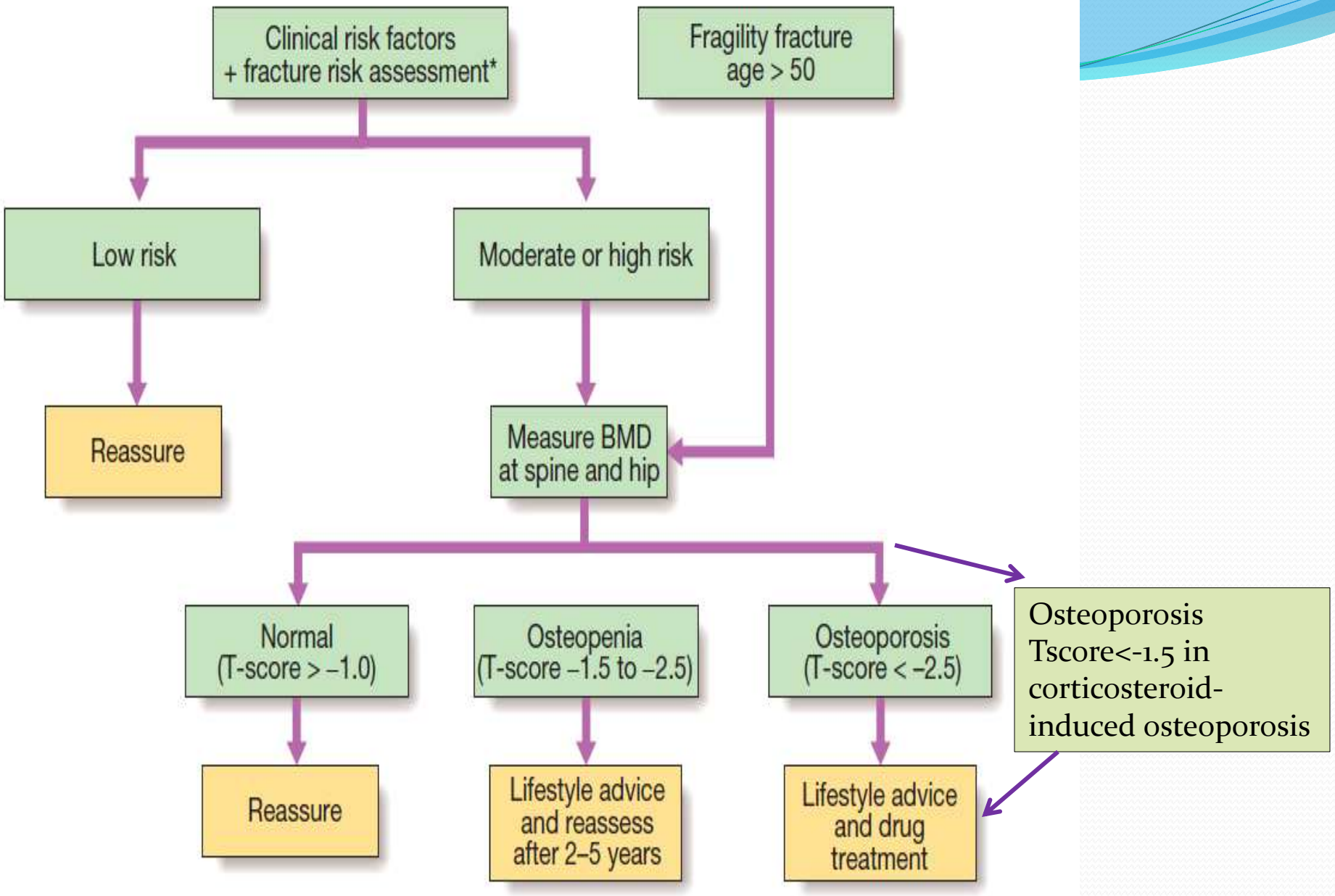
Difficulty rising?

Unsteady on standing?

Unsteady gait?

Unsteady on turning?

Unsteady on sitting down?



54 Algorithm for the investigation of patients with suspected osteoporosis. *Using FRAX® or QFracture (see Further information,
(BMD = bone mineral density)

25.76 Indications for bone densitometry

- Low trauma fracture age > 50 years*
- Clinical features of osteoporosis (height loss, kyphosis)
- Osteopenia on plain X-ray
- Corticosteroid therapy (> 7.5 mg prednisolone daily for > 3 mths)
- Family history of hip fracture
- Low body weight (BMI < 18)
- Early menopause (< 45 yrs)
- Diseases associated with osteoporosis
- Increased fracture risk on risk factor analysis (FRAX or QFracture)
- Assessing response of osteoporosis to treatment

*Defined as a fracture that occurs as the result of a fall from standing height or less.

25.79 Osteoporosis in old age

- **Bone loss**: due to increased bone turnover, with an age-related defect switch in differentiation of bone marrow stromal cells to form adipocytes as opposed to osteoblasts.
- **Fractures due to osteoporosis**: common cause of morbidity and mortality, although fracture healing is not delayed by age.
- **Recurrent fractures**: those who suffer a fragility fracture are at increased risk of further fracture, so should be investigated for osteoporosis and treated if this is confirmed.
- **Falls**: risk factors for falls (such as visual and neuromuscular impairments) are independent risk factors for hip fracture in elderly women, so intervention to prevent falls is as important as treatment of osteoporosis (p. 172).
- **Intravenous zoledronic acid**: reduces mortality and subsequent fracture in elderly patients with hip fractures.
- **Calcium and vitamin D**: reduce the risk of fractures in those who are housebound or living in care homes.

Drug treatment

Considered in patients:

- with BMD T-score values below –2.5
- below –1.5 in corticosteroid-induced steoporosis
- vertebral fractures, irrespective of BMD, unless they resulted from significant trauma.

25.77 Effects of drugs on the risk of osteoporotic fractures

Drug	Regimen	Vertebral fracture	Non-vertebral fracture	Hip fracture
Alendronic acid	70 mg/wk orally	+	+	+
Risedronate	35 mg/wk orally	+	+	+
Ibandronate	150 mg/mth orally 3 mg 3-monthly IV	+	+/–	–
Zoledronic acid	5 mg annually IV	+	+	+
Denosumab	60 mg 6-monthly SC	+	+	+
Strontium ranelate	2 g daily orally	+	+	+/–
Hormone replacement therapy	Various preparations	+	+	+
PTH 1-34	20 µg/day SC	+	+	–
PTH 1-84	100 µg/day SC	+	–	–
Raloxifene	60 mg/day orally	+	–	–
Tibolone	1.25 mg/day orally	+	+	–
Calcium/vitamin D	500 mg calcium and 800 U vitamin D orally	–	+/–	–

(+ effective, – not effective; +/– equivocal results, or efficacy based on post-hoc subgroup analysis of clinical trials.)

Bisphosphonates

- inhibit bone resorption by binding to hydroxyapatite crystals on the bone surface.
- increase in spine BMD of about 5–8% and in hip BMD of 2–4% during the first 3 years of treatment and plateaus thereafter.

25.78 Adverse effects of bisphosphonates

Common
• Upper gastrointestinal intolerance (oral) • Acute phase response (intravenous)
Less common
• Atrial fibrillation (intravenous zoledronic acid) • Renal impairment (intravenous zoledronic acid) • Atypical subtrochanteric fractures
Rare
• Uveitis • Osteonecrosis of the jaw → good oral hygiene

Osteonecrosis of the jaw (ONJ) necrotic bone in the mandible or maxilla: after tooth extraction

- Most cases in cancer patients with coexisting morbidity (infection and diabetes) + received high doses of intravenous bisphosphonates
- Very rare with the dose regimes used in osteoporosis.
- Bisphosphonates for any reason: good oral hygiene.
- Temporarily stopping medication in patients undergoing tooth extraction is not necessary or alters the occurrence of ONJ.

Atypical subtrochanteric fractures in long-term bisphosphonates,

Benefits of bisphosphonate therapy far outweigh the risks.

Denosumab

- Monoclonal antibody neutralises the effects of RANKL
- Subcutaneous injection every 6 months (osteoporosis).
- Reduces the risk of hip fractures by 40%, vertebral fractures by 70% and other non-vertebral fractures by 20%.
- few adverse effects but there are isolated reports of ONJ with long-term use.
- Short duration of action ⟶ long-term treatment.

Strontium ranelate

- Reduces after 3 years
  - vertebral fracture risk byabout 50%
  - non-vertebral fracture risk by 12%. The mechanism of action is poorly understood.
- Changes in BMD (12%), partly artefact (substitution of strontium for calcium).
- Common adverse effect: diarrhoea.
- Contraindicated cardiovascular disease: increases risk of
  - myocardial infarction.
  - venous thrombosis.
- Rarely, a severe rash occurs (indication to stop treatment).

PTH: 1-34 fragment of PTH (teriparatide)

- Single daily subcutaneous injection of 20 µg.
- Increases BMD by 10% or more in osteoporotic subjects
- Reduces risk of
  - vertebral fractures by about 65%
  - non-vertebral fractures by 50%.
- Expensive reserved for patients :
  - with severe osteoporosis (BMD T-score of –3.5 to –4.0 or below
  - failed to respond adequately to other treatments.
- Duration of treatment is 24 months, then antiresorptive drug, (bisphosphonate) to maintain the increase in BMD.
- Not be administered at the same time as bisphosphonates (blunts the anabolic effect).
- Teriparatide because of failure to respond, existing treatments should be stopped.

Hormone replacement therapy (HRT)

Cyclical HRT with oestrogen and progestogen:

- Prevents post-menopausal bone loss
- Reduces risk of vertebral and non-vertebral fractures in post-menopausal women.
- Indicated for.
  - prevention of osteoporosis in early menopause
  - treatment of women with osteoporosis in their early fifties menopausal symptoms.
- HRT should be avoided in older women with established osteoporosis
- increases the risk of breast cancer and cardiovascular disease.

Raloxifene and Tibolone

Raloxifene: partial agonist at oestrogen receptors in bone and liver, antagonist in breast and endometrium, It results in a modest

- increase in BMD (2%)
- 40% reduction in vertebral fractures,
- does not influence the risk of non-vertebral fracture
- provoke muscle cramps
- worsen hot flushes.
- increases the risk of VTE
- reduces the risk of breast cancer
- does not influence the risk of cardiovascular disease.

Tibolone is:

- steroid with partial agonist activity at oestrogen, progestogen and androgen receptors.
- similar effects on BMD to raloxifene
- prevent vertebral and non-vertebral fractures in post-menopausal osteoporosis.
- associated with a slightly increased risk of stroke but a reduced risk of breast cancer.

Calcitonin

- osteoclast inhibitor that has weak antifracture efficacy but is no longer used in the treatmentof osteoporosis because of concerns about an increased risk of cancer with long-term use.
- (unlicensed) in the short-term treatment of patients with acute vertebral fracture, (100–200 U daily).

Duration of therapy and monitoring response

- Periodic review at **5-yearly** intervals.
- Alendronate and risedronate: safe and effective for up to 10 years in most patients, one randomised trial with alendronate: overall fracture rates after 5 years = 10 years treatment .
- Intravenous **zoledronic** acid: **3 years**' treatment give **equal** protection from fractures as **6 years**' treatment.
- Duration of treatment for strontium has not been established.
- **PTH: 2-year course** of treatment and followed by long-term antiresorptive therapy.

Vertrbroplasty (VP) Kyphoplasty (KP)

- **(VP)**Treatment of painful vertebral compression fractures.
- injecting methyl methacrylate (MMA) into the affected
- vertebral body.

EBM 25.80 **Vertebroplasty in painful vertebral fractures**

'Meta-analysis of individual patient data from two placebo controlled trials of vertebroplasty showed no advantage of active treatment over a sham procedure.'

- Staples MP, et al BMJ 2011; 343:d3952.

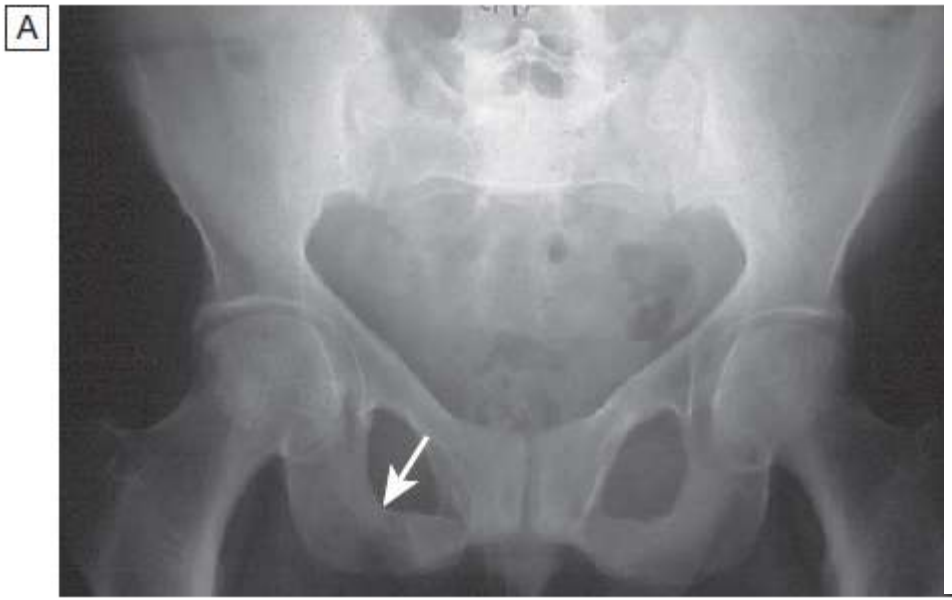
(KP) a needle is introduced into the affected vertebral body and a balloon is inflated,which is then filled with MMA.

- More effective than medical treatment at relieving pain in the
- short term, with results similar to VP.
- Both procedures are generally safe but serious adverse effects include
  - spinal cord compression,
  - fat embolus.

مريض عمره 65 سنة قيد العلاج منذ 3 سنوات من أجل تخلخل عظام (كشف بانخماص الفقرة القطنية الأولى) يراجع حالياً بكسر عنق فخذ. ما المقاربة؟

- Recurrent fractures whilst on treatment.
- DEXA:
  - increased, then treatment should be continued.
  - no BMD response or significant bone loss patient should be questioned about adherence, if yes different treatment should be considered.

Osteomalacia



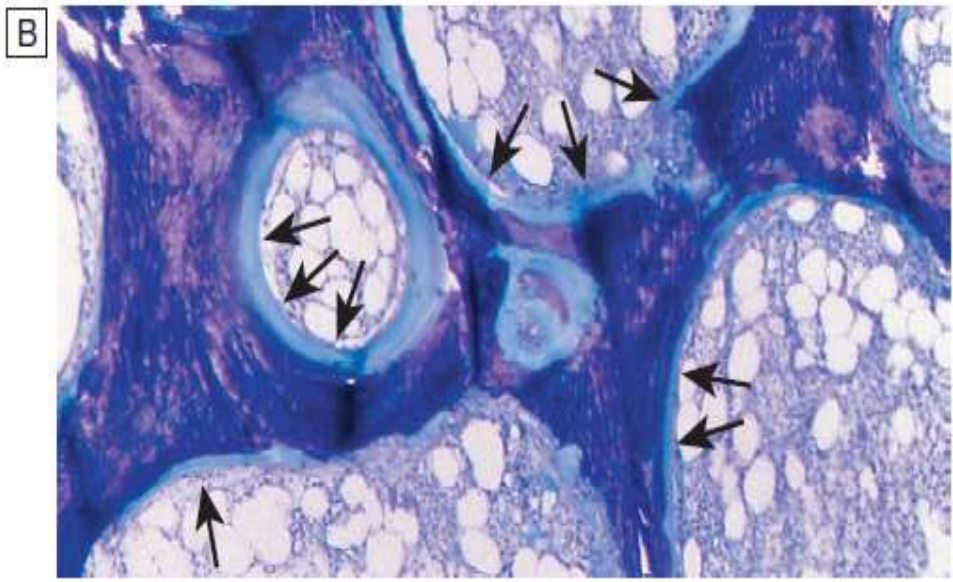


Fig. 25.56 Osteomalacia. A X-ray of the pelvis showing Looser's zones (arrow). B Photomicrograph of bone biopsy from osteomalacic patient showing thick osteoid seams (stained light blue) that cover almost all of the bone surface. Calcified bone is stained dark blue.

25.81 Causes of osteomalacia and rickets

Cause	Predisposing factor	Mechanism
Vitamin D deficiency		
Classical	Lack of sunlight exposure and poor diet	Reduced cholecalciferol synthesis in the skin/low levels of vitamin D in diet
Gastrointestinal disease	Malabsorption	Malabsorption of dietary vitamin D and calcium
Failure of 1,25 vitamin D synthesis		
Chronic renal failure	Hyperphosphataemia and kidney damage	Impaired conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$
Vitamin D-resistant rickets type I (autosomal recessive)	Loss-of-function mutations in renal 25(OH)D 1α-hydroxylase enzyme	Impaired conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$
Vitamin D receptor defects		
Vitamin D-resistant rickets type II (autosomal recessive)	Loss-of-function mutations in vitamin D receptor	Impaired response to $1,25(OH)_2D_3$
Defects in phosphate and pyrophosphate metabolism		
Hypophosphataemic rickets (X-linked dominant)	Mutations in *PHEX*	Increased FGF23 production (mechanism unclear)
Autosomal dominant hypophosphataemic rickets	Mutation in *FGF23*	Mutant FGF23 is resistant to degradation
Autosomal recessive hypophosphataemic rickets	*DMP1* mutation	Increased production of FGF23 Local deficiency of DMP1 inhibits mineralisation
Tumour-induced hypophosphataemic osteomalacia	Ectopic production of FGF23 by tumour	Over-production of FGF23
Hypophosphatasia	Mutations in bone-specific alkaline phosphatase	Inhibition of bone mineralisation due to accumulation of pyrophosphate in bone
Iatrogenic and other		
Bisphosphonate therapy	High-dose etidronate/pamidronate	Drug-induced impairment of mineralisation
Aluminium	Use of aluminium-containing phosphate binders or aluminium in dialysis fluid	Aluminium-induced impairment of mineralisation
Fluoride	High fluoride in water	Fluoride inhibits mineralisation

Paget's disease of bone (PDB)

- Focal areas of increased and disorganised bone remodelling.
- It mostly affects the axial skeleton, and bones that are commonly involved include the pelvis, femur, tibia, lumbar spine, skull and scapula.
- seldom diagnosed before the age of 40,
- up to 8% of the UK population by the age of 85.
- The disease is common in Caucasians from north-west and southern Europe but is rare in Scandinavians, Asians, Chinese and Japanese.

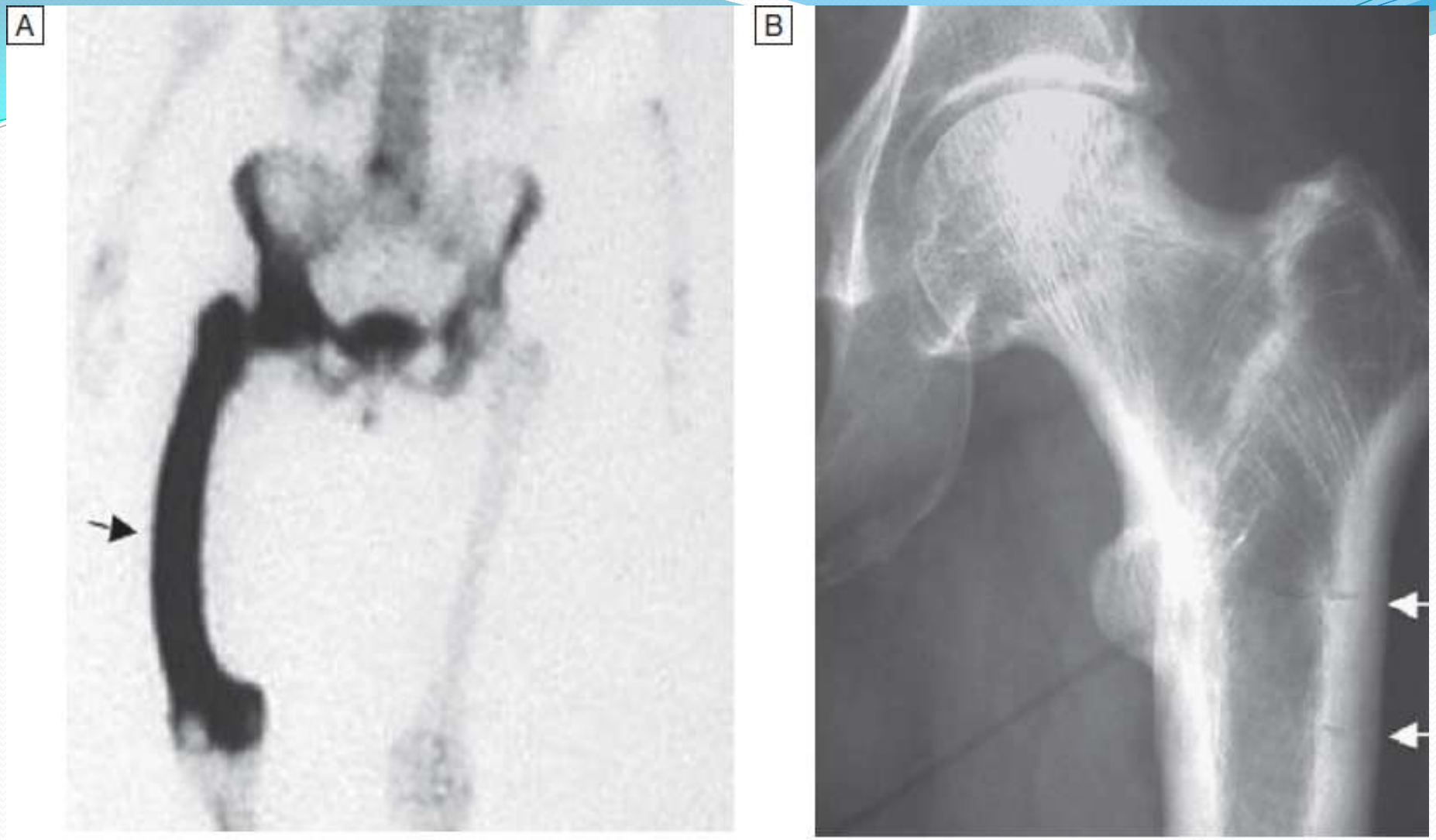


Fig. 25.57 Paget's disease. A Isotope bone scan from a patient with Paget's disease, illustrating the intense tracer uptake and deformity of the affected femur. B The typical radiographic features with expansion of the femur, alternating areas of osteosclerosis and radiolucency of the trochanter, and pseudofractures breaching the bone cortex (arrows).

Pathophysiology

- Increased :
  - osteoclastic bone resorption,
  - marrow fibrosis,
  - vascularity of bone
  - osteoblast activity.
- Bone in PDB is architecturally abnormal with reduced mechanical strength.
- Genetic factors: mutations in the *SQSTM1 gene are a common*
- Nuclear inclusionbodies in osteoclasts: slow virus infection with measles or distemper but the evidence is conflicting.
- Biomechanical factors may help determine the pattern of involvement,
- Involvement of subchondral bone can compromise the joint and predispose to OA ('Pagetic arthropathy').

Clinical features

- Bone pain, deformity, deafness and pathological fractures
- Asymptomatic and diagnosed from an abnormal X-ray or blood test performed for another reason.
- Clinical signs:
  - bone deformity and expansion (weightbearing bones)
  - increased warmth over affected bones,
  - pathological fracture.
  - cranial enlargement.
  - neurological problems (deafness, cranial nerve defects, nerve root pain, spinal cord compression and spinal stenosis)
  - high-output cardiac failure in elderly patients with limited cardiac reserve.
- The increased vascularity of Pagetic bone makes operative procedures difficult.

Investigations

- The characteristic features:
  - **elevated serum ALP**
  - bone expansion on X-ray,
  - alternating areas of radiolucency and osteosclerosis
- Bone biopsy help to exclude osteosclerotic metastases in cases of diagnostic uncertainty.

Management

25.82 Medical management of Paget's disease

Drug	Route of administration	Dose	Inhibitory effect on bone turnover
Etidronate	Oral	400 mg daily for 3–6 mths	+
Tiludronate	Oral	400 mg daily for 3–6 mths	+
Risedronate	Oral	30 mg daily for 2 mths	++
Pamidronate	IV	1–3 × 60 mg	++
Zoledronic acid	IV	1 × 5 mg	+++
Calcitonin	SC	100–200 U 3 times weekly for 2–3 mths	+

+ moderately effective; ++ effective; +++ highly effective.


شكراً
لإصغائكم